

Triggers and onset of acute myocardial infarction in the Middle East

The Myocardial Infarction Triggers and Onset in Jordan (MINTOR) Study

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Abstract

Background: In the West, acute myocardial infarction occurs after exposure to emotional or physical stress in about 20–30% of cases, and circadian variation has an incidence peak in the early morning hours, on Mondays, and during winter months. Whether similar frequency of triggers and circadian variation occurs in middle-eastern patients with acute myocardial infarction is largely unknown. **Methods and Results:** Consecutive patients (n=962) admitted with acute ST-elevation myocardial infarction were enrolled. Patients were interviewed within 24 h of admission and were asked about exposure to potential emotional or physical triggers prior to the onset of chest pain. Wake-up time, time, and date of pain onset were also recorded. There were 815 men and 147 women (mean ages of 53.8 and 62.7 years, respectively). Among them, there were 31% hypertensives, 36% diabetics, and 60% smokers. Exposure to a triggering event was reported by 411 patients (42.7%), including emotional trigger (25.9%; anger was the most common, 14.7%), physical exertion (10.5%), heavy meal (2%), sexual activity (1.8%), and smoking binge (0.5%). More than half of the patients (55%) had the onset of pain within the first 4 h after waking up. Friday (local weekend) was the day with the highest incidence of infarction with a 34% relative-risk increase ($p<0.05$) as compared with Sunday, the day with the least incidence. Incidence of infarction during the winter months did not differ significantly from those during the summer months. **Conclusions:** In this middle-eastern study, more than 40% of the patients admitted with acute myocardial infarction reported exposure to emotional or physical trigger. Anger was the most common trigger. We also observed that peak incidence of myocardial infarction in the early morning hours was similar to that obtained from western data. However, Friday not Monday was the day of peak incidence. Higher incidence was not observed during the winter months. In addition to coronary risk-factor control, stress management and behavioral therapy have a potential impact on the incidence of acute myocardial infarction.

Key words: Acute myocardial infarction; Triggers of myocardial infarction; Middle-eastern population

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Introduction

Exposure to emotional or physical stressful events can trigger acute myocardial infarction (AMI)¹⁻⁵. In the West, up to 20–30% of AMI cases are preceded by a triggering event such as extreme emotional event (i.e., death of a significant person, anger, anxiety, fear, work conflicts, and legal problems)⁶⁻⁸, or physical effort such as heavy physical exertion, lifting a heavy object, snow shoveling, and sexual activity⁹⁻¹². Moreover, when a whole community encounters stressful events such as natural disasters (i.e., earthquakes or hurricanes), war or air-raid alarms, and final matches of a championship, incidence of AMI increases in that community in the immediate period after the event¹³⁻¹⁶.

Circadian and seasonal variations in AMI occurrence have been documented, and indicate that triggering factors may play a role in causing cardiac events¹⁷. The circadian rhythm of circulating catecholamines and other stress hormones can explain the increase in AMI incidence among working individuals on Mondays in the early morning hours, and among housewives on the weekends¹⁸⁻²⁰. Seasonal variation in AMI incidence, with a winter peak and summer nadir, is also explained on the basis of certain meteorological triggers^{21,22}. It is largely unknown whether the triggers of AMI in the Middle East have the same frequency and nature as those in the West, and whether there are peaks of AMI incidence in a particular time of the day, day of the week, or season.

Methods

In the MINTOR (*Myocardial INfarction Triggers and Onset in JoRdan*) study, 962 consecutive patients with acute ST-elevation MI (STEMI) admitted to the coronary care units of 7 hospitals from January 2004 to December 2006 were enrolled. Acute STEMI was defined as the presence of typical chest pain, ST-segment elevation (≥ 2 mm) in at least two contiguous leads on the 12-lead electrocardiogram, and elevated cardiac troponin or CPK-isoenzyme-MB (CK-MB) > 2 times the upper limit of normal. For all patients, history of hypertension, diabetes, and smoking and past diagnosis of cardiovascular disease were recorded. Patients were interviewed at bedside within 24 h of admission and were asked about their personal exposure to potential triggering events in the 48-h period preceding AMI onset including (1) death of a significant person, (2) intense anger, sorrow, fear, or joy related to an event at a personal level such as family or work conflict, legal problem, financial stress, sickness of a relative, or emotional reaction to a local or regional event, (3) performing heavy physical effort, and (4) sexual activity, heavy meal, smoking binge, or presence of non-cardiac illness

or trauma. Patients were also asked about the time of onset of chest pain to exactly record the time and date of AMI, and whether onset of pain was during sleep or wake hours. The time elapsed from waking up to the onset of pain was also recorded. Frequency of reperfusion therapy, medication use, in-hospital complications, and deaths were also included.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) and were compared using the unpaired t-test. Categorical variables were expressed as percentages of the study population and were compared using the chi-square test. Statistical significance was defined as $p \leq 0.05$.

Results

Baseline characteristics of the 962 patients (15% women) are shown in Table 1. Sixty percent of men were younger and 74% of women were older than 55 years of age. As compared with men, women were older (mean age 73.7 and 53.8 years, respectively; $p < 0.05$), had higher prevalence of hypertension (51% and 23%; $p < 0.01$) and diabetes (59% and 32%; $p < 0.01$) and less prevalence of smoking (16% and 68%; $p < 0.01$). Prior cardiovascular disease was present in 8.9% of the patients. Reperfusion therapy for 815 eligible patients (84% of the whole group) was administered to 709 patients (87%), including thrombolytic therapy (342; 42%) and primary percutaneous coronary intervention (367; 45%). Aspirin and/or clopidogrel, statins, betablockers, and angiotensin converting enzyme inhibitors/angiotensin II blockers were used in 95, 84, 68, and 58%, respectively. Length of stay was < 3 days in 35% and 3–7 days in 54% of patients, and in-hospital mortality was 3.2%.

Of all patients, 411 (42.7%) confirmed the presence of a triggering event prior to the onset of chest pain. The most common triggers were emotional (25.9%) including anger, financial stresses, death of a significant person, and extreme sorrow or joy (Table 2). Other triggers reported by patients were heavy physical activity (10.5%), heavy meal (2%), non-cardiac illness or trauma (2%), sexual activity (1.8%), and smoking binge (0.5%). As compared to patients with non-triggered AMI, patients with triggered AMI showed non-significant (ns) difference in mean age (55 years in each group), percentage of men (84 and 86%; $p = ns$), percentage of anterior wall AMI (54 and 52%; $p = ns$), percentage of diabetics (32 and 39%; $p = ns$), or in-hospital mortality (2.5 and 4%; $p = 0.56$).

Onset of pain occurred during sleeping in 240 (25%)

Table 1. Clinical characteristics, therapy, and outcome of 962 consecutive patients with acute ST-elevation myocardial infarction.

Clinical features	N (%)
Men:Women	815 (85):147 (15)
Mean ages (years)	
Men	53.8
Women	62.7
Current cigarette smoking	577 (60)
Hypertension	298 (31)
Diabetes mellitus	344 (36)
Past cardiovascular history	86 (8.9)
Anterior-wall MI	504 (52)
Medication use during hospital stay	
Aspirin and/or clopidogrel	914 (95)
Statins	805 (84)
Beta-blockers	653 (68)
ACE inhibitors/angiotensin II blockers	562 (58)
Reperfusion and procedures during hospital stay	
Reperfusions*	709 (87)
Thrombolysis	342 (42)
Primary percutaneous coronary revascularization	367 (45)
Coronary procedures	
Diagnostic coronary angiography	792 (82)
Percutaneous coronary revascularizations*	606 (63)
Coronary bypass surgery	87 (9)
In-hospital mortality	31 (3.2)

*For the 815 eligible patients.

and while awake in 722 (75%) patients. Onset of chest pain occurred within the first 4 h of waking up in 532 patients (55.3%) and the remaining patients (44.7%) had the onset of pain after times ranging from >4 to 24 h after waking up.

There was a weekly variation in AMI with a 34% increase in the relative risk (RR) of AMI onset on Fridays ($p<0.05$) and a trough on Sundays as compared with the expected number of cases, if homogeneity was assumed. The same pattern of variation (i.e., Friday peak) was observed among men (37%-increase in RR; $p<0.05$), working individuals (34%-increase in RR; $p<0.05$), individuals with triggered AMI (39%-increase in RR; $p<0.05$) and working individuals with triggered AMI (51%-increase in RR; $p<0.001$). The small number of women with AMI precluded any conclusion regarding weekly variation in MI incidence.

The highest prevalence of MI occurred in January, with a 61%-increase in the RR as compared with August (9.8 and 6.1%; $p<0.02$), the month with the lowest incidence.

Table 2. Triggering events in acute myocardial infarction patients.

Triggers	N	%
No trigger	551	57.3
Trigger preceded chest pain	411	42.7
Emotional	249	25.9
Anger	141	14.7
Financial problem	50	5.2
Death of a significant person	28	2.9
Sorrow	19	2
Extreme fear	9	0.9
Extreme joy	2	0.2
Physical activity	101	10.5
Heavy meal	19	2
Non-cardiac illness/trauma	19	2
Sexual activity	17	1.8
Smoking binge	6	0.5

No significant seasonal variation was observed in AMI incidence between the winter (December to February) and summer months (June to August), with a 11.8%-increase in the RR ($p=ns$).

Discussion

Rupture of the coronary atherosclerotic plaque and subsequent formation of occlusive thrombus is the most common mechanism of acute STEMI. Usually, the ruptured coronary plaque is a minimally detectable lesion under angiography that does not produce any symptom before rupture²³. Such rupture can be either spontaneous or occur after exposure to an emotional or physical trigger. The potential mechanisms responsible for such plaque rupture include catecholamine surge causing increase in heart rate, blood pressure, and myocardial oxygen demand; hypercoagulability state; depressed fibrinolysis; increased platelet adhesiveness and aggregability; angiotensin II stimulation, baroreceptor reflexes inhibition; and increased vascular tone²⁴⁻²⁶.

In the West, 20–30% of STEMI are attributed to triggering events (Table 3). A meta-analysis of 17 studies that evaluated frequency of triggers in AMI found that the onset of symptoms was preceded by emotional stress in 6.8%, heavy physical exertion in 6.1%, eating in 8.2%, and sexual activity in 1.1% of cases⁶. Anger was reported to precede 2 and 8% of AMI in the 2- and 24-h periods, respectively, immediately before the onset of symptoms².

In the present study, more than four of every ten patients (42.7%) reported a triggering event prior to the onset

Table 3. Triggers of acute myocardial infarction.

Triggers	References
Anger	2,3,7,8
Circadian variation	17,19,20,23,34-36,40
Death of a significant person	8
Earthquake	13,28
Emotional stress	3-6
Holiday season (independent of cold weather)	47
Hostility	45,46
Lack of sleep	2
Meteorological stress (exposure to cold and windy weather, getting wet during rain)	21,37,44
Overeating	2,6
Physical exertion	10,11
Seasonal variation	18,22,37,38,40
Sexual activity	12
Sudden death from overwork (Karoshi), work stress, job strain	48,49
Surgery, anesthesia, and medical procedures	4,6
Traffic	50
War and large-scale attacks	14,15,27
World cup (soccer)	16

of chest pain. Regarding types of triggers, there is a difference between our patients and those in the West⁶. Our patients reported more emotional (26%) and less physical triggers (11%) and heavy meal intake (2%) prior to AMI onset.

Regarding our patients, only triggers reported to occur within the 48-h period preceding onset of chest pain were taken into consideration. For some investigators, duration of 2 h for hazard after episode of anger or sexual activity² and up to 1 h after physical activity were found to be considerably short¹². However, others found that duration of the pathophysiological changes induced by the trigger can extend from few days up one week or probably 30 days after exposure^{27,28}. Various cultural, social, and economical factors can account for regional and geographic differences in prevalence and types of trigger. Different ethnic groups living in the same geographic area show circadian variation in the onset of AMI²⁹. Exposure to a trigger does not unavoidably lead to AMI. Although presence of a vulnerable coronary plaque is a prerequisite for AMI, there is evidence that regular exercise, stress management, quitting smoking, controlling coronary risk factors, and use of aspirin, betablockers, and calcium channel blockers³⁰⁻³³ have a protective effect against trigger-induced coronary events.

The early morning and the first few hours after waking up witness more cases of AMI than other times of the day. More than half of our patients had onset of chest pain in the first 4 hours after waking up. Such circadian rhythm

is attributed to early morning hypercoagulability and catecholamine surge. Onset of AMI during sleep in our study (25%) was similar to that reported in the West (21%)⁶.

Western studies showed a weekly (circaseptal) variation in AMI onset with peak and nadir incidence on Mondays and weekends, respectively, mainly in the working population³⁴ and, to some extent, in the non-working population^{35,36}. As compared with the other days, especially Saturdays and Sundays (the start of the working days in the West), we observed that Friday (the local weekend) witnessed a significantly higher number of AMI cases among the whole study group, working individuals, and those with triggered AMI. It is possible that organized social events and family gatherings that take place on this day, more than on other days of the week, may favor more friction between individuals and thus trigger cardiac events. If this observation is confirmed by studies from other countries in the region, it will be important to emphasize that avoiding stressful events and inter-individual friction on this day (and other days) can lower the incidence of AMI.

Seasonal (circannular) variation in AMI incidence observed in the West is explained by certain meteorological factors, infection, and fluctuating cholesterol blood levels that increase in winter^{37,38}. In the present study, although there is a peak incidence of cases in January (one of the coldest months in the winter) and a nadir in the hot month

of August, significant difference between winter and summer months was not found in AMI incidence. Absence of seasonal variation in AMI was observed in diabetics and among individuals on betablocker or aspirin therapy³⁹ in regions without temperature extremes⁴⁰ similar to those observed in Jordan. Since AMI was found to increase in colder days in both winter and summer, season might not be the sole determining factor. Moreover, unequal seasonal variation in AMI in different subgroups of the same population suggests the presence of biological variables of racial, genetic, or cultural origin⁴¹.

Mortality was not different between patients with or without trigger. Mortality rate was low to start with, probably because of younger age-groups (especially among men) and the high rate of use of reperfusion therapy (which is higher than that reported by some Western studies)⁴².

Limitations of the study

The MINTOR study was not a registry, but rather a study on consecutive patients admitted mostly to tertiary centers. Thus it may not reflect the level of care offered at less-costly hospitals. Frequency of triggers could have been affected by several factors. Some patients may have over- or underestimated the impact of triggers because of individual variation in tolerance to daily life stress. Others may have even denied exposure to certain triggers. Furthermore, cases in which full information about triggers could not be obtained, such as patients who had sudden death or were arrested in the emergency room, were excluded. The recall bias is another potential limitation because patients did not report with the same accuracy episodes of stressful events occurred prior to the onset of chest pain. Similar to other studies, we relied on self-report of triggering events rather than on cumbersome scales⁴³. Larger studies are needed to confirm the frequency of triggers and weekly variation in AMI incidence observed in the present study.

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References

1. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol.* 2008 Apr 1;51(13):1237-46.

2. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman r, Benson H, Müller JE. Determinants of myocardial infarction onset study investigators. Triggering of acute myocardial infarction onset by episodes of anger. *N Eng J Med.* 1995 Oct 1;9(7):1720-5.
3. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice. The emerging field of behavioral cardiology. *J Am Coll Cardiol.* 2005 Mar 1;45(5):637-51.
4. Tofler GH, Stone PH, Maclure M, Edeiman E, Davis VG, Robertson T, Antman EM, Muller JE. Analysis of possible triggers of acute myocardial infarction (the MILLIS Study). *Am J Cardiol.* 1990 Jul 1; 66(1):22-7.
5. Stansfeld SA, Fuhrer R, Shipley MJ, Marmot MG. Psychological distress as a risk factor for coronary heart disease in the Whitehall II Study. *Int J Epidemiol.* 2002;31:248-55.
6. Culić V, Eterović D, Mirić D. Meta-analysis of possible external triggers of acute myocardial infarction. *Int J Cardiol.* 2005 Mar 10; 99(10):1-8.
7. Möller J, Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A. Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). *Psychosom Med.* 1999 Nov-Dec;61(6):842-9.
8. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child; a nationwide prospective study in Denmark. *Circulation.* 2002 Sep 24;106(13):1634-8.
9. Hammoudeh AJ, Haft JI. Coronary plaque rupture in acute coronary syndromes triggered by snow shoveling. *New Eng J Med.* 1996 Dec 26;335(26):2001.
10. von Klot S, Mittleman MA, Dockery DW, Heier M, Meisinger C, Hormann A, Wichmann HE, Peters A. Intensity of physical exertion and triggering of myocardial infarction: a case-crossover study. *Eur Heart J.* 2008 Aug;29(15):1881-8.
11. Willich SN, Lewis M, Lowel H, Arntz H, Schubert F, Schroder R, for Triggers and Mechanisms of Myocardial Infarction Study Group. Physical exertion as a trigger of acute myocardial infarction. *N Eng J Med.* 1993 Dec 2;329(23):1684-90.
12. Müller JE, Mittleman MA, Maclure M, Sherwood JB, Tofler GH. Triggering myocardial infarction by sexual activity: Low absolute risk and prevention by regular exercise. Determinants of Myocardial Infarction Onset Study Investigators. *JAMA.* 1996 May 8;275(18):1405-9.
13. Brown DL. Disparate effects of the 1989 Loma Prieta and 1994 Northridge earthquakes on hospital admissions for acute myocardial infarction: importance of superimposition of triggers. *Am Heart J.* 1999 May;137(5):830-6.
14. Bergovec M, Mihatov S, Prpić H, Rogan S, Batarelo V, Sjerobabski V. Acute myocardial infarction among civilians in Zagreb city area. *Lancet.* 1992 Feb 1;339(81,82):303.
15. Ornato JP, Muller JE, Froelicher ES, Kloner RA. Indirect and secondary cardiovascular effects of biological terrorism agents and diseases. *J Am Coll Cardiol.* 2007 Mar 27;49(12):1389-97.
16. Wilbert-Lampen U, Leistner D, Greven S, Pohl T, Sper S, Völk, et al. Cardiovascular events during world cup soccer. *N Eng J Med.* 2008 Jan 31;358(5):475-83.
17. Willich SN, Lowel H, Lewis M, Hormann A, Arntz HR, Keil U. Weekly variation of acute myocardial infarction: increase Monday risk in the working population. *Circulation.* 1994 Jul;90(1):87-93.
18. Spencer FA, et al. for the Participants in the National Registry of Myocardial infarction. Seasonal distribution of acute myocardial infarction in the Second National Registry of Myocardial Infarction. *J Am Coll Cardiol.* 1998 May;31(6):1226-33.
19. Cohen MC, Rohla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol.* 1997 Jun 1;79(11):1512-6.

20. Gneechi-Ruscione T, Piccaluga P, Guzzetti S, Contini M, Montano N, Nicolis E. Morning and Monday: critical periods for the onset of acute myocardial infarction: the GISSI II Study experience. *Eur Heart J*. Jul 1994;15(7):882-7.
21. Gerber Y, Jacobsen SJ, Killian JM, Weston SA, Roger VL. Seasonality and daily weather conditions in relation to myocardial infarction and sudden cardiac death in Olmsted County, Minnesota, 1979 to 2002. *J Am Coll Cardiol*. 2006 Jul 18;48(2):287-92.
22. Weerasinghe DP, MacIntyre CR, Rubin GL. Seasonality of coronary artery deaths in New South Wales, Australia. *Heart*. 2002 Jul;88(1):30-4.
23. Grønholdt ML, Dalager-Pederson S, Falk E. Coronary atherosclerosis: determinants of plaque rupture. *Eur Heart J*. 1998;19(suppl. C):C24-29.
24. Levine SP, Towell BL, Saurez AM, Khieriem LK, Harris MM, George JN. Platelet activation and secretion associated with emotional stress. *Circulation*. 1985 Jun;71(6):1129-34.
25. Kurnik PB. Circadian variation in the efficacy of tissue-type plasminogen activator. *Circulation*. 1995 March 1;91(5):1341-6.
26. Gertz SD, Roberts WC. Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques. *Am J Cardiol*. 1990 Dec 1;66(19):1368-72.
27. Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *J Am Coll Cardiol*. 2004 Sep 15;44(6):1261-4.
28. Trevisan M, Celentano E, Meucci C, Farinara E, Jossa F, Krogh V, et al. Short-term effects of natural disasters on coronary heart disease risk factors. *Arteriosclerosis*. 1986 Sep-Oct;6(5):491-4.
29. López F, Lee KW, Marin F, Roldán V, Sogorb F, Caturla J, Lip GY. Are there ethnic differences in the circadian variation in onset of acute myocardial infarction? A comparison of 3 ethnic groups in Birmingham, UK and Alicante, Spain. *Int J Cardiol*. 2005 Apr 8;100(1):151-4.
30. Blumenthal J, Sherwood A, Babyak M, Watkins LL, Waugh R, Georgiades A, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA*. 2005 Apr 6;293(13):1626-34.
31. Dimsdale JE, Mills P. An unanticipated effect of meditation on cardiovascular pharmacology and physiology. *Am J Cardiol*. 2002 Oct 15;90(6):908-9.
32. Culić V, Eterović D, Mirić D, Rumboldt Z, Hozo I. Gender differences in triggering of acute myocardial infarction. *Am J Cardiol*. 2000 Mar 15;85(6):753-6.
33. Tofler GH et al. for the TIMI Research Group. Modifiers of timing and possible triggers of acute myocardial infarction in Thrombolysis in Myocardial Infarction Phase II (TIMI II) Study Group. *J Am Coll Cardiol*. 1992;20:1049-1055.
34. Behar S, et al. for the SPRINT Study Group. Circadian variation and possible external triggers of onset of myocardial infarction. *Am J Med*. 1993 Nov 1;94(5):395-400.
35. Spielberg C, Falkenhahn D, Willich SN, Wegscheider K, Voller H. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. *Am Heart J*. 1996 Sep;132(9):579-85.
36. Massing W, Angermeyer MC. Myocardial infarction on various days of the week. *Psychol Med*. 1985 Nov;15(4):851-7.
37. Cheng TO. Mechanism of seasonal variation in acute myocardial infarction. *Int J Cardiol*. 2005 Apr 8;100(1):163-4.
38. Cheng TO. Seasonal variation in serum cholesterol levels may be another explanation for seasonal variation in acute myocardial infarction. *J Int Cardiol*. 2005 Sep 15;104(1):101.
39. Ku CS, Yang CY, Lee WJ, Chiang HT, Liu CP, Lin SL. Absence of a seasonal variation in myocardial infarction in myocardial infarction onset in a region without temperature extremes. *Cardiology*. 1998 May;89(4):277-82.
40. Marchant B, Ranjadyalan K, Stevenson R, Wilkinson P, Timmis AD. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmental temperature. *Br Heart J*. 1993 May;69(5):385-7.
41. Peters RW, Brooks MM, Zoble RG, Liebson PR, Seals AA for the CAST Investigators. Chronobiology of acute myocardial infarction: the CAST experience. *Am J Cardiol*. 1996 Dec 1;78(11):1189-1201.
42. Hammoudeh AJ, Izraiq M, Ismail Y, Tabbalat R, El-Harassis A, Al-Tarawneh H, Hamdan H, Al-mouse E. Utilization of reperfusion therapy in the Myocardial Infarction Triggers and Onset in JoRdan (MINTOR) Study. *Int J Cardiol*. 2007 Nov 15;122(2):156-7.
43. Ohlin B, Nilsson PM, Nilsson J-A, Berglund G. Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. *Eur Heart J*. 2004 May 25;25(10):867-73.
44. Culić V. Seasonal distribution of acute myocardial infarction: A need for a broader perspective. *Int J Cardiol*. 2006 May 10;109(2):265-6.
45. Matthews KA, Gump BB, Harris KF, Haney TL, Barefoot JC. Hostile behaviors predict cardiovascular mortality among men enrolled in the Multiple Risk Factor Intervention Trial. *Circulation*. 2004 Jan 6;109(1):66-70.
46. Surtees PG, Wainwright N, Luben R, Day NE, Khaw KT. Prospective cohort study of hostility and the risk of cardiovascular disease mortality. *Int J Cardiol*. 2005 Apr 8;100(1):155-61.
47. Phillips DP, Jarvinen JR, Abramson IS, Phillips RR. Cardiac mortality is higher around Christmas and new year's than at any other time. The holidays as a risk factor for death. *Circulation*. 2004 Dec 21;110(25):3781-8.
48. Fokoka, Fukouka Y, Dracup K, Froelicher ES, Ohno M, Hirayama H, Shiina H, Kobayashi F. Do Japanese workers who experience an acute myocardial infarction believe their prolonged working hours are a cause? *Int J Cardiol*. 2005 Apr 8;100(1):29-35.
49. Hammar N, Alfredsson L, Johnson JV. Job strain, social support at work, and incidence of myocardial infarction. *Occup Environ Med*. 1998 Aug;55(8):48-553.
50. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H. Exposure to traffic and the onset of myocardial infarction. *N Eng J Med*. 2004 Oct 21;351(17):1721-30.