Seasonal variation in enzymatic infract size and mortality in patients with ST-segment elevation myocardial infarction

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ABSTRACT

الأهداف: للتحقق من وجود أي تغيرات موسمية في حجم الإنزيم، معدل الوفيات، وموضع إحتشاء عضلة القلب في القطاع العلوي المستعرض (STEMI).

الطريقة: أجريت هذه الدراسة الوصفية خلال الفترة مابين مارس 2003م وحتى سبتمبر 2006م، تم فيها إدراج جميع المرضى الذين أدخلوا مستشفى مدني – إيران، ولديهم تشخيص إحتشاء حاد في عضلة القلب (AMI). تم تقسيم الحالات إلى أربعة مجموعات وفقاً للموسم الذي ظهر فيه الإحتشاء (MI)، وتم تحديد الحجم الإنزيمي وموضع الإحتشاء في كل مريض.

النتائج: تم تحليل إجمالي عدد 1206 حالة مصابة بالإحتشاء الحاد في عضلة القلب (AMI) خلال فترة الدراسة. لم يتم ملاحظة فرقاً موسمياً في دراستنا من ناحية الخصائص الجغرافية لدى المرضى. كما لم يتبين وجود تغير موسمي ملحوظ في حجم الإحتشاء وموضعة لعضلة القلب، وفي معدل الوفيات في المستشفى.

خاتمة: إن نتائجنا لا تدعم النظريات التي تقول أن حجم الإحتشاء، معدل الوفيات وموضع الإحتشاء STEMI تتغير نتيجة لتغير المواسم.

Objectives: To investigate any seasonal variation in enzymatic size, mortality rate, and localization of ST-segment elevation myocardial infraction (STEMI).

Methods: Between March 2003 and September 2006, all patients admitted to the Madani Heart Center, Tabriz, Iran with the diagnosis of acute myocardial infarction (AMI) were included in this observational prospective study. Cases were divided into 4 groups according to the season that MI occurred, and enzymatic size and location were determined for each patient.

Results: One thousand and two hundred six cases of AMI were analyzed during the study period. In our study, no seasonal difference was observed in demographic characteristics of patients. Also, no significant seasonal variation was found in enzymatic infract size, MI location, and in-hospital mortality rate.

Conclusions: Our findings does not support the hypothesis that enzymatic size, mortality rates, and location of STEMI varies by seasons.

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It is now well recognized that the onset of acute myocardial infarction (AMI) follows a marked circadian periodicity, with a peak incidence in the early to late morning hours.[1] Some studies also report a secondary peak in the onset of AMI in the late evening hours.[2] The concept of triggering AMI is a complex issue and likely involves the superimposition of multiple factors such as time of the day, season, and the stress of natural disasters.[3] Few data are available on the effects of temperature, months of the year, and seasons on cardiac events and death. Although some studies have revealed an increase in cardiac events during the winter,[4-7] those conducted in warmer regions of the United States have suggested an increase in cardiac events during the summer.[8,9] A recent analysis has shown that myocardial infract size is smallest during the summer.[10] On the contrary, another study has revealed absence of seasonal variations in the prevalence of heart failure at presentation, in myocardial perfusion, enzymatic infract size, and one year mortality in patients with ST-segment elevation myocardial infraction (STEMI) treated with primary angioplasty.[11] The purpose of our

study was to determine, when throughout the year, the incidence of STEMI, infarct region and size, and in-hospital mortality was highest in an area of the country, where temperatures are relatively cold during autumn and winter months (Tabriz, Iran), and whether these patterns have changed over a 3-year period.

Methods. Between March 2003 and September 2006, all patients admitted to Madani Heart Center, Tabriz, Iran with the diagnosis of AMI were evaluated. The criteria for the diagnosis of STEMI require that at least 2 of the following 3 elements be present: 1) a history of ischemic-type chest discomfort, 2) ST-segment elevation ≥1 mm in limb leads and/or ≥2 mm in the precordial leads and evolutionary changes on serially obtained ECG tracings, or new or presumed new left bundle branch block, and 3) a rise and fall in serum cardiac markers.[12] Location of infarction was categorized as either inferior, lateral, or anterior/septal. Demographic data of the patients were recorded, including the use of effective adjuvant therapies (aspirin, beta-blockers, statins, angiotensin converting enzyme [ACE] inhibitors, and fibrinolytics). Infract size was determined for each patient according to peak levels of creatine phosphokinase (CPK), creatine phosphokinase-MB (CK-MB), cardiac troponin I (cTnI), and mean levels of 3 CK-MB measurements obtained at 8 hour intervals. Left ventricular ejection fraction (LVEF) was semi-quantitatively analyzed by transthoracic echocardiography before discharge by an echocardiography expert who was blinded to the patient data and the location of infarction. Coronary artery narrowing was visually estimated and expressed as percent lumen diameter stenosis. Patients with a 50% diameter narrowing of the left main, left anterior descending, left circumflex, or right coronary arteries or their major branches were considered to have significant angiographic coronary artery diseases (CAD). Primary percutaneous coronary interventions (PCI) were not performed, but delayed PCI was carried out when indicated (ischemia-guided).[13] All patients gave written informed consents and the study were approved by our local Ethics Committee. For purposes of the study, we grouped patients according to MI occurrence season into: A) spring (March, April, and May); B) summer (June, July, and August); C) autumn (September, October, and November); D) winter (December, January, and February).[10]

Statistical analysis was performed with SPSS version 12.0. Continuous data were expressed as mean ± SD and categorical data as percentage. Differences in the distribution of selected categorical and continuous factors according to season were examined through the use of chi-square tests and analysis of variance for statistical significance. All analyses indicated significance at $p<0.05$.

Results. A total of 1206 cases of STEMI were included in this study. Eight hundred and nineteen (68%) of the cases were male (mean age = 59.2±13.7) and 387 (32%) were female (mean age = 65.1±12.9). The mean age of female patients was significantly higher than males ($p=0.0001$), but there was no significant difference in mean age of either gender in individual groups. As shown that the baseline characteristics in **Table 1**, no seasonal variation was observed according to gender ($p=0.086$), MI location ($p=0.682$), effective adjuvant medications [aspirin (mean 90.1%), beta-blockers (mean 51.3%), statin (mean 19.8%), ACEI/ARB (mean 51.9%); $p=0.768$], or thrombolytic therapy (TLT) ($p=0.456$). Door-needle time was 2.2 hours, and time from infarct to receiving TLT was approximately 9 hours. Approximately 92% (n=1112) of patients had chest pain during their admission. At summer season, the number of patients who had chest pain at presentation was significantly lower than other seasons ($p=0.008$). As described in **Table 1**, history of hypertension in group B and familial history of premature CAD in group D were significantly higher than other groups. As seen in **Table 2**, there was no significant difference in means of CPK peak level ($p=0.771$), CK-MB peak level ($p=0.655$), and cTn-I peak level ($p=0.690$) among all groups. This was also the case between those who received ($p=0.6$) or did not receive ($p=0.7$) TLT. No significant difference was present in the mean LVEF between seasons, both men, and women (36.48±11.26% versus 37.42±9.85%; $p=0.433$). Also, the prevalence of single, 2 and 3 vessel coronary involvement were statistically similar between seasons (34.5, 35.7, and 35.5%; $p=0.245$). Delayed PCI was carried out in 24.8% of patients and in 94.7% intracoronary stents were deployed. One hundred ninety-eight patients (8.9%) underwent coronary bypass surgery. The mean hospital stay was 9.8 days. Two hundred and thirteen (17.6%) patients died during the hospitalization. There was no significant difference in the in-hospital mortality between the groups (17.5% in groups A and D, and 17.7% in groups B and C; $p=0.496$). The mean age of those who died (67.7±12.6 years) was significantly higher ($p=0.008$) than those who were discharged (59.6±13.6 years). No significant difference was observed in means of CPK and CK-MB levels between those who died or were discharged; however, there was a strongly positive trend ($p=0.056$) in CPK and CK-MB levels in the former group (**Table 3**).

Table 1 - Patients' characteristics.

Charracteristics	Spring	Summer (%)	Winter	Year round *P*-value
Age (years) / mean ± SD	63.23 ± 13.83	61.73 ± 13.97	58.36 ± 12.67	NS
Male	(72.4)	(68.1)	(66.6)	NS
Smoking	(38.1)	(43.2)	(39.6)	NS
Hypertension	(32.1)	(52.5)	(43)	0.043
Diabetes mellitus	(23.7)	(20)	(24.2)	NS
Dyslipidemia	(21.2)	(24.6)	(25.1)	NS
Family history of CAD	(7.3)	(11.6)	(20.2)	0.014
Anterior MI	(50)	(58)	(52)	NS
Inferior MI	(43)	(39)	(48)	NS
Lateral MI	(16)	(14)	(12)	NS
Q-wave MI	(81.6)	(83.1)	(82.6)	NS
Prior MI	(9.1)	(8.6)	(8.7)	NS
KILLIP >I	(9.9)	(10.1)	(8.9)	NS
Aspirin use	(89.3)	(88.6)	(90.8)	NS
ACEI or ARB	(52.3)	(49.8)	(51.4)	NS
Beta blocker use	(55.3)	(51.8)	(48.5)	NS
Statin use	(21.2)	(18.6)	(20.5)	NS
Thrombolytic (STK)	(49.8)	(50.2)	(48.1)	NS
Time from Infarct to STK (h)	9.21	8.56	9.01	NS
Door-Needle Time (h)	2.12	2.08	2.36	NS
Time From infarct to treatment (h)	12.09	12.20	12.36	NS
Heart rate (bpm)	76.3	75.1	76	NS
SBP (mm Hg)	139.9	142.1	138.9	NS
DBP (mm Hg)	82.3	81.3	81.1	NS
Prior angina pectoris	(36.3)	(41)	(38.6)	NS
Chest pain at presentation	(96)	(84)	(95)	0.008

CAD - coronary artery disease, ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, STK - streptokinase, SBP - systolic blood pressures, DBP - diastolic blood pressures, MI - myocardial infraction

Table 2 - Enzymatic changes according to season.

Enzymatic changes	Spring	Summer	Autumn	Winter
Peak CPK level ± SD (IU/L)	1549.88 ± 1172.88	1735.96 ± 1249.09	1771.15 ± 2483.82	1846.97 ± 1140.44
Peak CK-MB level ± SD (IU/L)	195.23 ± 195.77	197.97 ± 159.06	194.92 ± 172.24	171.55 ± 138.15
Peak cTn-I level ± SD (ng/ml)	8.75 ± 8.4	6.8 ± 7.61	7.67 ± 7.21	7.42 ± 11.45

CPK - creatine phosphokinase, CK-MB - creatine phosphokinase-MB, cTnI - cardiac troponin I

Table 3 - Enzymatic changes of patients who died in the hospital or were discharged.

Enzymatic changes	Mortality group	Discharged group	*P*-value
Peak CPK level ± SD (IU/L)	2024.24 ± 1326.94	1617.58 ± 1656.29	0.056
Peak CK-MB level ± SD (IU/L)	255.01 ± 203.54	176.42 ± 154.29	

CPK - creatine phosphokinase, CK-MB - creatine phosphokinase-MB

Discussion. Acute myocardial infarction is a dynamic event resulting from rupture of a previous quiescent atherosclerotic plaque, producing an occlusive intracoronary thrombus. There have been great advances on understanding the key elements involved in the pathophysiologic events leading to plaque rupture. However, little is known on the initiating event or events that cause the actual plaque rupture.[14] Muller et al[1] has documented circadian variation in AMI onset long time ago. This work has shed light to understanding the sequence of events leading to AMI and eventual development of proper therapeutic and preventative measures. Previous reports have described seasonal variations in the incidence of STEMI, infract size and cardiac death.[10] The mechanism whereby infarct size varies with the season is unknown. During summer, warmth might contribute to reduced vascular resistance, with a decrease in afterload and preload. Left ventricular wall stress and oxygen demand would then be expected to be reduced, and this reduced oxygen demand might contribute to reduced infarct size. On the contrary, physiologic changes during winter (for example increased cardiac workload, higher coronary, and vascular resistance induced by cold, higher blood pressure, superimposed respiratory infections, and higher fibrinogen levels), could contribute to higher event rates in this season.[15] Kloner et al,[10] retrospectively examined 2 databases of large multicenter MI studies, and showed that, despite no seasonal difference in thrombolysis in myocardial infarction (TIMI) flow grades, there was a significant difference (but with marginal statistical significance) in infarct size, with smaller infarcts observed in the summer. This observation was true for patients treated during the prethrombolytic era (Multicenter Investigation of the Limitation of Infarct Size (MILIS) study)[16] as well as the thrombolytic era (TIMI-4 study).[17] However, this greater infarct size in the winter was not associated with higher in hospital mortality, reinfarction, or congestive heart failure. Definition of infarct size was different in this study with respect to ours, which were CPK, CK-MB, and cTn-I peak levels. For the MILIS study, infarct size was defined as areas under the curve based on plasma CK-MB and body surface area and for the TIMI-4 Study, infarct size was calculated as the average CK-MB taken over 14 time points that is proportional to area under the curve.[1] Mukamal and Mittleman,[18] study in the "onset study," did not support the hypothesis that infarct size varies by the season and they stated that chance appears to be a more likely explanation for the positive findings of the Kloner's results. The method used for definition of MI size, and the results were the same as ours. De Luca et al[11] recently reported the absence of any seasonal variation in myocardial perfusion, enzymatic infract size, and one-year mortality after primary angioplasty for STEMI. The absence of seasonal variation in infarct size in their analysis, may be explained by optimal reperfusion that is achieved by primary angioplasty, being unaffected by changes in platelet aggregation and fibrinogen observed across seasons, whereas these factors may affect the efficacy and results of thrombolysis. A limitation for De Luca's analysis was that enzymatic infarct size was estimated by cumulative release of lactate dehydrogenase, and the availability of CPK, CK-MB isoenzyme, and cTn-I measurements, such our method of infarct size estimation, would have improved their conclusion. However, the results are in concordance with our study on the absence of any seasonal variation in infarct size.

In our present study, similar to others,[11,18] no seasonal variation was observed in patient's demographic characteristics, enzymatic myocardial infract size, in-hospital mortality, or MI location. Although there is a possibility that differences in our methods and those of Kloner's[10] may explain the differences in our results, chance appears to be a more likely explanation for the positive findings of their exploratory analysis, particularly given the fact that their results had a marginal statistical significance, and there was no related seasonal variation in reinfarction rates, death, or congestive heart failure. We had an in hospital mortality rate of 17.6%, which may be seen as rather high compared to other registries. The short-term mortality rate of patients who receive aggressive pharmacologic reperfusion therapy as part of a randomized trial is in the range of 6.5-7.5%, whereas observational data bases suggest that mortality rate in STEMI patients in the community is 15-20%. In part this difference relates to the selection of patients without serious comorbidities for clinical trials.[3] The major reasons for the high mortality rate could be our relatively old patient population (mean 62.1 years), high prevalence of diabetes (mean 24%), the under-use of medications that have proven survival benefits in AMI (for example beta-blockers, statins, and thrombolytic therapy), prolonged door-needle time (mean 2.2 hours), long time from infarct to receiving TLT (mean 9 hours), relatively high incidence of anterior MI and, inevitably, low LVEF (mean 54.7% and 36.9%, respectively), and finally the fact that we were not performing primary PCI during the study period. At the time of this study, no patient received adjuvant therapy (for example clopidogrel and IIb-IIIa inhibitors), which has proved survival benefits in AMI.[19]

Results of this study must be interpreted in the face of certain limitations. First, it is a single tertiary referral center experience with a retrospective character and,

second, tertiary referral centers may not be representative of all hospitals within the region. Moreover, our study was not population based and data collection was from reports of hospital-specific data, so characterization of the group at risk for AMI and its variation by season may not be as much as needed. Another limitation may be the lack of including all risk factors for AMI. These risk factors have the potential for seasonal variation and becoming confounding variables in interpreting any possible trends in the occurrence of AMI.[14]

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Related topics

Zubaid M, Rashed WA, Al-Khaja N, Almahmeed W, Al-Lawati J, Sulaiman K, Al-Motarreb A, Amin H, Al-Suwaidi J, Al-Habib K. Clinical presentation and outcomes of acute coronary syndromes in the gulf registry of acute coronary events (Gulf RACE). ***Saudi Med J*** 2008; 29(2): 251-255.

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