The Impact of Time and Day on the Presentation of Acute Coronary Syndromes

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Summary

Background: The frequency of acute myocardial infarction (AMI) peaks on Mondays and in the mornings. However, the distribution of the types of acute coronary syndromes (ACS), including unstable angina (UA), has not been systematically evaluated.

Hypothesis: The distribution of the types of ACS and clinical presentations varies by time and day of admission.

Methods: A retrospective cohort study was conducted in 1,946 consecutive nontransfer ACS admissions (1999–2004) to a tertiary-care academic center to assess presenting clinical variables in patients admitted on days versus nights (6 p.m.–6 a.m.) and weekdays versus weekends (Friday 6 p.m.–Monday 6 a.m.).

Results: There were fewer ACS admissions than expected on nights and weekends (p < 0.001), but the proportion of patients with ACS presenting with ST-elevation myocardial infarction (STEMI) is 64% higher on weekends (p < 0.001) and 31% higher on nights (p = 0.022). This increased proportion with STEMI results in a greater proportion of ACS with AMI on weekends (↑10%, p = 0.006) and nights (↑7%, p = 0.033). Using multivariate modeling, the increase in patients with AMI on weekends was not explained by conventional risk predictors.

Conclusions: Although fewer patients with ACS presented on nights and weekends, patients at those times were more likely to have an AMI, driven largely by an increased proportion with STEMI at those times. Consideration should be given to these findings when developing clinical care paradigms, health care staffing needs, and when comparing new treatment outcomes in patients with ACS.

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Introduction

The timing of acute myocardial infarction (AMI) follows a circadian pattern, with a peak incidence in the morning. A meta-analysis found significantly increased events between 6 a.m. and noon, and attributed nearly 9% of all AMI to this morning increase.[1] The distribution of AMI by day appears nonrandom, with a peak on Monday[2,3] and a relative trough on Saturday.[2] The morning increase of AMI has prompted recommendations to blunt the morning surge in sympathetic tone with medications[4] and to reduce morning activity.

The distribution by type of acute coronary syndrome (ACS), including unstable angina (UA), has not been systematically evaluated in relation to time and day of presentation. It was hypothesized that differences could exist on nights and weekends secondary to alterations in physical or emotional stressors, prehospital delay, or pathophysiologic factors.

We sought to determine whether time or day of hospital presentation relate to the type of ACS (ST-elevation myocardial infarction [STEMI], non-STEMI [NSTEMI], or UA).

Methods

An ACS database[5] assessed major clinical variables in 1,946 consecutive adults admitted between 1999 and 2004 to the University of Michigan Hospital, Ann Arbor, Mich. Patients were identified retrospectively using ICD-9 codes for AMI or UA. Enrollment criteria required presenting symptoms of myocardial ischemia and one of the following: history of coronary artery disease (CAD), new documentation of CAD, ischemic electrocardiogram (ECG) changes, or elevated cardiac enzymes. Transfer patients were excluded. All 1,946 patients were included in the weekend versus weekday analysis; 1,869 patients were evaluated in the day versus night analysis, as 77 patients did not have an accurate time of arrival recorded. Prehospital delay (time from patient-reported symptom onset to hospital arrival) was available for 1,474 patients.

The initial ECG and peak troponin I and creatine kinase-MB (CK-MB) were used to establish the diagnoses of STEMI, NSTEMI, and UA. ST-elevation myocardial infarction was defined by an initial ECG demonstrating ST-elevations of ≥ 1 mm in consecutive leads, or a new left bundle-branch block (LBBB). Positive markers (a troponin I above the upper limit of normal or a CK-MB above twice the upper limit of normal) without ST-elevation or new LBBB were categorized as NSTEMI, with the remainder considered to be UA.

Statistical Methods

Analyses were performed to detect differences in days (6 A.M.–6 P.M.) versus nights (6 P.M.–6 A.M.), and weekdays (Monday 6 A.M.–Friday 6 P.M.) versus weekends (Friday 6 P.M.–Monday 6 A.M.). Logistic regression models were fitted to determine whether risk factors explained the increased frequencies of AMI on weekends and nights. Stepwise regression was conducted with all models adjusted by age (≥ 65), gender, and prehospital delay, where candidate variables had a univariate analysis $p < 0.10$, and the rule for retention of multivariate model terms was $p < 0.20$. Candidate variables included age, gender, CAD history, Killip class, home medications (aspirin, beta blockers, statins, diuretics, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers), prehospital delay, year of admission, weekend versus weekday presentation, night versus day presentation, and interactions of previous variables. With a c-statistic of 0.75 and a Hosmer-Lemeshow p value of 0.39, the model discrimination and fit are adequate. A p value of <0.05 was deemed significant. Statistics were performed with SAS software version 8.2 (SAS, Cary, N.C., USA).

Results

There were no meaningful differences in gender or age between groups (Table I). A greater number of patients with ACS presented during the week (1,376 compared with the 1,251 expected, $p < 0.001$). Of the

TABLE 1   Patient demographics and cardiovascular history in all acute coronary syndromes (ACS)

	Weekday n = 1376	Weekend n = 570	p Value	Days n = 1200	Nights n = 669	p Value
Demographics						
Female (%)	35.3	35.4		36.3	32.9	0.14
Age (mean ±SD)	64 ± 14	64 ± 14		65 ± 14	63 ± 14	0.003
Prehospital delay Median (h)	2.8	2.7		3.0	2.3	0.001
Medical history						
Angina (%)	47.3	39.8	0.003	47.9	42.6	0.03
AMI (%)	43.7	44.8		43.9	44.8	
CHF (%)	21.1	18.3		20.4	20.0	
PCI (%)	31.1	29.6		31.0	29.6	
CABG (%)	23.9	23.3		23.4	24.6	
Diabetes (%)	32.0	29.4		31.6	30.5	
Prior medications						
Diuretic (%)	34.7	34.2		34.5	33.8	
Aspirin (%)	57.2	56.7		57.8	54.7	
Statin (%)	46.4	42.3	0.09	44.0	46.8	
Beta blocker (%)	51.2	47.5	0.15	47.8	53.1	0.03
ACE-I/ARB (%)	39.8	43.3	0.14	38.8	42.9	0.09

P values provided for $p \leq 0.15$
Abbreviations: SD = standard deviation, AMI = acute myocardial infarction, CHF = congestive heart failure, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor-blocker.

TABLE 2   Diagnoses of acute coronary syndromes

	Weekday n = 1376	Weekend n = 570	p Value	Days n = 1200	Nights n = 669	p Value
Diagnosis						
Type of ACS			<0.001			0.02
STEMI (%)	11.8	19.3	—	12.3	16.1	—
NSTEMI (%)	54.4	53.3	—	54.5	55.5	—
UA (%)	33.8	27.4	—	33.2	28.4	—

P values provided for $p \leqslant 0.15$.
Abbreviations: ACS = acute coronary syndromes, STEMI = ST-elevation myocardial infarction, NSTEMI = non-STEMI, UA = unstable angina.

1,869 patients in whom time of presentation was available, only 35.8% presented during the 12 h defined as night (p < 0.001). Prior angina was more frequent among both weekday (↑18.8%) and daytime (↑12.4%) presenters. Prehospital delay was shorter on nights compared with days.

Although there were fewer ACS admissions on nights and weekends, a significant difference was found in the overall distribution of all three types of ACS on both nights and weekends (Table II). The proportion presenting with STEMI was 64.0% higher on weekends than on weekdays (p < 0.001) and 30.9% higher on nights than on days (p = 0.022), with corresponding significant decreases in UA on weekends and nights. As a result of the increase in STEMI, the proportion of patients with ACS presenting with AMI increased 9.7% on weekends (p = 0.006) and 7.1% on nights (p = 0.033).

A parsimonious multivariate model examined AMI versus UA. The surplus of AMI on weekends (odds ratio [OR] 1.62, 95% confidence interval [CI] 1.12–2.35, p = 0.010) and a trend toward increased AMI on nights (OR 1.25, 95% CI 0.97–1.63, p = 0.09) were not completely explained by variables in the model. In an analysis of raw data (Table II) it was estimated that 80% of the differential in AMI on nights (vs. days) and 100% of the differential in AMI on weekends (vs. weekdays) is due to an increase in STEMI. A subsidiary multivariate analysis analogous to the above would suggest a surplus of STEMI (vs. NSTEMI and UA) on weekends (OR 1.62, 95% CI 1.04–1.88, p = 0.028), and a null adjusted STEMI increase on nights (OR 1.04 95% CI 0.78–1.39, p = 0.80).

Discussion

We found a significant and important variability in the type of ACS based upon the time and day of presentation. Although fewer than expected patients with ACS presented on nights and weekends, those admitted at these times were considerably more likely to have AMI, largely attributed to an increased proportion with STEMI at these times. Multivariate modeling suggested conventional risk factors did not explain the AMI surplus on weekends but may explain this on nights.

There has been considerable previous study of circadian and circaseptan patterns of AMI. They are reported to occur more frequently on Mondays,[2,3] with a relative trough on Saturdays.[2] Several large observational studies and a subsequent meta-analysis of 30 studies identified an increase of AMI in the morning,[1] while the potential influence of time of day on non-ST-elevation ACS is less consistent.[6,7] The impact of night versus daytime presentation of AMI on the success of primary angioplasty is inconclusive.[8,9] Primary angioplasty for STEMI during nighttime has been associated with an increased failure rate and higher 30-day mortality.[9] A study of 33,647 patients undergoing angioplasty for STEMI found that 54% were treated at night and on weekends. These patients had longer door-to-balloon times than patients presenting during daytime and weekdays (116 vs. 95 min) and had a significant increase in adjusted in-hospital mortality.[10] As most hospitals do not have teams in-house at night and on weekends, the intrinsic delay in waiting for the interventional team to arrive may contribute to these findings.

Although previous studies have evaluated the frequency of AMI, there are few previous data on the distribution of the entire spectrum of ACS (including UA) when related to time and day. Our findings, combined with other studies, suggest that the pathobiology of ACS may differ considerably on nights and weekends. The well-studied peaks of AMI on Mondays and mornings are consistent with our peak of ACS noted during daytime and weekdays. By including UA and comparing the distribution of the types of ACS, we have found a greater proportion of ACS present with STEMI on nights and weekends, which to our knowledge has not been previously reported. The inclusion of patients with UA, and the use of the highly sensitive troponin assay in the diagnosis of AMI (increasing the number of patients diagnosed with NSTEMI rather than UA), differentiates this from previous studies.

Hypotheses to Explain the Findings

Potential explanations for our findings include differences in prehospital delay, physical or emotional stressors, pathophysiologic differences, and historical differences. Early hospital treatment should not influence these presenting findings, as markers of myonecrosis and the presenting ECG were used to characterize UA, NSTEMI, and STEMI. Previous studies have had conflicting results regarding prehospital delay in AMI when compared with time of presentation.[11,12] In our study, there was a shorter prehospital delay at night, possibly due to the more intense symptoms typically associated with STEMI and the influence of significant others. The less intense symptoms associated with NSTEMI or UA may lead some patients to wait during daytime and on weekdays, which could help explain the increased proportion with STEMI on nights and weekends.

Differences in physical or emotional stressors may impact on these results. Periods following heavy physical activity are associated with increased risks of AMI,[13] while emotional stress and physical activity are the most common precipitants.[14] The Monday increase of AMI described in working populations has been noted to be absent or decreased among retirees.[2,3] A second daytime peak of AMI has been described in workers at 4 P.M.,[2] possibly related to findings that traffic or public transportation exposure is associated with increased AMI in the following hour.[15] Patients may have greater physical activity, alcohol use, and emotional stress when at home on nights and weekends, which could contribute to the increased proportion with STEMI and AMI at these times.

Pathophysiologic factors may affect the timing and type of ACS. The complex interaction of plaque disruption, thrombosis, fibrinolysis, and endothelial function are not completely understood and may differ on nights and weekends. Circadian changes in catecholamines, cortisol, blood pressure, and pulse have been described, potentially altering coronary artery wall shear stress.[16] An increase in platelet aggregation has been described in the morning,[17] and the fibrinolytic system has marked circadian variation.[18] The mechanisms underlying the increase in STEMI, which is more often associated with an occlusive, fibrin-rich thrombus than NSTEMI and UA, may also underpin the resistance to thrombolytic therapy that has been observed in the early morning and late evening hours.[19] Morning and evening peaks of ischemia in patients with UA and with vasospasm and nonsignificant CAD have been described,[20] suggesting that differences in coronary vasospasm may play a role in the nighttime increase in STEMI. While the morning peak of AMI has been attributed to many of these factors, their interaction may also predispose to increased UA in the morning and increased AMI and STEMI at night. Although differences in the pathophysiology of ACS on weekends have not been described, it is possible that social activities including alcohol, later waking times, and presumptive later medication administration may impact on the incidence and response to plaque rupture on weekends.

That more of our patients presenting weekdays and at daytime had chronic stable angina may help explain the decreased proportion with STEMI. Brief periods of ischemia occurring during angina have been shown to protect against subsequent longer periods of ischemia as if occurs in ACS through both early and late ischemic preconditioning.[21] Patients with ACS and negative or mildly elevated cardiac enzymes are more likely to have had prodromal angina than those with higher levels, and the presence of UA symptoms in the two weeks prior to admission have been associated with an improved 5-year survival.[22]

Limitations

Our findings may not have general application and require further confirmation. While we excluded transfers from other hospitals, the use of data from a single center and the academic tertiary-care setting may not be representative of other environments.

Conclusion

The findings of our study are not simply a biologic curiosity. The success of treatment paradigms including angioplasty, antiplatelet and thrombolytic therapy, and the management of heart failure in ACS is dependent upon the availability of staff resources. Patients presenting with ACS on nights and weekends, whom we found to be more critically ill and who require greater care as a group, generally have less availability of physicians and ancillary support, as hospitals often decrease night and weekend staffing. Staffing of critical care services and personnel are generally based upon the overall number of patients and acuity. Persons responsible for staffing requirements in acute care settings should be aware of the possible increase in morbidity and mortality in patients with ACS admitted during "off hours." Furthermore, selection bias of patient enrollment into clinical trials in the daytime and on weekdays, when research teams are ordinarily available, may help explain the higher relative success of treatments demonstrated in clinical trials of ACS compared with usual clinical practice. In addition, studies of treatment modalities designed to reduce the progression of UA to infarction and limit myocardial damage must be cognizant of the differences in the natural history of patients with ACS presenting on nights and weekends.

References

1. Cohen MC, Rohtla 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;79:1512–1516

2. 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;132:579–585

3. Willich SN, Lowel H, Lewis M, Hormann A, Arntz HR, *et al*: Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. *Circulation* 1994;90:87–93

4. Manfredini R, Gallerani M, Salmi R, Fersini C: Circadian rhythms and the heart: Implications for chronotherapy of cardiovascular diseases. *Clin Pharmacol Ther* 1994;56:244–247

5. Granger C, Goldberg R, Dabbous O, Pieper KS, Eagle KA, *et al*: Predictors of hospital mortality in the global registry for acute coronary events. *Arch Intern Med* 2003;163:2345–2353

6. Cannon CP, McCabe CH, Stone PH, Schactman M, Thompson B, *et al*: Circadian variation in the onset of unstable angina and non-Q-wave acute myocardial infarction (The TIMI III registry and TIMI IIIB). *Am J Cardiol* 1997;79:253–258

7. Gilpin EA, Hjalmarson A, Ross J Jr: Subgroups of patients with atypical circadian patterns of symptom onset in acute myocardial infarction. *Am J Cardiol* 1990;66:7G–11G

8. Zahn R, Schiele R, Seidl K, Schuster S, Hauptmann KE, *et al*: Daytime and nighttime differences in patterns of performance of primary angioplasty in the treatment of patients with acute myocardial infarction. *Am Heart J* 1999;138:1111–1117

9. Henriques JPS, Haasdijk AP, Zijlstra F: Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. *J Am Coll Cardiol* 2003;41:2138–2142

10. Magid DJ, Wang Y, Herrin J, McNamara RL, Bradley EH, *et al*: Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. *J Am Med Assoc* 2005;294:803–812

11. Ladwig KH, Lehmacher W, Roth R, Breithardt G, Budde T, *et al*: Patient-specific determinants of delay in goal-oriented patient behavior in acute myocardial infarct. Results of the post-infarct late potentiaal study. *Z Kardiol* 1991;80:649–656

12. Goldberg RJ, Yarzebski J, Lessard D, Gore JM: Decade-long trends and factors associated with time to hospital presentation in patients with acute myocardial infarction. The Worcester Heart Attack Study. *Arch Intern Med* 2000;160:3217–3223

13. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, *et al*: Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of myocardial infarction onset study investigators. *N Engl J Med* 1993;329:1677–1683

14. Tofler GH, Stone PH, Maclure M, Edelman E, Davis VG, *et al*: Analysis of possible triggers of acute myocardial infarction (the MILIS study). *Am J Cardiol* 1990;66:22–27

15. Peters A, von Klot S, Heier M, Trentinaglia I, Hormman A, *et al*: Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 2004;351:1721–1730

16. Strike PC, Steptoe A: New insights into the mechanisms of temporal variation in the incidence of acute coronary syndromes. *Clin Cardiol* 2003;26:495–499

17. Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, *et al*: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 1987;316:1514–1518

18. Sayer JW, Gutteridge C, Syndercombe-Court D, Wilkinson P, Timmis AD: Circadian activity of the endogenous fibrinolytic system in stable coronary artery disease: Effects of beta-adrenoreceptor blockers and angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 1998;32:1962–1968

19. Kono T, Morita H, Nishina T, Fujita M, Hirota Y, *et al*: Circadian variations of onset of acute myocardial infarction and efficacy of thrombolytic therapy. *J Am Coll Cardiol* 1996;27:774–778

20. Onaka H, Hitota Y, Shimada S, Mishima T, Shimoyama H, *et al*: Circadian variation of myocardial ischemia in patients with unstable angina pectoris secondary to fixed and/ or spastic coronary narrowing. *Am J Cardiol* 1998;81:629–632

21. Kloner RA, Jennings RB: Consequences of brief ischemia: Stunning, preconditioning, and their clinical implications: Part 1. *Circulation* 2001;104:2981–2989

22. Bahr RD, Leino EV, Christenson RH: Prodromal unstable angina in acute myocardial infarction: Prognostic value of short- and long-term outcome and predictor of infarct size. *Am Heart J* 2000;140:126–133