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Arrhythmias in Patients with Acute Coronary Syndrome in the First 24 Hours of Hospitalization

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Abstract

Objectives—In patients with acute coronary syndrome (ACS), we sought to: 1) describe arrhythmias during hospitalization, 2) explore the association between arrhythmias and patient outcomes, and 3) explore predictors of the occurrence of arrhythmias.

Methods—In a prospective sub-study of the IMMEDIATE AIM study, we analyzed electrocardiographic (ECG) data from 278 patients with ACS. On emergency department admission, a Holter recorder was attached for continuous 12-lead ECG monitoring.

Results—Approximately 22% of patients had more than 50 premature ventricular contractions (PVCs) per hour. Non-sustained ventricular tachycardia (VT) occurred in 15% of patients. Very few patients (1%) had a malignant arrhythmia (sustained VT, asystole, torsade de pointes, or ventricular fibrillation). Only more than 50 PVCs/hour independently predicted an increased length of stay ($p<.0001$). No arrhythmias predicted mortality. Age greater than 65 years and a final diagnosis of acute myocardial infarction independently predicted more than 50 PVCs per hour ($p=.0004$).

Conclusions—Patients with ACS seem to have fewer serious arrhythmias today, which may have implications for the appropriate use of continuous ECG monitoring.

Keywords

Acute myocardial infarction; Electrocardiogram; Arrhythmia; Acute coronary syndrome; Outcomes

In the early years of coronary care (1960s – 1980s), patients with acute myocardial infarction (AMI) were provided supportive care with the main focus on surveillance and treatment of arrhythmias. Early reperfusion therapy using fibrinolytics or percutaneous

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coronary interventions (PCI) to limit the size of the infarction was introduced into clinical practice in the late 1980s, and has been shown to improve mortality.¹ Prior to the standard use of early reperfusion therapy, studies reported high rates of clinically important arrhythmias.^{2–8}

Knowledge of the occurrence of arrhythmias associated with acute coronary syndrome (ACS) is limited in contemporary clinical practice. Recent research on arrhythmias has been in the context of genetics and interventions, rather than centered on clinical conditions such as ACS. Many of the studies were designed to determine the efficacy of device-based therapies, catheter and surgical-based interventions for refractory arrhythmias, or electrophysiological testing for inherited abnormalities, such as long QT syndrome. In the beginning of the time when early reperfusion was used, the focus on ventricular arrhythmias was in the context of determining the associated risk for patients. In a few studies, such as the Cardiac Arrhythmia Suppression Trial (CAST)^{9,10} and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico study (GISSI-2),¹¹ investigators assessed the frequency of premature ventricular contractions (PVCs). Later, researchers^{12,13} involved in secondary analyses of large randomized controlled trials for medications (Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries [GUSTO-1] study; GISSI-2) and intervention studies (Primary Angioplasty in Myocardial Infarction [PAMI] trial)¹⁴ began to turn their attention to determine the prognostic significance of non-sustained ventricular tachycardia (VT), sustained VT, and ventricular fibrillation. Without a consensus on the on the short- or long-term significance of these arrhythmias, the therapeutic aim became mitigating the progression of ACS. Electrolyte imbalance, hemodynamic instability, and low cardiac output were the focus of treatment rather than the suppression of ventricular arrhythmias.

Over the last several decades, we have gone from monitoring and suppressing PVCs to the assessment and early treatment of ACS itself. It is now important to determine the nature of arrhythmias in contemporary patients with ACS, so that we are using the increasingly ubiquitous ECG monitoring effectively and only when clinically indicated. Alarm fatigue has become an important patient safety issue. Judicious use of ECG monitoring has the potential to decrease the occurrence of false and non-actionable alarms. Therefore, in this study we sought to: 1) describe the arrhythmias that occur during the first 24 hours in patients with ACS admitted through the emergency department (ED); 2) explore the association between arrhythmias and patient outcomes (inpatient complications and length of stay, readmission to the ED or hospital, and all-cause mortality); and 3) explore the demographic, clinical, and treatment characteristics that predict the occurrence of clinically important arrhythmias.

Methods

Design, Sample, and Setting

This is a prospective sub-study of the Ischemia Monitoring and Mapping in the Emergency Department in Appropriate Triage and Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM) study, which tested a new technique of estimated body surface potential mapping to diagnose myocardial ischemia. We obtained data from the University of California, San Francisco Medical Center between 2002 and 2004, with 1-year follow-up completed in 2005.¹⁵ Institutional review boards at the University of California, San Francisco and Yale University approved the study and patients gave informed consent. We asked all adult patients presenting to the medical center ED from 7am to 7pm, Monday through Friday who were evaluated for chest pain or suspected of having unstable angina or an AMI to participate in the study and to undergo 24-hour Holter electrocardiographic

(ECG) monitoring. There were 1,308 patients in the parent study, of whom 302 had ACS, as defined using standard ECG and biomarker criteria (troponin I and CK-MB).

Procedure

Research nurses applied radiolucent electrodes and attached a Holter recorder (Mortara Instruments, Milwaukee, WI) for continuous 12-lead ECG monitoring upon ED admission. The mean time from symptom onset (per patient report) to Holter attachment was 7 ± 9 (median 4) hours, and from ED admission to Holter attachment was 49 ± 27 (median 44) minutes. The electrodes and the wires were radiolucent to allow portable x-rays and angiographic procedures during continuous Holter monitoring. We collected the 12-lead ECG recordings prospectively and later downloaded them for computer-assisted analysis and manual evaluation.

We analyzed arrhythmias in leads II, V₁, V₅, and in full 12-lead configuration over the length of the monitoring time period (mean: 21 ± 6 hours). We documented the underlying rhythm (e.g., sinus rhythm, sinus tachycardia, sinus bradycardia, atrial fibrillation) and arrhythmias and conduction abnormalities were categorized: atrial flutter, supraventricular tachycardia, PVCs, non-sustained VT (6 – 14 consecutive beats), sustained VT, torsade de pointes, junctional rhythms, atrioventricular blocks, ventricular fibrillation, asystole, and bundle branch blocks. We accessed the arrhythmias stored on the Mortara H-Scribe system remotely and analyzed the type, the frequency, and the time period that they occurred. We established ranges for categories of PVCs and non-sustained VT, based on those established by CAST.⁹

Local co-investigators (DS, JZH) oriented the principal investigator (CW) to the patient's medical record and the Mortara H-Scribe system. We used a data collection form on which we categorized arrhythmias and noted their frequency and timing prior to entry into a database. We pilot tested and revised the data collection form. Co-investigators performed episodic data checks on approximately 10% of patients (DS) and reviewed complicated ECG recordings (DS, BJD). We collected demographic, clinical, and ECG data during admission. We obtained information on outcomes by telephone interviews conducted at 1 month and 1 year after the initial hospitalization, and by review of medical records and death registries.

Data Analysis

We performed all analyses using SAS version 9.1 (SAS Institute, Cary, NC) and considered an alpha of .05 to be significant. We described the sample using frequencies and standard measures of central tendency and dispersion. For aim 1, we used frequencies to describe the occurrence of arrhythmias during the first 24 hours of hospitalization.

For aim 2, we explored the association between arrhythmias and patient outcomes. We selected the arrhythmias that occurred most frequently or those that were clinically important (potentially hemodynamically unstable): more than 50 PVCs per hour; non-sustained VT; malignant arrhythmias (sustained VT, ventricular fibrillation, torsade de pointes, asystole); and any intraventricular conduction block (right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block). For the dichotomous outcomes (cardiovascular-related ED and hospital readmission at 30 days and 1 year, and all-cause mortality during inpatient stay and within 30 days and 1 year), we used chi square analysis followed by stepwise logistic regression, with confirmation by forward selection and backward elimination, to determine independent arrhythmia predictors of these outcomes. To evaluate the association between arrhythmias and length of stay, we used

independent t-test after log transformation to normalize the data, and then used stepwise multiple regression, with confirmation by forward selection and backward elimination.

For aim 3, we explored the demographic, clinical, diagnostic, and treatment characteristics that predict the occurrence of clinically important arrhythmias. We used chi square analysis followed by stepwise logistic regression, with confirmation by forward selection and backward elimination.

Results

Sample Characteristics

Of the 302 patients with ACS, 24 were eliminated because they were readmissions of the same patients or were missing ECG recordings. The final sample for this sub-study contained 278 unique patients with ACS. The majority of the patients (n=229; 83%) had a near complete Holter recording of at least 20 hours and 171 (62%) had a full 24 hours recorded. We included recordings of all patients in the analysis. The mean duration of continuous 12-lead Holter recording was 21±6 (median 24) hours.

The mean patient age was 66 years and half of the patients identified White as their race (Table 1). There were more males than females and most patients (92%) experienced chest pain as one of the presenting symptom to the ED. Over half of the patients experienced shortness of breath (68%) and jaw, neck, arm, or back pain (55%). Hypertension was the most frequently occurring cardiovascular risk factor (76%), followed by hypercholesterolemia (63%) and family history of coronary artery disease (53%). A majority had a personal history of coronary artery disease (63%) and 19% had a history of arrhythmias.

Peak serum troponin values, CK-MB, and ECG changes resulted in 8.63% of the patients diagnosed with a ST elevation MI, 26.62% with a non-ST elevation MI, and 64.75% with unstable angina. A little over one quarter of the patients had a PCI, and of those, only 5% had a PCI within 90 minutes of arrival in the ED. Only 6% were treated with an anti-arrhythmic medication.

We categorized patient outcomes into four groups: 1) inpatient complications (of which some patients may have experienced more than one); 2) inpatient length of stay; 3) readmission to either the ED or the hospital within 30-days and 1-year of initial hospitalization; and 4) death during hospitalization, within 30-days, and 1-year after discharge (Table 2). These are outcomes that are reported in many contemporary studies of patients with ACS. Thirty-two patients (11.5%) were lost to 1-year follow-up, resulting in a sample size for the analysis of 1-year outcomes of 246 patients. The most frequently occurring inpatient complication was AMI in patients admitted with unstable angina (8%). The median length of stay was 4 days. The all-cause mortality rate at 1 year was 11%.

Occurrence of Arrhythmias

Patients' arrhythmias and conduction defects are listed in Table 3. Approximately 22% of patients had more than 50 PVCs per hour. Non-sustained VT (6 – 14 consecutive PVCs) occurred in 15% of patients. Very few patients had a malignant arrhythmia (sustained VT, asystole, torsade de pointes, or ventricular fibrillation). No patients had a junctional rhythm or atrial flutter. Conduction defects occurred infrequently, with no patients having a third degree atrioventricular block.

Association of Arrhythmias with Patient Outcomes

There were statistically significant bivariate associations between at least one of the arrhythmias and the outcomes of length of stay and all-cause mortality within 1 year. The only arrhythmias significantly ($p < .05$) associated with length of stay by independent t-test was more than 50 PVCs per hour. Non-sustained VT, malignant arrhythmias (sustained VT, ventricular fibrillation, torsade de pointes, and asystole), and bundle branch blocks were not associated with length of stay. More than 50 PVCs per hour was the only arrhythmia that remained in the final model for the prediction of length of stay after controlling for relevant demographic and clinical factors by multiple regression analyses (Table 4).

More than 50 PVCs per hour was the only arrhythmia significantly associated with all-cause mortality within 1 year by chi square analysis. Logistic regression analysis revealed that no arrhythmias were independently associated with all-cause mortality.

Arrhythmias or groups of arrhythmias were not significantly associated with any of the other outcomes examined.

Predictors of Arrhythmias

We examined the relationship between demographic and clinical characteristics and inpatient interventions and the one arrhythmia (more than 50 PVCs per hour) that independently predicted an adverse outcome (longer length of stay). Bivariate analyses of the demographic and clinical factors shown in Table 1 revealed that only age greater than 65 years, absence of chest pain, a final diagnosis of AMI (vs. unstable angina), and use of anti-arrhythmic medications were significantly related to more than 50 PVCs per hour. The only factors that independently predicted a patient having more than 50 PVCs per hour were age greater than 65 years and a diagnosis of an AMI ($p = .0004$) (Table 5).

Discussion

We found that very few patients with ACS had life-threatening arrhythmias, but 22% experienced isolated PVCs. There was a significant independent association between PVCs and longer length of stay. Age older than 65 years and a diagnosis of AMI were independent predictors of PVCs.

Recent research, although limited, indicates that ventricular arrhythmias were less common today than in the era before early reperfusion became the standard, with reports of ventricular arrhythmia rates of 7.5%¹⁶ and 18%.¹⁷ PVCs that were counted and documented hourly, as was done in this study, were last reported this way in a secondary analysis of CAST¹⁰ and in a study reported by Heidebüchel et al. in 1994.¹⁸ In CAST,^{9,10} more than 50 PVCs per hour were reported to have occurred in almost half (45%) of patients in the study. Heidebüchel and colleagues¹⁸ found that the median PVC frequency per hour was 8.7 (90% confidence interval 0.1 – 92/hour) in their randomized trial of thrombolytic therapy and beta-blockers.

Only 22% of the patients in our cohort had more than 50 PVCs per hour. This is despite the fact that, unlike prior investigators, we counted PVCs with computer and manual over-read of 24-hours of continuous 12-lead ECG data that were obtained soon after ED admission. Heidebüchel and colleagues¹⁸ placed patients on a Holter monitor on day 1 and most were recorded for 24 hours; however, patients were not attached to the Holter until after they had received the fibrinolytic agent and the Holter did not record 12 leads. In our study, there were fewer interruptions of data acquisition and we collected data early in the patient's clinical course. Further, we obtained the ECG recordings continuously, even during interventions such as PCI and intra-hospital transfers. We obtained the recordings promptly,

with patients attached to the monitor at a mean time of 7 (median 4) hours from the onset of symptoms, and within 49 (median 44) minutes of arrival to the ED. Because PVCs commonly develop during ischemia, it would follow that arrhythmias would be more likely to occur early in the patient's clinical course.

Non-sustained VT, defined as 6 to 14 consecutive PVCs, occurred in 15% of patients. Research from the era before early reperfusion became the standard of care revealed a broad range of rates of non-sustained VT: 6–7% in patients with ACS^{11,19}, 22% in CAST¹⁰, and 75% in patients with AMI.¹⁸ These differences may be due to variations in definition of non-sustained VT.

The rarity of sustained VT (1%) and ventricular fibrillation (<1%) in our cohort is in stark contrast to the frequent occurrence of these arrhythmias before early reperfusion became the norm. Sustained VT occurred in 6–31% of patients in these early cohorts,^{2,4,6–8} while VF occurred in 4–20% of patients.^{2–7} Our rates of these life-threatening arrhythmias are also better than rates in contemporary cohorts: 4.3%–10.2% for VT/ventricular fibrillation combined,^{12,14,20} 2.6%–6% for VT^{21–23} and 3.5–5.4% for ventricular fibrillation.^{23,24} Our better rates may be attributed to patients having smaller infarctions and fewer ensuing complications from electrical and pump malfunction.

The samples in the studies of arrhythmias from the era before early reperfusion was the standard consisted only of patients with AMI.^{2–8} Reports of arrhythmias after the onset of the use of early reperfusion therapies were from secondary analyses from large randomized controlled drug trials with carefully selected patients.^{9–12,14,18,19,23} Our study included all patients presenting to an ED with a discharge diagnosis of ACS, resulting in a more diverse sample.

Inpatient length of stay was the only patient outcome that was associated with an arrhythmia independent of demographic and clinical factors. The duration of inpatient hospital stay has declined over the years for all patients, including those with ACS.²⁵ This may be attributed to improvements in the management of patients, such as better diagnostic testing and reperfusion therapy. In this study patients who had more than 50 PVCs per hour had a longer length of stay, which may be due to extended telemetry monitoring when there was no longer a clinical indication for it. Perhaps frequent PVCs serve only as a marker for more severe heart disease that may have prolonged hospitalization, rather than an independent predictor for adverse outcomes.

In this study, age older than 65 years and a final diagnosis of AMI were significantly and independently associated with the occurrence of frequent PVCs. This finding is not surprising as age is a known risk factor for PVCs. In addition, the increased occurrence of frequent PVCs in patients with AMI is likely due to the presence of infarcted versus ischemic myocardium, where there are changes in the myocardial substrate and electrophysiological structure. These changes adversely affect the mechanical and electrical function of the heart, increasing the risk for the development of arrhythmias.

Limitations

Although we refer to the current time as the early reperfusion era, not all patients with AMI had fibrinolytics or PCI during the first 24 hours while the Holter monitor was in place. Of note, two-thirds of the patients had unstable angina vs. AMI and may not have been appropriate for an early reperfusion intervention.

Anti-arrhythmic medication started during hospitalization could not be used in some analyses because we did not know if the medication was given before or after the

arrhythmia. Also, we did not know the type of arrhythmia that was the indication for its use. However, use of these medications was rare.

We also did not note the location or the size of the infarction based on a rise in cardiac biomarkers or echocardiogram. The location and size of the infarction may have influenced the occurrence of arrhythmias.

Patients who came to the ED at night or on the weekend were not included in the sample. It is possible that patients who report to the ED at night or on the weekend for symptoms suggestive of ACS may be more likely to delay coming to the hospital, which may result in more ischemia and arrhythmias. There is considerable evidence for circadian variation in ischemic events – with more occurring in the early morning hours. We may have missed some arrhythmias by including only daytime hours.

This study took place in one hospital in an urban setting, thus potentially limiting the generalizability of the findings. Sample size was a limitation because some of the arrhythmias occurred infrequently, thus precluding multivariate analysis.

Implications for Practice and Research

Despite these limitations, the results of this study have important implications for practice. The settings on monitors in many units are defaulted to alarm for PVCs. Perhaps this is not necessary because since the CAST⁹ results were published, we do not try to suppress PVCs. Turning off PVC alarms, except for patients at risk for torsade de pointes, would result in a quieter environment. More importantly, with the reduction in non-actionable alarms, the total alarm burden would be less, which may result in a faster response to meaningful alarms. With the recent release of the Joint Commission's new National Patient Safety Goal on Alarm Management,²⁶ hospitals will soon be required to take a focused approach to reducing non-actionable alarms, such as PVCs.

Additional research on arrhythmias in the context of ACS is necessary. Research is needed to determine if the findings of this study are generalizable to other settings and other populations. A larger sample of patients with ACS would enable separate analyses of arrhythmia categories that, although are clinically important, were too small for further analysis in this study.

It is important that research in this area continue as we re-evaluate the use of ECG monitoring in the inpatient setting to determine the arrhythmias that have hemodynamic consequences or are of prognostic importance. ECG monitoring could be used more efficiently to monitor for important arrhythmias and avoid over-monitoring with the resulting excessive false or non-actionable alarms. With implementation of the National Patient Safety Goal on Alarm Management,²⁶ perhaps hospitals will also begin to take a more thoughtful approach to the appropriateness of monitoring as a way to decrease alarms and the resulting sentinel events related to alarm fatigue. For patients with ACS, continuing monitoring beyond the recommendations of the ECG monitoring practice standards²⁷ may prolong a patient's hospital stay. Perhaps frequent PVCs as a recognized marker of severity of heart disease in patients who have ACS should prompt nurses and physicians to monitor these patients closely in the short-term and to discontinue monitoring in a timely manner if the frequent PVCs appear to be benign.

Conclusions

Life-threatening arrhythmias are rare in patients with ACS, but almost one quarter of the sample experienced isolated PVCs. There was a significant independent association between

PVCs and a longer length of stay, but PVCs were not related to other adverse outcomes. Rapid treatment of the underlying ACS should remain the focus, rather than extended monitoring for arrhythmias we no longer treat.

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Table 1

Demographic and clinical characteristics of the sample (N = 278)

Characteristic	N	%
Gender		
Male	158	57
Female	120	43
Race		
White	143	51
Asian	60	22
Black	50	18
American Indian	23	8
Pacific Islander	2	< 1
Presenting symptoms to the ED (may have > 1)		
Chest pain	255	92
Shortness of breath	189	68
Jaw, neck, arm, or back pain	152	55
Diaphoresis	116	42
Nausea and vomiting	96	35
Syncope	11	4
Cardiovascular risk factors (may have > 1)		
Hypertension	211	76
Hypercholesterolemia	175	63
Family history of CAD	148	53
Diabetes	81	29
Smoking (current)	56	20
Cardiovascular medical history (may have > 1)		
Personal history of CAD	176	63
History of unstable angina	124	45
Previous acute myocardial infarction	114	41
Previous percutaneous coronary intervention	85	31
Previous CABG surgery	54	19
History of arrhythmias	53	19
Final diagnosis		
Unstable angina	180	65
Non-ST elevation myocardial infarction	74	27
ST elevation myocardial infarction	24	9
Interventions during 24-hour Holter recording		
PCI 90 minutes of ED admission	14	5
PCI > 90 minutes of ED admission	3	1

Characteristic	N	%	
Thrombolytic medication	3	1	
Interventions anytime during hospitalization			
PCI	76	27	
Treated with anti-arrhythmic medication	16	6	
CABG surgery	22	8	
	Mean (SD)	Median	Range
Age (years)	66 (14)	66	30–102
ECG recording time (hours)	21 (6)	24	2–25

ED, emergency department; CAD, coronary artery disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SD, standard deviation; ECG, electrocardiogram

Table 2

Outcomes during inpatient stay, and within 30-days and 1-year of hospitalization (N = 278)

Outcomes	N	%	
Inpatient complications (may have > 1)			
AMI post-admission for patients admitted with UA	21	8	
Transfer to intensive care unit	17	6	
Cardiac arrest	7	3	
AMI extension (detected by 2 nd rise in CK-MB)	6	2	
Cardiogenic shock	5	2	
New severe heart failure/pulmonary edema	2	1	
Readmission [*]			
30-day			
To ED for a cardiovascular reason	42	15	
To hospital for ACS	13	5	
1-year (N = 246)			
To ED for a cardiovascular reason	108	44	
To hospital for ACS	24	10	
All-cause mortality ^{**}			
Inpatient	10	4	
30-day	13	5	
1-year (N = 246)	27	11	
	Mean (SD)	Median	Range
Length of stay	5.37 (7.02)	4	1–93

AMI, acute myocardial infarction; UA, unstable angina; CK-MB, creatinine kinase-myocardial band; ED, emergency department; ACS, acute coronary syndrome; SD, standard deviation

* Readmission: 1-year data includes 30-day data

** All-cause mortality: 30-day data includes inpatient data; 1-year data includes both 30-day and inpatient data

Table 3

Arrhythmias and conduction defects (N = 278)

Arrhythmia and Conduction Defect	N	%
Arrhythmias (may have > 1)		
PVCs (> 50 per hour)	60	22
Non-sustained VT (6–14 consecutive PVCs)	42	15
Supraventricular Tachycardia (< 150 bpm)	37	13
Atrial fibrillation (predominant rhythm or intermittent)	28	10
Sustained VT (> 14 consecutive PVCs or > 30 seconds VT)	3	1
Asystole	2	1
Torsade de Pointes	1	< 1
Ventricular Fibrillation	1	< 1
Conduction defects (may have > 1)		
Atrioventricular Block 2 nd Degree	3	1
Right Bundle Branch Block	26	9
Left Anterior Fascicular Block	13	5
Left Bundle Branch Block	8	3
Left Posterior Fascicular Block	2	< 1

PVCs, premature ventricular contractions; VT, ventricular tachycardia

Table 4

Factors significantly associated with length of stay by multiple regression (N = 278)

Factor	* <i>F value</i>	* <i>p</i>
Final diagnosis of acute myocardial infarction	36.32	<.0001
CABG during admission	118.50	<.0001
PVCs (> 50/hour)	12.28	.0005
<i>F value</i> = 58.12; <i>p</i> = <.0001		

CABG, coronary artery bypass graft; PVCs, premature ventricular contractions

* These statistics represent analyses using the log transformation of length of stay.

Variables significantly related to length of stay by t-test analysis, but were not significant in final multivariate model: non-sustained ventricular tachycardia (6–14 consecutive PVCs), age > 65 years, absence of diaphoresis.

Table 5

Factors significantly associated with the occurrence of > 50 PVCs per hour by multivariate logistic regression

Factor	X ²	p	Odds Ratio (95% CI)
Final diagnosis of acute myocardial infarction	6.24	.0125	2.14 (1.18, 3.88)
Age > 65 years	7.36	.0067	2.35 (1.27, 4.35)
-2 Log Likelihood = 271.240			
Model Chi-square (<i>df</i> = 2) = 15.68			
<i>p</i> = .0004			

CI, confidence interval

Absence of chest pain was significantly related to the occurrence of > 50 PVCs per hour by chi square analysis, but was not significant in the final multivariate model