Clin. Cardiol. 27, 80–86 (2004)

Does Initial and Delayed Heart Rate Predict Mortality in Patients with Acute Coronary Syndromes?

DAVID KOVAR, M.D., CHRISTOPHER P. CANNON, M.D.,* JANE H. BENTLEY, B.SC.,† ANDREW CHARLESWORTH, B.SC.,† WILLIAM J. ROGERS, M.D.

Division of Cardiology, University of Alabama at Birmingham, Birmingham, Alabama; *Division of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts, USA; †Nottingham Clinical Trials Data Centre, Nottingham, United Kingdom

Summary

Background: Lower admission heart rate (HR) is known to predict favorable outcome in ST-elevation acute myocardial infarction. However, there are limited short-term and no long-term data available regarding the prediction value of the initial HR in patients with the full spectrum of acute coronary syndromes (ACS). In addition, it is unknown whether the HR obtained later during hospitalization for ACS (i.e., Day 2 or 3) remains prognostically valuable.

Hypothesis: The aim of this study was to investigate the utility of the initial and delayed HR in predicting outcome in patients with ACS.

Methods: We examined mortality at 30 days and 10 months in 10,267 patients with ACS enrolled in the oral glycoprotein IIb/IIIa inhibition with Orofiban in Patients with Unstable coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 trial. Patients were stratified by HR and day from onset of ACS into the following groups: (1) HR < 60 beats/min, (2) HR 60–80 beats/min, (3) HR 80–100 beats/min, (4) HR > 100 beats/min; and HR obtained on (1) Day 1, (2) Day 2, and (3) Day 3.

Results: By univariate analysis, mortality at 30 days and at 10 months increased progressively with higher HR strata (1.4 vs. 1.6 vs. 2.3 vs. 5.6%, $p < 0.001$, and 2.6 vs. 4.2 vs. 6.5 vs. 11.8%, $p < 0.001$, respectively). Elevated HR remained associated with mortality irrespective of time from onset of ACS.

Conclusions: Higher initial and delayed HR is highly predictive of higher short- and long-term mortality in patients with ACS. This is a simple marker that could be easily used in risk assessment.

Key words: acute coronary syndromes, heart rate, prognosis

Introduction

Effective management of acute coronary syndromes (ACS) requires early identification of patients at high risk for an unsatisfactory outcome. It has been reported that admission heart rate (HR) values independently predict mortality in patients with ST-elevation acute myocardial infarction (STEMI).[1–9] Recently, Boersma *et al.* identified HR as a significant predictor of 30-day mortality in patients with ACS without persistent ST-segment elevation.[10] However, there are no data regarding the long-term predictive value of the initial HR in patients with the full spectrum of ACS. In addition, it is unknown whether an elevated HR obtained later during hospitalization for ACS (i.e., on Days 2, 3) is also associated with adverse outcomes.

The primary objectives of our study were as follows: (1) to quantify the short and long-term prognostic significance of initial HR on mortality and other endpoints in a large population of patients hospitalized for ACS, and (2) to assess the prediction value of HR by day from onset of ACS. We hypothesized that there would be a progressive increase in mortality with increasing HR irrespective of the time interval from onset of the index event.

Methods

Data Sources

The oral glycoprotein IIb/IIIa inhibition with Orofiban in Patients with Unstable coronary Syndromes-Thrombolysis

Address for reprints:

David Kovar, M.D.
Sydney Cardiology Group
Suite 2303, Level 23
25 Bligh Street
Sydney, NSW 2000
Australia
e-mail: david_kovar@yahoo.com

Received: March 8, 2002
Accepted with revision: February 18, 2003

In Myocardial Infarction (OPUS-TIMI)-16 trial was a prospective, randomized, multicenter study of patients with ACS (unstable angina, non-ST-elevation myocardial infarction [NSTEMI]) conducted in 888 hospitals in 29 countries worldwide. The protocol and main results of the OPUS-TIMI-16 trial have been reported previously.[11] Briefly, the study was designed to compare two doses of the oral glycoprotein IIb/IIIa platelet receptor blocker, orbofiban, with placebo for management of patients with ACS. In all, 10,302 patients were randomized into the trial within 72 h of the onset of ACS from October 10, 1997, to November 5, 1998. The exclusion criteria were reported previously[11] and included patients with cardiogenic shock. All patients received aspirin; other therapy was at the discretion of the attending physician. Patients were seen in follow-up at 14 and 30 days, and every 3 months thereafter. Treatment and follow-up were planned to continue for an average of 1 year. Because of higher mortality in one of the dose groups treated with orbofiban, the Data and Safety Monitoring Committee recommended ending enrollment prematurely on November 5, 1998. Follow-up was terminated on January 18, 1999.

Patients

We studied 10,267 patients with ACS. Twenty-one additional patients were excluded from our analyses because they had no baseline HR measurement recorded. Heart rate was measured either by physical examination or by electrocardiogram (ECG) as close to randomization as possible. Patients were divided into four groups based on their admission HR: (1) HR < 60 beats/min, (2) HR 60–80 beats/min, (3) HR 80–100 beats/min, and (4) HR > 100 beats/min. To evaluate whether elevated HR obtained later during the initial hospital stay remains a predictor of increased mortality, patients were stratified according to whether their admission HR was obtained (1) within 24 h of ACS, (2) 24–48 h after onset of ACS, and (3) 48–72 h after onset of ACS. Clinical events were compared between the groups at 30 days and 10 months.

Definitions

Acute coronary syndrome was defined as ischemic discomfort at rest associated with positive cardiac markers, and/or acute ECG changes, and/or evidence of coronary artery disease.[11]

Statistical Analysis

For each group in the general population and specific subgroups of patients including the elderly, diabetics, women, and patients with congestive heart failure (CHF), STEMI, NSTEMI, and unstable angina (UA), outcome results are presented with Kaplan-Meier event rates. Probability values were determined from log-rank tests with follow-up censored at time indicated (i.e., 30 days or 10 months). Multivariate analyses were performed to adjust for confounding variables and to assess the independent prognostic value of admission HR on subsequent mortality and other endpoints. The following variables were included in the multivariate models: age, gender, history of hypertension, diabetes mellitus, hypercholesterolemia, prior MI, prior revascularization, history of heart failure, smoking, ECG changes, elevated cardiac enzymes, and use of heparin, aspirin, and nitrates. Patients with unknown value for any variable were excluded from multivariate analyses. All statistical analyses were performed using S-Plus 2000.

Results

Baseline Characteristics

Baseline characteristics of all four HR groups are shown in Table I. Patients were, on average, about 60 years old. Patients with admission HR > 100 beats/min were older and more likely to be female and black compared with other HR groups. Prevalence of hypertension, diabetes mellitus, peripheral vascular diseases, and heart failure was higher in patients with higher HRs. In contrast, patients with admission HR < 60 beats/min had higher occurrence of previous MI, prior angina, and prior percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery. Patients with higher HR strata were more likely to be treated with diuretics and angiotensin-converting enzyme (ACE) inhibitors. Elevated HR was associated with higher frequency of CHF of any severity and lower ejection fraction. Patients with elevated HR also had higher mean systolic and diastolic blood pressure on admission, increased troponin level, and longer duration of discomfort and hospitalization. There were no significant differences in frequency of revascularization between groups.

Thirty-Day Results

At 30 days, mortality increased progressively with higher admission HR strata (1.4 vs. 1.6 vs. 2.3 vs. 5.6%, $p < 0.001$) (Fig. 1). Rate of recurrent MI was significantly higher in patients with HR > 100 beats/min than in patients with HR < 60 beats/min (5.7 vs. 2.7%, $p = 0.004$). The rate of recurrent ischemia leading to urgent revascularization was not significantly different among the four groups ($p = 0.35$). Cox proportional hazards multivariate analysis is shown in Table II. In patients with HR > 100 beats/min, relative risk (RR) for mortality was more than three-fold higher compared with the group with HR < 60 (RR 3.08, 95% confidence interval [CI] 1.54–6.17). There was no significant difference in mortality rate between patients with HR 60–80 and 80–100 beats/min compared with patients with HR < 60 beats/min (RR 1.09, 95% CI 0.66–1.79 and RR 1.61, 95% CI 0.94–2.79, respectively). Besides HR > 100 beats/min, other independent predictors of death at 30 days were ST-segment depression (RR 2.1, 95% CI 1.11–3.96), elevated creatine kinase (RR 1.84,

TABLE I Baseline characteristics

Characteristics	< 60 beats/min (n = 2,214)	60–80 beats/min (n = 5,854)	80–100 beats/min (n = 1,893)	> 100 beats/min (n = 306)	p Value
Age (mean, year)	61.1	60.2	60.1	62.0	0.001
Male sex (%)	76.9	71.6	69.6	62.7	< 0.001
White race (%)	91.5	90.9	89.6	88.6	0.003
Black race (%)	2.3	2.7	3.8	5.2	0.003
Medical history (%)					
Previous MI	30.1	27.4	23.6	28.9	< 0.001
Previous UA	27.7	23.6	20	24.3	< 0.001
Prior PTCA	14	10.7	7.9	9.5	< 0.001
Prior CABG	12.6	10.9	8.1	8.5	< 0.001
Heart failure	3.3	5	6.4	12.1	< 0.001
PVD	6.7	6.7	7.2	10.5	< 0.001
Prior nonhemorrhragic stroke	3.1	2.5	2.9	3.9	0.26
Risk factors (%)					
Hypertension	39.8	43.1	45.7	48.7	< 0.001
Hypercholesterolemia	29.9	28.2	25.9	26.8	0.03
Diabetes mellitus	14.6	20.8	27.1	35.6	< 0.001
Family history of CAD	39.6	40.5	40.2	41.3	0.9
Current smoker	37.2	36.3	35.7	33.4	0.69
Drugs used in 2 weeks before randomization (% of patients)					
Beta blockers	20.7	15.8	12.1	13.1	< 0.001
Nitrates	13.2	12.2	11.6	15.7	< 0.001
Diltiazem	7.2	7.8	7.7	12.4	0.003
Amlodipine	4.7	4.3	4.6	5.2	< 0.001
Nifedipine	5.2	5.4	4.9	5.6	0.89
Lipid-lowering therapy	16.1	14.9	11.4	13.7	< 0.001
Aspirin	23.7	21.8	19.2	19.9	< 0.001
ACE inhibitors	11.7	13.7	15.8	19.9	< 0.001
Diuretics	7.6	10	11.8	12.1	< 0.001
Drugs used for management of event (% of patients)					
Beta blockers	36	41.5	43	38.6	< 0.001
Nitrates	51.1	54.8	55.7	46.1	< 0.001
Aspirin	47.5	52.7	57.9	52	< 0.001
Unfractionated heparin	79.6	79.4	79.8	80	0.98
LMWH	17.7	17.1	17.3	16.3	0.91
Physical examination					
Systolic BP, mean (mmHg)	125.16	128.76	133.23	138.61	< 0.001
Diastolic BP, mean (mmHg)	71.32	74.42	77.53	80.57	< 0.001
Heart rate, mean (beats/min)	56.04	71.25	88.94	111.89	< 0.001
Killip I (%)	95.3	92.8	86	68.8	< 0.001
Killip II (%)	4	6.5	12.6	24.7	< 0.001
Killip III (%)	0.4	0.5	1.3	5.9	< 0.001
Killip IV (%)	0.3	0.2	0.2	0.7	< 0.001
Duration of discomfort, mean (min)	186.59	223.57	240.43	276.88	< 0.001
Duration of hospitalization, mean (days)	8.8	8.87	9.46	10.57	< 0.001
CK > ULN (%)	54	61	67.7	64.6	< 0.001
CK-MB > ULN (%)	69.4	74.3	78.6	78.2	< 0.001
Positive troponin (%)	16	19.5	21.7	27	< 0.001
LVEF (mean)	56.25	54.07	50.71	47.86	< 0.001
Coronary arteriography (%)	17.1	18	20	13.1	0.01
Revascularization attempted (%)	51.6	56.9	57.6	62.5	0.21

Abbreviations: ACE = angiotensin-converting enzyme, BP = blood pressure, CABG = coronary artery bypass graft, CAD = coronary artery disease, CK = creatine kinase, LMWH = low molecular weight heparins, MI = myocardial infarction, LVEF = left ventricular ejection fraction, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, UA = unstable angina, ULN = upper limit normal.

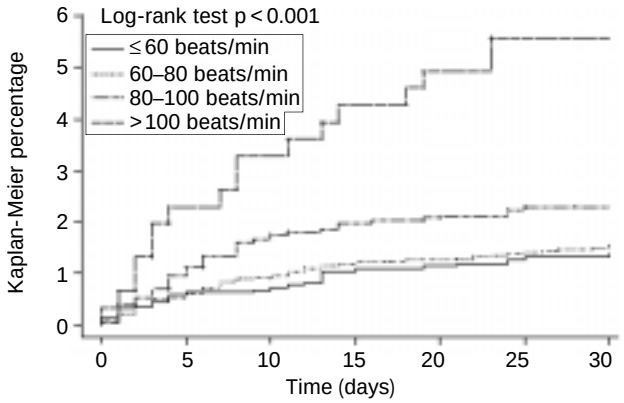

FIG. 1 Thirty-day Kaplan-Meier mortality rates for patients with different heart rates.

95% CI 1.09–3.12), and advanced age (RR 1.06 per year, 95% CI 1.04–1.08).

Ten-Month Results

As shown in Figure 2 , at 1 year the rate of death remained significantly higher in higher HR groups (2.6 vs. 4.2 vs. 6.5 vs. 11.8%, p < 0.001). There was no significant difference in the rate of recurrent MI (p = 0.16) and recurrent ischemia leading to urgent revascularization (p = 0.46) between the four groups. When adjusted for confounding variables, RRs of death for patients with HR > 100, HR 80–100, and HR 60–80 beats/min were 3.25 (95% CI 1.88–5.6), 1.91 (1.24–2.94), and 1.39 (0.94–2.05), respectively (Table II). At 10-month follow-up, in addition to HR > 80 beats/min, other independent predictors of mortality were history of heart failure (RR 1.86, 95% CI 1.28–2.7), ST depression (RR 1.63, 95% CI 1.07–2.48), elevated creatine kinase (RR 1.53, 95% CI 1.06–2.21), diabetes mellitus (RR 1.43, 95% CI 1.09–1.88), and advanced age (RR 1.07 per year, 95% CI 1.05–1.08).

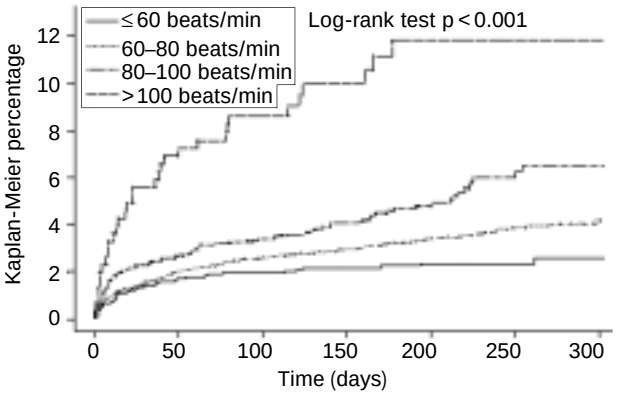

FIG. 2 Ten-month Kaplan-Meier mortality rates for patients with different heart rates.

TABLE II Cox proportional hazards multivariate analysis comparing relative risk for mortality among heart rate groups at 30 days and 10 months

	Relative risk for mortality		p Value	
	30 Days	10 Months	30 Days	10 Months
HR 60–80 [a]	1.09 (0.66–1.79)	1.39 (0.94–2.05)	0.73	0.09
HR 81–100 [a]	1.61 (0.94–2.79)	1.91 (1.24–2.94)	0.08	0.003
HR > 100 [a]	3.08 (1.54–6.17)	3.25 (1.88–5.6)	0.001	< 0.001

[a] vs. HR < 60.

Abbreviation: HR = heart rate.

Relation between Heart Rate and Time from Onset of Acute Coronary Syndrome

As demonstrated in Figure 3, increased short- and long-term mortality was associated with elevated HR not only during the initial presentation but also on the second and third hospital day.

Subgroup Analysis

The relationship of increased risk of death with higher HR strata at 30 days and 10 months also applied to specific population subgroups, including patients with and without diabetes (Fig. 4), patients with and without history of CHF (Fig.

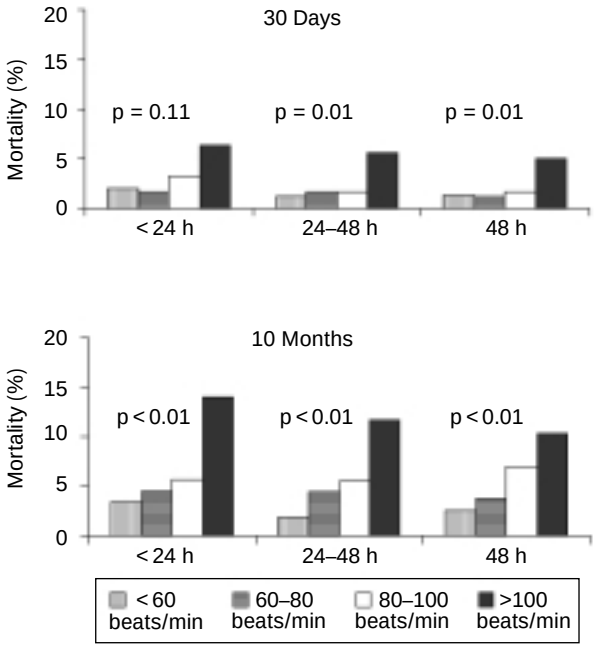

FIG. 3 Relation between heart rate and time from onset of acute coronary syndromes; 30-day and 10-month data.

5), older and younger patients (Fig. 6), men and women (Fig. 7), and patients with the full spectrum of ACS (Fig. 8) comprising STEMI (32.4% of all patients), NSTEMI (23.1%), and UA (44.5%).

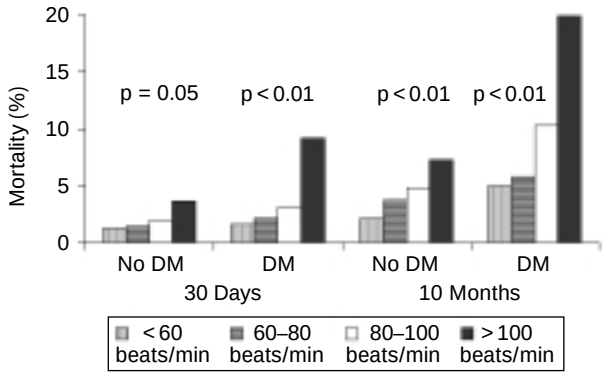

FIG. 4 Relation between heart rate and mortality in patients with and without diabetes mellitus (DM).

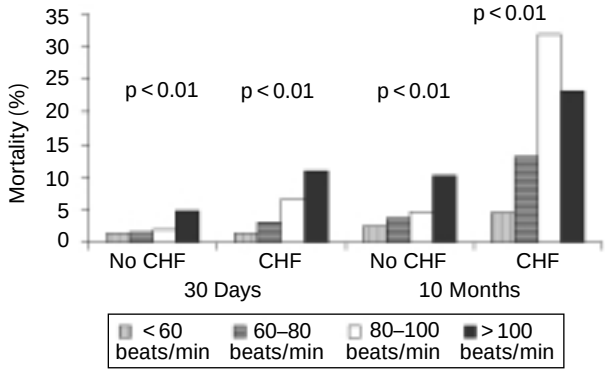

FIG. 5 Relation between heart rate and mortality in patients with and without history of congestive heart failure (CHF).

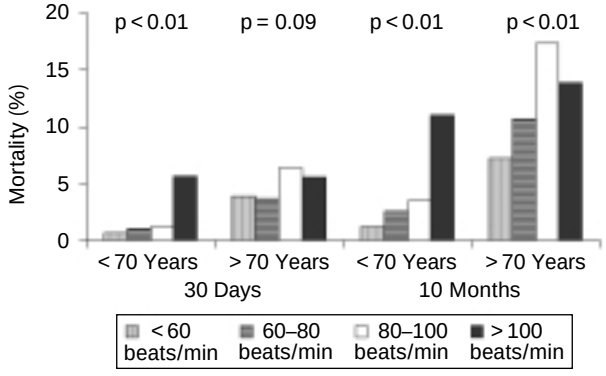

FIG. 6 Relation between heart rate and mortality in patients aged < 70 years and > 70 years.

Discussion

Our study demonstrates that higher initial HR (especially HR > 100 beats/min) is highly predictive of higher short- and long-term mortality in patients with ACS. Patients with initial HR > 100 beats/min have a greater than three-fold increased risk of death at both 30 days and 10 months compared with patients with HR < 60 beats/min. The results of our study are very consistent, as demonstrated by progressive increase of mortality with increasing HR strata in various patient populations (i.e., diabetics vs. nondiabetics, CHF vs. no CHF, > 70 years vs. < 70 years old, women vs. men, and STEMI vs. NSTEMI vs. UA).

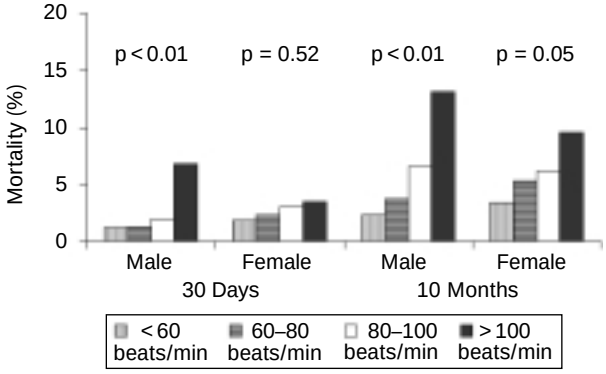

FIG. 7 Relation between heart rate and mortality in female and male patients.

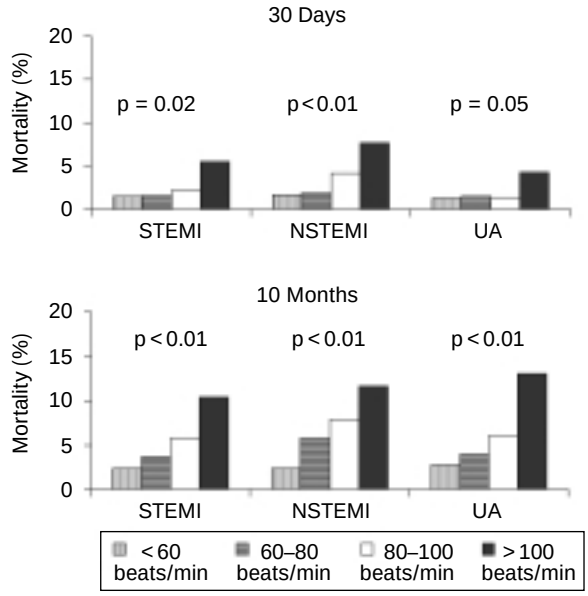

FIG. 8 Relation between heart rate and mortality in patients with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA); 30-day and 10-month data.

Timing of Heart Rate Assessment

To estimate the risk of death in patients with ACS, multiple risk stratification scores have been developed recently.[12–23] The majority of these included elevated cardiac markers and ECG changes as independent predictors of adverse outcomes. Unfortunately, there are limited data on risk assessment of "subacute" patients with ACS after initial presentation. Our study is unique because it demonstrates that HR is a very useful mortality predictor, not only during the initial presentation but also later during hospitalization (i.e., on hospital Days 2 and 3). As most patients with ACS are being monitored continuously while in the hospital, a simple hemodynamic parameter such as HR might be used as an uninterrupted risk prognosticator. We believe that patients with elevated HR might have additional benefit from aggressive therapy. It is interesting that, in our study, HR > 100 beats/min was the most potent predictor of 30-day and 10-month mortality.

The present study confirms and extends observations derived from the analysis performed by Boersma *et al.*[10] They showed that elevated HR increases risk of death by 36% for patients with NSTEMI and by 12% for patients with UA. However, their study was limited to a 30-day follow-up.[10] Our study is the first to evaluate long-term prediction capability of admission HR on mortality in patients with the full spectrum of ACS, including STEMI and UA/NSTEMI. Our study is unique in evaluating the relation of HR to the rate of recurrent MI and ischemia in patients with ACS. Furthermore, we have found similar results in different population subgroups, which strengthens the generalization of this finding. As our patients were younger than the patients in the study by Boersma *et al.* (average age 60 vs. 64 years), with lower prevalence of associated comorbidities (i.e., hypertension, diabetes, hypercholesterolemia, history of MI, and heart failure), our study expands the applicability of HR as a predictor of adverse outcomes to a less acutely ill population.

Increased mortality with increased HR strata has also been reported previously in patients with STEMI.[1–9] Hjalmarson *et al.* showed that total 1-year mortality was 15% for patients with admission HR between 50 and 60 beats/min, 41% for HR > 90 beats/min, and 48% for HR > 110 beats/min.[5] The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) study group reported an increase in admission HR of 15 beats/min to be associated with average estimated increases of in-hospital and 1-year postdischarge mortality of 36 and 45%, respectively.[6] Findings in both studies were specifically adjusted for presence of CHF. Analyses of Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) studies showed a progressive increase in mortality with increasing HR in the STEMI population receiving thrombolytic therapy.[7, 9] Furthermore, a number of epidemiologic studies have reported a relationship between a high resting HR and cardiovascular mortality and morbidity in relatively healthy subjects.[24, 25] The Framingham study showed increased HRs in older patients and progressively higher overall and cardiovascular mortality in patients with increased resting HR.[24] Similar findings were reported by Dyer *et al.* in three Chicago epidemiologic studies.[25]

Pathophysiologic Mechanisms

The explanation for the observed association between rapid HR and increased mortality is complicated. Tachycardia may indicate subclinical loss of cardiac reserve as a result of impaired myocardial function, leading to the observed higher case fatality rates in coronary attacks and propensity to sudden deaths.[24] Heart rate is one of the most important determinants of the energy requirements of the myocardium. A high HR increases myocardial oxygen requirements and may potentiate myocardial ischemia.[24] High HRs may indicate poor physical fitness, which has been shown to be associated with increased cardiovascular mortality rates,[26] and may also reflect autonomic imbalance, indicating excessive sympatho-adrenergic activity, described to be associated with adverse outcome.[9, 27] Holtzman *et al.* reported that a higher HR may derive from an increase in norepinephrine or hypersensitivity to it.[28] Ewing *et al.* described HR changes as a result of compromised parasympathetic activity in diabetes mellitus.[29] It has also been suggested that severe arteriosclerosis is associated with elevated HR, with atherosclerotic thickening of the arterial tree the possible culprit in this phenomenon.[30, 31]

The beneficial effect of HR-lowering therapy (i.e., beta blockers) supports the findings of our study. Three double-blind, randomized trials have compared beta blockers with placebo in UA.[32–34] Meta-analysis of the available trials indicates a 13% reduction in risk of progression to acute MI.[35, 36]

Study Limitations

Several limitations of our study must be acknowledged. Our study is a substudy of a multicenter trial analyzing a preselected group of patients with specific entry criteria. Therefore, our data may not apply to patients who were excluded from the study (e.g., patients with renal insufficiency or other comorbidities that were exclusion criteria for the trial). Also, retrospective analysis may have led to information bias, even though the high number of patients from multiple sites should minimize this type of error. In spite of the inclusion of multiple variables in the multivariate analysis, it is possible that an elevated HR is a consequence of another cause of increased mortality that we did not account for.

Conclusions

In patients with acute coronary syndromes, elevated initial as well as delayed heart rate is highly predictive of higher short- and long-term mortality. Heart rate is a readily available variable and may be useful in the selection of high-risk patients for more aggressive treatment.

References

1. Madsen EB, Gilpin E, Henning H: Prediction of late mortality after myocardial infarction from variables measured at different times during hospitalization. *Am J Cardiol* 1984;53:47–54
2. Willers JL, Pardaens J, De Geest H: Early risk stratification using clinical findings in patients with acute myocardial infarction. *Eur Heart J* 1984;5: 130–139
3. Henning H, Gilpin E, Covell JW: Prognosis after acute myocardial infarction: A multivariate analysis of mortality and survival. *Circulation* 1979;59: 1124–1136
4. Gilpin E, Olshen R, Henning H: Risk prediction after myocardial infarction, comparison of three multivariate methodologies. *Cardiology* 1983;70: 73–84
5. Hjalmarson A, Gilpins EA, Kjekshus J, Schieman G, Nicod P, Henning H, Ross J: Influence of heart rate on mortality after acute myocardial infarction. *Am J Cardiol* 1990;65:547–553
6. Disegni E, Gouldbourt U, Reicher-Reiss H, Kaplinsky E, Zion M, Boyko V, Behar S: The predictive value of admission heart rate on mortality in patients with acute myocardial infarction. SPRINT study group. Secondary Prevention Reinfarction Israeli Nifedipine trial. *J Clin Epidemiol* 1995;48: 1197–1205
7. Zuanetti G, Mantini L, Hernandez-Bernal F, Barlera S, di Gregorio D, Latini R, Maggioni AP: Relevance of heart rate as a prognostic factor in patients with acute myocardial infarction: Insight from the GISSI-2 study. *Eur Heart J* 1998;19(suppl F):19–26
8. Gundersen T, Grottum P, Pederson T, Kjekshus JK: Effect of timolol on mortality and reinfarction after acute myocardial infarction: Prognostic importance of heart rate at rest. *Am J Cardiol* 1986;58:20–24
9. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM, for the GUSTO-I investigators: Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: Results from an international trial of 41,021 patients. *Circulation* 1995;91:1659–1668
10. Boersma E, Pieper KS, Steyerberg EW: Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: Results from an international trial of 9,461 patients. *Circulation* 2000;101: 2557–2567
11. Cannon CP, McCabe CH, Wilcox RG, Langer A, Caspi A, Berink P, Lopez-Sendom J, Toman J, Charlesworth A, Anders RJ, Alexander JC, Skene A, Braunwald E, for the OPUS-TIMI 16 Investigators: Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149–156
12. Holmvang L, Lusher MS, Clemmensen P, Thygesen K, Granse P: Very early risk stratification using combined ECG and biochemical assessment in patients with unstable coronary artery disease. *Circulation* 1998;98:2004–2009
13. Lloyd-Jones DM, Camargo CA, Lapuerta P: Electrocardiographic and clinical predictors of acute myocardial infarction in patients with unstable angina pectoris. *Am J Cardiol* 1998;81:1182–1186
14. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fisher GA, Fung AY, Thompson C, Wybenga D, Braunwald E: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342–1349
15. Lindahl B, Toss H, Venge P, Wallentin L: Troponin T is a strong prognostic marker for subsequent cardiac events in patients with unstable angina. *Eur Heart J* 1995;16(suppl):40
16. Cannon CP, Thompson B, McCabe CH, Mueller HS, Kirshenbaum JM, Herson S, Nasmith JB, Chaitman BR, Braunwald E: Predictors of non-Q-wave acute myocardial infarction in patients with acute ischemic syndromes: An analysis from the Thrombolysis in Myocardial Ischemia (TIMI) III trials. *Am J Cardiol* 1995;75:977–981
17. Ravkilde J, Nissen H, Horder M, Thygesen K: Independent prognostic value of serum creatine kinase isoenzyme MB mass, cardiac troponin T and myosin light chain levels in suspected acute myocardial infarction. *J Am Coll Cardiol* 1995;25:574–581
18. Hamm CW, Ravkilde J, Gerhart W: The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146–150
19. Ravkilde J, Horder M, Gerhardt W: Diagnostic performance and prognostic value of serum troponin T in suspected myocardial infarction. *Scand J Clin Lab Invest* 1992;53:677–685
20. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE Jr, Calif RM, Topol EJ: Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996;335:1333–1341
21. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schachtman M, Thompson BW, Pearce DJ, Divers DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E, for the TIMI III Registry ECG Ancillary Study Investigators: The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q-wave myocardial infarction: Results of the TIMI III registry ECG ancillary study. *J Am Coll Cardiol* 1997;30:133–140
22. Hamm C, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML: Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;340:1623–1629
23. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E: The TIMI risk score for unstable angina/non-ST elevation MI. A method for prognostication and therapeutic decision making. *J Am Med Assoc* 2000;2000;284:835–842
24. Kannel WB, Kannel C, Paffenbarger RS, Cupples AL: Heart rate and cardiovascular mortality: The Framingham Study. *Am Heart J* 1987;11:1489–1494
25. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA: Heart rate as a prognostic factor for coronary heart disease and mortality: Findings in three Chicago epidemiologic studies. *Am J Epidemiol* 1980;112:736–749
26. Kannel WB, Wilson P, Blaire SN: Epidemiologic assessment of the role of physical activity and fitness in development of cardiovascular disease. *Am Heart J* 1985;109:876–885
27. Conway J: Hemodynamic aspects of essential hypertension in humans. *Physiol Rev* 1984;64:617–660
28. Holtzman E, Gouldbourt U, Rosenthal T: Hypertension in middle aged men. Associated factors and mortality experience. *Isr J Med Sci* 1983;19:25–33
29. Ewing DJ, Campbell IW, Clarke BF: Heart rate changes in diabetes mellitus. *Lancet* 1981;1:183–185
30. Persky A, Olsson G, Landon C, deFaire U: Minimum heart rate and coronary atherosclerosis. Independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. *Am Heart J* 1992;123:609–616
31. Bonaa KH, Arnessen E: Association between heart rate and atherogenic blood lipid fractions in a population—the Tromso Study. *Circulation* 1992; 86:394–405
32. Lubsen J, Tijssen JG: Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: Findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987;60:18A–25A
33. Gottlieb SO, Weisfeldt ML, Ouyang P: Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: A randomized, double-blind, placebo-controlled trial. *Circulation* 1986;73:331–337
34. Telford AM, Wilson C: Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet* 1981;1: 1225–1228
35. Yusuf S, Wittes J, Friedman L: Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *J Am Med Assoc* 1988;260: 2259–2263
36. Braunwold E, Antman EM, Beasley JW, Cliff RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC: ACC/AHA guidelines for management of patients with unstable angina and non-ST-segment elevation myocardial infarction: A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000;36:970–1062