Acute myocardial infarction treatment : from prehospital care to secondary prevention

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Chapter 8

Prognostic value of heart rate in patients after acute myocardial infarction treated with Primary percutaneous coronary intervention.

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ABSTRACT

Objectives

The aim was to evaluate the prognostic value of heart rate in patients with acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention (PCI).

Background

Recently, heart rate has been described as an important risk factor for reinfarction, revascularization and heart failure in patients with left ventricular dysfunction. Currently, most patients with AMI are treated with primary PCI and left ventricular function is relatively preserved. The clinical relevance of heart rate in this patient population is unknown.

Methods

A total of 1102 consecutive AMI patients treated with primary PCI were evaluated. Heart rate was measured by 12-lead electrocardiography at time of admission. The endpoint was a composite of all-cause mortality, nonfatal reinfarction, coronary revascularization and hospitalization for heart failure.

Results

During a mean follow-up of 20 months, 89 patients died (8%), 38 patients (3%) had a nonfatal reinfarction, 169 patients (15%) underwent revascularization and 45 patients (4%) were hospitalized for heart failure. After adjustment for known risk factors, a heart rate of 72bpm or higher was associated with a significant increased risk for the composite endpoint and all separate events. In addition, every increase of 5bpm resulted in an increased adjusted relative risk of 8% for the composite endpoint, 9% for mortality, 17% for reinfarction, 7% for revascularization and 11% for hospitalization for heart failure.

Conclusions

Baseline resting heart rate is a strong risk factor for adverse outcome in AMI patients and preserved left ventricular function. The present study provided further evidence for targeting low heart rate in patients after AMI.

INTRODUCTION

Resting heart rate is a simple cardiovascular parameter and has been well established as a strong predictor of mortality in patients with coronary artery disease.[1,2] Recently, heart rate has also been described as a risk factor for cardiovascular morbidity including reinfarction, revascularization and hospitalization for heart failure in patients with left ventricular dysfunction. The BEAUTIFUL study demonstrated that an elevated heart rate of 70 bpm or greater identified patients at increased risk of cardiovascular outcomes in patients with coronary heart disease and left ventricular dysfunction.[3] Acute myocardial infarction (AMI) is a major health problem in the western world despite the improved treatment strategies including reperfusion therapy.[4] Currently, most patients with AMI are treated with primary percutaneous coronary intervention (PCI), and therefore, left ventricular function is relatively preserved. The clinical relevance of resting heart rate in that currently growing population of post-AMI patients with preserved left ventricular function is unknown. Accordingly, the aim of the current study was to evaluate the relation between resting heart rate and long-term mortality and cardiovascular morbidity in patients with AMI treated with primary PCI. Importantly, all patients in the present patient population were treated with structurized evidence-based medical therapy including a high level of beta-blockers, initiated early after admission.[5,6]

METHODS

Patient population and study design

Since February 2004 consecutive patients admitted with an AMI with ST-segment elevation to our university hospital were included in an ongoing registry. All patients were treated with primary PCI according to the institutional AMI protocol, which is based upon the most recent American College of Cardiology/American Heart Association guidelines.[7] This protocol, designed to improve care around AMI, includes structurized evidence-based medical therapy, two-dimensional echocardiography and standardized follow-up at the outpatient clinic during 1 year after the index infarction, as described previously.[5] Echocardiography was performed within 48 hours of admission to quantify left ventricular ejection fraction according to the recommended biplane Simpson's method.[8] In addition, resting heart rate was measured by 12-lead electrocardiography at time of admission.

Follow-up and endpoint definitions

All patients were followed prospectively according to the institutional protocol and the occurrence of adverse cardiac and non-cardiac events after the index infarction was noted.[5] Patients of whom more than 6 months follow-up data were lacking, were considered as lost to follow-up, and were excluded from further analysis. The primary endpoint was a composite

of all-cause mortality, nonfatal reinfarction, coronary revascularization and admission to hospital for new-onset of worsening heart failure. In addition, all clinical outcomes included in the composite endpoint were evaluated as individual endpoints. Nonfatal reinfarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram.[9] All coronary revascularizations after discharge of the index infarction were included for the secondary endpoint.

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as frequencies and percentages. Differences between groups were evaluated using the unpaired Student's *t* test and chi-square test, where appropriate.

Elevated baseline heart rate was analyzed as a continuous variable, dichotomized according to a cutoff value of 72 bpm and categorized into intervals of 5 bpm. The cutoff of 72 bpm was derived from the patient population as the median heart rate of the total population and is in line with previous studies assessing the risk associated with an elevated heart rate.[1-3,10] Cox proportional hazards regression analyses were performed to relate elevated baseline heart rate to the different endpoints, adjusting for all variables with significant baseline differences between the patients with a heart rate less than 72 bpm and 72 bpm or greater. Peak creatine phosphokinase level and diastolic blood pressure were excluded from multivariate analysis to avoid co-linearity with peak cardiac troponin T level and systolic blood pressure.

Event rates were plotted in Kaplan-Meier curves for the composite endpoint and all separate clinical outcomes and the study population divided by the cutoff of 72bpm, and groups were compared using the log-rank test.

Finally, the incremental value of baseline resting heart rate as a continuous variable in addition to clinical risk factors for adverse outcome was assessed by comparison of model chi-square values. For this purpose, those characteristics were entered in the Cox proportional hazard model in a stepwise fashion. Subsequently, heart rate was entered individually. All statistical tests were two-sided, and a *P* value <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics and follow-up

A total of 1193 patients were included. Four (0.3%) patients died before an electrocardiogram could be performed and 87 (7.3%) patients were lost to follow-up and were excluded from further analysis. The final patient population therefore comprised 1102 patients. The baseline characteristics of the patients are shown in Table 1. Patients with a heart rate of 72 bpm or greater were more likely to have diabetes, the left anterior descending coronary

Table 1. Baseline characteristics of patients

	All Patients (n =1102)	Heart rate <72 bpm (n=537)	Heart rate ≥72 bpm (n=565)	*P**
Age (years)	61 ± 12	61 ± 12	60 ± 12	0.32
Male gender	852 (77%)	422 (79%)	430 (76%)	0.33
Killip class ≥2	76 (7%)	30 (6%)	48 (9%)	0.06
Current smoking	536 (49%)	270 (49%)	284 (53%)	0.19
Diabetes	127 (12%)	47 (9%)	80 (14%)	0.004
Family history of CAD	454 (43%)	226 (43%)	228 (42%)	0.89
Hyperlipidemia	214 (20%)	95 (18%)	119 (22%)	0.12
Hypertension	351 (32%)	169 (32%)	182 (33%)	0.63
Prior myocardial infarction	91 (8%)	40 (7%)	51 (9%)	0.34
LAD culprit vessel	513 (47%)	214 (40%)	299 (53%)	<0.001
Multivessel disease	551 (50%)	256 (48%)	295 (52%)	0.13
Peak CPK level (U/l)	2406 ± 3132	2154 ± 3659	2685 ± 2471	0.01
Peak cTnT level (µg/l)	6.4 ± 6.9	5.6 ± 5.5	7.1 ± 7.9	<.001
Heart rate at admission (bpm)	74 ± 18	60 ± 9	88 ± 14	
TIMI flow	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	0.15
Systolic blood pressure (mm Hg)	135 ± 25	133 ± 25	137 ± 24	0.001
Diastolic blood pressure (mm Hg)	81 ± 16	78 ± 15	83 ± 16	<0.001
Left ventricular ejection fraction (%)	45 ± 9	46 ± 8	44 ± 9	<0.001
ACE inhibitor / ARB at admission	173 (16%)	81 (15%)	92 (16%)	0.57
Antiplatelets at admission	171 (16%)	81 (15%)	90 (16%)	0.68
Beta-blocker at admission	203 (19%)	111 (21%)	92 (16%)	0.07
Statins at admission	181 (17%)	82 (15%)	99 (18%)	0.28
ACE inhibitor / ARB at discharge	1037 (97%)	513 (97%)	524 (98%)	0.24
Antiplatelets at discharge	1065 (100%)	530 (100%)	535 (100%)	1.00
Beta-blocker at discharge	1003 (94%)	490 (93%)	513 (96%)	0.02
Statins at discharge	1056 (99%)	528 (100%)	528 (99%)	0.10

*P values are given for the comparison of patients who died of all-cause mortality versus patients who survived.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; LAD = left anterior descending coronary artery.

artery as the culprit vessel, higher peak cardiac enzymes, higher blood pressures, lower left ventricular ejection fraction and were less likely to be treated with beta-blockers at discharge.

During a mean follow-up duration of 20 ± 14 months, 277 patients (25%) reached the composite endpoint: 89 patients died (8%), 38 patients (3%) had a nonfatal reinfarction, 169 patients (15%) underwent revascularization and 45 patients (4%) were hospitalized for heart failure.

Increased risk of adverse outcome associated with elevated heart rate

Table 2 shows the increased risk of adverse events associated with an elevated heart rate adjusted for all variables with significant differences between the groups with a heart rate less than 72 bpm and 72 bpm or greater. A resting heart rate of 72 bpm or higher was associated with a significant increased risk of all endpoints (Table 2). In addition, analyses with heart rate as a continuous variable showed that every increase of 5 bpm resulted in a significant higher risk for every endpoint. An increased adjusted relative risk of 8% was observed for the composite endpoint, 9% for mortality, 17% for reinfarction, 7% for revascularization and 11% for hospitalization of heart failure for every increase of 5 bpm.

Table 2. Adjusted hazard ratios for elevated heart rate at admission

	Events, n (%)	Heart rate ≥72 versus <72 bpm		Heart rate higher by 5 bpm	
		Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Composite endpoint	277 (25%)	1.57 (1.20 – 2.05)	0.001	1.08 (1.04 – 1.12)	<.001
Mortality	89 (8%)	1.94 (1.04 – 3.63)	0.04	1.09 (1.02 – 1.16)	0.01
Reinfarction	38 (3%)	2.41 (1.16 – 5.00)	0.02	1.17 (1.09 – 1.25)	<0.001
Revascularization	169 (15%)	1.40 (1.02 – 1.91)	0.04	1.07 (1.03 – 1.11)	0.001
Heart Failure	45 (4%)	2.50 (1.21 – 5.16)	0.01	1.11 (1.03 – 1.19)	0.006

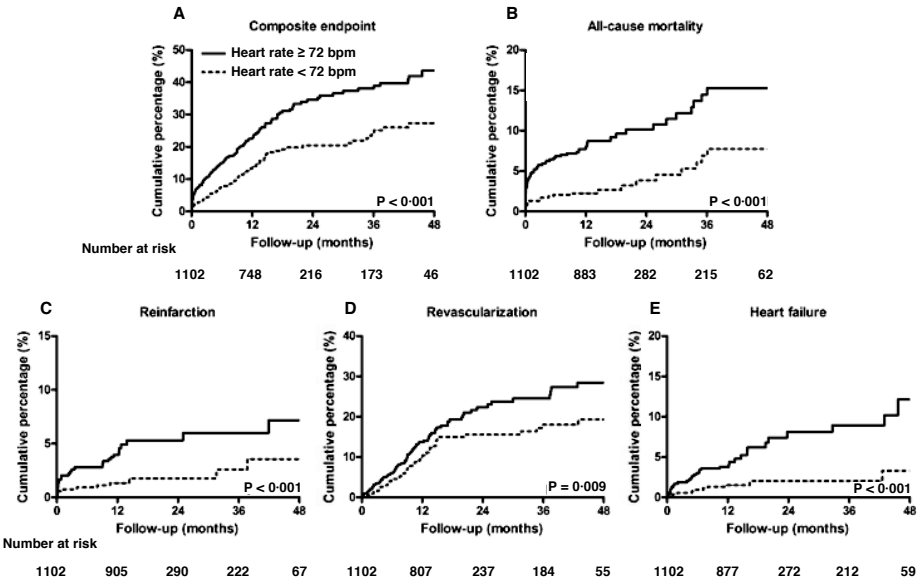

Figure 1. Cumulative risk of adverse events after acute myocardial infarction.
Kaplan-Meier time-to-event plots for baseline resting heart rate with a cutoff of 72 bpm and the composite endpoint, all-cause mortality, reinfarction, revascularization and hospitalization for heart failure.

Kaplan-Meier curves for the cutoff of 72 bpm and all endpoints are shown in Figure 1. The 4 year event rate in patients with a heart rate lower than 72 bpm compared to patients with a heart rate of 72 bpm or higher was 28% vs. 45% (P <.001) for the composite endpoint, 8% vs. 17% (P <0.001) for all-cause mortality, 4% vs. 7% (P <0.001) for reinfarction, 19% vs. 28% (P = 0.009) for revascularization and 3% vs. 12% (P <.001) for hospitalization of heart failure.

Analyses of more comprehensive classification of baseline resting heart rates relative to a heart rate lower than 67 bpm are shown in Table 3. Interestingly, for all endpoints only a heart rate of 77 bpm or higher showed a significant increase in relative risk and the intermediate heart rate groups of 67 – 72 bpm and 72 – 77 bpm showed no increased risk.

The incremental prognostic value of baseline resting heart rate was assessed by calculating global chi-square values. Figure 2 shows that heart rate demonstrated to provide incremental value to baseline clinical information (diabetes, left anterior descending coronary artery as the culprit vessel, peak cardiac troponin T level, systolic blood pressure, left ventricular ejection fraction and treatment with beta-blockers at discharge) for the prediction of all clinical endpoints.

Table 3. Hazard ratios according to heart rate group

		Hazard Ratio (95% CI)	*P*
Composite endpoint	Heart rate <67 bpm	1.00	
	Heart rate 67 – 72 bpm	0.92 (0.58 – 1.44)	0.70
	Heart rate 72 – 77 bpm	1.18 (0.73 – 1.90)	0.50
	Heart rate ≥77 bpm	1.96 (1.49 – 2.59)	<0.001
Mortality	Heart rate <67 bpm	1.00	
	Heart rate 67 – 72 bpm	0.57 (0.19 – 1.66)	0.30
	Heart rate 72 – 77 bpm	0.79 (0.27 – 2.31)	0.67
	Heart rate ≥77 bpm	2.72 (1.64 – 4.51	<0.001
Reinfarction	Heart rate <67 bpm	1.00	
	Heart rate 67 – 72 bpm	0.28 (0.04 – 2.18)	0.22
	Heart rate 72 – 77 bpm	1.19 (0.33 – 4.34)	0.79
	Heart rate ≥77 bpm	2.20 (1.05 – 4.59)	0.04
Revascularization	Heart rate <67 bpm	1.00	
	Heart rate 67 – 72 bpm	0.92 (0.54 – 1.57)	0.76
	Heart rate 72 – 77 bpm	1.18 (0.67 – 2.06)	0.57
	Heart rate ≥77 bpm	1.41 (1.00 – 1.99)	0.05
Heart failure	Heart rate <67 bpm	1.00	
	Heart rate 67 – 72 bpm	1.88 (0.53 – 6.66)	0.33
	Heart rate 72 – 77 bpm	2.01 (0.50 – 8.05)	0.32
	Heart rate ≥77 bpm	5.13 (2.14 – 12.28)	<0.001

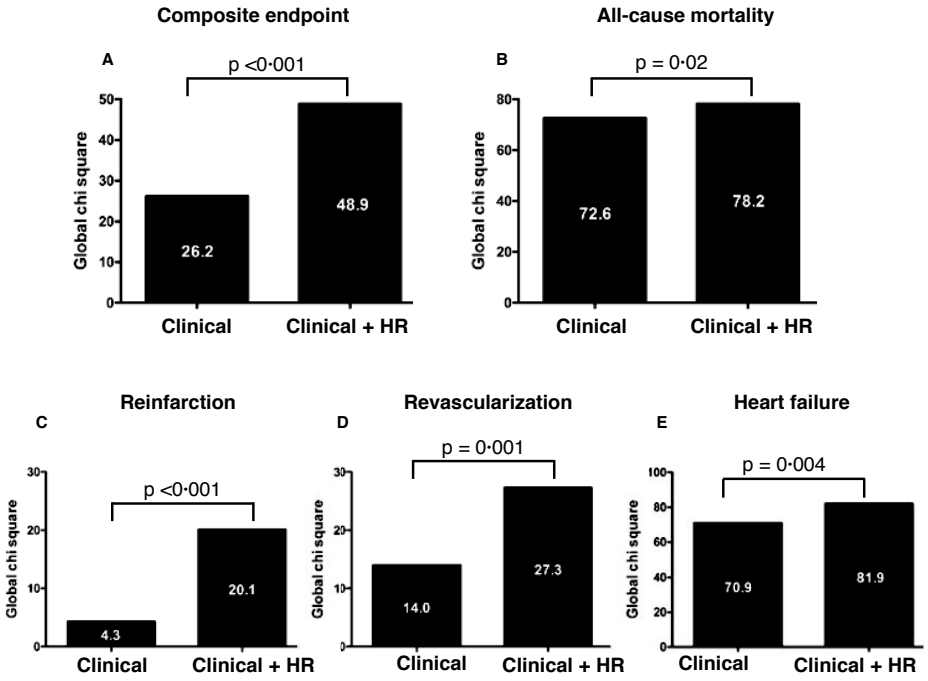

Figure 2. Incremental value of heart rate for the prediction of adverse events.
Incremental value of heart rate to baseline clinical information (diabetes, left anterior descending coronary artery as the culprit vessel, peak cardiac troponin T level, systolic blood pressure, left ventricular ejection fraction and treatment with beta-blockers at discharge) for the prediction of the composite endpoint, all-cause mortality, reinfarction, revascularization and hospitalization for heart failure.
HR = heart rate.

DISCUSSION

The major finding of the current study was that baseline resting heart was a strong predictor of all-cause mortality, reinfarction, revascularization and heart failure in patients with AMI and relatively preserved left ventricular function. Moreover, for the prediction of all endpoints, resting heart rate provided incremental value to the traditional risk factors including the presence of diabetes, the left anterior descending coronary artery as culprit vessel, peak cardiac enzymes, blood pressure, left ventricular ejection fraction and treatment with beta-blockers.

The current results indicate for the first time the importance of heart rate control in patients with AMI and preserved left ventricular function. In patients with left ventricular dysfunction, an elevated heart rate has been described as an important risk factor for mortality and adverse events.[3] However, data about the relation between heart rate and patients with preserved left ventricular function after AMI are scarce. Several large trials have demonstrated the

relation between beta-blocker treatment and decreased mortality after AMI.[11,12] Of note, in the current population, all patients were treated according to the institutional protocol with evidence-based medical therapy including a high level of beta-blocker usage, and resting heart rate at admission remained an independent predictor of all endpoints after adjusting for treatment with beta-blockers at discharge. Every increase of 5 bpm in resting heart rate resulted in a significant higher adjusted risk ranging from 7% to 17% for each individual endpoint. These findings suggest that more aggressive lowering of heart rate in patients after AMI may have a beneficial effect on adverse events.

Although the association of heart rate and outcome has been investigated extensively, understanding the relation between heart rate and adverse events remains challenging. It is likely that heart rate is both a causative factor and an indicator of pathophysiologic processes. Heart rate influences myocardial oxygen demand and supply and consequently, also myocardial perfusion which may explain the strong relationship observed in the current study with outcome in patients after AMI.[13,14] In addition, an elevated heart rate has been associated with an increased risk of plaque rupture. Heidland et al. analyzed 106 patients who underwent 2 coronary angiography procedures within 6 months and reported a positive association between plaque rupture and a mean heart rate higher than 80 bpm, whereas medication with beta-blockers was associated with a reduced incidence of disruption of vulnerable plaques.[15]

Recently, the BEAUTIFUL investigators reported that ivabradine reduced the incidence of myocardial infarction and revascularization in patients with stable coronary artery disease, left ventricular dysfunction and a heart of 70 bpm or higher.[3,16] Conversely, ivabradine did not affect mortality and hospitalization for heart failure, suggesting that ivabradine protects patients more from ischaemia than from heart failure. A high resting heart is a modifiable risk factor, but existing medications including beta-blockers and calcium-channel blockers have other cardiovascular effects besides decreasing the heart rate. Ivabradine has been reported not to affect blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarisation and therefore may provide pure lowering of the heart rate.[17-19] Thus far, only 1 study has been performed in patients after AMI with ivabradine demonstrating that the treatment was safe, feasible and well tolerated by the patients. Fasullo et al. investigated 155 patients with first anterior AMI randomized to metoprolol or ivabradine and reported a significant improvement in left ventricular volumes and ejection fraction in patients randomized to ivabradine compared to patients treated with metoprolol, but no difference in achieved heart rate.[20] In addition, several experimental studies in pigs and rats have demonstrated promising results including preservation of coronary reserve, attenuation of the decline in ejection fraction after AMI and significant reduction in infarct size.[21-23] Evidently, large prospective studies are needed to further determine whether a reduction in heart rate by ivabradine, beta-blockers or another strategy is the best approach to reduce the occurrence of adverse events in patients after AMI.

Limitations

Finally, although baseline resting heart rate was a strong predictor of outcome in patients after AMI, the predictive value of heart rate at different periods after AMI could not be addressed. The assessment of the time course and changes in resting heart rate in relation to adverse events during follow-up would be interesting and will provide more insight in the mechanism between heart rate and adverse events. Another potential limitation of the study is that all-cause mortality rather than cardiac mortality was examined, because the classification of cardiac death is often problematic. However, because the mean age of the current population was 61 ± 12 years, it is likely that most deaths were cardiac in origin.

CONCLUSION

In patients after AMI treated with primary PCI and preserved left ventricular function, resting heart rate at admission was a strong independent risk factor for all-cause mortality, reinfarction, revascularization and hospitalization for heart failure. The present study provides further evidence for targeting low heart rate in the currently growing population of post-AMI patients with preserved left ventricular function.

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