Improving risk stratification after acute myocardial infarction : focus on emerging applications of echocardiography

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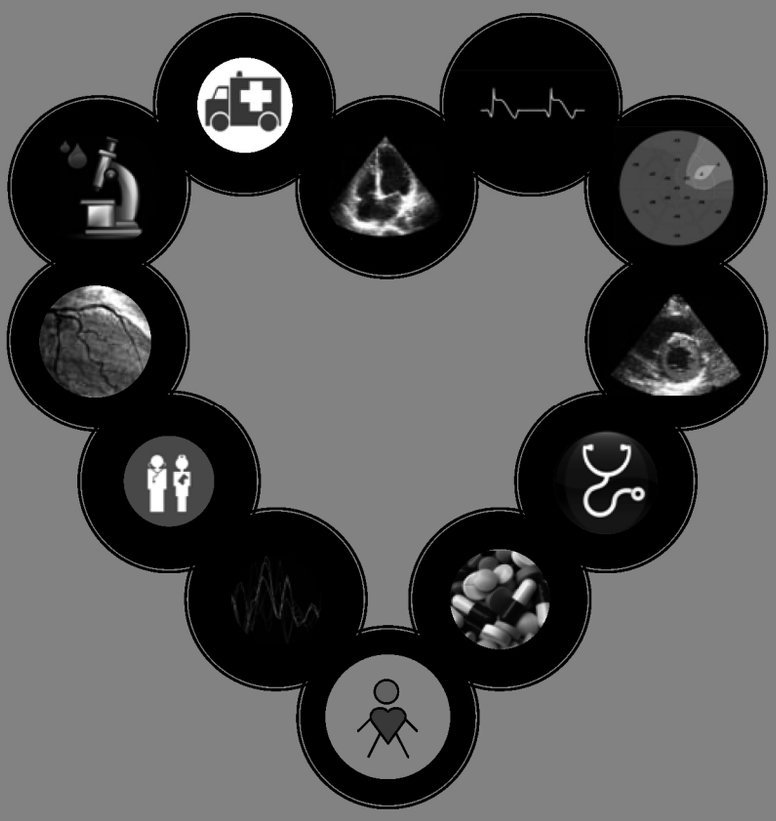

Chapter 4

Elevated Admission Heart Rate in Patients with ST-Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention Predicts Increased Infarct Size

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Abstract

Objectives

Recently, heart rate has been described as an important risk factor for adverse outcome in patients with left ventricular dysfunction. Currently, patients with ST-elevation myocardial infarction (STEMI) are treated with primary percutaneous coronary intervention (PCI) and left ventricular function is largely preserved. The purpose of the current study was to evaluate the clinical relevance of heart rate at admission in this contemporary cohort of patients, in particular in relation to infarct size and 30-day outcome.

Methods and results

Consecutive STEMI patients were evaluated and heart rate was measured at time of admission. Infarct size was assessed during hospitalization with peak cardiac enzymes and left ventricular ejection fraction. In addition, patients were followed prospectively for the occurrence of adverse events (cardiovascular mortality, reinfarction and hospitalization for heart failure) at 30 days. A total of 1492 patients were evaluated and the median heart rate at admission was 72 beats/min. After adjustment for known risk factors, an admission heart rate of ≥72 beats/min was associated with a larger infarct size as assessed with both peak cardiac enzymes and left ventricular ejection fraction. In addition, the event rate at 30 days was significantly higher in patients with a heart rate of ≥72 beats/min compared to patients with a heart rate <72 beats/min (3.3% vs. 8.9%, $p < 0.001$). Moreover, elevated admission heart rate was an independent predictor of adverse 30-day outcome.

Conclusions

Heart rate at admission is a strongly related to infarct size and 30-day outcome in STEMI patients treated with primary PCI.

Introduction

Resting heart rate has been well established as a 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 was related to an increased risk of cardiovascular outcomes in patients with coronary heart disease and left ventricular dysfunction.[3]
ST-segment elevation acute myocardial infarction (STEMI) is a major health problem in the western world despite the improved treatment strategies including reperfusion therapy.[4] Previous studies assessing the prognostic value of heart rate, have been mostly performed in patients with STEMI treated with thrombolysis and left ventricular dysfunction.[5-10] However, currently most patients with STEMI are treated with primary percutaneous coronary intervention (PCI) in the Western countries, and therefore, left ventricular function is largely preserved and outcome has improved significantly.[11] In addition, the patients included in the current study were treated aggressively with a high level of evidence-based medical therapy initiated early during hospitalization. The clinical relevance of resting heart rate at admission in this contemporary cohort of patients presenting with STEMI is unknown, in particular in relation to infarct size.
Accordingly, the aim of the current study was to evaluate the relationship between admission heart rate and infarct size and 30-day outcome in a consecutive population of STEMI patients treated with primary PCI and structurized evidence-based medical therapy including a high level of beta-blockers, initiated early after admission.[12 13]

Methods

Patient population and data collection

Since February 2004 consecutive patients admitted with STEMI were included in an ongoing registry. All patients were treated with primary PCI according to the institutional STEMI (MISSION!) protocol, which is based upon the most recent American College of Cardiology/American Heart Association guidelines/European Society of Cardiology.[12 14-16] This protocol, designed to improve care around STEMI, includes a prehospital, inhospital and outpatient clinical framework, as described previously.[12 17] The prehospital phase is

focused on rapid diagnosis, minimal treatment delay and aggressive reperfusion. Abciximab, clopidogrel and aspirin were started in the ambulance before primary PCI. If no contraindications exist, angiotensin-converting enzyme inhibitors, beta-blockers and statins were administrated within 24 hours of admission. After discharge, patients visit the outpatient clinic at 1 month follow-up and the occurrence of adverse cardiac events was noted.[12] Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands).

The aim of the current study was twofold: first, to assess the relationship between admission heart rate and infarct size estimated by peak cardiac enzymes and left ventricular ejection fraction; second, to relate admission heart rate to 30-day outcome. For this purpose, resting heart rate was measured from 12-lead electrocardiography at time of admission and peak creatine phosphokinase level and peak cardiac troponin T level were obtained during hospitalization. Patients who presented with atrial fibrillation or cardiogenic shock were not included in the present study. Two-dimensional echocardiography was performed within 48 hours of admission to quantify left ventricular ejection fraction according to the recommended biplane Simpson's method.[18]

Follow-up and endpoint definitions

The primary endpoint was infarct size as assessed with peak cardiac troponin T level, peak creatine phosphokinase level and left ventricular ejection fraction. Laboratory testing was performed according to the protocol, where the first blood sample is taken at arrival at the catheterization laboratory before the intervention. Thereafter, blood samples are acquired every 6 hours until the biomarkers have reached the highest value.[12 16]

In addition, patients were followed prospectively according to the institutional protocol at the outpatient clinic, or if not possible, by telephone inquiry.[12 17] The occurrence of 30-day adverse cardiac and non-cardiac events after the index infarction was noted. Follow-up was completed in 1461 (98%) patients. The remaining patients did not show up at the outpatient clinic and could not be reached by telephone, and therefore survival status of patients was retrieved through the municipal civil registries. The clinical endpoint was a composite of cardiovascular mortality, reinfarction and admission to hospital for new-onset or worsening

heart failure at 30 days. All deaths were defined as cardiac unless unequivocally proven noncardiac. Myocardial reinfarction was defined as recurrent typical clinical symptoms with new typical changes on the electrocardiogram and elevation of cardiac markers.[19]

Statistical analysis

Continuous data are presented as mean ± standard deviation or median and 25th and 75th percentiles as appropriate. Categorical data are presented as frequencies and percentages. Elevated heart rate at admission was analyzed as a continuous variable, dichotomized according to a cut-off value of 72 beats/min and categorized into 4 groups by quartiles. The cut-off value of 72 beats/min 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.[2 3 20] Differences in baseline characteristics between patients with a heart rate less than 72 beats/min and 72 beats/min or higher were evaluated using the unpaired Student's t-test and chi-square test. Non-normally distributed data (number of diseased vessels, symptoms to balloon time, peak creatine phosphokinase level and peak cardiac troponin T level) were compared using the Wilcoxon's rank-sum test.

The relationship between heart rate and infarct size was assessed by comparison between the patient groups divided according to the quartiles of heart rate <60 beats/min, 60–27 beats/min, 72–85 beats/min and ≥85 beats/min) using ANOVA and Kruskal-Wallis tests, where appropriate. Of note, eleven patients (0.7%) died before the echocardiogram could be performed and in another 74 patients (4.9%) the echocardiogram was not available within 48 hours of admission due to logistic reasons. These patients were excluded from following analyses where left ventricular ejection fraction was used as an endpoint.

Event rates were plotted in Kaplan-Meier curves for the composite endpoint and the study population divided by the cut-off of 72 beats/min, and groups were compared using the log-rank test. Thereafter, univariable and multivariable analysis were performed with heart rate as a continuous variable and dichotomized to the cut-off of 72 beats/min in relation to the composite endpoint. Multivariable models were constructed with all variables with significant differences between patients with a heart rate <72 beats/min and ≥72 beats/min using Cox proportional hazards regression analyses. More in detail, Killip class ≥2, diabetes, glucose level, systolic blood pressure, left anterior descending coronary artery as

the culprit vessel, symptoms to balloon time, peak cardiac troponin T level, left ventricular ejection fraction and treatment with beta-blockers at admission and discharge were included in the model. 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. The last date of clinical follow-up consisting of either a visit or telephone call was used for the composite endpoint at 30 days in order to confirm both fatal and non-fatal outcomes. All statistical tests were two-sided, and a P value <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 1496 patients were included. Four (0.3%) patients died before an electrocardiogram could be performed and were excluded from further analysis. The final sample therefore comprised 1492 patients. Table 1 shows the baseline characteristics of the patients and divided according to an admission heart rate of 72 beats/min. Patients with a heart rate of 72 beats/min or higher were more likely to present with a Killip class ≥2 (46 (6%) vs. 24 (3%), p = 0.01), diabetes (107 (14% vs. 75 (10%), p = 0.03), higher glucose level (8.8±3.5 vs. 8.2±2.6 mmol/l, p = 0.002)) and higher systolic and diastolic blood pressures (137±24 and 82±16 vs. 132±24 and 78±15 mmHg, both p <0.001). In addition, patients with a heart rate of 72 beats/min or higher were more likely to present with the left anterior descending coronary artery as the culprit vessel (406 (53%) vs. 279 (38%), p <0.001) and longer symptoms to balloon time (185 (129,281) vs. 167 (124, 251) min, p = 0.008).

Admission heart rate versus infarct size

Patients with a heart rate of 72 beats/min or higher had significantly higher peak creatine phosphokinase and cardiac troponin T levels (1663 (750, 3480) vs. 1343 (596, 2554)U/l, P <0.001 and 4.2 (1.6, 8.9) vs. 3.6 (1.3, 7.2)µg/l, p = 0.001). In addition, left ventricular ejection fraction was significantly lower in patients with a heart rate of 72 beats/min or higher (44±9 vs. 47±8%, p <0.001), suggesting that an elevated admission heart rate is related to the final infarct size.

Table 1. Patient characteristics

	All Patients (N =1492)	***Heart rate <72 bpm (N = 730)***	***Heart rate ≥72 bpm (N = 762)***	***P***
Age (years)	61 ± 12	61 ± 12	61 ± 12	0.25
Male gender	1131 (76%)	553 (76%)	578 (76%)	0.96
Killip class ≥2	70 (5%)	24 (3%)	46 (6%)	0.01
Current smoking	709 (48%)	337 (46%)	372 (49%)	0.31
Diabetes	182 (12%)	75 (10%)	107 (14%)	0.03
Family history of CAD	610 (41%)	310 (43%)	300 (39%)	0.22
Hyperlipidemia	295 (20%)	140 (19%)	155 (20%)	0.57
Hypertension	519 (35%)	250 (34%)	269 (35%)	0.67
Prior myocardial infarction	131 (9%)	65 (9%)	66 (9%)	0.58
Glucose (mmol/l)	8.5 ± 3.1	8.2 ± 2.6	8.8 ± 3.5	0.002
eGFR (ml/min/1,73m^2)	97 ± 34	97 ± 35	98 ± 34	0.51
Heart rate at admission (bpm)	74 ± 18	60 ± 9	88 ± 14	
Systolic blood pressure (mmHg)	135 ± 25	132 ± 24	137 ± 24	<0.001
Diastolic blood pressure (mmHg)	80 ± 16	78 ± 15	82 ± 16	<0.001
LAD culprit vessel	685 (46%)	279 (38%)	406 (53%)	<0.001
Number of diseased vessels	691/512/289	352/236/142	339/276/147	0.29
Symptoms to balloon time (min)	175 (126, 264)	167 (124, 251)	185 (129, 281)	0.008
Peak CPK level (U/l)	1506 (656, 3050)	1343 (596, 2554)	1663 (750, 3480)	<0.001
Peak cTnT level (µg/l)	3.8 (1.5, 8.1)	3.6 (1.3, 7.2)	4.2 (1.6, 8.9)	0.001
TIMI 2–3 flow	1468 (98%)	721 (99%)	747 (98%)	0.26
LV ejection fraction (%)	45 ± 8	47 ± 8	44 ± 9	<0.001
Medication at admission				
β -blockers	282 (19%)	160 (22%)	122 (16%)	0.004
Calcium-channel blockers	149 (10%)	70 (10%)	79 (10%)	0.59
Nitrates	45 (3%)	25 (3%)	20 (3%)	0.37
β-blockers <24 h of admission	1325 (91%)	648 (89%)	677 (91%)	0.42
Medication at discharge				
ACE inhibitors/ARBs	1417 (98%)	698 (96%)	719 (98%)	0.10
Antiplatelets	1453 (100%)	721 (100%)	732 (100%)	1.00
β -blockers	1377 (95%)	92 (93%)	705 (96%)	0.008
Statins	1440 (99%)	716 (99%)	724 (99%)	0.42

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CPK: creatine phosphokinase; cTnT: cardiac troponin T; eGFR: glomerular filtration rate estimated with the Cockcroft-Gault formula; LAD: left anterior descending coronary artery.

To further analyze the relationship between a higher heart rate and infarct size, we divided the heart rate according to quartiles (<60 beats/min, 60–72 beats/min, 72–85 beats/min and ≥85 beats/min, Table 2). Both peak creatine phosphokinase and cardiac troponin T levels demonstrated a significant gradual increase for every quartile of increasing heart rate (from 1211 (535, 2484) to 1774 (810, 3701) U/l, p <0.001 and from 3.3 (1.3, 7.0) to 4.5 (1.7, 10.4) µg/l, p = 0.003 for patients with a heart rate <60 beats/min to a heart rate of ≥85 beats/min). In line, left ventricular ejection fraction showed a significant decrease for every quartile of increasing heart rate from 48±8% for patients with a heart rate <60 beats/min to 44 ± 9% for patients with a heart rate of 85 beats/min or higher, p <0.001.

Table 2. Relation between admission heart rate and infarct size as assessed with peak CPK, peak cTnT and LVEF

	Heart rate at admission divided by quartiles				
	<60 bpm	***60–72 bpm***	***72–85 bpm***	***≥85 bpm***	***P***
Peak CPK level (U/l)	1211 (535, 2484)	1477 (620, 2575)	1605 (659, 3233)	1774 (810, 3701)	<0.001
Peak cTnT level (µg/l)	3.3 (1.3, 7.0)	3.8 (1.4, 7.4)	4.1 (1.6, 8.1)	4.5 (1.7, 10.4)	0.003
LVEF (%)	48 ± 8	46 ± 8	45 ± 9	44 ± 9	<0.001

CPK: creatine phosphokinase; cTnT: cardiac troponin T; LVEF: left ventricular ejection fraction. (median, 25th, 75th quartile)

Admission heart rate versus 30-day adverse outcome

Survival status was available for 1489 (99.8%) patients and clinical status for 1461 (98%) patients at 30-day follow-up. During the follow-up period, 94 patients (6%) reached the composite endpoint. Fifty-one patients died (3%, cardiovascular mortality accounted for 98% (50 patients) of all deaths, 26 patients (2%) had a reinfarction and 28 patients (2%) were hospitalized for new-onset or worsening of heart failure.

Kaplan-Meier curves for heart rate at admission divided by the cut-off of 72 beats/min and the composite endpoint at 30 days are shown in Figure 1.

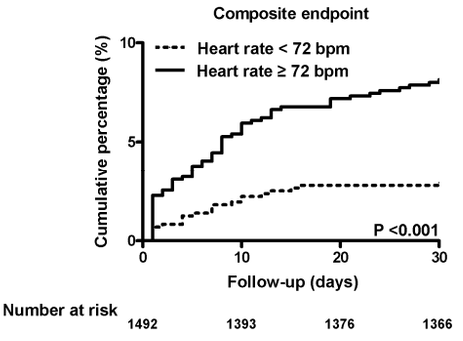

Figure 1.
Kaplan-Meier time-to-event plots for baseline resting heart rate at admission divided by the cut-off value of 72 beats/min and the composite endpoint at 30 days.

Table 3. Adjusted hazard ratios for elevated heart rate at admission as related to adverse 30-day outcome

	Hazard Ratio (95% CI)	***P***
Heart rate ≥72 versus <72 beats/min	2.70 (1.37–5.31)	0.004
Heart rate higher by 5 beats/min	1.09 (1.01–1.17)	0.02
Heart rate by quartiles		0.04
Heart rate <60 beats/min	1.00	
Heart rate 60–72 beats/min	0.96 (0.30–3.07)	0.95
Heart rate 72–85 beats/min	2.68 (0.97–7.38)	0.06
Heart rate ≥85 beats/min	2.60 (0.93–7.24)	0.07

Multivariable models were constructed with the following parameters: Killip class ≥2, diabetes, glucose level, systolic blood pressure, left anterior descending coronary artery as the culprit vessel, peak cardiac troponin T level, left ventricular ejection fraction and treatment with beta-blockers at admission and discharge.

The event rate in patients with a heart rate lower than 72 beats/min compared to patients with a heart rate of 72 beats/min or higher was significantly lower at 30-day follow-up (3.3% vs. 8.9% (p <0.001). Table 3 shows the increased risk of adverse events associated with an elevated heart rate at admission. Multivariate analysis demonstrated that a resting heart rate of 72 beats/min or higher was associated with a more than 2-fold increased risk of the composite endpoint (HR 2.70, 95%CI 1.37–5.31, p = 0.004) compared to patients with a heart rate lower than 72 beats/min. Multivariate analyses with heart rate as a continuous variable showed that every increase of 5 beats/min resulted in a 9% increased risk of the

composite endpoint (HR 1.09, 95% CI 1.01–1.17, p = 0.02). To further investigate the relation between an increased heart rate and adverse events, heart rate at admission was divided into quartiles (<60 beats/min, 60–72 beats/min, 72–85 beats/min and ≥85 beats/min). In line with the other results, patients in the quartiles of 72–85 beats/min and ≥85 beats/min demonstrated 2- and 3-fold increased risk of the composite endpoint compared to patients with a heart rate <60 beats/min at univariate analysis (HR 2.48, 95%CI 1.17–5.25, p = 0.02 and HR 3.73, 95% CI 1.82–7.67, p <0.001, respectively). At multivariate analysis, similar results were observed, but statistical significance was not reached for each quartile.

Discussion

The major findings of the current study can be summarized as follows: 1) Elevated admission heart rate in patients with STEMI treated with primary PCI is associated with a larger infarct size as assessed by peak cardiac enzymes and left ventricular ejection fraction. 2) Elevated admission heart rate was an independent predictor of adverse 30-day outcome and provided incremental value to known risk factors for the composite endpoint.

Admission heart rate and infarct size

Previous studies have demonstrated the relationship between heart rate and myocardial ischaemia in patients with stable coronary artery disease.[21-23] In 50 patients with stable angina, Andrews et al. showed that baseline resting heart rate was related to the likelihood of myocardial ischaemia and the risk was 2 times higher in patients with a heart rate of ≥90 beats/min compared to patients with a heart rate of <60 beats/min.[21] In addition, Pratt et al. demonstrated that ischaemia occurred twice as often in patients with coronary artery disease and a heart rate of >80 beats/min compared to patients with a heart rate of <70 beats/min.[24] The findings of the current study support the relationship between heart rate and myocardial ischaemia, extending the relationship of admission heart rate to myocardial infarct size. Several early beta-blocker trials have shown the relationship between heart rate and infarct size determined by accumulated creatine kinase release in patients with STEMI from the thrombolytic era.[25] However, most patients are currently treated aggressively with primary PCI and infarct size is relatively preserved. The clinical relevance of heart rate in

that growing population of patients is unknown. The results of the current study show that admission heart rate shows a strong relationship with infarct size as assessed by peak creatine phosphokinase level, peak cardiac troponin T level and left ventricular ejection fraction. Every increasing quartile in admission heart rate showed significantly higher peak cardiac enzymes and worse left ventricular ejection fraction, confirming the value of admission heart rate in patients treated with primary PCI. Although the current study demonstrates the strong association between heart rate and infarct size, explaining the relationship remains challenging and is only partially understood. It could be hypothesized that an elevated heart rate just reflects infarct size and therefore is solely a surrogate marker of infarct size. However, previous experimental studies with coronary artery occlusions have shown that hemodynamic status and neurohumoral status at the time of occlusion can alter the extent and severity of myocardial ischemic damage and myocardial necrosis.[26] As a consequence, patients with an elevated heart rate at admission may develop more extensive infarction due to an increased vulnerability of the border zone. Most likely, an elevated heart rate both reflects a larger infarct size and makes the border zone more prone to an extension of the infarct due to an increased myocardial oxygen demand.

Admission heart rate and 30-day outcome

In the present study, admission heart rate was an independent predictor of 30-day outcome including cardiovascular mortality, reinfarction and hospitalization for heart failure. It must be acknowledged that several previous studies have examined the prognostic value of heart rate leading to the inclusion of this parameter in several risk scores. For example, the GRACE risk model was recently validated for hospital mortality in patients presenting with acute coronary syndromes and only minimal changes in the model's discrimination were observed over a time period of 7 years.[27] However, the population described in the present study differs significantly from previous studies.[5-7] In the current population, all patients were treated according to the institutional protocol with primary PCI and evidence-based medical therapy including a high level of beta-blocker usage. Since therapeutic regimen was the same in all patients after PCI and at discharge, 30-day outcome is most likely predominantly dictated by the infarct size. The current results are interesting and accumulating evidence is being presented for the relationship between heart rate and infarct

size which translates into 30-day outcome. Several studies have shown that beta-blocker treatment in patients with post myocardial infarction has a beneficial effect on mortality, which is partly related to the achieved reduction in heart rate.[25 28] More recently, Parodi et al. have also demonstrated that an elevated admission heart rate of 80 beats/min or higher was related to an increased mortality at 6 months in patients with STEMI treated with primary PCI.[29] Although there are differences in both populations, the results of Parodi et al. also demonstrate that infarct size is related to admission heart rate.[29] The current study demonstrates a stepwise increase in infarct size as assessed with left ventricular ejection fraction and peak cardiac enzymes and every increasing quartile of admission heart rate. In addition, all other parameters associated with infarct size (Killip class, diabetes, glucose level, the left anterior descending coronary artery as the culprit vessel and systolic and diastolic blood pressure) differed significantly in patients with and without an elevated heart rate. Moreover, heart rate at admission was an independent predictor of the composite endpoint. These findings emphasize the importance of admission heart rate in the patients after STEMI treated with primary PCI.

Clinical implications

The results of the present study demonstrate that an elevated admission heart rate is strongly related to infarct size at admission and the final infarct size in a contemporary population of STEMI patients treated with primary PCI. Admission heart rate consistently correlated with all parameters reflecting infarct size indicating that heart rate is strongly related to infarct size and may influence the underlying pathophysiologic determinants of the final infarct size. From a clinical point of view, the current results therefore could suggest that the extent of myocardial damage could be altered by early reduction of the heart rate and thereby reduction of myocardial oxygen demand; this needs to be investigated in clinical trials. Moreover, early reduction of heart rate before the occurrence of a myocardial infarction, thus in stable angina patients, may limit infarct size when patients develop a myocardial infarction; again this needs to be tested. Although these results are promising, more studies are needed to evaluate the importance of heart rate in patients with STEMI treated with primary PCI. Particularly, future studies have to focus on

the therapeutic implications, mainly the potential benefit of early reduction of heart rate on limiting the extent of the final infarct size.

Limitations

Quantification of infarct size is complex and the assessment of infarct size with peak levels of cardiac enzymes has limitations. Several cardiac imaging techniques including nuclear imaging and magnetic resonance imaging are considered as precise methods to quantify infarct size; however, these methods are not widely available in most centers and are costly for routine use in clinical practice. Serial measurements of cardiac troponin T level and creatine phosphokinase level to determine peak values are commonly used in clinical practice. However, peak values can be missed due to rapid washout after reperfusion and correlations between area under the curve of peak values and infarct size are difficult. On the other hand, the rapid washout may result in a higher peak, but potentially smaller area under the curve, which is a more accurate reflection of infarct size. However, all clinical parameters of increased infarct size (including Killip class, diabetes, glucose level, the left anterior descending coronary artery as the culprit vessel and systolic and diastolic blood pressure) correlated very closely with an elevated heart rate and support the results of the current study. Nevertheless, prospective studies are needed to confirm our results using accurate measurements of infarct size. The exclusion of patients presenting with congestive heart failure could be seen as a limitation of the current study. However, this is in line with previous studies evaluating the value of heart rate and it is already well known that patients with congestive heart failure have a worse prognosis.[30] Finally, left ventricular ejection fraction was assessed early after STEMI and therefore may be underestimated due to myocardial stunning. However, several studies have demonstrated the prognostic value of left ventricular ejection fraction assessed early after STEMI.[31 32]

Conclusions

In patients after STEMI treated with primary PCI, admission heart rate is strongly related to the size of the infarction and 30-day outcome.

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