Prognosis of In-Hospital Myocardial Infarction Course for Diabetic and Nondiabetic Patients Using a Noninvasive Evaluation of Hemodynamics and Heart Rate Variability

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Summary. *Background and Objective. The objective of our study was to investigate whether the combination of markers of heart rate variability (HRV) and impedance cardiography (ICG) help evaluate the risk of in-hospital death, ventricular arrhythmia, or complicated course secondary to myocardial infarction (STEMI) and to clarify whether combined analysis of HRV and ICG improve prognosis of STEMI, comparing 3 groups: 1) diabetic, 2) nondiabetic, and 3) diabetes-unselected patients.*

Material and Methods. The parameters reflecting heart rate variability and central hemodynamics were estimated from a 24-hour synchronic electrocardiogram and thoracic impedance signal recordings in 232 patients (67 diabetic) on the third day after myocardial infarction. Logistic regression analysis was used to determine the predictors of selected outcomes. Different prognostic models were compared with the receiver operating characteristic curve analysis.

Results. The model consisting of low- and high-frequency power ratio (LF/HF) and cardiac output (CO) was elaborated for the prognosis of in-hospital death in the group 3 (odds ratios [ORs] were 9.74 and 4.85, respectively). Very low-frequency power (VLF), cardiac index (CIN), and cardiac power output (CPO) were the predictors of ventricular arrhythmia in the group 2 (ORs of 1.005, 5.09, and 66.7, respectively) and the group 3 (ORs of 1.004, 3.84, and 37.04, respectively). The predictors of the complicated in-hospital course in the group 1 were the baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals (TINN) and stroke volume (SV) (ORs of 1.006, and 1.009, respectively); in the group 2, the mean of the standard deviations of all NN intervals for all 5-minute segments of the recording (SDNN index) and CPO (ORs of 1.06 and 2.44, respectively); and in the group 3, SDNN index, VLF, LF/HF, CIN (ORs of 1.04, 1.004, 2.3, and 3.49, respectively).

Conclusions. The patients with decreased HRV and low estimates of central hemodynamics evaluated by ICG are at an increased risk of the adverse in-hospital course of STEMI. The combined analysis of HRV and ICG hemodynamic estimates contributes to the risk assessment of the complicated in-hospital course of STEMI, in-hospital hemodynamically significant ventricular arrhythmia, and in-hospital death secondary to STEMI. The in-hospital prognostic value of the combined estimates of HRV and ICG is lower in the STEMI patients with diabetes mellitus as compared with the nondiabetic patients.

Introduction

Ischemic heart disease and diabetes mellitus (DM) are highly prevalent and remain among the leading causes of death in European countries (1, 2). Diabetic patients with myocardial infarction (MI) are at a particularly high risk of poor outcomes. The adverse prognosis of patients with DM after acute MI has been reported in several studies despite adjustment for age, sex, comorbidities, and other coronary risk factors (3–5). Therefore, optimal risk stratification is very important particularly in this population.

In the general post-MI population, left ventricular ejection fraction (LVEF) has been the gold standard measure for the risk stratification so far (6). However, it has rather low sensitivity and specificity. Several risk scores have been proposed in order to improve risk stratification with the Thrombolysis In Myocardial Infarction (TIMI) risk score and the Global Registry of Acute Coronary Events (GRACE) risk score being most extensively investigated to date (7, 8). Tools for an additional risk

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evaluation and their various combinations have extensively been analyzed in the post-MI population, including autonomic dysfunction indexes. Noninvasive monitoring of hemodynamics using impedance cardiography (ICG) also provides a good substitute for LVEF in the prognostic models for patients after ST-segment elevation myocardial infarction (STEMI) (9, 10).

In postinfarction patients with DM, the autonomic heart function is usually affected by both the preexisting autonomic cardiac neuropathy and myocardial ischemia. It affects the risk-predictive value of the autonomic markers. In unselected post-MI patients, the standard deviation of all normal-to-normal intervals (SDNN) helped indicate a higher risk of death after MI, and the combination of SDNN with cardiac power output (CPO), a noninvasive hemodynamic estimate, helped improve the accuracy of the prognosis (10, 11). Controversial data exist whether the inclusion of various autonomic markers in prognostic models help improve risk stratification in diabetic patients with acute MI. Some authors have stated that heart rate variability (HRV) measures have good prognostic power in diabetic patients (12–14), while others have claimed that excluding patients with DM improves prognostic HRV power for the STEMI course in the rest of the patients (15, 16). Clarification is needed in this field.

Our study aimed to investigate whether the combination of markers of autonomic dysfunction (HRV) and left ventricular systolic function (impedance cardiography monitoring) helped evaluate the risk of the adverse in-hospital course of STEMI, i.e., in-hospital death, hemodynamically unstable ventricular arrhythmia or complicated MI course, and to clarify whether the combined analysis of HRV and ICG improved the prognosis in the clinical setting of MI when patients with type 2 DM were analyzed separately from nondiabetic patients versus the diabetes-unselected patients' population.

Material and Methods

Study Population. Between January 2003 and February 2009, a total of 232 patients with STEMI were prospectively enrolled in our study. The inclusion criteria were as follows: 1) the symptoms of acute STEMI persisting less than 24 hours at the time of inclusion; 2) sinus heart rhythm; and 3) none of the exclusion criteria applicable. The exclusion criteria were as follows: 1) arrhythmia with a pulse deficit of 10 beats per minute (bpm) or more; 2) uncontrolled significant tachycardia with a pulse of 120 bpm or more; 3) heart conduction disturbances (second- or third-degree atrioventricular block or sick sinus syndrome); 4) ongoing treatment with antiarrhythmic medications (exclusive of the stable dose of a beta-blocker or a calcium channel blocker); 5) an implanted cardiac pacemaker or a cardioverter-defibrillator; 6) severe structural heart valve disease; 7) heart transplantation; and 8) body mass index equal or more than 40 kg/m^2. Data were analyzed in the following 3 different categories: group 1, consisting of 67 patients (28.9%) with type 2 DM; group 2, 165 nondiabetic patients (71.1%); and group 3, the diabetes-unselected group that included all study participants.

Study Methods. A baseline medical history was recorded, and all the patients underwent a physical examination. The diagnosis of acute MI was confirmed according to the criteria provided by the European Society of Cardiology (17). All patients had type 1 STEMI as defined in the report by Thygesen et al. (17). Type 2 DM was diagnosed if there was a history of type 2 DM and treatment (diet, tablets, and/or insulin) was prescribed or if the repeated fasting plasma glucose level was $\geqslant$7 mmol/L and/or the repeated random plasma glucose level was $\geqslant$11 mmol/L (18). Sedentary lifestyle was defined as a mode of living with the activities in the sitting or lying positions for much of the day with little or no vigorous physical exercise. Other relevant clinical data were collected from medical records. The Charlson comorbidity index was calculated to estimate the severity of comorbidities (10, 19).

After informed consent was signed, a 24-hour parallel one-lead electrocardiogram was recorded, and thoracic electrical bioimpedance monitoring was performed in all study patients on the third day of acute MI by using the noncommercial system "HeartLab" (certificate of correspondence, No. LS.08.02.1957; date of issue, February 12, 2004). The patients also underwent regular cardiac monitoring in an intensive care unit. All measurements were taken in the supine resting position.

The analysis of the impedance cardiogram and HRV was performed as described elsewhere (10). The standard deviation of all normal-to-normal intervals (SDNN), standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), mean of the standard deviations of all NN intervals for all 5-minute segments of the recording (SDNN index), standard deviation of differences between adjacent NN intervals (SDSD), number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50), total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 1/128 seconds (HRV triangular index), baseline width of the minimum square difference triangular interpolation of the highest peak

of the histogram of all NN intervals (TINN), power in very low-, low-, or high-frequency ranges (VLF, LF, and HF, respectively), LF or HF power in normalized units (LF norm and HF norm), and LF-to-HF ratio (LF/HF) were used as the measures for HRV. Stroke volume (SV), cardiac output (CO), cardiac index (CIN), stroke volume index (SVI), cardiac power output (CPO), and cardiac power index (CPI) were central hemodynamic estimates computed from ICG recordings.

All participants underwent coronary angiography using the standard Judkins technique. Most patients (90.1%) underwent direct angioplasty at the time of index MI or coronary artery bypass grafting (CABG) during the same hospitalization as index MI (6.1%). The patients revascularized via CABG were excluded from the further study as many surgical factors may influence the outcomes and prognosis. The study patients had transthoracic echocardiography performed at a stable convalescent phase. All measurements and estimations were performed according to the criteria of the American Society of Echocardiography (20). LVEF was determined during echocardiography. Patients were reviewed on the day of discharge from the hospital (clinical course of STEMI and in-hospital complications were evaluated).

In-hospital mortality was considered a primary outcome. The secondary outcomes were hemodynamically unstable ventricular arrhythmias and the complicated in-hospital course. Hemodynamically unstable ventricular arrhythmia was described as ventricular tachycardia, causing hemodynamical instability and/or ventricular fibrillation. The complicated course of STEMI was described as the in-hospital presence of at least one of the following complications: hemodynamically unstable arrhythmia, cardiogenic shock, pulmonary edema, clinically significant recurrent myocardial ischemia, or death.

This study was carried out at the Clinic of Cardiology, Hospital of Lithuanian University of Health Sciences. The study protocol was approved by the Kaunas Regional Ethics Committee for Biomedical Research.

Statistical Analysis. Binary logistic regression analysis was used to determine the significance of HRV and ICG parameters in predicting in-hospital mortality or secondary outcomes. First, for the selection of HRV and ICG measures that might independently predict primary and secondary outcomes, univariate analyzes were performed. Univariate analysis was followed by forward stepwise multivariate logistic regression: the variables with a P value of <0.05 in the univariate analysis were entered into the model and those with P>0.1 were removed; odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. The variables in the final equation were considered as significant determinants of the investigated outcome. Various clinical variables were also tested for the possible significant association with the outcomes. The predictive models of HRV and ICG variables were adjusted for the clinically significant variables in order to maximize their predictive power.

Areas under receiver operating characteristic (ROC) curves (AUC) were obtained for all prognostic models in order to evaluate the accuracy of different measurements and the discriminatory power of the models (C statistic). The DeLong z test was used to statistically compare different ROC curves and to determine the differences between AUCs.

A P value of <0.05 was regarded as statistically significant.

The majority of statistical analyzes were performed with the SPSS software, version 17.0 (SPSS Inc., Chicago, Ill, USA). The MedCalc version 12.4.0 software was used to statistically compare different ROC curves and AUCs.

Results

Table 1 describes the clinical characteristics of all patients and compares them in the groups 1 and 2 (diabetic vs. nondiabetic patients). The diabetic subgroup was older and had a greater proportion of women compared with the nondiabetic subgroup. They also had more cardiovascular risk factors than the nondiabetic patients (4.42 [SD, 1.17] vs. 2.77 [SD, 1.17], P<0.001). Overweight, sedentary lifestyle, and hypertension were more prevalent in the diabetic population, and smoking was more common in the nondiabetic patients (P<0.05). Both groups were similar according to the history of previous MI; however, previous reperfusion treatment (percutaneous coronary intervention [PCI] or CABG) was more common in the diabetic patients. As a result, the incidence of 3-vessel disease diagnosed during coronary angiography was higher in this group. Time from the onset of acute MI to the arrival to the hospital was greater in the diabetic than the nondiabetic subgroup: 49.3% and 68.5% of diabetic and nondiabetic patients, respectively, arrived to the hospital within less than 6 hours from the onset of symptoms (P=0.006); similarly, 16.4% and 6.1% of the diabetic and nondiabetic subjects, respectively, presented within more than 12 hours (P=0.021). The groups were similar regarding comorbidities, localization and Killip class of index MI, GRACE score, PCI or CABG treatment of the index MI, and administration of thrombolytics, glycoprotein IIb/IIIa inhibitors, and adjuvant medications.

All impedance cardiography estimates were significantly lower in the diabetic patients as compared with the nondiabetic patients (Table 2).

Table 1. Patients' Characteristics at Baseline

Characteristic	All Patients (n=232)	Nondiabetic Patients (n=165)	Diabetic Patients (n=67)	*P*
Demographics				
Age, years	62.8 (10.7)	61.1 (11.4)	64.1 (9.0)	0.034
Male, %	69.8	73.9	59.7	0.032
Cardiovascular risk factors, %				
Overweight or obesity (BMI >25 kg/m^2)	82.3	75.8	98.5	<0.001
Dyslipidemia	71.4	68.9	77.3	NS
Smoking	32.3	39.4	14.9	<0.001
Sedentary lifestyle	24.6	20.0	35.8	0.011
Family history of CAD	37.1	37.0	37.3	NS
History of hypertension, %	78.0	70.9	95.5	<0.001
Charlson comorbidity index	0.89 (1.25)	0.85 (1.21)	0.97 (1.37)	NS
History of prior MI, %	14.2	12.7	17.9	NS
Previous PCI/CABG, %	8.2	5.5	14.9	0.017
Index MI, %				
Anterior location	49.6	47.9	53.7	NS
Killip class III or IV	13.4	12.1	16.4	NS
Revascularization				
Time from symptoms to revascularization	7.9 (6.3)	6.4 (5.3)	10.6 (6.9)	<0.001
PCI, %	90.1	90.3	89.6	NS
CABG, %	6.1	4.9	9.1	0.055
Thrombolytic therapy, %	3	3	3	NS
Glycoprotein IIb/IIIa inhibitor, %	6.5	4.9	10.4	NS
Admission information				
Symptom duration, h	6.1 (5.4)	4.8 (4.6)	8.2 (6.0)	0.001
Hear rate on arrival, bpm	78.5 (20.0)	75.1 (19.7)	84.4 (19.2)	0.004
GRACE score (in-hospital)	164 (41.8)	163.9 (43.4)	164.1 (37.9)	NS
GRACE score (6 months)	128.8 (32.7)	128.2 (34.0)	130.2 (29.7)	NS
Angiography information, %				
1-vessel disease	35.5	38.3	28.2	NS
2-vessel disease	23.2	23.5	22.7	NS
3-vessel disease	35.5	30.9	47.0	0.021
LM disease	5.3	6.8	1.5	NS
LVEF, %	40.4 (9.4)	41.2 (8.8)	38.9 (10.3)	NS

Values are mean (standard deviation) unless otherwise indicated.
BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GRACE, the Global Registry of Acute Coronary Events; LM, left main coronary artery; LVEF, left ventricular ejection fraction; NS, not significant.

Table 2. Comparison of the Direct and Derived Impedance Cardiography Hemodynamic Measures in Patients With and Without Diabetes Mellitus

ICG Measure	All Patients (n=216)	Nondiabetic Patients (n=156)	Diabetic Patients (n=60)	*P*
CO, L/min	4.49 (1.51)	4.81 (1.51)	3.83 (1.34)	<0.001
CIN, L·min^{-1}·m^{-2}	2.31 (0.83)	2.5 (0.83)	1.88 (0.68)	<0.001
SV, mL	61.9 (29.5)	68.4 (31.4)	47.8 (19.9)	<0.001
SVI, mL/m^2	31.9 (16.1)	35.6 (17.1)	23.6 (10.4)	<0.001
CPO, W	1.24 (0.47)	1.3 (0.48)	1.1 (0.4)	0.005
CPI, W/m^2	0.63 (0.25)	0.67 (0.25)	0.54 (0.2)	<0.001

Values are mean (standard deviation).
CO, cardiac output; CIN, cardiac index; SV, stroke volume; SVI, stroke volume index; CPO, cardiac power output; CPI, cardiac power index; ICG, impedance cardiography.

The results of HVR evaluation are presented in Table 3. All time domain measures were significantly lower in the diabetic subgroup (SDNN, SDANN, RMSSD, SDNN index, SDSD, pNN50, HRV triangular index, and TINN). Some frequency domain measures (e.g., TP, HF, and HF norm) were lower in the diabetic patients, while LF norm and LF/HF were lower in the nondiabetic subgroup. VLF and LF did not differ significantly between the groups.

The incidence of in-hospital clinical outcomes in the study population is shown in Table 4.

Prognosis of In-Hospital Mortality. LF/HF, derived from HRV, was the strongest independent single predictor of the primary outcome in the group 1. Although univariate binary logistic regression analysis revealed 3 HRV measures (LF norm,

Table 3. Heart Rate Variability Measures of the Study Patients

HRV Measure	All Patients (n=216)	Nondiabetic Patients (n=156)	Diabetic Patients (n=60)	*P*
NN mean, ms	775.6 (122.9)	784.4 (122.6)	753.6 (121.9)	0.031
SDNN, ms	116.8 (34.7)	123.4 (33.1)	100.3 (33.6)	<0.001
SDANN, ms	76.6 (25.1)	80.8 (24.3)	66.1 (24.1)	<0.001
RMSSD, ms	29.9 (10.6)	31.7 (9.8)	25.4 (11.4)	<0.001
SDNN index, ms	61.3 (19.2)	64.6 (17.7)	53.0 (20.4)	<0.001
SDSD, ms	28.4 (10.0)	30.4 (9.6)	23.5 (9.3)	<0.001
pNN50, %	0.08 (0.04)	0.09 (0.04)	0.07 (0.05)	0.003
HRV triangular index	21.7 (6.5)	22.7 (6.4)	19.2 (6.0)	0.001
TINN, ms	627.3 (177.7)	650.7 (180.2)	568.4 (157.9)	0.001
TP, ms^2	249.9 (142.4)	265.6 (161.5)	210.5 (61.0)	0.044
VLF, ms^2	165.0 (107.3)	174.3 (120.5)	141.8 (57.4)	NS
LF, ms^2	40.6 (33.2)	42.9 (36.9)	34.9 (20.8)	NS
HF, ms^2	34.6 (27.4)	37.6 (30.1)	26.9 (17.0)	0.011
LF norm, n.u.	48.2 (13.6)	47.0 (11.8)	51.1 (17.2)	0.017
HF norm, n.u.	41.1 (10.4)	42.0 (9.4)	38.8 (12.2)	0.002
LF/HF	1.26 (0.52)	1.18 (0.43)	1.46 (0.67)	0.005

Values are mean (standard deviation).
HRV, heart rate variability; NN, normal-to-normal intervals; NN mean, mean value of NN interval; SDNN, standard deviation of all NN intervals; SDANN, standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN index, mean of the standard deviations of all NN intervals for all 5-minute segments of the recording; SDSD, standard deviation of differences between adjacent NN intervals; pNN50, number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; HRV triangular index, total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 1/128 s; TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; TP, total power; VLF, LF, HF, power in very low-, low-, or high-frequency ranges, respectively; LF norm, HF norm, LF or HF power in normalized units; LF/HF, LF-to-HF ratio; n.u., normalized unit; NS, not significant.

Table 4. In-Hospital Clinical Outcomes of ST-Segment Elevation Myocardial Infarction in Study Patients

Outcome	All patients (n=216)	Nondiabetic Patients (n=156)	Diabetic Patients (n=60)	*P*
Death	3.2	1.9	6.7	NS
Hemodynamically significant ventricular arrhythmia	11.6	12.8	8.3	NS
Recurrent ischemia	6	5.1	8.3	NS
No complications	67.1	63.5	76.7	NS

Values are percentage.
NS, not significant.

HF norm, and LF/HF) and all ICG estimates (except for SV) to have a significant association with in-hospital mortality, multivariate regression analysis failed to demonstrate that the combination of HRV and ICG measures improved the prediction of in-hospital death for diabetic patients.

In the group 2, a univariate logistic regression analysis demonstrated a significant association of VLF and HF norm, obtained from HRV, and all ICG estimates with in-hospital death. However, the combination of these parameters did not add any power to the prediction of this outcome.

The majority of HRV measures (except for SDNN, SDANN, SDNN index, pNN50, HRV triangular index, LF, HF) and all measures of ICG were significant independent predictors of in-hospital mortality in the univariate logistic regression analysis in all patients, independently of the MD status. Multivariate analysis revealed that combined LF/HF and CO added to the precision of the mortality prediction (Table 5). In the group 3, clinical variables such as age, Killip class, presence of DM, blood glucose on admission, mean arterial pressure, and LVEF were significantly associated with in-hospital mortality. The association between in-hospital mortality and combined LF/HF and LVEF remained significant after adjustment for all of the abovementioned clinical variables. The adjusted model is shown in Table 5. Table 6 summarizes the discrimination measures and accuracy of the models.

Prognosis of Hemodynamically Unstable Ventricular Arrhythmias. Binary logistic regression analysis with a hemodynamically unstable ventricular arrhythmia as a dependent variable in the univariate analysis revealed that none of the HRV measures and only 2 ICG measures (CO and CIN) were significantly associated with this STEMI complication in the DM subgroup.

In the nondiabetic group, 3 HRV measures (SDNN, SDNN index, and VLF) and only 2 ICG estimates

Table 5. Prognosis of In-Hospital Mortality

Model	Variable	OR	95% CI	*P*
In-hospital death, group 3 (unadjusted)	LF/HF (↑ 1 unit)	9.74	1.71–55.57	0.010
	CO (↓ 1 L/min)	4.85	1.38–16.95	0.014
In-hospital death, group 3 (adjusted*)	LF/HF (↑ 1 unit)	11.53	2.16–61.63	0.004
	LVEF (↓ 1%)	1.14	1.03–1.37	0.009

*LF/HF and CO were adjusted for age, Killip class, presence of DM, blood glucose on admission, mean arterial pressure, and LVEF (clinical variables that were significantly associated with in-hospital mortality). Group 3, diabetes-unselected patients.
OR, odds ratio; CI, confidence interval; LF/HF, ratio of the power in low- and high-frequency ranges; CO, cardiac output, DM, diabetes mellitus, LVEF, left ventricular ejection fraction.

(CPO and CIN) were found to be significant predictors of hemodynamically significant ventricular arrhythmias. A prognostic model, including VLF, CIN, and CPO, in the multivariate analysis was developed (Table 7). Clinical variables, including Killip class, overweight, mean blood pressure, leukocytosis, glycemia on admission, and LVEF, were independently associated with the occurrence of hemodynamically significant ventricular arrhythmia in the group 2. After adjustment for these variables, only VLF remained a strong predictor. CPO could only be adjusted for overweight and leukocytosis, and other clinical variables were stronger predictors than CPO. CIN remained a significant variable after adjustment for leukocytosis. The adjusted composite model for the group 2 is shown in Table 7.

In the analysis of the DM-unselected data, the results of univariate and multivariate binary logistic regression analyzes were very similar to those in the nondiabetic subgroup. The same HRV and ICG measures (VLF, CIN, and CPO) aided in the risk estimation for the occurrence of hemodynamically significant ventricular arrhythmia (Table 7). The same clinical variables, as listed above for the nondiabetic subgroup, were significant predictors of

Table 6. Comparison of the Discrimination Measures and Accuracy of Prognostic Models and Recognized ST-Segment Elevation Myocardial Infarction Risk Scores for the Risk Stratification of In-Hospital Mortality

Characteristics	LF/HF, CO (Unadjusted)	LF/HF, LVEF (Adjusted)	GRACE (In-Hospital)	TIMI
C-index	0.923	0.936	0.891	0.868
Overall accuracy, %	98.6	98.0	96.3	96.8
Sensitivity, %	40.0	20.0	0	0
Specificity, %	100	100	99.5	100
PPV, %	100	100	0	0
NPV, %	98.5	98.0	96.7	96.8

In-hospital death was chosen as dependent variable for all prognostic models and risk scores. Group 3 (diabetes-unselected patients) was analyzed.
LF/HF, ratio of the power in low and high frequency ranges; CO, cardiac output; LVEF, left ventricular ejection fraction; GRACE, the Global Registry of Acute Coronary Events risk score; TIMI, Thrombolysis In Myocardial Infarction risk score; PPV, positive predictive value; NPV, negative predictive value.

Table 7. In-Hospital Prognosis of Hemodynamically Unstable Ventricular Arrhythmia

Model	Variable	OR	95% CI	*P*
Hemodynamically unstable ventricular arrhythmia, group 2 (unadjusted)*	VLF (↓ 1 ms^2)	1.005	1.001–1.008	0.007
	CIN (↓ 1 $L{\cdot}min^{-1}{\cdot}m^{-2}$)	5.09	1.63–15.85	0.005
	CPO (↓ 1 W)	66.7	6.13–100.0	0.001
Hemodynamically unstable ventricular arrhythmia, group 2 (adjusted‡)†	VLF (↓ 1 ms^2)	1.005	1.001–1.009	0.008
	Overweight (yes, no)	4.69	1.42–15.63	0.011
	LVEF (↓ 1%)	1.08	1.02–1.14	0.014
Hemodynamically unstable ventricular arrhythmia, group 3 (unadjusted)	VLF (↓ 1 ms^2)	1.004	1.001–1.008	0.008
	CIN (↓ 1 $L{\cdot}min^{-1}{\cdot}m^{-2}$)	3.84	1.45–10.17	0.007
	CPO (↓ 1 W)	37.04	4.98–250.0	<0.001
Hemodynamically unstable ventricular arrhythmia, group 3 (adjusted§)	VLF (↓ 1 ms^2)	1.004	1.001–1.008	0.011
	CPO (↓ 1 W)	5.15	1.61–16.67	0.006
	Overweight (yes, no)	6.02	2.26–16.13	<0.001

Group 2, nondiabetic patients; group 3, diabetes-unselected patients.
*VLF, CIN, and CPO, unadjusted model for nondiabetic patients: C-index of 0.773, overall accuracy of 87.8%, sensitivity of 10%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 87.7%.
†VLF and clinical variables, adjusted model for nondiabetic patients: C-index of 0.865, overall accuracy of 90.1%, sensitivity of 45.0%, specificity of 97.5%, positive predictive value of 75%, and negative predictive value of 91.5%.
‡VLF, CIN, and CPO were adjusted for Killip class, overweight, mean blood pressure, leukocytosis, glycemia on admission, and LVEF (clinical variables that were significantly associated with in-hospital hemodynamically significant ventricular arrhythmia in the group 2).
§VLF, CIN, and CPO were adjusted for Killip class, overweight, mean blood pressure, and LVEF (clinical variables that were significantly associated with in-hospital hemodynamically significant ventricular arrhythmia in the group 3).
OR, odds ratio; CI, confidence interval; VLF, power in very low frequency range; CIN, cardiac index; CPO, cardiac power output; LVEF, left ventricular ejection fraction.

Table 8. Comparison of the Discrimination Measures and Accuracy of Prognostic Models and Left Ventricle Ejection Fraction for the Risk Stratification of In-Hospital Ventricular Arrhythmia

Characteristic	VLF, CIN, CPO (Unadjusted)	VLF, CPO, Overweight (Adjusted)	LVEF*	LVEF†
C-index	0.739	0.770	0.627	0.594
Overall accuracy, %	89.4	89.2	88.7	88.4
Sensitivity, %	8.3	16.7	0	0
Specificity, %	100	98.9	100	100
PPV, %	100	66.7	0	0
NPV, %	89.3	89.9	88.7	88.4

In-hospital hemodynamically unstable ventricular arrhythmia was chosen as a dependent variable for all prognostic models and LVEF. The group 3 (diabetes-unselected patients) was analyzed.
*LVEF was analyzed as a continuous variable, for LVEF decrease by 1%: OR, 1.06; 95% CI, 1.02–1.11; P=0.008;
†LVEF was analyzed as a categorical binary variable (LVEF ⩽35% vs. >35%): OR, 2.32; 95% CI, 1.0–5.46; P=0.050;
VLF, power in very low-frequency range; CIN, cardiac index; CPO, cardiac power output; LVEF, left ventricular ejection fraction; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval.

hemodynamically significant ventricular arrhythmia for the group 3, except for leukocytosis and glycemia on admission. VLF and CPO remained strong enough predictive variables after adjustment for these clinical variables (Table 7). Overweight was also significant in prognosis. The discriminative power and accuracy of the models are disclosed in Tables 7 and 8.

Prognosis of Complicated In-Hospital STEMI Course. Six HRV variables (SDNN, RMSSD, SDNN index, SDSD, TINN, and LF) along with all ICG variables were selected by univariate binary logistic regression as possible predictors of the complicated STEMI course in diabetic patients. The results of multivariate analysis are described in Table 9. Age, Killip class, mean blood pressure, leukocytosis, blood creatinine, and LVEF were also identified as significant determinants of the complicated in-hospital STEMI course by multivariate analysis in the group 1. TINN and SV remained significant after adjustment for every clinical variable. After adjustment for all clinical variables, TINN and SV retained significance along with Killip class. The adjusted model is described in Table 9.

Table 9. Prognosis of the Complicated In-Hospital ST-Segment Elevation Myocardial Infarction Course

Model	Variable	OR	95% CI	P
Complicated in-hospital course of STEMI, group 1 (unadjusted)	TINN (↓ 1 ms)	1.006	1.001–1.011	0.019
	SV (↓ 1 mL)	1.099	1.031–1.170	0.004
Complicated in-hospital course of STEMI, group 1 (adjusted*)	TINN (↓ 1 ms)	1.006	1.000–1.012	0.042
	SV (↓ 1 mL)	1.079	1.003–1.160	0.041
	Killip class (↑ 1 class)	9.65	1.11–84.21	0.040
Complicated in-hospital course of STEMI, group 2 (unadjusted)	SDNN index (↓ 1 ms)	1.06	1.03–1.08	<0.001
	CPO (↓ 1 W)	2.44	1.02–5.85	0.045
Complicated in-hospital course of STEMI, group 2 (adjusted†)	SDNN index (↓ 1 ms)	1.08	1.04–1.11	<0.001
	Age (↑ 1 year)	1.05	1.002–1.09	0.039
	Killip class (↑ 1 class)	4.0	1.64–9.72	0.002
	Time MI to PCI (↑ 1 hour)	1.19	1.05–1.34	0.005
Complicated in-hospital course of STEMI, group 3 (unadjusted)	SDNN index (↓ 1 ms)	1.04	1.02–1.06	<0.001
	VLF (↓ 1 ms^2)	1.004	1.001–1.008	0.008
	LF/HF (↓ 1 unit)	2.30	1.17–4.55	0.016
	CIN (↓ 1 $L{\cdot}min^{-1}{\cdot}m^{-2}$)	3.49	1.64–7.44	0.001
	CPO (↓ 1 W)	27.8	6.02–125	<0.001
Complicated in-hospital course of STEMI, group 3 (adjusted‡)	SDNN index (↓ 1 ms)	1.06	1.03–1.09	<0.001
	Killip class (↑ 1 class)	4.18	1.83–9.50	0.001
	Overweight (yes vs. no)	4.02	1.25–12.99	0.020
	Time MI to PCI (↑ 1 hour)	1.13	1.02–1.27	0.024

*TINN and SV were adjusted for the age, Killip class, mean blood pressure, leukocytosis, blood creatinine, and LVEF (clinical variables that were significantly associated with complicated in-hospital course of STEMI in group 1);
†SDNN index, TINN, and CPO were adjusted for the age, Killip class, overweight, mean blood pressure, leukocytosis, glycemia on admission, time from the onset of STEMI symptoms to PCI, LVEF, and the Charlson comorbidity index (clinical variables, that were significantly associated with complicated in-hospital course of STEMI in group 2);
‡SDNN index, VLF, LF/HF, CIN, and CPO were adjusted for the age, Killip class, overweight, previous MI, mean blood pressure, leukocytosis, blood creatinine, time from the onset of STEMI symptoms to PCI, LVEF, and the Charlson comorbidity index (clinical variables, that were significantly associated with complicated in-hospital course of STEMI in group 3).
Group 1, diabetic patients; group 2, nondiabetic patients; group 3, diabetes-unselected patients. STEMI, ST-segment elevation myocardial infarction; NN, normal-to-normal intervals; TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; SV, stroke volume; SDNN index, mean of the standard deviations of all NN intervals for all 5-minute segments of the recording; CPO, cardiac power output; MI, myocardial infarction; PCI, percutaneous coronary intervention; VLF, power in very low frequency range; LF/HF, ratio of the power in low and high frequency ranges; CIN, cardiac index; OR, odds ratio; CI, confidence interval, LVEF, left ventricular ejection fraction.

In nondiabetic patients, the majority of HRV measures (except for pNN50, VLF, and HF) and the majority of ICG measures (except for CIN, SV, and SVI) were independently associated with the complicated in-hospital STEMI course. The best prognostic model obtained in the multivariate logistic regression is shown in Table 9. Age, Killip class, overweight, mean blood pressure, leukocytosis, glycemia on admission, time from the onset of STEMI symptoms to PCI, LVEF, and the Charlson comorbidity index were also significant predictors of the complicated in-hospital STEMI course for the group 2. After adjustment for clinical variables, The SDNN index was the strongest predictor (Table 9). CPO could be adjusted for overweight, leukocytosis, ejection fraction, and the Charlson comorbidity index. The adjusted model is presented in Table 9.

In the DM-unselected population, the same HRV measures as in the nondiabetic patients and the majority of ICG measures (except for SV and SVI) were individually associated with the complicated in-hospital STEMI course. Table 9 shows the multivariate logistic regression-derived prognostic model. The following clinical variables were independently associated with the complicated course of STEMI in the group 3: age, Killip class, overweight, previous MI, mean blood pressure, leukocytosis, blood creatinine, time from the onset of STEMI symptoms to PCI, LVEF, and the Charlson comorbidity index. After adjustment for these clinical variables, the SDNN index retained its significance. After adjustment for all clinical variables, the SDNN index remained significant in the model along with Killip class, overweight, and time from the onset of MI to PCI (Table 9).

The discrimination measures and accuracy of all models are presented in Table 10.

Discussion

Despite lower ICG measures (Table 2) as well as the majority of HRV measures (Table 3) in the diabetic patients, the prognostic power of combined ICG and HRV measures was not higher in the diabetic group. In contrast, none of the combinations of HRV and ICG parameters were associated with the primary outcome and hemodynamically unstable ventricular arrhythmias in the diabetic patients. It could be hypothesized that decreased HRV reflected more severe autonomic heart dysfunction due to diabetes mellitus and resultant higher risk status, but was not predictive of outcome during the in-hospital period.

The HRV and ICG measures helped predict the risk of in-hospital death in the patients with STEMI only if they were not selected by the presence or absence of DM. In our patients, the combination of LF/HF and CO was the best predictor of in-hospital death. This is consistent with the findings of Stein et al., who also found the LF/HF ratio to be the best predictor of the HRV measures of mortality in diabetes-unselected patients after MI (15). The accuracy and discriminative power of the obtained prognostic model was rather high (Table 6). During the last decades, scientists suggested several risk scores for STEMI. D'Ascenzo et al. have recently performed the meta-analysis of more than 80 prognostic studies and have concluded that TIMI and GRACE are most extensively investigated scores and as with the other acute coronary syndromes, the GRACE score performed better than the TIMI score in STEMI patients (7). As demonstrated in Table 6, we compared the discrimination measures and accuracy of our prognostic models (both unadjusted and adjusted) with the GRACE and TIMI risk scores for the risk stratification of in-hospital mortality in the DM-unselected patients' group. In our study population, LF/HF and CO or adjusted LF/HF and LVEF prognostic models were at least as accurate as the GRACE or TIMI scores for the prediction of in-hospital mortality due to STEMI (statistical significance between the C indexes of different models was not achieved though the absolute C index values were

Table 10. Comparison of the Discrimination Measures and Accuracy of Prognostic Models for the Risk Stratification of Complicated In-Hospital Course of ST-Segment Elevation Myocardial Infarction

Characteristic	TINN, SV (Unadjusted)*	TINN, SV, CLV (Adjusted)*	SDNN index, CPO (Unadjusted)†	SDNN index, CLV (Adjusted)†	SDNN index, VLF, LF/HF, CIN, CPO (Unadjusted)‡	SDNN index, CLV (Adjusted)‡
C-index	0.893	0.927	0.786	0.852	0.809	0.830
Overall accuracy, %	88.3	86.8	73.0	80.2	76.3	80.4
Sensitivity, %	64.3	61.5	50.0	64.7	53.7	61.7
Specificity, %	95.7	95.0	86.2	90.0	87.1	89.6
PPV, %	81.8	80.0	67.5	80.5	66.7	74.4
NPV, %	89.8	88.4	75.0	80.0	79.7	82.7

*Diabetic patients (group 1); †nondiabetic patients (group 2); ‡diabetes-unselected patients (group 3).
NN, normal-to-normal intervals; TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; SV, stroke volume; SDNN index, mean of the standard deviations of all NN intervals for all 5-minute segments of the recording; CPO, cardiac power output; CLV, clinical variables; VLF, power in very low-frequency range; LF/HF, ratio of the power in low- and high-frequency ranges; CIN, cardiac index; PPV, positive predictive value; NPV, negative predictive value.

higher in the unadjusted LF/HF and CO or adjusted LF/HF and LVEF prognostic models).

None of the combined HRV and ICG parameters were found as the significant predictors of hemodynamically unstable arrhythmia in the diabetic patients. However, in the nondiabetic subgroup or the DM-unselected group, the prognostic models were constructed using the combined measures of HRV and ICG. The combination of HRV-derived VLF and ICG-derived CIN and CPO showed the highest predictive power for in-hospital hemodynamically unstable ventricular arrhythmias both in the nondiabetic and DM-unselected subjects. The discriminative power of models were similar in the nondiabetic subgroup and the DM-unselected group, hence our results support the conclusion that the selection of patients according to their diabetes status does not improve the prognosis of hemodynamically unstable ventricular arrhythmias after STEMI.

Left ventricular systolic dysfunction, as described by decreased EF (⩽35% or <40%), is the gold measure for the risk of hazardous ventricular arrhythmias after STEMI currently and has become the basis for determining patient's eligibility for the prophylactic implantation of a cardioverter-defibrillator (8, 21). Though for prognostic purposes it is recommended to repeat the measurement of LVEF in at least 40 days after STEMI and in our patients, it was measured within 3.9 days (SD, 2.2) from the onset of STEMI, in the absence of better prognostic markers we compared the discriminative prognostic power of LVEF with the combined HRV and ICG measures with an in-hospital hemodynamically unstable ventricular arrhythmia chosen as a dependent variable. The results of such a comparison are demonstrated in Table 8 and Fig. It is obvious that the biggest limitation of LVEF as a prognostic marker for in-hospital ventricular arrhythmias was insufficient sensitivity and the lack of positive predictive power, regardless of the form of LVEF in analysis (continuous or binary categorical). Similar limitations are described in other studies (6, 22). The sensitivity of the prognostic model with the combined VLF, CIN and CPO parameters was also rather low, but other measures and discriminative power were sufficient, especially for the adjusted composite model, which performed significantly better than LVEF (Fig.).

As demonstrated in Table 9, the combined measures of HRV and ICG have a prognostic value in the prediction of the complicated in-hospital course of STEMI and can be applied in the diabetic, nondiabetic, and DM-unselected patients' populations. Prognostic parameters had different prognostic power in all patients' subgroups. In the diabetic patients, the best prognostic model was obtained using the combination of TINN and SV. In the nondiabetic patients, the best results were achieved using

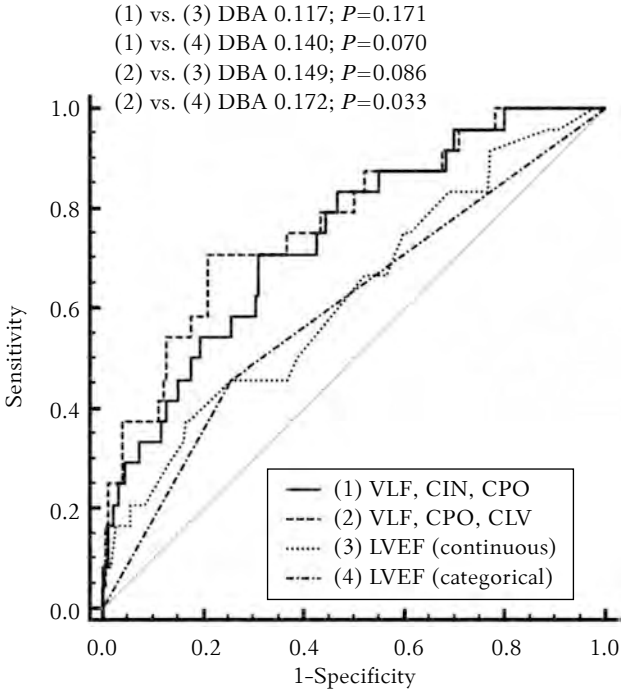

Fig. Statistical comparison of the discriminative power of the prognostic models and left ventricular ejection fraction for the risk stratification of in-hospital hemodynamically unstable ventricular arrhythmia

(1) VLF, CIN, CPO, a prognostic model for risk stratification of in-hospital ventricular arrhythmia in the DM-unselected patients with STEMI, including the combination of HRV-derived VLF and ICG-derived CIN and CPO (unadjusted for clinical variables);
(2) VLF, CPO, CLV, a prognostic model for risk stratification of in-hospital ventricular arrhythmia in the DM-unselected patients with STEMI, including combination of HRV-derived VLF, ICG-derived CPO and significant clinical variables (adjusted model);
(3) LVEF (continuous) and (4) LVEF (categorical), use of LVEF (in continuous or categorical form with a cutoff point at 35%) for the prognosis of in-hospital ventricular arrhythmia in DM-unselected patients with STEMI.
VLF, power in very low-frequency range; CIN, cardiac index; CPO, cardiac power output; CLV, clinical variables; LVEF, left ventricular ejection fraction; DBA, difference between areas under the curve; DM, diabetes mellitus; STEMI, ST-segment elevation myocardial infarction; HRV, heart rate variability; ICG, impedance cardiography.

the combination of the SDNN index and CPO. In the DM-unselected patients, the prognostic model included the SDNN index, VLF, LF/HF, CIN, and CPO. The accuracy and discriminative power was sufficient in all models, irrespectively of the patients' subgroup. The predictive value of some clinical characteristics for the complicated in-hospital course of STEMI was superior to the HRV or ICG variables; in the adjusted model of nondiabetic patients, CPO was substituted by age, Killip class, and the time from the onset of STEMI symptoms to PCI. Similarly, in the adjusted model of DM-unselected patients, VLF, LF/HF, CIN, and CPO

were substituted by Killip class, overweight, and the time from the onset of STEMI symptoms to PCI. Such composite models were more accurate and had higher discriminative power determining the complicated in-hospital course of STEMI. When compared with the widely used GRACE score (for the complicated in-hospital course of STEMI), the following results were obtained: C index of 0.813 ($P<0.001$), overall accuracy of 79.7%, sensitivity of 91.4%, specificity of 58%, positive prognostic value of 78.3%, and negative prognostic value of 80.2%.

The combined analysis of the selected HRV measures, such as a statistical time domain measure (SDNN index), a geometrical time domain measure (TINN), frequency domain measures (VLF and LF/HF), and ICG measures (SV, CO, CIN, and CPO), provided the most valuable in-hospital prognostic information for the patients with STEMI. Since many of the HRV measures correlate closely with others (because of both mathematical and physiological relationships), the majority of other authors used just several selected HRV parameters for prognostic purposes (such as SDNN, SDANN, HRV triangular index, frequency domain measures). Although, the values of other HRV measures (SDNN, SDSD, LF, and LF norm) varied significantly in the patients with complicated STEMI and were independently associated with the selected outcomes, their overall predictive value was lower than that of SDNN index, TINN, VLF and LF/HF. The SDNN index measures variability due to cycles shorter than 5 minutes. TINN expresses overall HRV measured during 24 hours and is more influenced by lower than higher frequency (23). Both the SDNN index and TINN were predictive of the complicated in-hospital STEMI course. Although, VLF physiological correlates are still uncertain, it was predictive of hemodynamically unstable ventricular arrhythmia and complicated in-hospital STEMI course. The LF/HF ratio is considered by some investigators to mirror sympathovagal balance or to reflect the sympathetic modulations (23). LF/HF was predictive of in-hospital mortality due to STEMI and the complicated in-hospital STEMI course. Some HRV measures (RMSSD, pNN50, and HF) did not have any prognostic value for STEMI patients. This coincides with the data of other authors stating that HRV measures reflecting respiratory-dependent parasympathetic heart rhythm control are rarely associated with the outcomes of MI (24).

Talking about the prognosis of the in-hospital STEMI course, using noninvasive measures or ICG and HRV, in summary it could be stated that it was possible to predict only the complicated in-hospital course of STEMI in the diabetic patients' group. The risk of individual STEMI complications could not be assessed using the measures of HRV and ICG in this group. The exclusion of diabetic patients from risk stratification models did not improve accuracy for the prognosis of in-hospital mortality (a prognostic model for nondiabetic patients could not be constructed using binary logistic regression), hemodynamically unstable ventricular arrhythmias (a difference between AUCs [DBA] was 0.004 [$P=0.999$] for unadjusted models and DBA of 0.024 [$P=0.491$] for adjusted models for the group 2 and group 3, respectively) and the complicated in-hospital course of STEMI (DBA of 0.014 [$P=0.597$] for unadjusted models and DBA of 0.008 [$P=0.696$] for adjusted models for the groups 2 and 3, respectively) for the rest of the patients using the measures of HRV and ICG.

Study Limitations. Our study has several potential limitations. First, it was accomplished in a single hospital and could be subject to the inherent biases of this type of study.

The study population was limited by the inclusion and exclusion criteria, which were established for the HRV and ICG measures to be reliable. Therefore, the STEMI patients with permanent arrhythmias, severe heart conduction disturbances, and severe structural heart valve diseases were excluded from our study. Consequently our findings may not reflect the characteristics of the overall population with STEMI.

Although this was a prospective study, some data were collected from a comprehensive medical documentation review after discharge and was subject to the missing data. However, the missing data represented a very small proportion ($\leqslant 1\%$) of all data, and these cases were excluded from the further analysis.

The recruitment period was rather long due to technical reasons. However, the treatment strategy and outcomes of the patients, enrolled during 2003–2005 and 2006–2009, were similar.

Conclusions

The patients with both impaired autonomic heart regulation, demonstrated by decreased HRV, and reduced systolic function, demonstrated by the low estimates of central hemodynamics evaluated by ICG, are at an increased risk of the adverse in-hospital course of STEMI.

The combined analysis of HRV and ICG hemodynamic estimates contributes to the risk assessment of the complicated in-hospital course of STEMI, in-hospital hemodynamically significant ventricular arrhythmias, and in-hospital death secondary to STEMI.

The in-hospital prognostic value of the combined estimates of HRV and ICG is lower in the STEMI patients with diabetes mellitus as compared with the nondiabetic patients.

Statement of Conflict of Interest

The authors state no conflict of interest.

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