Impedance Cardiography and Heart Rate Variability for Long-Term Cardiovascular Outcome Prediction After Myocardial Infarction

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Key words: *myocardial infarction; prognosis; risk stratification; mortality; impedance cardiography; heart rate variability.*

Summary. *Background and Objective. The objective of our study was to evaluate the predictive power of a combined assessment of heart rate variability (HRV) and impedance cardiography (ICG) measures in order to better identify the patients at risk of serious adverse events after ST-segment elevation myocardial infarction (STEMI): all-cause or cardiac mortality (primary outcomes) and in-hospital recurrent ischemia, recurrent nonfatal MI, and need for revascularization (secondary outcomes).*

Material and Methods. A total of 213 study patients underwent 24-hour electrocardiogram (used for HRV analysis) and thoracic bioimpedance monitoring (used for calculation of hemodynamic measures) immediately after admission. The patients were examined on discharge and contacted after 1 and 5 years. Cox regression analysis was used to determine the predictors of selected outcomes.

Results. The standard deviation of all normal-to-normal intervals (SDNN) and cardiac power output (CPO) were found to be the significant determinants of 5-year all-cause mortality (SDNN ⩽100.42 ms and CPO ⩽1.43 W vs. others: hazard ratio [HR], 11.1; 95% CI, 4.48–27.51; P<0.001). The standard deviation of the averages of NN intervals (SDANN) and CPO were the significant predictors of 5-year cardiac mortality (SDANN ⩽85.41 ms and CPO ⩽1.43 W vs. others: HR, 11.05; 95% CI, 3.75–32.56; P<0.001). None of the ICG measures was significant in predicting any secondary outcome.

Conclusions. The patients with both impaired autonomic heart regulation and systolic function demonstrated by decreased heart rate variability and impedance hemodynamic measures were found to be at greater risk of all-cause and cardiac death within a 5-year period after STEMI. An integrated analysis of electrocardiogram and impedance cardiogram helps estimate patient's risk of adverse outcomes after STEMI.

Introduction

Ischemic heart disease, as well its complications, is the leading cause of morbidity and mortality in Lithuania. Cardiovascular mortality in Lithuania is substantially higher compared with overall cardiovascular mortality in Europe (56.1% and 48%, respectively), and cardiovascular diseases remain the leading cause of death in our country (1, 2). In 2010, death due to acute myocardial infarction (MI) accounted for 3% of all deaths (1). The management of acute coronary syndromes should be guided by an early estimate of patient risk. The majority of MI complications appear in the acute phase of the disease, but the risk of adverse cardiac events, such as cardiac death, nonfatal MI, progressive heart failure, need for revascularization remains high for a long time (3). In the absence of an ideal single risk marker, several scoring systems are available for risk stratification (4), but a reliable identification of patients at risk of adverse long-term outcomes after MI still remains uncertain. High mortality rates suggest the need for further studies analyzing adverse cardiac events and survival in relation to different clinical risk markers in patients after MI.

Noninvasive measures of autonomic regulation, such as heart rate variability (HRV), have been developed to identify the patients at higher risk of serious arrhythmias and death after MI, but they are limited by rather low sensitivity (5–7). Combining the multiple measures of autonomic tone alone has not been shown to improve prognostic accuracy. A combined testing of various HRV parameters with other noninvasive methods has been advocated in many previous studies and reviews in order to improve predictive accuracy and achieve better sensi-

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tivity and specificity (5, 8, 9). It was earlier demonstrated that a combined assessment of the various measures of impaired autonomic tone and reduced systolic function improved a long-term prognosis of cardiac death (5).

Noninvasive hemodynamic monitoring using impedance cardiography (ICG) reflects left ventricular systolic function. Previous studies revealed that cardiac power output (CPO), a measure derived from impedance cardiography, helped identify patients with acute ST-segment elevation myocardial infarction (STEMI) at higher risk for in-hospital death (10, 11). The advantage of ICG for a combined assessment of both autonomic tone and systolic function is that only one examination is needed, as an impedance cardiogram is always registered parallel to a 1-lead electrocardiogram. It is anticipated that a concomitant impairment of autonomic tone and contractile function, as expressed by diminished HRV and various decreased ICG parameters, would help better identify the patients after MI at risk of serious adverse events. To our knowledge, no previous studies have addressed this issue.

The objective of our study was to evaluate the short- and long-term predictive power of a combined assessment of various noninvasive HRV and hemodynamic monitoring (ICG) measures, obtained immediately after the onset of STEMI, in order to identify patients at risk of serious adverse events: all-cause or cardiac death and ischemic complications, such as in-hospital recurrent ischemia, recurrent nonfatal MI, and need for revascularization.

Material and Methods

This prospective observational study was carried out at the Clinic of Cardiology, Hospital of Lithuanian University of Health Sciences, during 2003–2012. The patients were enrolled from January 2003 through February 2009. The follow-up was completed in January 2012. The study protocol was approved by the Kaunas Regional Ethics Committee for Biomedical Research.

Study Population. A total of 213 nonconsecutive adult patients with STEMI (150 men [70.4%]; median age, 63 years) were enrolled in the study if they fulfilled the inclusion criteria: a) symptoms of acute STEMI persisting less than 24 hours at the time of inclusion; b) sinus heart rhythm; and c) none of the exclusion criteria applicable. The exclusion criteria were as follows: a) arrhythmia with a pulse deficit of 10 beats per minute or more; b) uncontrolled significant tachycardia with a pulse of 120 beats per minute or more; c) heart conduction disturbances (degree 2 or 3 atrioventricular block or sick sinus syndrome); d) ongoing treatment with antiarrhythmic medications (exclusive of a stable dose of a beta-blocker or calcium blocker); e) an implanted cardiac pacemaker or cardioverter-defibrillator; f) severe structural heart valve disease; g) heart transplantation; and h) body mass index equal or more than 40 kg/m^2.

Study Methods. After informed consent was signed, 24-hour parallel 1-lead electrocardiogram (ECG) and thoracic electrical bioimpedance monitoring was performed for all study patients on the first and third days of acute MI, using a noncommercial system "HeartLab" (certificate of correspondence No. LS.08.02.1957 issued on February 12, 2004). The patients also underwent regular monitoring in a cardiac intensive care unit. All the measurements were carried out in a supine resting position.

Baseline medical history was obtained, and physical examination was performed for all patients. The diagnosis of acute MI was confirmed according to the criteria provided by the European Society of Cardiology (12). Other relevant clinical data were collected from medical records. The Charlson comorbidity index was used to estimate the severity of comorbidities (13). According to this index, comorbidities were categorized as normal (total score of Charlson comorbidity index, 0), moderate (total score, 1), severe (total score, 2), and very severe (total score, $\geqslant$3).

All the participants underwent coronary angiography using a standard Judkin's technique. Most patients (94.7%) underwent direct angioplasty at the time of index MI or revascularization soon after index MI. The study patients underwent transthoracic echocardiography during a stable convalescent phase. All the measurements and estimations were performed according to the criteria of the American Society of Echocardiography (14).

During the study, the patients were examined on discharge from the hospital and contacted by phone or mail after 1 year and 5 years (patients' caregivers were contacted if applicable). At each follow-up, patient-related data were collected (clinical status, NYHA class, unplanned hospitalizations, arrhythmia occurrence, and changes in medical treatment). The corresponding medical data were also reviewed on clinical databases currently used in the Hospital of Lithuanian University of Health Sciences (KMUK KARDIO and Soarian MedSuite [K2-HIS, version 0.40]). Mortality data were collected through medical records and from interviews with patient's caregivers where appropriate.

The primary outcome considered was short-term (in-hospital) and long-term (1 to 5 years) mortality (both all-cause death and cardiac death). The secondary outcomes were ischemic complications: recurrent in-hospital ischemia, recurrent nonfatal MI, and need for revascularization procedures (percuta-

neous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). The study population was categorized into the subgroups by the development of the clinical outcomes, with the differential characteristics of each subgroup being studied.

Analysis of Impedance Cardiogram. A standard 8 skin surface electrode system (2 outer pairs and 2 inner pairs located at both sides of the root of the neck and at both sides of thorax at the level of the xiphoid process) was connected to an impedance measurement device (system "HeartLab") and used for impedance cardiography signal processing. The outer electrodes transmitted a constantly low-amplitude (1.2 mA), high-frequency (42 kHz) current, which is safe and unsensed; the inner electrodes were for resistance sensing. The analysis of impedance cardiography signal and cardiac output (CO) calculations were performed automatically and averaged during the 10-second periods using the original software incorporated into the system "HeartLab." Stroke volume (SV) and CO were computed using the Sramek-Bernstein formula (15). For the estimation of CO on the first and third days, the first 5 minutes of impedance cardiogram was used, and the mean CO was calculated. All derived hemodynamic measures were further computed as described in Table 1.

Analysis of Heart Rate Variability. One-lead ECG was used to analyze HRV. ECG recordings were excluded from further analysis if they showed more than 10% nonsinus rhythm (1 patient) or less than 50% of the original ECG recording was available for analysis (4 patients). The analysis of 208 patients' ECGs was performed using original custom-made software. Supraventricular and ventricular premature beats, atrial fibrillation episodes, electrical noise, and other aberrant ECG signals were excluded from HRV analysis. Traditional statistical methods and power-spectral analysis were used to describe HRV.

Table 1. Derived Hemodynamic Measures (Impedance Cardiography)

Measure	Units of Measurement	Formula
Cardiac index	L/min/m^2	$CI=\frac{CO}{BSA}$
Stroke volume index	mL/m^2	$SVI=\frac{CI}{HR}\times 1000$
Heart power output	W	$CPO=\frac{CO\times MAP}{451}$
Heart power index	W/m^2	$CPI=\frac{CI\times MAP}{451}$

CI, cardiac index; SVI, stroke volume index; CPO, heart power output; CPI, heart power index; HR, heart rate; MAP, mean arterial blood pressure; BSA, body surface area (according to D. DuBois and E. F. DuBois).

Both time and frequency domain measures were analyzed using the accepted methods (8). All HRV measures were abbreviated as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: 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), the 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), 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) (8).

Statistical Analysis. Continuous variables were described using median and interquartile range, and categorical variables were presented as percentages, unless otherwise noted. Differences between the parameters of the two patients' groups were tested by the unpaired *t* test for normally distributed continuous variables at the 95% confidence level (two-tailed). Categorical characteristics were compared using the chi-square test and the Mann-Whitney test for ordinal variables as well as nonnormally distributed continuous variables. A paired *t* test was used to compare the corresponding HRV and ICG measures recorded on the first and third days of index MI. Pearson correlation coefficient (*r*) was used to evaluate correlations between different variables, and an $|r|\geqslant 0.4$ was interpreted to show a substantial correlation.

Cox proportional hazards regression analyses were used to determine the significance of HRV and ICG parameters in predicting 1- and 5-year mortality, recurrent nonfatal MI, and need for revascularization. First, univariate analyses were performed to select HRV and ICG measurements that might independently predict primary and secondary outcomes. To maximize the predictive power, selected HRV and ICG measures were dichotomized at optimal threshold values and were further analyzed as continuous variables. Univariate analysis was followed by stepwise Cox multivariate regression: the variables with a *P* value of <0.05 in the univariate analysis were entered into a stepwise forward selection model and those with a *P* value of >0.1 were removed; hazard

ratios (HR) and 95% confidence intervals (CI) were calculated. The variables in the final equation were considered as the significant determinants of investigated outcome. The final model fit was assessed using –2 log likelihood tests and analysis of residuals. Binary logistic regression was used for analysis of in-hospital mortality and recurrent ischemia, as the censored data were absent in this case.

Receiver operating characteristic (ROC) curves with the Youden index and optimal binning procedure were used to find the optimal threshold values for the dichotomization of variables in order to obtain their maximal predictive power. Areas under receiver operating characteristic curves (AUC) were obtained in order to evaluate the sensitivity and specificity of different measures and discriminatory power of the prognostic models (C statistics).

The time to development of selected outcomes was graphically displayed by constructing Kaplan-Meier time-to-event curves, and differences in hazard were assessed using the log-rank test.

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

All statistical analyzes were performed with SPSS software, version 17.0 (SPSS Inc., Chicago, Ill, USA).

Results

The demographic and clinical characteristics of all patients are summarized in Table 2.

Table 2. The Baseline Characteristics of Patients

Characteristic	All Patients (n=208)	5-Year All-Cause Death (n=22)	5-Year Cardiac Death (n=15)
Demographic			
Age, years	63 (53–70)	64 (56–73.8)	65 (53–76)
Male, %	71.2	86.4	80.0
Cardiovascular risk factors, %			
Overweight or obesity (BMI >25 kg/m^2)	79.8	77.3	80
Diabetes mellitus	21.2	18.2	13.3
Dyslipidemia	70.2	68.4	66.7
Smoking	35.1	40.9	40
Ex-smoker	15.4	9.1	6.7
Impaired mobility	23.1	36.4*	33.3
Family history of CAD	38.9	45.5	46.7
History of prior MI, %	13.9	36.4*	26.7
Previous PCI/CABG, %	8.2	13.6	13.3
History of hypertension, %	76.0	81.8	73.3
Comorbidity category, %			
Normal	52.9	22.7	33.3
Moderate	17.3	13.6	20
Severe	17.8	40.9*	20
Very severe	12.1	22.7	26.6
Index MI, %			
Anterior location	49.6	77.3*	73.3
Killip class III or IV	13.0	31.8*	33.3*
Revascularization			
Time from symptoms to revascularization, hours	5 (3–8.4)	5 (3–9.3)	4.5 (3–9.9)
PCI, %	89.9	90.9	93.3
Successful PCI, %	80.1	77.3	73.3
Coronary artery bypass, %	4.9	9.1	6.7
Thrombolytic therapy, %	2.4	9.1*	6.7
Glycoprotein IIb/IIIa inhibitor, %	5.3	4.5	6.7
Admission information			
Symptom duration, hours	3.5 (2–7)	3.8 (1.9–6.5)	3 (1.5–6)
Body mass index, kg/m^2	28.4 (25.7–31.4)	28.2 (25.2–30.8)	28.1 (25.4–29.8)
Heart rate on arrival, bpm	77.5 (64–90)	82.5 (71–90)	82 (75–90)
GRACE score (in-hospital)	160.5 (129.0–187.8)	179.5 (156.3–202.5)*	173 (154–214)*
GRACE score (6 months)	126.5 (100.0–149.8)	141.5 (117.5–161.5)*	135 (116–165)
Angiography findings, %			
1-vessel disease	36.8	27.3	26.7
2-vessel disease	25.5	18.2	20
3-vessel disease	31.9	50	46.7
LM disease	5.4	4.5	6.7
LVEF, %	40 (35–48)	34.5 (25.8–41.5)*	34 (25–39.3)*

Values are median (interquartile range) unless otherwise stated. *P<0.05 as compared with survivors.
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.

Table 3. Cumulative Incidence of Primary and Secondary Outcomes

Outcome Available for Follow-up	In-hospital n=208	1 Year n=183	5 Years n=147
All-cause death	4 (1.9)	7 (3.8)	22 (15.0)
Cardiac death	4 (1.9)	7 (3.8)	15 (10.2)
Recurrent ischemia	11 (5.3)	NA	NA
Nonfatal MI	NA	8 (4.4)	22 (15.0)
Revascularization (PCI or CABG)	NA	22 (12.0)	43 (29.3)

Values are number (percentage).
MI, myocardial infarction; PCI, percutaneous coronary intervention; CAB, coronary artery bypass grafting; NA, not applicable.

Table 3 shows the incidence of clinical outcomes in the study population.

As compared with the patients who survived with no corresponding clinical outcome considered, all subgroups (as indicated in Table 3) were similar according to the demographic characteristics (age and gender) and majority of cardiovascular risk factors except for hypertension, which was less prevalent in 1-year nonfatal MI subgroup (37.5% vs. 78%, P=0.009) and impaired mobility, which was more prevalent in the 5-year all-cause mortality subgroup (36.4% vs. 17.8%, P=0.049). A greater percentage of patients had a history of previous MI in the 5-year all-cause mortality (36.4% vs. 10.2%, P=0.001) and 5-year nonfatal MI (27.3% vs. 10.3%, P=0.032) subgroups as compared with the corresponding survivors, but there were no significant differences between the subgroups regarding previous revascularization procedures.

The most prevalent Charlson comorbidities were congestive heart failure (27.9%), diabetes (21.2%), ulcer disease (8.2%), stroke (7.1%), peripheral vascular disease (7.1%), cancer (7.1%), chronic pulmonary disease (4.8%), and other (1.9%). A severe and very severe Charlson comorbidity category was documented more frequently in the 5-year all-cause mortality and 1-year mortality subgroups than their corresponding groups of survivors (63.6% vs. 25.4%, P<0.001, and 57.1% vs. 29.9%, P=0.04, respectively).

The patients in the 5-year all-cause mortality subgroup had index MI of anterior location more frequently than their corresponding group of survivors (77.3% vs. 43.2%, P=0.033), and all other subgroups did not differ according to the location of STEMI. Killip class III or IV MI was more prevalent in all mortality subgroups as compared with survivors, but similar in all nonfatal MI and revascularization subgroups as compared to the event-free study population. Symptom duration from the onset of index MI to hospitalization as well as to PCI was similar in all the subgroups. None of the patients in the 1-year revascularization subgroup underwent CABG during the acute phase of index MI, while 6.6% of patients who were not hospitalized due to the need for revascularization within the first year after index MI underwent this procedure. No significant differences in the percentages of patients treated for index MI with other revascularization treatment modalities (including fibrinolytic therapy and use of glycoprotein IIb/IIIa antagonist) were found comparing the subgroups.

The comparison of the corresponding HRV and ICG measures recorded on the first and third days of index MI revealed that the majority of HRV measures did not vary significantly comparing the days except for the SDANN and HRV triangular index, which were higher on the third day (SDANN: 76.5±25.3 ms vs. 74.8±25.5 ms, P=0.026; HRV triangular index: 21.6±6.4 vs. 21.0±6.4, P=0.030) in contrast to the ICG measures, most of which significantly increased on the third day.

PCI was less common among the patients enrolled during 2003–2005 as compared with those enrolled during 2006–2009 (86.8% vs. 97.0%, P=0.021), and CABG was performed more often in the 2003–2005 subgroup (17.1% vs. 4.5%, P=0.015). Secondary preventive treatment was similar in both subgroups (Table 4). A significantly greater percentage of the patients enrolled during 2006–2009 than those enrolled 2003–2005 were administered clopidogrel, but if the administration of both clopidogrel and oral anticoagulant was compared, no significant difference was found comparing the groups (89.2% vs. 96.9%, P=0.064). Both the subgroups were similar regarding the investigated outcomes.

Prognosis of Mortality

5-Year All-Cause Mortality. Univariate Cox regression analysis selected 9 HRV measures (SDNN, SDANN, RMSSD, SDNN index, SDSD, HRV triangular index, TINN, VLF, and LF norm) and 6 ICG measures recorded on the first day (CO, CI, SV, SVI, CPO, and CPI) as the possible significant predictors of 5-year all-cause mortality. Other variables associated with this outcome were the mean heart rate (as expressed by the mean NN interval), history of previous MI, impaired mobility, localization of index MI, Killip class, left ventricular ejection fraction (LVEF), and Charlson comorbidity index.

Table 4. Comparison of Secondary Preventive Treatment in Patients Recruited During 2003–2005 and 2006–2009

Secondary Prevention Medicine	Enrolment Period 2003–2005	Enrolment Period 2006–2009	*P*
Antiplatelet/anticoagulant			
Aspirin	129 (92.8)	62 (95.4)	0.483
Clopidogrel	116 (83.5)	61 (93.8)	0.042
Oral anticoagulant	9 (6.5)	3 (4.6)	0.600
β-Blocker	128 (92.1)	61 (93.8)	0.654
ACE inhibitor or ARB	133 (95.7)	60 (92.3)	0.321
Statin	121 (87.1)	61 (93.8)	0.146

Values are number (percentage).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Stepwise forward Cox multivariate survival analysis was performed with the variables mentioned above (in their continuous form); however, the HRV measures recorded on the third day were excluded, as they did not significantly differ compared with the corresponding HRV measures recorded on the first day. The variables with substantial Pearson correlation were also excluded, and only the strongest independent predictors remained in the further analysis. SDNN and CPO were the most significant and strongest independent determinants of 5-year all-cause mortality. To maximize their diagnostic power, they were dichotomized at the optimal threshold values using the ROC curves. Multivariate Cox regression analysis was repeated with the dichotomized variables; HR with 95% CI were recalculated for each parameter as well as cumulative HR for all parameters (Table 5).

Both selected variables (SDNN and CPO) remained the significant predictors of 5-year all-cause mortality after adjustment for the mean NN interval, history of previous MI, impaired mobility, localization of index MI, Killip class, left ventricular ejection fraction, and Charlson comorbidity index.

The 5-year all-cause mortality cumulative hazard ratios for the dichotomized values of both variables indicated in Table 5 is disclosed in Fig. 1.

Heart rate expressed by a mean NN interval of $\leqslant$736.4 ms (i.e., heart rate $\geqslant$81 bpm) was other significant independent predictor of 5-year all-cause mortality (HR, 4.76; 95% CI, 1.94–11.69; P=0.001). The mean NN interval provided additional prognostic information to our model (Table 5).

Charlson comorbidity category was significant in predicting 5-year all-cause mortality. The univariate Cox regression analysis showed that the patients

Table 5. Hazard Ratios for 5-Year All-Cause and Cardiac Mortality (Cox Regression)

Variable	HR	95% CI	P
5-year all-cause mortality			
SDNN $\leqslant$100.42 ms vs. >100.42 ms	4.36	1.68–11.35	0.003
CPO $\leqslant$1.43 W vs. >1.43 W	4.33	1.73–10.84	0.002
SDNN $\leqslant$100.42 ms and CPO $\leqslant$1.43 W vs. others*	11.10	4.48–27.51	<0.001
SDNN $\leqslant$100.42 ms and CPO $\leqslant$1.43 W and mean NN interval $\leqslant$736.4 ms vs. others†	11.39	4.15–31.23	<0.001
5-year cardiac mortality			
SDANN $\leqslant$85.41 ms vs. >85.41 ms	9.65	1.27–73.4	0.029
CPO $\leqslant$1.43 W vs. >1.43 W	6.25	2.12–18.41	0.001
SDANN $\leqslant$85.41 ms and CPO $\leqslant$1.43 W vs. others‡	11.05	3.75–32.56	<0.001
SDANN $\leqslant$85.41 ms and CPO $\leqslant$1.43 W and mean NN interval $\leqslant$736.4 ms vs. others§	14.18	4.46–45.06	<0.001

Model discrimination (C statistics) and calibration by an unadjusted logistic regression model to the prespecified dichotomy limits:
*AUC, 0.646; positive predictive accuracy, 31.8%, negative predictive accuracy, 97.5%;
†AUC, 0.605; positive predictive accuracy, 22.7%, negative predictive accuracy, 98.3%;
‡AUC, 0.650; positive predictive accuracy, 33.3%, negative predictive accuracy, 96.6%;
§AUC, 0.625; positive predictive accuracy, 26.7%, negative predictive accuracy, 98.3%.
HR, hazard ratio; CI, confidence interval; SDNN, standard deviation of all NN intervals; CPO, cardiac power output; AUC, area under receiver operating characteristic curve (=C index).

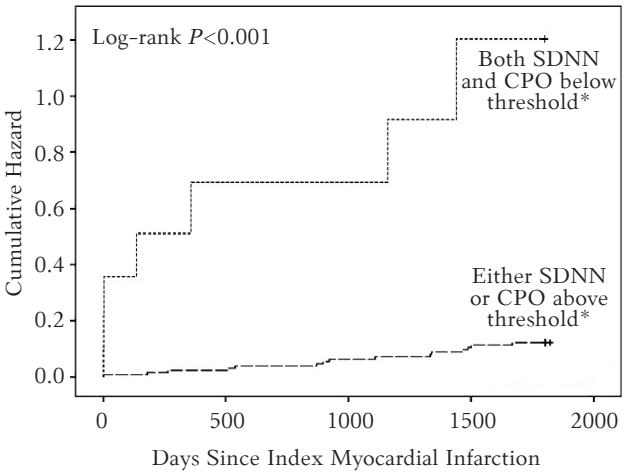

Fig. 1. Cumulative hazard for 5-year all-cause mortality
*Thresholds for selected variables: SDNN ⩽100.42 ms and CPO ⩽1.43 W.
SDNN, standard deviation of all normal-to-normal intervals; CPO, cardiac power output.

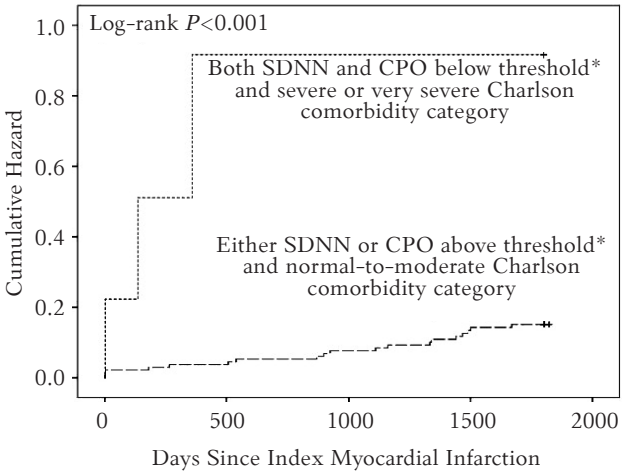

Fig. 2. Impact of Charlson comorbidity category on 5-year all-cause mortality
*Thresholds for selected variables: SDNN ⩽100.42 ms and CPO ⩽1.43 W.
SDNN, standard deviation of all normal-to-normal intervals; CPO, cardiac power output.

with the severe or very severe Charlson comorbidity category were at higher risk of 5-year all-cause mortality than those with the normal or moderate comorbidity category (HR, 4.29, 95%; CI 1.80–10.25; P=0.001). SDNN, CPO, and Charlson comorbidity category were all significant independent predictors of 5-year all-cause mortality (cumulative HR, 7.56; 95% CI, 2.22–25.75; P=0.001) (Fig. 2).

5-Year Cardiac Mortality. In the univariate Cox regression analysis, 7 HRV measures (SDNN, SDANN, RMSSD, SDNN index, SDSD, TINN, and LF) as well as 4 ICG measures (SV, SVI, CPO, and CPI) were significant in the prediction of 5-year cardiac mortality. Killip class was other significant independent predictor of 5-year cardiac mortality (HR, 2.28; 95% CI, 1.38–3.78; P=0.001). Multivariate analysis revealed that combined SDANN and CPO added to the precision of the aforementioned mortality prediction (Table 5). The value of both parameters below the threshold had a cumulative HR of 11.05, which remained significant after adjustment for Killip class.

Heart rate was other significant independent predictor of 5-year cardiac mortality (mean NN interval of ⩽736.4 ms vs. others: HR, 6.20; 95% CI, 1.97–9.48; P=0.002). Table 5 shows that the mean NN interval provided additional prognostic information to the model.

1-Year Mortality. Although the univariate Cox regression analysis revealed several HRV measures (SDNN, SDANN, RMSSD, SDNN index, SDSD and TINN) and CPO and CPI to be associated with 1-year mortality, no combination of these HRV and ICG measures appeared to improve the prediction of this outcome. The RMSSD was the strongest single HRV predictor of 1-year mortality (RMSSD ⩽20.9 ms vs. >20.9 ms: HR, 9.69; 95% CI, 1.88–49.95; P=0.007). Killip class was also an independent predictor of 1-year mortality (HR, 3.12; 95% CI, 1.49–6.54; P=0.003). The RMSSD remained a significant predictor of 1-year mortality after adjustment for Killip class (adjusted HR, 7.25; 95% CI, 1.38–38.23; P=0.020). An unadjusted logistic regression model applied to the prespecified RMSSD dichotomy limits showed an AUC of 0.762; however, the sensitivity was very low.

In-hospital Mortality. Three HRV and all ICG measurements were identified in the univariate regression analysis as the possible independent predictors of in-hospital mortality together with the Global Registry of Acute Coronary Events (GRACE) risk score and Killip class. However, none of these measures was strong enough as a single predictor, and the combination of the parameters did not add power to the prediction of this outcome. Optimal binning analysis was also used to check a prognostic significance of the measurements mentioned above. Weak or no association with in-hospital mortality as a guide variable was found in optimal binning analysis, and no bins were possible to create whatever HRV or ICG measures. A small number of cases were most likely the reason for the insufficient power of logistic regression to reveal the associations between HRV or ICG measures and in-hospital mortality.

Prognosis of Ischemic Complications. None of the ICG measures was significant in the prognosis of any secondary outcome considered (risk of recurrent MI, need for revascularization, and in-hospital recurrent ischemia). Though several HRV measures had a potential impact on the prediction of the ischemic complications in the univariate Cox regression analysis, their sensitivity for the defined outcome was very

low, particularly for the 1-year event prognosis.

The SDNN was the strongest independent predictor of the risk for recurrent nonfatal MI within 5 years (SDNN ⩽123.43 ms vs. >123.43 ms: HR, 4.1; 95% CI, 1.54–11.32; P=0.005); an unadjusted logistic regression model applied to the prespecified SDNN dichotomy limits showed an AUC of 0.676, but the sensitivity of the model was very low. The SDNN was also the strongest independent predictor of the need for revascularization within a 5-year period after index MI with an optimal threshold value of ⩽125.7 ms (HR, 4.79; 95% CI, 2.13–10.78; P<0.001) and an AUC of 0.695; however, the sensitivity was very low.

Multivariate binary logistic regression analysis indicated that the LF/HF was the strongest significant predictor of in-hospital recurrent ischemia even after adjustment for other covariates and Charlson comorbidity index (LF/HF ⩽0.66 vs. >0.66: HR, 22.94; 95% CI, 5.45–96.53; P<0.001). An unadjusted logistic regression model applied to the prespecified LF/HF dichotomy limits showed an AUC of 0.804; however, the sensitivity of the model was low.

All noninvasive HRV and ICG measures had a weak association with the risk of recurrent nonfatal MI and the need for revascularization within 1 year after index MI.

Discussion

The main objective of our study was to assess the power of combined autonomic tone and cardiac contractile function measures to predict the development of serious adverse short- and long-term outcomes after MI. The selected HRV and ICG measures, assessed within a 3-day period after the onset of STEMI, best predicted 5-year all-cause and 5-year cardiac mortality. The combination of SDNN and CPO or both, and the mean NN interval significantly predicted a higher risk of 5-year all-cause mortality. Similarly, a combined assessment of SDANN and CPO significantly predicted a higher risk of 5-year cardiac mortality. A combined assessment of various HRV and ICG measures did not add to the prediction of ischemic complications: recurrent nonfatal MI, the need for revascularization, and in-hospital recurrent ischemia.

In general, the HRV measures were stronger and more significant predictors of selected outcomes than the ICG measures. However, in coincidence with other studies, the predictive power of all HRV measures was limited by low sensitivity (10), as estimated by the analysis of ROC curves. In contrast, the ICG measures were characterized by suboptimal specificity and rather high sensitivity in respect of selected outcomes. A combined assessment of both improved an overall sensitivity and specificity of the developed model.

The optimal threshold value maximizing the predictive power of the derived ICG CPO measure was higher than demonstrated in other studies (10, 11). CPO is directly proportional to the mean arterial pressure, which was measured on admission to the Cardiac Intensive Care Unit (CPO and CPI recorded on the first day were used for prognostic purposes). Arterial hypertension was highly prevalent in our study population (76%) and was even higher in the 5-year all-cause mortality subgroup (81.8%), hence the mean arterial pressure used to estimate CPO was high (median 140.5 mm Hg [IQR, 124.3–160.0], 89.5 mm Hg [IQR, 78.3–100.0], and 124.0 mm Hg [IQR, 109.3–139.6] for systolic, diastolic, and mean blood pressure, respectively). This was most likely the reason for higher CPO and CPI values observed.

A diagnostic value of various noninvasive parameters varies depending on their evaluation time in regard to the onset of MI (10, 13). The majority of previously published studies analyzed HRV from the ECG recordings obtained at 1 to 2 weeks after the onset of symptoms (9). Studies, analyzing the value of various HRV parameters or LVEF measured very early after MI, are scarce (16). Optimal timing for HRV analysis after acute MI remains uncertain. In our study, HRV and ICG measures were registered at serial points very early after MI (on the first and third days after the onset of symptoms), and the parameters of impaired HRV and systolic function obtained even so early in the course of STEMI were decreased significantly and correlated with the late complications and adverse course of the disease.

Previous studies have demonstrated that a combined assessment of the various measures of impaired autonomic tone and LVEF, obtained early after MI, improved a prognosis of cardiac death during a median duration of 4 years (5, 6). Both LVEF and ICG measures reflect left ventricular systolic function. In our study, LVEF correlated with the ICG measures; however, the correlation was only moderate (CO, r=0.431; CPO, r=0.426; and CPI, r=0.409, all P<0.001). The advantage of the suggested approach is that only one examination is needed for the combined assessment of both autonomic tone and systolic function if the direct or derived ICG measures are used as the markers of left ventricular contractile function, in contrast to 2 separate examinations if LVEF is used.

Comorbidity burden was a strong prognostic factor for short-term and long-term mortality in a large cohort study recently conducted in Denmark (13). Our documentation of a more severe Charlson comorbidity category in the subgroups of all-cause mortality within the first year and particularly 5 years after STEMI supports these findings.

Study Limitations. Our study has several potential limitations. First, it was carried out in a single hospital and was subject to the inherent biases of

this type of study. However, it does represent otherwise unselected population of patients with STEMI treated in routine clinical practice at a Lithuanian tertiary referral institution within the framework of inclusion criteria.

Although this was a prospective study, some data were retrospectively collected from comprehensive medical documentation records after patients' discharge and was subject to the missing data. However, the missing data accounted for a very small proportion of the data on this population (⩽1%), and these cases were excluded from the further analysis. Some patients were lost to follow-up: 12% of all patients were lost to follow-up at 1 year and 14.1% at 5 years. The data of these patients were excluded from the corresponding analysis.

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

A rather low rate of in-hospital and 1-year mortality limited our study by reducing the power to detect a possible association between the selected noninvasive parameters and the considered outcomes. A rather small number of patients with some selected outcomes restricted the number of covariates we could control in order to assess the independent predictive power of HRV and ICG measures.

Conclusions

The patients with both impaired autonomic heart regulation and systolic function demonstrated by decreased heart rate variability and impedance hemodynamic measures were found to be at greater risk of serious events, particularly all-cause and cardiac death, within a 5-year period after ST-segment elevation myocardial infarction.

An integrated analysis of simultaneously obtained electrocardiogram and impedance cardiogram early after ST-segment elevation myocardial infarction helps estimate patient's risk of serious long-term adverse outcomes.

Statement of Conflicts of Interest

The authors state no conflict of interest.

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