Int J Clin Exp Med 2015;8(12):22440-22449
www.ijcem.com /ISSN:1940-5901/IJCEM0013554

Original Article

A pilot study of prognostic value of non-invasive cardiac parameters for major adverse cardiac events in patients with acute coronary syndrome treated with percutaneous coronary intervention

Min-Jie Yuan*, Ye-Sheng Pan*, Wei-Guo Hu, Zhi-Gang Lu, Qing-Yong Zhang, Dong Huang, Xiao-Li Huang, Meng Wei, Jing-Bo Li

Department of Cardiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.
**Equal contributors.*

Received July 28, 2015; Accepted November 11, 2015; Epub December 15, 2015; Published December 30, 2015

Abstract: The objective of this study was to determine the combination of left ventricular ejection fraction (LVEF) and individual electrocardiographic parameters related to abnormal depolarization/repolarization or baroreceptor sensitivity that had the best predictive value for major adverse cardiac events (MACE) in patients with acute coronary syndrome (ACS). Patients with ACS who underwent coronary angiography and percutaneous coronary intervention (PCI) were included in this prospective study. Ventricular late potential (VLP), heart rate turbulence (HRT), heart rate variability (HRV), and T wave alternans (TWA) parameters were measured using 24 h Holter monitoring 2-4 weeks after onset of ACS. Initial and follow-up LVEF was measured by ultrasound. Patients were followed for at least 6 months to record the occurrence of MACE. Models using combinations of the individual independent prognostic factors found by multivariate analysis were then constructed to use for estimation of risk of MACE. In multivariate analysis, VLP measured as QRS duration, HRV measured as standard deviation of normal RR intervals, and follow-up LVEF, but none of the other parameters studied, were independent risk factors for MACE. Areas under ROC curve (AUCs) for combinations of 2 or all 3 factors ranged from 0.73 to 0.76. Combinations of any of the three independent risk factors for MACE in ACS patients with PCI improved prediction and, because these risk factors were obtained non-invasively, may have future clinical usefulness.

Keywords: Acute coronary syndrome, ventricular late potential, heart rate turbulence, heart rate variability, LVEF

Introduction

Acute coronary syndrome (ACS) patients have a high risk for major adverse cardiac events (MACE), including sudden coronary death (SCD). Common, non-invasively determined parameters used for risk assessment of these patients include left ventricular ejection fraction (LVEF) [1], ventricular late potential (VLP) [2], T-wave alternans (TWA) [3], heart rate variability (HRV) [4-7], and heart rate turbulence (HRT) [8].

LVEF, for example, has recently been reported to be an independent predictor of in-hospital death in patients with ACS undergoing percutaneous coronary intervention (PCI) [9]. VLP and TWA, markers of abnormal ventricular depolarization and repolarization, have been reported to predict life-threatening ventricular arrhythmias in ACS patients during coronary reperfusion therapy [10, 11]. HRV and HRT are indicators of baroreceptor sensitivity and autonomic nervous system input to the sinus node [12]. HRV has been reported to be a predictor of mortality [13] and HRT has been reported to be a predictor of sudden cardiac death [14, 15]. The indicators mentioned above vary in odds ratio (OR), sensitivity, and specificity. For example, low LVEF is a good predictor of over-all mortality, but whether it is specific for SCD is not completely clear [16]. The negative predictive value of VLP for SCD is very high, but its sensitivity for prediction of SCD is low [17].

Table 1. Characteristics distribution of subjects

	Total valid N	No MACE (n=171)	MACE (n=31)	*P*-value
Age (years)	202	62.87±10.81	64.29±10.34	0.499
Gender	202			0.366
Female		37 (21.64%)	9 (29.03%)	
Male		134 (78.36%)	22 (70.97%)	
proBNP	195	161.25 (67.71-524.23)	234.1 (82.18-634.1)	0.119
LDL	182	2.76 (2.14-3.47)	2.64 (2.22-3.02)	0.389
SBP (mmHg)	202	130 (117-140)	128 (116-135)	0.554
DBP (mmHg)	202	75 (67-82)	78 (64-89)	0.76
HR	202	75 (68-80)	78 (68-83)	0.294
BMI (kg/m^2)	202	24.42±2.86	25.44±3.81	0.164
Anterior MI	201			0.376
No		133 (78.24%)	22 (70.97%)	
Yes		37 (21.76%)	9 (29.03%)	
Killip grade[a]	202			0.061
I		160 (93.57%)	26 (83.87%)	
II		8 (4.68%)	3 (9.68%)	
III		3 (1.75%)	1 (3.23%)	
IV		0 (0%)	1 (3.23%)	
Smoker	200			0.801
No		75 (44.38%)	13 (41.94%)	
Yes		94 (55.62%)	18 (58.06%)	
ACEI/ARB	202			0.198
No		37 (21.64%)	10 (32.26%)	
Yes		134 (78.36%)	21 (67.74%)	
β-blocker	202			0.034
No		22 (12.87%)	0 (0%)	
Yes		149 (87.13%)	31 (100%)	
Statins[a]	202			1
No		3 (1.75%)	0 (0%)	
Yes		168 (98.25%)	31 (100%)	
Hypertension	202			0.022
No		70 (40.94%)	6 (19.35%)	
Yes		101 (59.06%)	25 (80.65%)	
Diabetes	202			0.378
No		119 (69.59%)	24 (77.42%)	
Yes		52 (30.41%)	7 (22.58%)	
HRT-TO	110	-1.08 (-2.48-0)	-0.84 (-1.24-1.04)	0.2
HRT-TS	110	5.05 (2.45-8.08)	5.3 (2.35-8.03)	0.943
HRV (SDNN)	167	108.64±30.54	93.68±31.17	0.034
TWA	99	45.5 (39-66.75)	59 (48-64)	0.184
VLP	151			< 0.001
Negative		121 (70.76%)	8 (25.81%)	
Positive		14 (8.19%)	8 (25.81%)	
VLP-fQRSd	151	87 (80-92)	92.5 (82-117.75)	0.031
VLP-RMS (40)	151	28.9 (23.7-39.85)	27.95 (18.03-36.1)	0.269
VLP-LAS (40)	151	30 (24-34)	32.5 (26.75-45.5)	0.039
LVEF (admission status)	178	61 (57-64)	59 (55.75-63)	0.24

LVEF (follow-up)	180	62 (59-64)	56 (51-64)	0.002

[a]Analyzed by Fisher exact test for group comparison. Continuous variables without normal distribution are presented as median and inter-quartile range (IQR), and Mann-Whitney tests used for group comparisons; continuous variables with normal distribution are presented as mean and standard deviation (SD) and independent t tests used for group comparisons. Categorical variables are presented as counts and percentages. Chi-square tests or Fisher exact tests were applied for comparisons.

Table 2. ROC results for optimal cutoff value and MACE discrimination

	Optimal cut-off value	AUC (95% CI)	Sensitivity	Specificity	*P*-value
HRT-TO	≥ -1.17	0.61 (0.46-0.75)	78.57	48.96	0.200
HRT-TS	≤ 12.1	0.51 (0.35-0.66)	12.50	100	0.943
HRV(SDNN)	≤ 74.5	0.64 (0.51-0.77)	91.03	36.36	0.036
TWA	≥ 47.5	0.61 (0.45-0.76)	80.00	54.76	0.184
VLP-fQRSd	≥ 97.5	0.64 (0.50-0.79)	45.45	89.92	0.031
VLP-RMS(40)	≤ 21.9	0.57 (0.43-0.72)	86.82	36.36	0.269
VLP-LAS(40)	≥ 39	0.64 (0.50-0.78)	36.36	93.80	0.039
LVEF(follow-up)	≤ 56.5	0.68 (0.56-0.81)	87.42	55.17	0.002

Receiver operating characteristic (ROC) analyses were performed to find the optimal cutoff values for each continuous variable. Youden indexes, defined as (sensitivity + specificity-1) were set to determine the cutoff values for optimal MACE prediction. Area under ROC curve (AUC) with null hypothesis (AUC=0.5) was analyzed by using the Wilcoxon rank sum test.

Because ACS patients have a high rate of later cardiac events, it would be important to develop a non-invasive, rapid, simple, and inexpensive method for risk stratification that can be used widely in clinical practice. These non-invasive electrocardiographic prognostic indicators have been studied individually, but data are lacking on how they all compare with each other in a single defined clinical cardiac condition, and whether a combination of these risk factors might increase the reliability of risk prediction.

In the current study, we evaluated the association with MACE of LVEF and 8 electrocardiographic parameters (HRV, TWA, VLP and its three constituent markers, and the two markers for HRT) in ACS patients who had received percutaneous coronary intervention (PCI), and constructed receiver operating curves (ROC) to determine the area under the curve (AUC), sensitivity, and specificity for MACE of each parameter. We then performed univariate and multivariate regression analysis on those factors that had shown statistically significant association with MACE. Finally, we constructed ROC curves using different combinations of the three factors found to be independent risk factors in multivariate regression in order to determine the combination with the highest sensitivity and specificity for prediction of MACE.

Patients and methods

Patient selection

ACS patients undergoing PCI and standard drug therapy were enrolled as subjects. Inclusion criteria: 1. Fulfillment of the ACS diagnostic criteria (acute ST-elevation myocardial infarction, acute non ST-elevation myocardial infarction and unstable angina); 2. No more than 90 years old; 3. Baseline rhythm was sinus rhythm. 4. Ventricular premature contraction (VPC) more than twice within 24 h (to enable HRT calculation). Exclusion criteria: 1. Sinoatrial block; 2. Atrioventricular block; 3. Temporary and permanent pacemaker implantation; 4. Long-term use of anti-arrhythmic drugs; 5. Malignant tumor; 6. Serious electrolyte disorder interfering with 24 h Holter monitoring; 7. Part or all of the Holter monitor data missing; 8. No myocardial injuries with unstable angina pectoris.

Two hundred eighty-six of the total of 517 ACS patients were selected for the study, based on the inclusion and exclusion criteria. Forty-seven of these patients declined to participate, leaving a total of 239 patients. Of these patients, 37 did not complete the study either because they did not complete the diagnostic procedures or because they were lost to follow-up, leaving a final enrollment of 202 patients. Of these patients, 99 provided TWA results, 150 provided VLP results, 158 provided initial and follow-up LVEF measurements and 48 provided complete results for all 5 markers: LVEF, HRT, HRV, VLP, and TWA.

Institutional review board (IRB) approval for the study was obtained from Shanghai Jiao Tong

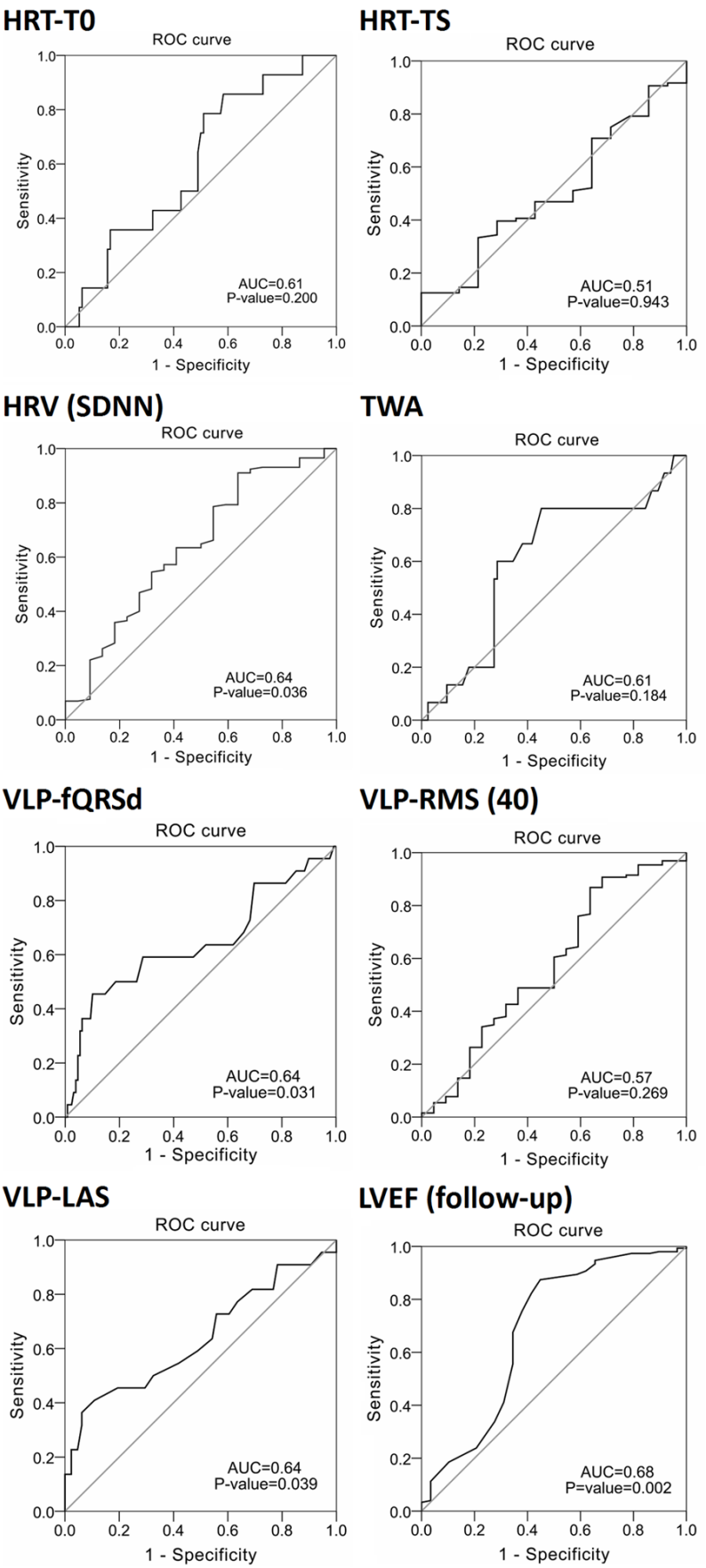

Figure 1. ROC for Electrocardiographic Parameters and Follow-up LVEF for Prediction of MACE. Receiver operating characteristic (ROC) analyses were performed to find the optimal cutoff value for each continuous variable. Youden indexes, defined as (sensitivity + specificity -1) were set to determine the cutoff values for optimal MACE prediction. Area under ROC operating curve (AUC) with null hypothesis (AUC=0.5) was analyzed by the Wilcoxon rank sum test.

University Affiliated Sixth People's Hospital, Shanghai, China. Informed consent was obtained in advance from all patients.

Study protocol

During hospitalization of patients identified with ACS onset, an ECG workstation (GE, USA) was used to test patients in a resting state, and a DELMAR Avionics DCG Holter monitoring system (USA) was used to perform 24 h dynamic electrocardiography. HRT and HRV analysis systems were also used. During outpatient visits 2-4 weeks after exit from hospitalization, routine ECG examinations and Holter monitoring were given to patients, and follow-up records were established. Follow-up was continued for at least 6 months, and the occurrence of major adverse cardiac events (MACE) was recorded. Initial and follow-up ECG were also recorded using ultrasound.

Definition of MACE

MACE was defined as: 1. All-cause mortality, including sudden cardiac death

Table 3. Results of univariate logistic regression to detect risk factors

	β±SE	OR (95% CI)	*p*-value
β-blocker	12.41±230.9	NA	0.957
Hypertension	1.06±0.48	2.89 (1.13-7.41)	0.027
VLP (ref=negative)	2.16±0.57	8.64 (2.81-26.63)	< 0.001
HRV(SDNN) (ref ≥ 74.5)	1.76±0.53	5.8 (2.05-16.4)	0.001
VLP-fQRSd (ref ≤ 7.5)	2.01±0.52	7.44 (2.69-20.55)	< 0.001
VLP-LAS (40) (ref ≤ 39)	2.16±0.57	8.64 (2.81-26.63)	< 0.001
LVEF (follow-up) (ref ≥ 56.5)	2.15±0.45	8.55 (3.56-20.53)	< 0.001

NA: non-available for unstable estimates. Univariate logistic regression analyses were performed to investigate risk factors for MACE. If statistically significant differences between those with MACE and those without MACE were found, they were included in the univariate logistic regression analyses.

(SCD); 2. Serious ventricular arrhythmia, including sustained ventricular tachycardia and ventricular fibrillation; 3. The recurrence of non-fatal ACS. 4. Rehospitalization due to reasons 2 and 3 was also defined as MACE if the events due to these reasons were not recorded as MACE elsewhere.

VLP measurement and diagnostic criteria

The duration of the QRS complex (fQRSd) was obtained from an average ECG at high frequency [18]. The root mean square value of the voltage in the last 40 mSec of the QRS complex (RMS (40)) and the duration below 40 μV in the last 40 mSec period (LAS (40)) were also calculated. Technically, the noise ratio was required l to be < 1 μV, with a frequency response of 40-250 Hz. The diagnostic criteria for VLP were fQRSd > 110 ms; RMS (40) < 20 μV; LAS (40) > 38 ms, and if VLP met 2 of these criteria, it was considered positive.

Definition and measurement of TWA

T wave alternans (TWA) refers to the alternation of amplitude and shape of the T wave with every beat in the ECG. According to ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, TWA is defined as class IIa of fatal ventricular arrhythmia risks [19]. The electrocardiographic signal was pretreated (removal of ECG interference, baseline drift, power frequency interference, etc.) before TWA calculation. The heart beat was then divided into an odd and an even group. According to the update strategy, heartbeats of the two groups are corrected with asymptotic increment. T wave alternans was calculated as the maximum absolute difference between the two groups, which is the quantitative index of TWA [20].

HRV

HRV, defined as the standard deviation of normal RR intervals (SDNN) during a continuous 24 h period, was calculated through the HRV analysis system.

HRT

Turbulence onset (T) and turbulence slope (TS) were obtained through the HRT analysis system. The neutral point for TO was defined as 0; TO < 0 referred to an accelerated initial heart rate after the premature ventricular contraction; and TO ≥ 0 referred to a decelerated initial heart rate after the premature ventricular contraction; the neutral point for TS was defined as 2.5, TS > 2.5 referred to the deceleration after the acceleration of sinus rhythm, while TS ≤ 2.5 referred to the absence of deceleration [14].

Statistical analysis

Continuous variables without normal distribution were presented as median and inter-quartile range (IQR), and Mann-Whitney U tests used for group comparisons; continuous variables with normal distribution were presented as mean and standard deviation (SD), and independent t tests were used for group comparisons. Categorical variables were presented as counts and percentages. Chi-square tests or Fisher exact tests were applied for group comparisons. Receiver operating characteristic (ROC) analyses were performed to find the optimal cutoff value for each continuous variable and used to detect the effects of different combinations of risk factors of MACE. Youden indexes, defined as (sensitivity + specificity-1), were set to determine the cut-off values for optimal MACE prediction. Area under ROC curve (AUC) with null hypothesis (AUC=0.5) was analyzed by using the Wilcoxon rank sum test. Univariate and multivariate logistic regression analyses were performed to investigate risk factors for MACE. If statistically significant differences between those with MACE and those without

Table 4. Results of multivariate logistic regression to detect risk factors

	β±SE	OR (95% CI)	*p*-value
HRV (SDNN) (ref ≥ 74.5)	1.86±0.78	6.41 (1.4-29.35)	0.017
VLP-fQRSd (ref ≤ 97.5)	1.79±0.66	5.99 (1.64-21.84)	0.007
LVEF (follow-up) (ref ≥ 56.5)	1.58±0.69	4.85 (1.27-18.59)	0.021

Multivariate logistic regression with stepwise model selection method were performed to investigate risk factors for MACE. Factors that reached statistical significance in univariate analysis were included in multivariate regression analysis. Factors included in multivariate logistic regression were as follows: gender, age, hypertension, VLP, HRV (SDNN), VLP-fQRSd, VLP-LAS (40), LVEF (follow-up). This final result was conducted by stepwise model selection.

Table 5. Area under ROC curve in different combinations of risk factors

Combined factors	AUC	95% CI
HRV (SDNN) & VLP-fQRSd	0.73	0.59-0.87
HRV (SDNN) & LVEF (follow-up)	0.73	0.60-0.87
VLP-fQRSd & LVEF (follow-up)	0.73	0.59-0.87
HRV (SDNN) & VLP-fQRSd & LVEF (follow-up)	0.76	0.62-0.91

CI: Confidence Interval. Receiver operating characteristic (ROC) analyses were used to detect the effects of different combinations of risk factors for MACE. The larger area under the ROC curve (AUC) indicates the better combination.

MACE were found, they were included in univariate logistic regression analyses. Factors that reached statistical significance in univariate analysis were included in multivariate logistic regression analysis. Factors included in multivariate logistic regression were as follows: gender, age, hypertension, VLP, HRV (SDNN), VLP-fQRSd, VLP-LAS (40), LVEF (follow-up). The stepwise model selection method was used to investigate the influence of factors for MACE diagnosis during multivariate logistic regression analysis. Statistical analyses were performed with SPSS software version 17 (SPSS Inc, Chicago, IL, US), and two-tailed P < 0.05 indicated statistical significance.

Results

Baseline demographic characteristics

Baseline characteristics of subjects with and without MACE are shown in **Table 1**. Hypertension and use of β-blockers were significantly more common in those with MACE (*P*=0.022, *P*=0.034, respectively). The MACE and no MACE groups showed no significant difference in any other baseline demographic characteristic.

LVEF, fHRV (SDNN), VLP, and VLP-fQRSd were potential risk factors of MACE

Table 1 also shows values for LVEF and the 8 electrocardiographic parameters investigated as possible risk factors of MACE. LVEF, although not significantly different between the two groups at hospital admission, was significantly smaller at follow-up in those with MACE (MACE vs. no MACE, 56% vs. 62%, *P*=0.002). Beat-to-beat variability in rate (fHRV (SDNN)) was lower in those with MACE (MACE vs. no MACE, 93.68 vs 108.64, *P*=0.034), and those with MACE were more likely to have a positive VLP (*P* < 0.001), and a longer ventricular depolarization period (VLP-fQRSd 92.5 vs. 87, *P*=0.031; VLP-LAS (40) 32.5 vs, 30, *P*=0.039). The other parameters studied, VLP-RMS (40), HRT-TO, HRT-TS, and TWA, had no significant association with the occurrence of MACE.

ROC results showed significant predictive power for VLP-fQRSd, VLP-LAS (40), HRV (SDNN) and follow-up LVEF

ROC analyses for the 8 potential parameters are shown in **Table 2**, and the individual ROC for each parameter is shown in **Figure 1**. Significant predictive power and similar AUCs (0.65 to 0.68) were seen for VLP-fQRSd, VLP-LAS (40), HRV (SDNN), and LVEF (follow-up). The other parameters, HRT-TO, HRT-TS, TWA, and VLP-RMS (40), had no significant discriminatory power.

Values for HRV (SDNN) below the optimal value of 74.5 identified those with MACE with a sensitivity of 91.03%, but a specificity of only 36.3%. Values above than the optimal VLP-fQRSd cut-off value of 97.5 identified patients with MACE were with a sensitivity of only 45.45%, but with a specificity of 89.92%. Values higher than the optimal VLP-LAS (40) value of 39 identified patients with MACE with a sensitivity of 36.36%, but a high specificity (93.8%). LVEF values smaller than the optimal cut-off value of 56.5% identified those with MACE with a sensitivity

and specificity of 87.42% and 55.17% respectively.

Six parameters in univariate analysis and three in multivariate analysis were significantly related to MACE

In univariate analysis (**Table 3**), six parameters, hypertension, VLP, VLP-fQRSd, VLP-LAS (40), HRV (SDNN), and LVEF (follow-up), were significantly related to diagnosis of MACE. Step-wise multivariate analysis was performed with the six parameters plus gender and age. **Table 4** shows only 3 of these parameters, HRV (SDNN), VLP-fQRSd, and LVEF (follow-up) to be significantly and independently related to MACE. With adjustment for the other 2 parameters, the odds for MACE were significantly higher in those with HRV (SDNN) ≤ 74.5 (adjusted OR=6.41, P=0.017), in those with VLP-fQRSd ≥ 97.5 (adjusted OR=5.99, P=0.007), and in those with LVEF (follow-up) ≤ 56.5 (adjusted OR=4.85, P=0.021). The highest odds for MACE were observed with HRV (SDNN) ≤ 74.5.

The combination of HRV (SDNN), VLP-fQRSd, and follow-up LVEF produced the highest AUC

The AUC results for combinations of the 3 parameters found through multivariate analysis to be independent risk factors for MACE are shown in **Table 5**. Combinations of any 2 of these parameters produced the same AUC, 0.73. The combination of all 3 factors produced a somewhat higher AUC, 0.76. The logit equation for the 3 parameter combination is shown below:

Logit (MACE/No MACE) = -0.49 + 1.86 × HRV (SDNN) + 1.79 × VLP-fQRSd + 1.58 × LVEF (follow-up)

All combinations show good discriminatory power compared to the discriminatory power (AUC 0.64) seen when either of the three is used alone.

Discussion

In the current study, three non-invasively determined, significant, independent risk factors for MACE were identified in ACS patients who had undergone PCI. These were an indicator of cardiac contractile function (LVEF), an indicator of the sensitivity of cardiac ANS regulation (HRV (SDNN)), and an indicator of the speed of action potential conduction in the ventricles (fQRSd).

Continuation of the QRS signal beyond its normal termination is a sign of slow action potential conduction at some location in the ventricle and of arrhythmogenic potential. We studied four parameters by which the lengthening of the QRS can be quantified: VLP, VLP-LAS (40), VLP-RMS (40), and VLP-fQRSd. Of these parameters, only the total duration of the QRS complex, VLP-fQRSd, was a significant and independent predictor of MACE. VLP (the combination of at least 2 of the 3 other markers) and the markers using information from the last 40 ms of the QRS complex (that is, VLP-LAS (40) and VLP-RAM (40)) were not independent related factors in multivariate analysis. A prolonged QRS has previously been reported to be predictive of cardiac death in suspected coronary artery disease patients and in post-MI patients, but to have no prognostic significance in non-ischemic cardiomyopathy [11, 21-23].

Changes in ventricular repolarization (that is, TWA) were not related to of MACE in any of the statistical analyses performed here. In other studies, TWA, the beat-to-beat fluctuation in the T wave, has been shown to be a long term predictor of arrhythmia [10, 24, 25], and a predictor for post-MI cardiac death [8, 26]. However, the mechanistic link between repolarization and arrhythmia is less direct than the link between depolarization and arrhythmia. Further studies are needed to clarify the use of TWA as a predictor.

The sensitivity of the heart to ANS control decreases with age and in the failing heart [14, 27]. Heart rate variability, that is, the oscillation in the interval between heart beats, and the two markers of heart rate turbulence are indicators of this sensitivity. In our study HRV was within the range reported by others for the elderly and sick [15, 28-30] and was an independent marker for MACE, but the two turbulence markers, HRV-TO and HRV-TS, showed no significant association with MACE in any of our statistical analyses. In previous studies, decreased HRV has consistently been associated with increased risk of death and cardiac death, results consistent with ours. However, turbulence markers have also been reported to predict cardiac events [31]. In one previous study, HRV and HRV-TS predicted non-fatal car-

diac events [32], and in another study, if both HRV-TO and HRV-TS were abnormal, this combination was found to be as good a predictor of post-MI death as decreased LVEF [14, 32]. These results do not correspond to ours.

Multivariate analysis yielded 3 significant and independent predictive factors for MACE. Of these factors, the marker for poor ANS sensitivity (that is, HRV (SDNN)) had the highest OR for MACE and showed high sensitivity and low specificity in MACE analysis. The marker for abnormal ventricular depolarization speed (VLP-fQRSd) had very high specificity for MACE, but low sensitivity, and an OR of 5.99. LVEF, the marker for abnormal pumping function, showed intermediate sensitivity and specificity compared to the other 2 parameters. And combinations of any 2 or of all three parameters gave higher ROC values than those for any individual parameter.

This study has several limitations. It was limited by the relatively small number of samples. The sample size and number of events included in the multivariate regression model was even lower due to missing data. The relatively mild severity of the patients' cardiovascular disease, and thus the overall low occurrence rate of MACE may have caused a lack of baseline differences in some variables between the MACE and non-MACE patient groups. Additional limitations were that no filtering method was described for the time series, and there was no detailed explanation of the clinical characteristics of the cardiovascular disease of individual patients (we felt that inclusion of individual clinical characteristics would detract from the focus of the study).

In conclusion, identification of patients with MACE using a combination of any two or all three risk factors (VLP-fRQSd, HRV (SDNN) and LVEF) in ACS patients with PCI was more powerful (AUC 0.73 to 0.76) than identification using only one of the risk factors (each AUC 0.64). It improves predictability and has the potential to become a useful clinical tool.

Acknowledgements

This study was funded by Science and Technology Commission of Shanghai Municipality (fund number: 114119a8900).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Jing-Bo Li and Meng Wei, Department of Cardiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishang Road, Shanghai 200233, China. Tel: +86-18930170413; +86-13501731990; Fax: +86-64735588; +86-64701932; E-mail: mj_yuan1988@163.com; ljbsjtu6h@hotmail.com

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