CARDIOVASCULAR MEDICINE

Prognostic value of ventricular arrhythmias and heart rate variability in patients with unstable angina

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Heart 2006;**92**:1055–1063. doi: 10.1136/hrt.2005.070714

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Accepted 13 December 2005
Published Online First 30 December 2005

Objectives: To assess the prognostic value of ventricular arrhythmias (VA) and heart rate variability (HRV) in patients with unstable angina.
Design: Multicentre prospective study.
Setting: 17 cardiological centres in Italy.
Patients: 543 consecutive patients with unstable angina and preserved left ventricular function (ejection fraction ⩾40%) enrolled in the SPAI (Stratificazione Prognostica dell'Angina Instabile) study.
Methods: Patients underwent 24 h ECG Holter monitoring within 24 h of hospital admission. Tested variables were frequent ventricular extrasystoles (⩾10/h), complex (that is, frequent or repetitive) VA, and bottom quartile values of time-domain and frequency-domain HRV variables. Primary end points were in-hospital and six-month total and cardiac deaths.
Results: Eight patients died in hospital (1.5%) and 32 (5.9%, 29 cardiac) during follow up. Both complex VA and frequent extrasystoles were strongly predictive of death in hospital and at follow up, even after adjustment for clinical (age, sex, cardiac risk factors and history of myocardial infarction) and laboratory (troponin I, C reactive protein and transient myocardial ischaemia on Holter monitoring) variables. At univariate analysis bottom quartile values of three HRV variables (standard deviation of RR intervals index, low-frequency amplitude and low to high frequency ratio) were associated with in-hospital death, and bottom quartile values of most HRV variables predicted six-month fatal events. At multivariate Cox survival analysis reduced low-frequency amplitude was consistently found to be independently associated with fatal end points.
Conclusion: In patients with unstable angina with preserved myocardial function, both VA and HRV are independent predictors of in-hospital and medium-term mortality, suggesting that these factors should be taken into account in the risk stratification of these patients.

Ventricular arrhythmias (VA),[1–6] and impaired cardiac autonomic function, as indicated by depressed heart rate variability (HRV),[7–13] have been shown to predict mortality among patients recovering from acute myocardial infarction (MI).

Despite the recent wave of interest in risk stratification of patients with non-ST segment elevation acute coronary syndrome,[14 15] no study has assessed the prognostic value of VA in patients with unstable angina. HRV was investigated only in small studies that were not sufficiently powered to assess its relationship with survival.[16–19]

The SPAI (Stratificazione Prognostica dell'Angina Instabile) study is a prospective, multicentre Italian study designed to investigate the prognostic value of clinical, biohumoral and ECG variables in patients admitted to a coronary care unit with a diagnosis of unstable angina. In this report we focus on the role of VA and HRV in predicting in-hospital and six-month survival in this group of patients.

METHODS

Patients

Consecutive patients admitted to coronary care units of participating centres (see appendix) with a clinical diagnosis of unstable angina from December 1997 to December 2001 were recruited in the SPAI study. For patients to be enrolled in the study, however, the diagnosis of unstable angina had to be confirmed during their hospital stay by one or more of the following findings: (1) ischaemic ECG changes during recurrent chest pain; (2) evidence of myocardial ischaemia during exercise ECG stress test or during exercise radionuclide studies or pharmacological echocardiographic stress tests (with either dipyridamole or dobutamine); and (3) documentation of obstructive (> 50%) stenosis in at least one major epicardial artery during coronary angiography. If the diagnosis of unstable angina could not be confirmed by any of the previous clinical and laboratory findings, patients were excluded from the SPAI study.

Unstable angina was defined as new onset angina (< 2 months) ensuing either at low levels of effort or at rest (new onset unstable angina), resting or worsening effort angina occurring in patients with either an old MI or a known history of stable coronary artery disease (worsening unstable angina), and readmission to hospital because of recurrent angina within three months after discharge for an acute MI (post-MI unstable angina).

An acute MI, according to the definition of the World Health Organization,[20] was excluded by monitoring 12-lead ECG and assaying standard serum cardiac enzymes (creatine kinase and its MB isoform) at admission and after 6, 12 and

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; LV, left ventricular; MI, myocardial infarction; NPV, negative predictive value; NSVT, non-sustained ventricular tachycardia; PPV, positive predictive value; RR, relative risk; SDNNi, mean of the standard deviations of RR intervals of all 5 min segments in 24 h; SPAI, Stratificazione Prognostica dell'Angina Instabile; VA, ventricular arrhythmias

24 h. Patients with evidence of reduced left ventricular (LV) function (LV ejection fraction < 40%) on two dimensional echocardiography were excluded from the study.

A standard ECG and a venous blood sample were obtained on admission. Blood was centrifuged, and serum and plasma samples were frozen at −80°C until assayed at a core laboratory. Plasma troponin I was measured by an enzyme immunological assay (Boehringer Mannheim, Mannheim, Germany), with the lowest detection limit of 0.1 ng/ml. Serum C reactive protein was assayed by a high-sensitivity nephelometric method (Nephelometric 100 Analyzer; Behring, Scoppito, Italy), with the lowest detection limit of 0.05 mg/l. Patients were managed according to local standard protocols.

Holter monitoring

Patients underwent 24 h ECG Holter monitoring within 24 h of admission with two-channel tape recorders (Oxford Medilog MR45; Oxford Instruments) and monitoring two bipolar chest leads. All Holter monitoring tapes were analysed independently by two expert cardiologists at a core laboratory with the Oxford Medilog Excel 3.0 device.

Transient myocardial ischaemia was diagnosed when one or more episodes of horizontal or downsloping ST segment depression or of ST segment elevation ⩾ 1 mm lasting for ⩾ 1 min were detected.

For each patient the total number of ventricular extrasystoles, couplets and episodes of non-sustained ventricular tachycardia (NSVT, defined as ⩾ 3 consecutive extrasystoles with a rate > 100 beats/min) were obtained.

HRV was assessed for the entire 24 h in both the time domain and the frequency domain after careful revision and editing of beats in the Oxford V.7.0 HRV analysis package.[13] RR interval interpolation was applied in case of extrasystoles. Time-domain HRV variables were mean RR interval; standard deviation of all RR intervals; standard deviation of the mean RR intervals of all 5 min segments in 24 h; and mean of the standard deviations of RR intervals of all 5 min segments in 24 h (SDNNi). In the frequency domain, HRV was assessed in the range of frequencies of 0–0.5 Hz with a fast Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz. Data were analysed in 10 min epochs throughout the 24 h and results from all epochs were averaged to form a composite spectrum. The amplitude of the following frequency-domain HRV variables was obtained: very low frequency (0.0033–0.04 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz). Furthermore, the LF:HF ratio was calculated.

Clinical follow up

Patients were followed up at each centre three and six months after discharge by outpatient clinical visits or by a telephone interview. In case of death, detailed information about the causes were obtained from clinical records or from the patient's physician or relatives. Death was considered of cardiac origin when it was consequent to acute MI or heart failure or when it occurred suddenly (within 1 h of symptom onset).

In-hospital death and six-month death were the primary end points of this study, but in-hospital and cardiac death were also analysed separately. Furthermore, as a secondary end point, we considered the occurrence of non-fatal acute MI. Acute MI was diagnosed in case of chest pain > 30 min, with ischaemic ST segment or T wave changes on the ECG and the typical rise of creatine kinase MB.[20]

Statistical analysis

The following clinical and laboratory variables were regarded as potential risk predictors in statistical analyses: age (dichotomised in ⩾ 70 and < 70 years), sex, family history of coronary artery disease, active smoking, hypertension (blood pressure > 140/90 mm Hg or use of hypertension drugs), hypercholesterolaemia (> 5.7 mmol/l or use of lipaemia drugs), diabetes, previous acute MI, type of unstable angina (new onset or worsening), prolonged duration (> 20 min) of the qualifying angina episode, serum C reactive protein concentrations (dichotomised in concentrations ⩾ 3 or < 3 mg/l), plasma troponin I concentrations (dichotomised in concentrations ⩾ 0.4 or < 0.4 ng/ml), drug treatment started in the coronary care unit, presence of basal ST segment depression (> 0.5 mm) in at least one of the Holter monitor chest leads and detection of transient myocardial ischaemia on Holter monitoring. For the analysis, the few patients with post-MI unstable angina (table 1) were included in the group with worsening unstable angina. The cut off concentrations of 3 mg/l for C reactive protein and of 0.4 ng/ml for troponin I were chosen because, in preliminary analyses, they were found to be those best for predicting six-month mortality.

Patients were also divided into groups with or without frequent (⩾ 10/h) ventricular extrasystoles, with or without NSVT episodes, and with or without complex VA (defined as frequent or repetitive extrasystoles—either couplets or NSVT episodes). Lastly, patients were dichotomised according to each HRV parameter into groups with values in the bottom quartile and with values in the three upper quartiles.

Univariate and multivariate logistic regression analyses were applied to assess the association of variables with clinical end points, whereas univariate and multivariate survival Cox regression analyses were applied to assess the

Table 1 Main clinical data of patients with unstable angina included in the study and of patients excluded from the Holter study

	Study patients (n = 543)	Excluded patients (n = 143)	p Value
Age (years)	65.2 (10)	67.0 (10)	0.06
Age >70	201 (37%)	61 (43%)	0.25
Men	356 (66%)	86 (60%)	0.27
CAD risk factors			
Active smoking	133 (25%)	28 (20%)	0.26
Systemic hypertension	294 (54%)	65 (45%)	0.08
Family history of CAD	221 (41%)	54 (38%)	0.59
Hypercholesterolaemia	258 (48%)	80 (56%)	0.09
Diabetes mellitus	103 (19%)	33 (23%)	0.33
Previous AMI	181 (33%)	39 (27%)	0.20
Type of unstable angina			
De novo	210 (39%)	52 (36%)	0.68
Worsening	309 (57%)	81 (57%)	0.97
Post-AMI	24 (4%)	8 (6%)	0.71
Preadmission angina ⩾20 min	252 (46%)	70 (49%)	0.65
Drug treatment in the coronary care unit*			
β blocking agents	348 (65%)	89 (65%)	0.95
Calcium antagonists	356 (66%)	93 (68%)	0.72
Nitrates	519 (97%)	123 (90%)	0.004
Antiplatelet agents	513 (96%)	128 (94%)	0.64
Heparin/LMWH	449 (84%)	96 (71%)	0.006
ACE inhibitors	226 (42%)	67 (49%)	0.16
Statins	153 (29%)	37 (27%)	0.85
Troponin I >0.4 ng/ml	168 (32%)	28 (21%)	0.022
C reactive protein >3 mg/l	335 (63%)	83 (64%)	0.76
STd >0.5 mm at basal ECG	86 (16%)	NA	NA
TMI on Holter monitoring	135 (25%)	NA	NA

Age data are mean (SD).
*Drug treatment, troponin I and C reactive protein available for 537, 528 and 532 patients included in the study and for 136, 130 and 130 patients excluded from the study, respectively.
ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; CAD, coronary artery disease; LMWH, low molecular weight heparin; NA, not applicable; STd, ST segment depression; TMI, transient myocardial ischaemia.

Table 2 Variables significantly predictive of in-hospital death at univariate analysis

	Odds ratio (95% CI)	p Value
Age >70	12.3 (1.5 to 10.12)	0.02
⩾10 extrasystoles/h	7.25 (1.69 to 30.9)	0.007
SDNNi <39 ms	4.99 (1.18 to 21.1)	0.029
LF <15.7 ms	4.94 (1.16 to 20.9)	0.030
LF:HF <1.12	5.14 (1.21 to 21.8)	0.026

Complex ventricular arrhythmias are excluded, as all patients who died had these forms of arrhythmias on Holter monitoring.
HF, high frequency; LF, low frequency; NSVT, non-sustained ventricular tachycardia; SDNNi, mean of the standard deviations of RR intervals of all 5 min segments in 24 h.

association of variables with six-month mortality and non-fatal MI. The predictive value of VA and HRV variables at follow up was also adjusted, in a separate model of multivariate Cox regression analysis, for coronary revascularisation procedures (either coronary bypass surgery or percutaneous interventions) performed during follow up. Data for patients lost at follow up were censored at the time of the last visit or contact. Survival curves were constructed by the Kaplan–Meier method and compared by log rank test.

A stepwise backward procedure was applied for multivariate analyses (both for logistic regression and for Cox regression). All considered variables were included in the models and progressively removed, leaving only variables with $p \leqslant 0.1$ in the final models. The independent predictive value of frequent extrasystoles and of complex VA in multivariate models was assessed separately. Similarly, the independent predictive value was assessed individually for each of the considered HRV variables.

Patients included in the study and those who had undergone Holter monitoring but were excluded (see below) from analyses were compared by unpaired t test or Mann–Whitney U test (as indicated) for continuous variables and by χ^2 test for proportions. Data were statistically analysed by SPSS V.12.01 statistical software (SPSS Inc, Chicago, Illinois, USA). Data are reported as mean (SD), unless otherwise indicated. A value of $p < 0.05$ was always required for significance.

RESULTS

General results

Overall, 843 patients were included in the SPAI study, 686 of whom (81.4%) underwent Holter monitoring. Overall, 143 patients (20.8%) were excluded from the present study for the following reasons: technical deficiencies of Holter monitor recordings (n = 73); Holter monitoring duration < 18 h (n = 34); persistent supraventricular arrhythmias (n = 10); left bundle branch block (n = 16); pacemaker rhythm (n = 8); and lack of data about clinical outcome (n = 2). Thus, 543 patients formed the final cohort of the present study (64.4% of the original SPAI cohort and 79.1% of those with Holter monitoring). Troponin I and C reactive protein concentrations were available for 528 (97%) and 531 (98%) patients, respectively.

Patients included in the study tended to be younger but had higher troponin I values and more commonly received nitrates than the patients excluded from the study, suggesting a slightly more severe form of unstable angina (table 1).

Table 3 Multivariate analysis of in-hospital death, including frequent ventricular extrasystoles and, separately, significant heart rate variability parameters in the logistic regression models

	Odds ratio (95% CI)	p Value
First model		
Age >70 years	8.60 (1.02 to 72.3)	0.047
⩾10 extrasystoles/h	5.13 (1.16 to 22.6)	0.031
SDNNi <39 ms	4.43 (1.01 to 19.4)	0.048
Second model		
Age >70 years	8.04 (0.96 to 68.5)	0.056
⩾10 extrasystoles/h	5.27 (1.19 to 23.3)	0.029
LF <15.7 ms	4.49 (1.02 to 19.7)	0.047
Third model		
Age >70 years	7.44 (0.86 to 64.3)	0.068
⩾10 extrasystoles/h	4.29 (0.96 to 19.1)	0.056
LF:HF ratio <1.12	2.76 (0.61 to 12.4)	0.18

HF, high frequency; LF, low frequency; SDNNi, mean of the standard deviations of RR intervals of all 5 min segments in 24 h.

VA during Holter monitoring

The median number of ventricular extrasystoles in 24 h for the group as a whole was 10 (range 0–40 163); 105 patients (19.3%) had frequent extrasystoles on Holter monitoring. Couplets were found in 142 patients (26.1%; median 0, range 0–769) and NSVT episodes were found in 61 patients (11.2%; median 0, range 0–66). Overall, complex VA (that is, frequent or repetitive extrasystoles) were detected in 188 patients (34.6%).

In-hospital mortality

Eight (1.5%) patients died in hospital, seven (1.3%) of cardiac causes. All of the patients who died had complex VA during Holter monitoring. Furthermore, only old age, frequent extrasystoles and bottom quartile values of three HRV variables (SDNNi, LF and LF:HF ratio) were significantly predictive of death (table 2). Results were similar for cardiac deaths (data not shown).

Frequent ventricular extrasystoles and, among HRV variables, SDNNi and LF maintained independent significant association with in-hospital mortality in multivariate logistic regression models including ⩾ 10 extrasystoles/h as an arrhythmic variable, with only age ⩾ 70 years adding independent prognostic information among all other clinical, ECG and laboratory variables (table 3).

As all of the patients who died had complex VA, we evaluated whether HRV variables might help to identify those at the highest risk among patients with complex VA. Among HRV variables, LF best predicted mortality in this subgroup: five of 57 (9.6%) patients with LF amplitude < 15.7 ms died compared with two of 136 (2.2%) patients with LF amplitude ⩾ 15.7 ms (odds ratio 4.72; 95% confidence interval (CI) 1.08 to 20.5, p = 0.038).

Six-month mortality

Complete follow up at six months was available for 489 (93.5%) patients. Thirty two (5.9%) patients died, 29 (5.3%) of cardiac causes. Several baseline clinical and laboratory variables were significantly associated with fatal end points at follow up at univariate analysis (table 4). Furthermore, ⩾ 10 extrasystoles/h, complex VA and bottom quartile values of most HRV variables were found to predict total and cardiac deaths (table 5). Figure 1 shows the curves for event-free survival from cardiac deaths of patients with, compared with those without, frequent extrasystoles or complex VA. Fig 2 shows the curves for patients with LF or LF:HF in the bottom quartile compared with those in the three upper quartiles.

On multivariate Cox survival analysis, ⩾ 10 extrasystoles/h and complex VA, separately, maintained a significant association with total and cardiac mortality. Among HRV variables, LF only was found to be independently associated with fatal end points (table 6), with low LF:HF ratio being of independent significance for cardiac death in the multivariate model including complex VA (relative risk (RR) 2.36, 95% CI

Table 4 Univariate association of clinical and laboratory variables with fatal events at six-month follow up

	Total deaths	p Value	Cardiac deaths	p Value
Men	0.68 (0.34 to 1.36)	0.27	0.75 (0.36 to 1.53)	0.75
Age >70 years	8.14 (3.35 to 19.8)	0.00001	9.01 (3.44 to 23.06)	0.00001
Active smoking	0.32 (0.10 to 1.03)	0.06	0.23 (0.05 to 0.96)	0.013
Hypertension	1.00 (0.49 to 2.03)	0.99	0.91 (0.43 to 1.92)	0.91
Family history of CAD	1.14 (0.59 to 2.29)	0.71	1.35 (0.55 to 2.84)	0.40
Hypercholesterolaemia	0.73 (0.36 to 1.49)	0.73	0.65 (0.31 to 1.40)	0.27
Diabetes mellitus	3.77 (1.86 to 7.65)	0.0002	4.57 (2.18 to 9.59)	0.0001
Previous MI	2.69 (1.34 to 5.40)	0.006	2.96 (1.41 to 6.19)	0.004
Worsening unstable angina	3.47 (1.34 to 9.02)	0.011	5.57 (1.69 to 18.4)	0.005
Angina >20 min	1.31 (0.65 to 2.82)	0.45	1.42 (0.68 to 2.95)	0.35
β blocking agents	0.65 (0.32 to 1.31)	0.23	0.62 (0.29 to 1.30)	0.20
Calcium antagonists	1.41 (0.63 to 3.14)	0.41	1.47 (0.62 to 3.46	0.38
ACE inhibitors	1.20 (0.59 to 2.44)	0.23	1.09 (0.52 to 2.31)	0.81
Basal ST changes	1.81 (0.81 to 4.03)	0.15	2.07 (0.92 to 4.68)	0.08
Troponin I >0.4 ng/ml	2.01 (0.99 to 4.06)	0.052	2.24 (1.22 to 4.11)	0.009
C reactive protein >3 mg/l	2.60 (1.07 to 6.34)	0.036	2.71 (1.32 to 5.56)	0.007
TMI on Holter monitoring	2.72 (1.36 to 5.45)	0.005	2.50 (1.20 to 5.20)	0.014

ACE, angiotensin converting enzyme; CAD, coronary artery disease; MI, myocardial infarction; TMI, transient myocardial ischaemia. Data are presented as relative risk with 95% confidence intervals.

1.08 to 5.16, p = 0.03) and of borderline significance in the model including ⩾ 10 extrasystoles/h (RR 1.97, 95% CI 0.88 to 4.40, p = 0.1). Other variables independently predictive of fatal end points were old age, diabetes and (for cardiac deaths only) basal persistent ST depression on the Holter monitor ECG (table 6), but not a history of MI.

During the whole period of the study 257 patients (47.3%) underwent coronary revascularisation (142 percutaneous coronary interventions, 112 coronary artery bypass surgery, 3 both). Frequent extrasystoles, complex VA and bottom quartile LF amplitude maintained a significant association with total (RR 3.60, 95% CI 1.72 to 7.52, p = 0.001; RR 6.50, 95% CI 2.77 to 15.2, p = 0.00002; RR 2.86, 95% CI 1.38 to 5.92, p = 0.005, respectively) and cardiac (RR 3.81, 95% CI 1.75 to 8.29, p = 0.001; RR 8.69, 95% CI 3.27 to 23.0, p = 0.00001; RR 3.06, 95% CI 1.42 to 6.60, p = 0.004, respectively) mortality even after adjustment for coronary interventions.

Figures 3 and 4 illustrate the incremental prognostic value of complex VA combined with established clinical and laboratory

Table 5 Association of ventricular arrhythmias and heart rate variability parameters with six-month fatal events according to univariate Cox regression analysis

		Total deaths			Cardiac deaths		
	Total number	Number	RR (95% CI)	p Value	Number	RR (95% CI)	p Value
Extrasystoles							
⩾10/h	105	14 (13.3)	3.5	0.000	13 (12.4)	3.66	0.001
<10/h	428	18 (4.1)	(1.74 to 7.03)		16 (3.6)	(1.76 to 7.60)	
Non-sustained ventricular tachycardia							
Yes	61	5 (8.2)	1.47	0.43	5 (8.2)	1.65	0.31
No	482	27 (8.2)	(0.57 to 3.82)		24 (5.2)	(0.63 to 4.30)	
Complex ventricular arrhythmias							
Yes	188	24 (12.8)	6.14	0.00001	23 (12.2)	7.84	0.00001
No	355	8 (2.2)	(2.76 to 13.66)		6 (1.7)	(3.19 to 19.3)	
RR interval <833 ms							
Yes	135	13 (9.6)	2.06	0.044	12 (8.8)	2.12	0.046
No	408	19 (4.7)	(1.02 to 4.18)		17 (4.2)	(1.01 to 4.44)	
SDNN <80 ms							
Yes	135	10 (7.4)	1.56	0.23	10 (7.4)	1.82	0.12
No	408	22 (5.4)	(0.75–3.24)		19 (4.7)	(0.86 to 3.86)	
SDANN <62 ms							
Yes	135	11 (8.1)	1.84	0.09	11 (8.1)	1.97	0.077
No	408	21 (5.1)	(0.90 to 3.74)		18 (4.4)	(0.93 to 4.16)	
SDNNi <39 ms							
Yes	135	16 (11.8)	3.00	0.002	15 (11.1)	3.21	0.002
No	408	16 (3.9)	(1.50 to 5.99)		14 (3.4)	(1.55 to 6.54)	
Very low-frequency amplitude <31 ms							
Yes	138	16 (11.6)	3.07	0.002	15 (10.9)	3.28	0.001
No	405	16 (3.9)	(1.53 to 6.14)		14 (3.5)	(1.58 to 6.80)	
LF <15.7 ms							
Yes	136	16 (11.8)	3.09	0.001	15 (10.9)	3.31	0.001
No	407	16 (3.9)	(1.54 to 6.17)		14 (3.5)	(1.60 to 6.85)	
HF <11.2 ms							
Yes	135	12 (8.9)	1.80	0.11	12 (8.9)	2.12	0.046
No	408	20 (4.9)	(0.88 to 3.69)		17 (4.2)	(1.01 to 4.44)	
LF:HF <1.12							
Yes	138	17 (12.3)	3.57	0.0003	16 (14.6)	3.87	0.0003
No	405	15 (3.7)	(1.78 to 7.15)		13 (3.2)	(1.86 to 8.04)	

HF, high frequency; LF, low frequency; RR, relative risk; SDANN, standard deviation of the mean RR intervals of all 5 min segments in 24 h; SDNN, standard deviation of all RR intervals; SDNNI, mean of the standard deviations of RR intervals of all 5 min segments in 24 h.

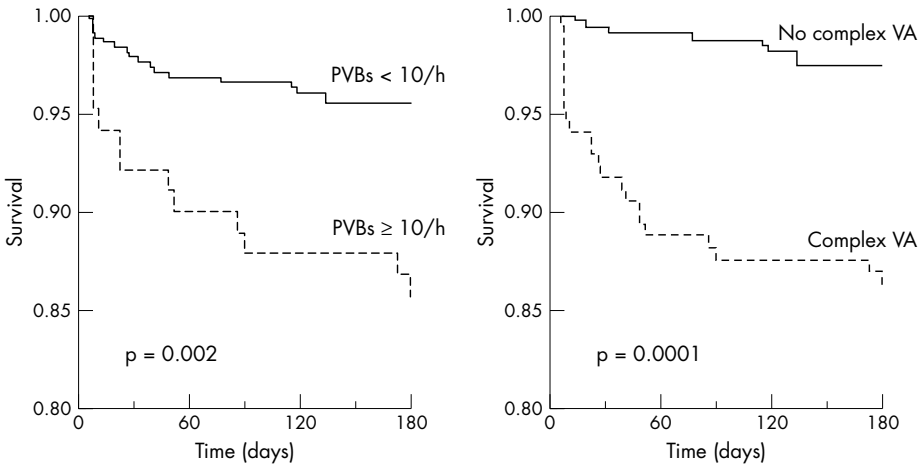

Figure 1 Cardiac death-free survival according to the presence or absence of frequent ventricular extrasystoles (left) and the presence or absence of complex ventricular arrhythmias (VA; right) on 24 h ECG Holter monitoring of patients with unstable angina.

predictors of risk and with LF value. Table 7 shows sensitivity, specificity and positive (PPV) and negative (NPV) predictive values for total mortality of the most important arrhythmic and HRV variables. Individual variables had high NPV but low PPV. Combining complex VA with low HRV variables resulted in a significant but limited improvement in PPV (25.4% for complex VA and low LF:HF ratio), with only a mild reduction in NPV.

Non-fatal acute MI

There were 8 (1.5%) non-fatal acute MIs during hospital stay and 23 (4.7%) from discharge to the six-month follow up. Neither VA nor reduced HRV was significantly associated with the occurrence of non-fatal MI, both in hospital (data not shown) and at the six-month follow up (table 8).

DISCUSSION

This study, to the best of our knowledge, is the first to show in a large population of patients that both VA and low HRV, as detected on Holter monitoring started within 24 h after admission for unstable angina, are predictors of in-hospital and medium-term mortality in patients with unstable angina and preserved LV function. Of note, only patients with complex VA died in hospital, and in multivariate models frequent extrasystoles and two HRV parameters (SDNNi and LF) maintained an independent association with in-hospital mortality, despite the low incidence of deaths. Only old age added independent prognostic information to VA and HRV parameters for in-hospital death.

Frequent or complex VA on Holter monitoring started within 24 h after admission for unstable angina was also a strong predictor of total and cardiac mortality at six-month follow up, and most HRV variables had a significant univariate association with fatal events. Notably, frequent extrasystoles, complex VA and bottom quartile values of LF amplitude were found to be predictors of six-month mortality independent of several common prognostic indicators, including transient myocardial ischaemia, C reactive protein and troponin I, which were not independently associated with mortality in this study when VA and HRV were taken into account. Combination of laboratory prognostic variables showed that the subgroup of patients with both complex VA and low HRV parameters had the highest risk of death (fig 3). In contrast with the high specificity and NPV, however, PPV remained insufficiently low, being at best 25.4% when complex VA and low LF:HF ratio were combined. The low PPV, however, is a limitation that has consistently been shown to concern all prognostic variables in patients with acute coronary syndromes.[1–13 16–19]

The group of patients included in this study had preserved LV function (ejection fraction ⩾40%). VA and HRV were predictive of death independently of a history of MI, which was documented for only 33% of patients. In contrast to mortality, no significant association was found in this cohort of patients with unstable angina between VA or reduced HRV and the occurrence of non-fatal acute MI in the in-hospital phase and at the six-month follow up.

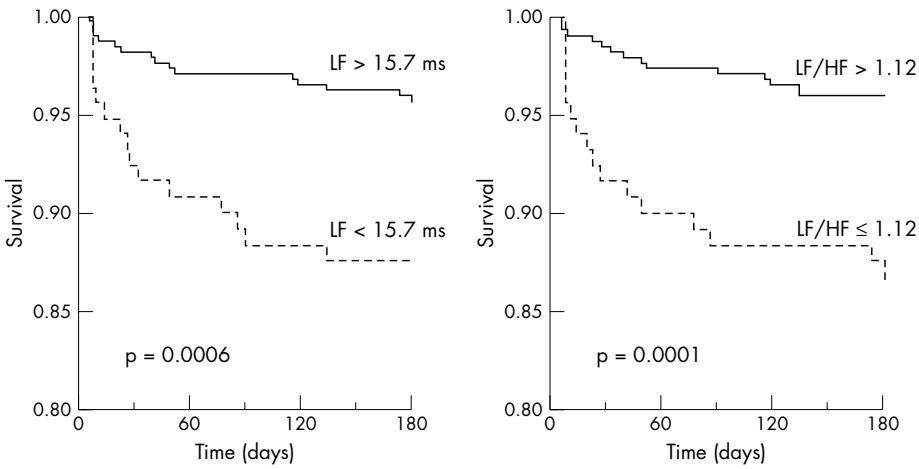

Figure 2 Cardiac death-free survival according to low-frequency (LF) amplitude values in the bottom versus the three upper quartiles (left) and ratio of low frequency to high frequency (LF:HF) in the bottom versus the three upper quartiles (right) on frequency-domain heart rate variability analysis for patients with unstable angina.

Table 6 Results of multivariate Cox survival analysis of fatal end points at six-month follow up

	Total deaths		Cardiac deaths	
	RR (95% CI)	p Value	RR (95% CI)	p Value
Model with ⩾10 extrasystoles/h				
Age >70 years	8.61 (3.24 to 22.9)	0.00002	10.96 (3.63 to 33.0)	0.00002
Diabetes	4.29 (2.06 to 8.93)	0.0001	6.39 (2.83 to 14.5)	0.00001
Worsening UA	2.34 (0.89 to 6.14)	0.085	3.90 (1.15 to 13.1)	0.028
Persistent ST depression	NA	NA	3.07 (1.24 to 7.59)	0.015
Troponin I >0.4 ng/ml	NA	NA	2.18 (0.97 to 4.64)	0.06
⩾10 extrasystoles/h	2.52 (1.22 to 5.21)	0.012	2.40 (1.10 to 5.20)	0.027
LF <15.7 ms	2.14 (1.03 to 4.44)	0.04	2.29 (1.00 to 5.28)	0.05
Model with complex VA				
Age >70 years	8.27 (3.13 to 21.9)	0.00002	9.38 (3.18 to 27.7)	0.0001
Diabetes	4.44 (2.14 to 9.24)	0.0001	6.31 (2.87 to 13.9)	0.00001
Worsening UA	2.30 (0.88 to 6.00)	0.09	3.53 (1.06 to 11.8)	0.04
Persistent ST depression	NA	NA	3.17 (1.30 to 7.72)	0.011
Complex VA	4.99 (2.13 to 11.7)	0.0002	6.38 (2.38 to 17.1)	0.0002
LF <15.7 ms	2.23 (1.08 to 4.60)	0.03	2.90 (1.30 to 6.46)	0.009

LF, low frequency; NA, not applicable; RR, relative risk; UA, unstable angina; VA, ventricular arrhythmias.

Comparison with previous studies

The predictive prognostic value of predischarge VA and HRV was consistently observed in most studies of patients recovering from acute MI,[1–13] but our study is the first to show an association between VA and mortality also in patients with unstable angina.

HRV was previously investigated in studies of patients with unstable angina, showing a significant association with composite cardiac end points,[16–19] but the limited number of patients recruited precluded the assessment of the predictive value of HRV for total and cardiac mortality.

In our study several HRV variables were significantly associated with six-month mortality, although only a frequency-domain variable, LF, was independently associated with both in-hospital and six-month mortality in multivariate survival analyses. Notably, a low LF:HF ratio was also independently associated with cardiac death when complex VA were taken into account (table 6) and its combination with complex VA resulted in the highest PPV for mortality (table 7). Thus, our findings complement the observations of the prognostic value of low LF amplitude and LF:HF ratio observed in other populations of patients.[8 10 13 21 22]

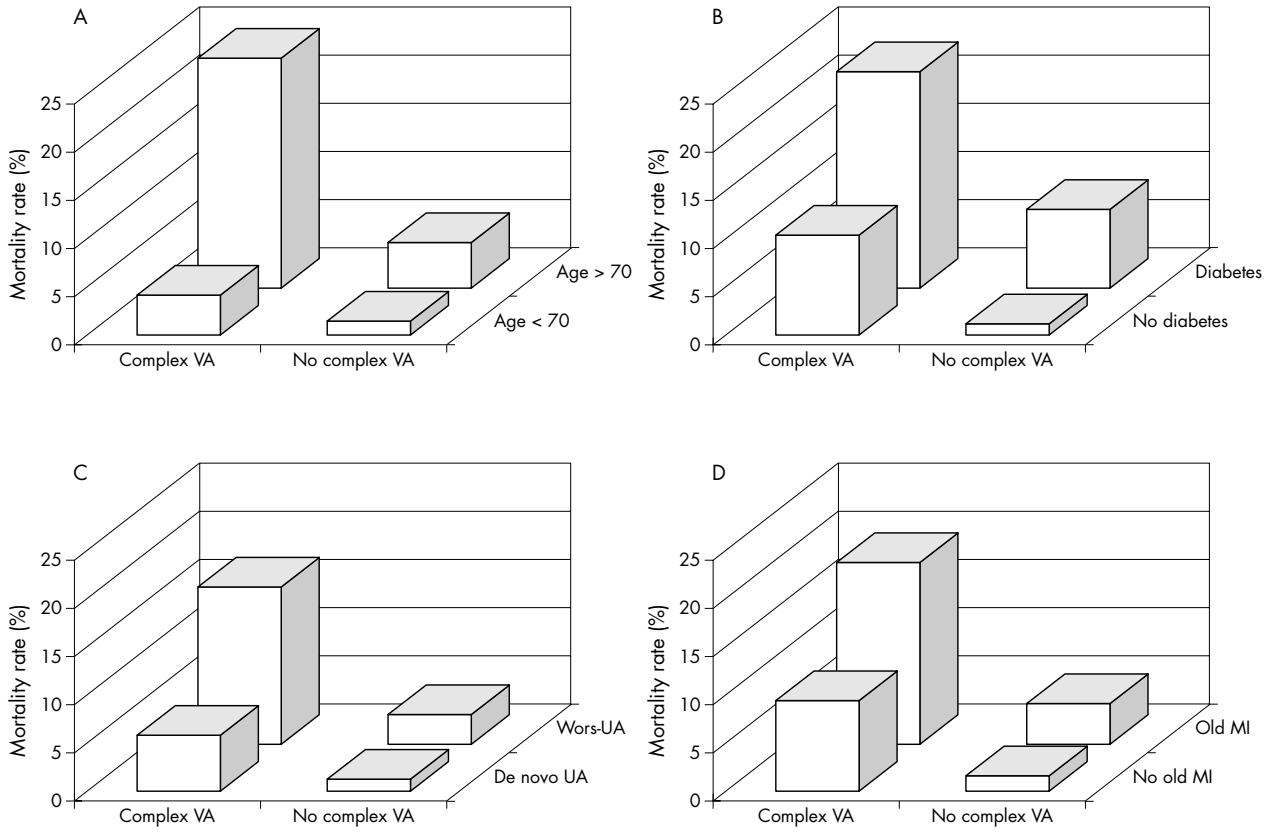

Figure 3 Crude six-month mortality according to complex ventricular arrhythmias (VA) in groups of patients with presence or absence of established clinical risk predictors. (A) Age, (B) diabetes, (C) type of unstable angina (UA) and (D) previous myocardial infarction (MI). Wors, worsening; $p < 0.001$ for data in each graph.

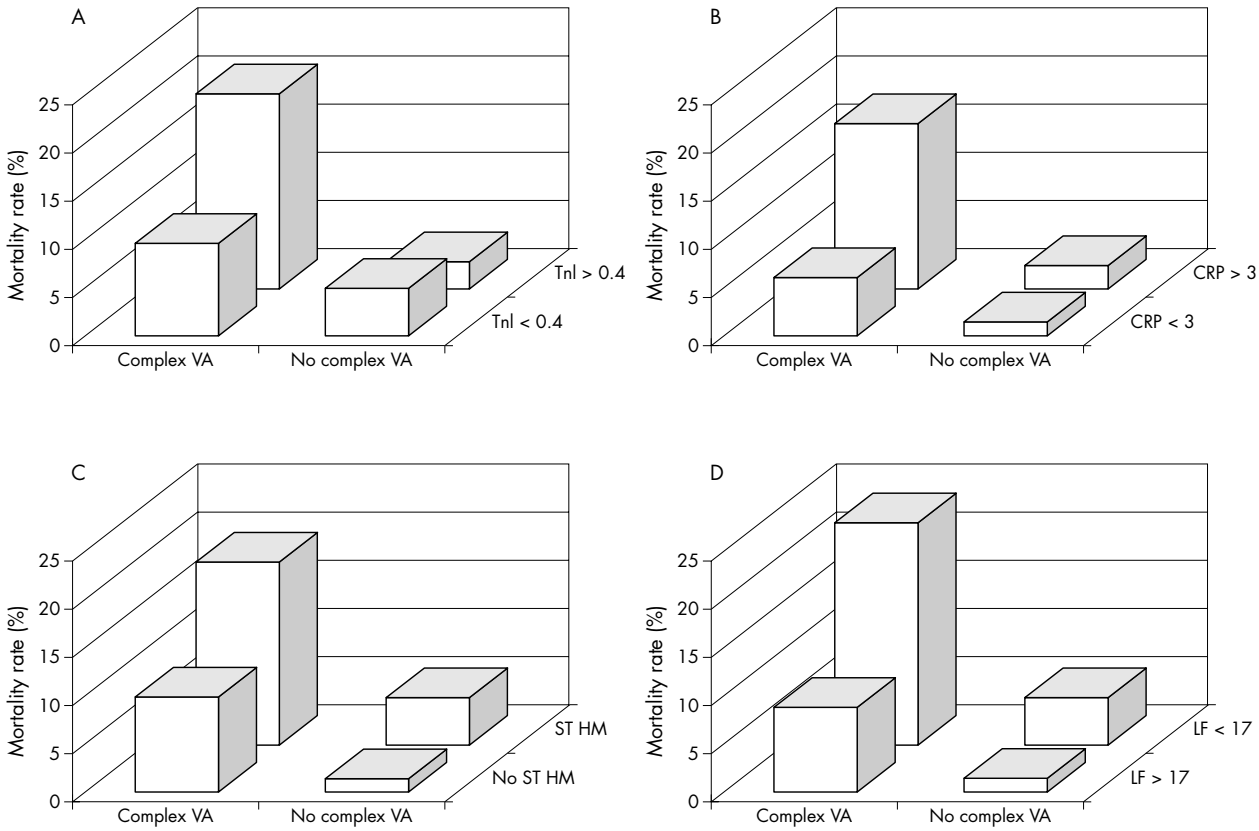

Figure 4 Crude six-month mortality according to complex ventricular arrhythmias (VA) in groups of patients with presence or absence of established prognostic laboratory variables. (A) Troponin I (TnI), (B) C reactive protein (CRP), (C) transient myocardial ischaemia on Holter monitoring (ST-HM), and (D) low-frequency (LF) amplitude. $p < 0.001$ for data in each graph.

Pathophysiological mechanisms

The reasons why non-sustained VA and impaired HRV are strongly predictive of mortality in patients with unstable angina are speculative. They may reflect impaired LV function,[23–26] but LV ejection fraction was normal or only mildly reduced in our cohort of patients, 39% of whom had a history of de novo unstable angina and 67% of whom had no history of MI, thus strongly limiting the possible role of impaired LV function.

HRV is also reduced in patients with diabetes,[27 28] which was a strong predictor of death in our study, but decreased LF amplitude was associated with fatal end points also independently of diabetes.

The relationship between depressed HRV and mortality is also difficult to ascertain as the exact physiological mechanisms responsible for the various HRV components are still incompletely known.[29 30] Decreased values of HRV variables, including LF, may reflect reduced vagal tone or predominant sympathetic influence to the heart.[31 32] The presence of

Table 7 Sensitivity, specificity, positive predictive value and negative predictive value for all cause mortality in the study group

	Sens (%)	Spec (%)	PPV (%)	NPV (%)
⩾10 extrasystoles/h	43.7	81.8	13.3	95.8
Complex VA	75.0	67.9	12.8	97.7
LF amplitude <15.7 ms	50.0	76.5	11.8	96.1
LF:HF ratio <1.12	53.1	76.3	12.3	96.3
Complex VA and low LF	37.5	92.2	23.1	95.6
Complex VA and low LF:HF	43.7	92.0	25.4	94.4

HF, high frequency; LF, low frequency; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; VA, ventricular arrhythmias.

Table 8 Relationship of major potential prognostic variables with non-fatal acute myocardial infarction at six-month follow up (univariate Cox regression)

	RR (95% CI)	p Value
Age >70 years	0.80 (0.32 to 2.0)	0.64
Men	1.33 (0.22 to 4.0)	0.42
Active smoking	2.49 (1.06 to 5.76)	0.033
Hypertension	1.13 (0.49 to 2.61)	0.78
Family history of CAD	1.15 (0.49 to 2.69)	0.75
Hypercholesterolaemia	1.14 (0.47 to 2.76)	0.77
Diabetes mellitus	1.40 (0.50 to 3.91)	0.52
Previous AMI	0.96 (0.38 to 2.45)	0.94
No de novo unstable angina	0.74 (0.32 to 1.71)	0.48
Angina >20 min	0.92 (0.39 to 2.15)	0.85
β blocking agents	1.02 (0.43 to 2.40)	0.97
Calcium antagonists	0.62 (0.27 to 1.42)	0.26
ACE inhibitors	0.79 (0.34 to 1.67)	0.79
Basal ST changes	0.52 (0.12 to 2.22)	0.38
Troponin I >0.4 ng/ml	2.17 (0.94 to 5.0)	0.069
C reactive protein >3 mg/l	2.20 (0.82 to 5.92)	0.12
TMI on Holter monitoring	1.66 (0.71 to 3.9)	0.24
⩾10 extrasystoles/h	0.42 (0.10 to 1.78)	0.24
Complex VA	0.71 (0.28 to 1.80)	0.47
LF amplitude <15.7 ms	0.64 (0.22 to 1.88	0.42
HF amplitude <11.2 ms	0.28 (0.07 to 1.19)	0.086
LF:HF ratio <1.12	0.91 (0.34 to 2.45)	0.85

ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; CAD, coronary artery disease; HF, high frequency; LF, low frequency; RR, relative risk; TMI, transient myocardial ischaemia; VA, ventricular arrhythmias.

frequent or complex non-sustained VA in the context of sympathovagal imbalance can increase the susceptibility to fatal VA, in particular during myocardial ischaemia.[33 34] On the other hand, VA and depressed HRV are unlikely to be associated with the triggers of acute MI, as they were not predictive of non-fatal MI in hospital or at six-month follow up.

Limitations of the study

A significant number of patients (47%) during follow up underwent percutaneous or surgical revascularisation. Both VA and low LF amplitude, however, continued to be significantly associated with death after adjustment for revascularisation procedures.

The SPAI study was designed to assess the predictive value of prognostic variables in patients with unstable angina with sufficiently preserved LV myocardial function. Although all SPAI patients had LV ejection fraction $\geqslant$ 40% on admission, however, the exact value was not obtained. Thus, we cannot exclude some influence of LV function on clinical outcome among our patients, although it is unlikely, as the effect on mortality of differences in LV ejection fraction for values $\geqslant$ 40% is well known to be negligible in patients with coronary artery disease.[35 36]

Conclusions

This study shows that, in patients with unstable angina, early assessment of VA and of cardiac autonomic function by ECG monitoring adds incremental prognostic information above that provided by established clinical and laboratory markers of risk; indeed, these variables can identify patients at extremely low risk and those at high risk of in-hospital and six-month death, and therefore should be considered in risk stratification of patients with non-ST segment elevation unstable angina.

ACKNOWLEDGEMENTS

We thank Helen Raiswell BSc for the design and administration of the SPAI database.

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The SPAI study was supported financially by the Regione Calabria and by the Fondazione per il Cuore ONLUS.

APPENDIX

List of participant centres in the SPAI study: Ancona, Azienda Ospedaliera ''G M Lancisi'' (Purcaro A, Perna G, Costantini C, Moretti S); Aosta, Ospedale Civile (De Marchi M, Leone G, Giudice M); Bologna, Policlinico Universitario ''Sant'Orsola'' (Bugiardini R, Manfrini O, Pizzi C); Brescia, Policlinico Universitario Ospedale Civili (Dei Cas L, Metra M, Gaiti M, Fiorini C); Castelnuovo Garfagnana, Ospedale ''Santa Croce'' (Bernardi D, Volterrani C); Firenze, Ospedale Santa Maria Nuova (Marchi F, Ciriello G, Crisano S); Frascati, Ospedale San Sebastiano Martire (Giorgi G, Ciavolella M, Sarli G); Genova, Policlinico Universitario ''San Martino'' DI MI, (Brunelli C, Spallarossa P, Ferraris F); Livorno, Ospedale Riuniti (Magini G, Galli M, Di Giorgio A); Padova, Policlinico Universitario Giustinianeo (Iliceto S, Nava A, Maddalena F, Babuin L, Pedrocco A); Roma, Policlinico Universitario A Gemelli (Maseri A, Crea F, Cianflone D, Rebuzzi AG, Angeloni G, Lanza GA, Sestito A); Roma, Ospedale San Filippo Neri (Santini M, Tubaro M); Roma; Ospedale Santo Spirito (Ceci V, Aspromonte N, Leone F); San Giovanni Rotondo, Ospedale ''Casa Sollievo della Sofferenza'' (Fanelli R, Cianfrone N, Santoro T); Teramo, Ospedale Civile ''G Mazzini'' (Iacovoni F, Delle Monache S, Iacovoni A); Torino, Ospedale ''Le Molinette'' (Trevi GP, Pistono M, Bianchi F, Bergerone S); Verona, Ospedale Borgotrento (Zardini P, Destro G, Brighetti G, Zorzi A); Viareggio, Ospedale Civile (Pesola A, Comella A).

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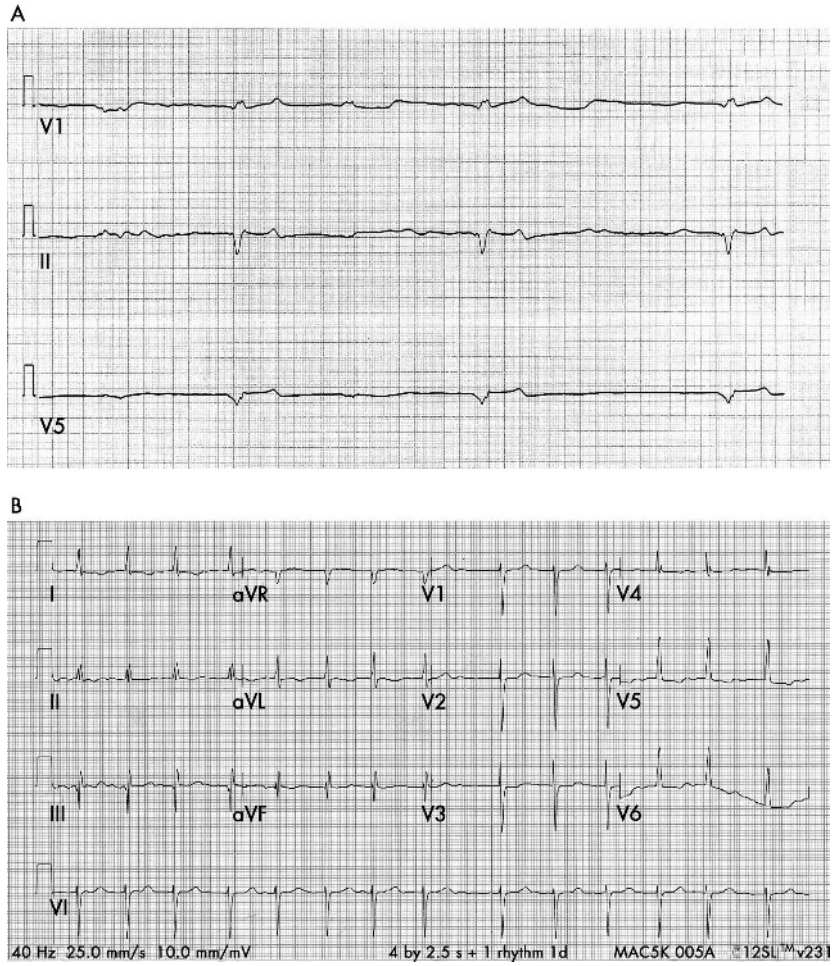
IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2005.071803

Hyperkalaemia causing profound bradycardia

Two elderly patients presented with profound bradycardia. Both were taking angiotensin converting enzyme (ACE) inhibitors for widespread vascular disease. One had diarrhoea and the other recently started spironolactone. The first patient's ECG showed regular broad QRS complexes with no P waves (panel A). She was paced without improvement. The second patient had a ventricular rate of 20/min with irregular broad QRS complexes and absent atrial activity, consistent with slow atrial fibrillation (ECG not shown). Initial treatment was with atropine and an external pacemaker. Serum potassium in the first patient was 9.4 mmol/l with urea 42.6 mmol/l and creatinine 598 umol/l. Corresponding values for the second patient were potassium 7.7 mmol/l, urea 20.2 mmol/l and creatinine 231 umol/l. The heart rate in both cases responded to intravenous calcium chloride (shown for first patient in panel B).

When patients collapse and are found to be bradycardic it is likely that an ECG will be available before the serum biochemistry. Clinicians should be aware that life threatening hyperkalaemia may cause profound bradycardia and bear a superficial resemblance to complete heart block. The clue to the correct diagnosis is the broad QRS complex with absence of P waves. True second and third degree atrioventricular (AV) block have been described in hyperkalaemia but are uncommon because the P wave usually disappears before such advanced AV block occurs. If the ECG is available before the serum potassium and is consistent with life threatening hyperkalaemia, then it would seem sensible to give calcium chloride speculatively while waiting for the biochemistry results.



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