

Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction

Georg Schmidt, Marek Malik, Petra Barthel, Raphael Schneider, Kurt Ulm, Linda Rolnitzky, A John Camm, J Thomas Bigger Jr, Albert Schömig

Summary

Background Identification of high-risk patients after acute myocardial infarction is essential for successful prophylactic therapy. The predictive accuracy of currently used risk predictors is modest even when several factors are combined. Thus, establishment of a new powerful method for risk prediction independent of the available stratifiers is of considerable practical value.

Methods The study investigated fluctuations of sinus-rhythm cycle length after a single ventricular premature beat recorded in Holter electrocardiograms, and characterised the fluctuations (termed heart-rate turbulence) by two numerical parameters, termed turbulence onset and slope. The method was developed on a population of 100 patients with coronary heart disease and blindly applied to the population of the Multicentre Post-Infarction Program (MPIP; 577 survivors of acute infarction, 75 deaths during a median follow-up of 22 months) and to the placebo population of the European Myocardial Amiodarone Trial (EMIAT; 614 survivors of acute myocardial infarction, 87 deaths during median follow-up of 21 months). Multivariate risk stratification was done with the new parameters and conventional risk factors.

Findings One of the new parameters (turbulence slope) was the most powerful stratifier of follow-up mortality in EMIAT and the second most powerful stratifier in MPIP: MPIP risk ratio 3.5 (95% CI 2.2–5.5, $p < 0.0001$), EMIAT risk ratio 2.7 (1.8–4.2, $p < 0.0001$). In the multivariate analysis, low left-ventricular ejection fraction and turbulence slope were the only independent variables for mortality prediction in MPIP ($p < 0.001$), whereas in EMIAT, five variables were independent mortality predictors: abnormal turbulence onset, abnormal turbulence slope, history of previous infarction, low left-ventricular ejection fraction, and high mean heart rate ($p < 0.001$). In both MPIP and EMIAT, the combination of abnormal onset and slope was the most powerful multivariate risk stratifier: MPIP risk ratio 3.2 (1.7–6.0, $p < 0.0001$), EMIAT risk ratio 3.2 (1.8–5.6, $p < 0.0001$).

Interpretation The absence of the heart rate turbulence

after ventricular premature beats is a very potent postinfarction risk stratifier that is independent of other known risk factors and which is stronger than other presently available risk predictors.

Lancet 1999; **353**: 1390–96

See Commentary page 1377

Introduction

Clinical trials^{1,2} suggest that in high-risk patients with ischaemic heart disease, mortality can be effectively reduced by implantation of a cardioverter-defibrillator. Since the selection of high-risk patients is a crucial part of prophylaxis, risk stratification strategies are important. In patients surviving acute myocardial infarction, the predictive value of currently used risk factors, such as left-ventricular dysfunction,^{3–5} frequent ventricular ectopic beats (VPB),⁶ non-sustained ventricular tachycardia,⁵ positive late potentials,⁷ heart-rate variability,⁸ and mean heart rate⁹ is modest¹⁰ even when several predictors are combined and methodological issues of such a combination solved.¹¹ Establishment of a new risk predictor independent of the presently available stratifiers is therefore of considerable practical value.

We describe a new method for risk stratification based on a simple expression of ventriculophasic sinus arrhythmia,^{12–14} namely fluctuations of sinus-rhythm cycle length after a single VPB. We term such fluctuations heart-rate turbulence. In low-risk patients, we observed that after a VPB, sinus rhythm shows a characteristic pattern of early acceleration and subsequent deceleration. Such a characteristic pattern does not occur in high-risk patients. We propose to characterise this phenomenon by two descriptors, both of which contain independent information on the risk of subsequent mortality.

The new risk predictors were developed in an open study with a training sample of 100 patients accumulated at the medical department of the Technical University in Munich and validated blind, in both univariate and multivariate analyses, in two large independent populations of myocardial-infarction survivors, namely the population of the Multicentre Post-Infarction Program (MPIP) study⁴ and in the placebo group of the European Myocardial Infarction Amiodarone Trial (EMIAT).¹⁵

Methods

Training sample

100 patients with coronary artery disease (78 of whom had a history of myocardial infarction and 26 a history of multiple infarctions) and presenting with sinus rhythm and more than ten VPBs per hour during 24 h Holter monitoring were used to design the method and to optimise the risk prediction power of the new indices. Characteristics of these patients have previously been published¹⁶ and are listed in table 1. During a 2-year follow-up period, 17 of these patients died.

In each patient, a 24 h Holter recording was obtained

Erste Medizinische Klinik (G Schmidt MD, P Barthel MD, R Schneider MEng, A Schömig MD); and **Institut für Medizinische Statistik und Epidemiologie, Technischen Universität München, München, Germany** (K Ulm PhD); **Department of Cardiological Sciences, St George's Hospital Medical School, London, UK** (M Malik PhD, A J Camm MD); and **Division of Cardiology, Department of Medicine, Columbia University, NY, New York, USA** (L Rolnitzky MSA, J T Bigger Jr MD)

Correspondence to: Dr Georg Schmidt, Erste Medizinische Klinik der Technischen Universität München, Ismaninger Straße 22, 81675 München, Germany (e-mail: gschmidt@med1.med.tu-muenchen.de)

	Training sample (n=100)	MPIP population (n=577)	EMIAT population (n=614)
Age (years)	62.8 (9.7)	57.2 (8.7)	60.8 (9.3)
Women	15 (15.0%)	126 (21.8%)	89 (14.5%)
Previous myocardial infarction	26 (26.0%)	149 (25.8%)	161 (26.2%)
LVEF (%)	46.4 (14.6)	45.4 (14.8)	29.9 (9.3)
VPB count per h	176 (210)	16 (49)	48 (186)
β -blocker treatment	55 (55.0%)	185 (32.1%)	272 (44.3%)
Thrombolytic treatment	0	0	366 (59.6%)

Data are mean (SD) or number (%) of patients.

Table 1: Patients' characteristics

during a stable phase of coronary artery disease (at least 3 months after acute myocardial infarction). An Oxford Excel Holter system (Oxford Instruments, Abingdon, UK) was used to process the Holter recordings. After manual review and revision, computer files were generated containing the duration of individual RR intervals and morphology classifications of individual QRS complexes (normal, supraventricular, and ventricular premature complexes, supraventricular and ventricular escape beats).

In patients surviving follow-up, we observed a typical pattern of sinus-rhythm RR interval series following singular VPBs. The VPBs were followed by an early acceleration and a late deceleration of the sinus rhythm. Figure 1 A gives a typical example of this pattern in a long-term survivor. The acceleration starts immediately after an ectopic beat and lasts for only a few RR intervals. Subsequent deceleration reaches a maximum between the third and seventh sinus cycle; the longest RR interval occurs usually near to the tenth cycle after a VPB. These variations are subtle and can be recognised only after computer algorithm.

In patients who died during the follow-up period, the extent of this turbulence response to VPBs was substantially smaller and often absent (figure 1B).

Numerical descriptors were investigated characterising both phases of the heart-rate turbulence (that is initial acceleration and subsequent deceleration) with the aim of obtaining descriptors that were independent each of the other, separated patients who did and did not die during follow-up, and were predictors of mortality independent of age, left-ventricular ejection fraction (LVEF), and other Holter-based risk factors.

The numerical factors characterising the chronotropic response to VPBs were dichotomised into normal and abnormal values. Cut-off points for the dichotomisation were determined by the method of maximising the log-rank test statistic for all possible cut-off values within the 10–90 percentiles of each predictor. The approach is identical to recursive partitioning or the use of classification and regression trees as introduced by Breiman and colleagues¹⁷ and adapted to use for survival data by LeBlanc and Crowley¹⁸ in the context of Cox's proportional-hazards model.¹⁹

In each patient, LVEF was assessed either by radionuclide or contrast radiographic ventriculography (35% and 65% respectively). Other recognised risk factors were obtained from the Holter recordings and included mean heart rate, frequency of ventricular ectopathy, and 24 h heart-rate variability (HRV). HRV was expressed by the so-called HRV triangular index, an established measure of global 24 h HRV that is, compared with other measures, relatively insensitive to the precision with which the Holter tapes are analysed.

Validation sample

The MPIP study⁴ enrolled 715 survivors of acute myocardial infarction (age ≤ 70 years). Of these, 138 patients were excluded from the analysis of the heart-rate turbulence after VPBs because of atrial fibrillation, no VPB during Holter monitoring, missing LVEF, or because of technically insufficient or missing Holter recordings. The remaining 577 patients were used in this study (table 1). The patients were followed up for a median of 22 months. During this period, 75 of the patients died.

The EMIAT trial¹⁵ randomised 743 patients into the placebo

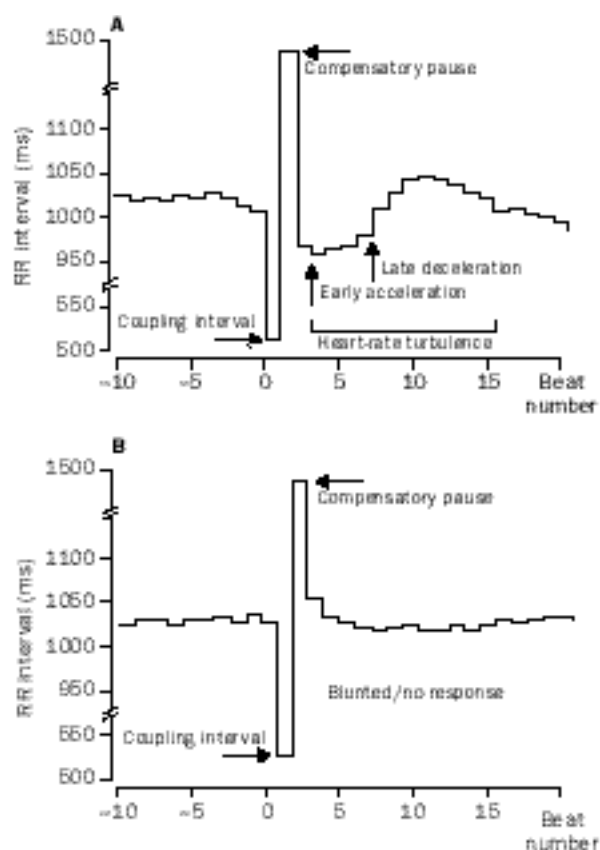


Figure 1: Examples of heart-rate turbulence patterns in two patients from training sample

A: Typical acceleration-deceleration sequence of RR intervals after coupling interval and compensatory pause of a VPB recorded in a 64-year-old woman with anterior myocardial infarction who survived during follow-up. B: Almost random pattern recorded in a 77-year-old man with inferior myocardial infarction who suddenly died 7 months after the index infarction.

group. The patients were survivors of a recent myocardial infarction with LVEF of 40% or less, aged 75 years or younger, free of bradyarrhythmia, and free of contraindications to amiodarone therapy. Of these, 129 patients were excluded from our analyses because of atrial fibrillation, no VPB during Holter monitoring, or because the Holter tape was not available. The remaining 614 patients were studied (table 1). During median follow-up of 21 months, 87 patients died.

In the MPIP population, Holter recordings were done in the second week after the index infarction; in the EMIAT population, the recordings were obtained in the second or third week after the infarction. Initially, the Holter tapes were processed at Columbia University, New York (MPIP data) and by EMIAT investigators. In both populations, a Laser Holter 8000 System (Marquette Medical System, WI, USA) was used to obtain, after visual inspection and manual editing, computer files listing RR interval duration (sampling frequency 128 Hz) and QRS morphological classifications on a beat-to-beat basis.

The RR interval and beat-type files of individual MPIP and EMIAT Holter recordings were transferred to the Technical University of Munich for the computation of characteristics of heart-rate turbulence. The same dichotomies as derived from the training samples were applied without knowledge of patients' characteristics and the results provided to the collaborating centres (Columbia University, New York, for the MPIP data, and St George's Hospital Medical School, London, for the EMIAT data) who did the survival analyses.

To eliminate any possible bias, the centre in Munich has never received individual clinical data (clinical variables and mortality) of the MPIP and EMIAT populations and the collaborating centres were not aware of the principle of the analysis and measurement involved until the statistical analyses

Variable	Training sample			MPIP population			EMIAT population		
	Survived (n=83)	Died (n=17)	p	Survived (n=502)	Died (n=75)	p	Survived (n=527)	Died (n=87)	p
Age (years)	62 (10)	67 (9)	0.03	57 (9)	60 (8)	0.008	60 (9)	63 (8)	0.006
Previous myocardial infarction (%)	24	35	0.2	24	39	0.006	23	39	0.0017
Mean RR interval (ms)	892 (150)	836 (182)	0.16	859 (138)	829 (147)	0.06	839 (134)	764 (143)	<0.0001
HRV index (units)	32.0 (12.8)	25.8 (10.6)	0.08	28.4 (13.4)	21.9 (8.7)	<0.0001	27.1 (10.3)	22.6 (9.6)	<0.0001
Arrhythmia on Holter (%)*				28	47	0.0008	38	60	<0.0001
LVEF (%)	48.6 (13.6)	37.3 (15.1)	0.005	46.7 (14.4)	36.6 (14.6)	<0.0001	30.5 (7.3)	26.5 (7.9)	<0.0001
Turbulence onset (%)	-1.0 (2.4)	0.2 (1.3)	0.003	-1.2 (2.2)	-0.6 (1.6)	0.005	-1.2 (2.4)	0 (1.6)	<0.0001
Turbulence slope (ms per RR interval)	7.6 (6.3)	4.4 (7.0)	0.005	9.0 (10.1)	4.9 (5.4)	<0.0001	6.6 (7.8)	4.7 (9.1)	<0.0001

*Due to inclusion criteria, arrhythmia on Holter was present in every patient of the training sample.

Table 2: Statistical association of risk variables with mortality

were completed.

In both MPIP and EMIAT populations, LVEF was assessed by radionuclide ventriculography,^{4,15} mean heart rate was taken as the mean of all sinus rhythm cycles in the Holter recordings, and HRV triangular index expressing the global 24 h HRV was calculated from the Holter recording by previously described technology.²⁰

For the purpose of multivariate analysis, age (dichotomised at <65 years vs ≥65 years), history of previous myocardial infarction, LVEF (dichotomised at ≥30% vs <30%), arrhythmia sign on Holter (defined as ten or more VPBs per h or at least one non-sustained ventricular tachycardia of three or more beats on the Holter recording), mean heart rate (dichotomised at >75 beats per min vs ≤75 beats per min), and HRV (HRV triangular index dichotomised at >20 vs ≤20 units) were also assessed. Their cut-off points were based on previous risk stratification investigations.^{4,9,15,20}

Statistical analyses

The endpoint of the study was total mortality. Continuous and categorical variables were compared by the Kruskal-Wallis test and the χ² test, respectively. Kaplan-Meier survival functions were calculated to test the association of heart-rate turbulence characteristics with total mortality. The main survival analyses were done with the Cox proportional-hazards model with a stepwise forward procedure.

In MPIP and EMIAT datasets, sensitivity, specificity, and positive and negative predictive accuracy of follow-up mortality prediction were also evaluated for conventional and heart-rate-turbulence-based predictors of mortality (with dichotomies as above).

Results of all survival analyses are presented as relative risks with corresponding 95% CI. A significance level of 0.05 was used for the analyses.

Results

Training sample

Of the number of possibilities tested, two factors were selected to characterise the chronotropic response of sinus rhythm to VPBs. The immediate initial acceleration was quantified by the relative change of RR

intervals immediately after compared with immediately before a VPB and is termed here the turbulence onset. The speed of the subsequent deceleration was quantified by the steepest regression line between the RR interval count and duration. The corresponding factor is termed here the turbulence slope. In precise numerical terms, we used the following formulae:

Turbulence onset is defined as the difference between the mean of the first two sinus RR intervals after a VPB and the last two sinus RR intervals before the VPB divided by the mean of the last two sinus RR intervals before the VPB. In other words:

$$\text{Turbulence onset} = \frac{(RR_i + RR_{i+1}) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})}$$

where RR_i is the i-th sinus rhythm after (i>0) the compensatory pause of the VPB or preceding (i<0) the coupling interval of the VPB. For convenience, the value of turbulence onset is expressed as a percentage. For instance, in figure 1A, the coupling interval of the ectopic is preceded by RR intervals of 1017 ms and 1014 ms and its compensatory pause is followed by RR intervals of 974 ms and 963 ms. Thus, in this case,

$$\text{Turbulence onset} = \frac{(974+963) - (1017+1014)}{(1017+1014)} = -4.6\%$$

These measurements were first performed for each individual singular VPB and then averaged to obtain the value characterising the patient. Positive values of turbulence onset mean sinus rhythm deceleration after a VPB, and negative turbulence onset means sinus rhythm acceleration after a VPB.

Turbulence slope is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after a VPB. The value of

Variable	Training sample		MPIP population				AMIAT population							
	Relative hazard (95% CI)	p	Relative hazard (95% CI)	p	Sen	Spc	Ppa	Npa	Relative hazard (95% CI)	p	Sen	Spc	Ppa	Npa
Age >65 years	3.6 (1.3-9.7)	0.01	1.8 (1.1-3.0)	0.02	29	82	19	89	1.6 (1.1-2.5)	0.02	53	61	18	89
Previous MI	1.8 (0.7-4.9)	0.3	1.9 (1.2-3.0)	0.008	39	76	20	89	1.9 (1.2-2.8)	0.004	39	76	21	88
Mean RR <800 ms	1.9 (0.7-4.9)	0.2	1.5 (0.9-2.3)	0.1	47	63	16	89	2.6 (1.7-4.1)	<0.0001	66	60	21	91
HRV index ≤20 units	3.5 (1.3-9.6)	0.01	2.4 (1.5-3.8)	0.0002	46	76	22	90	2.5 (1.7-3.9)	<0.0001	51	73	24	91
Arrhythmia on Holter			2.2 (1.4-3.5)	0.0008	46	72	20	90	2.2 (1.4-3.4)	0.0003	60	62	20	90
LVEF <30%	5.8 (2.1-15.9)	0.0006	4.0 (2.5-6.4)	<0.0001	43	85	30	91	2.2 (1.4-3.5)	0.0004	66	56	20	91
Turbulence onset ≥0%	4.8 (1.8-13.1)	0.002	2.1 (1.3-3.4)	0.002	42	74	19	90	2.4 (1.5-3.6)	0.0001	45	76	23	89
Turbulence slope ≤2.5 ms per RR interval	7.1 (2.7-18.9)	<0.0001	3.5 (2.2-5.5)	<0.0001	47	81	27	91	2.7 (1.8-4.2)	<0.0001	51	74	25	90
Combined turbulence onset and slope*	7.4 (3.1-17.3)	<0.0001	5.0 (2.8-8.8)	<0.0001	30	91	33	90	4.4 (2.6-7.5)	<0.0001	29	89	31	87

MI=myocardial infarction. *Turbulence onset ≥0 and turbulence slope ≤2.5 per RR interval; Sen=sensitivity, Spc=specificity, Ppa=positive predictive accuracy, Npa=negative predictive accuracy (%).

Table 3: Association of risk variables with total mortality in a univariate analysis

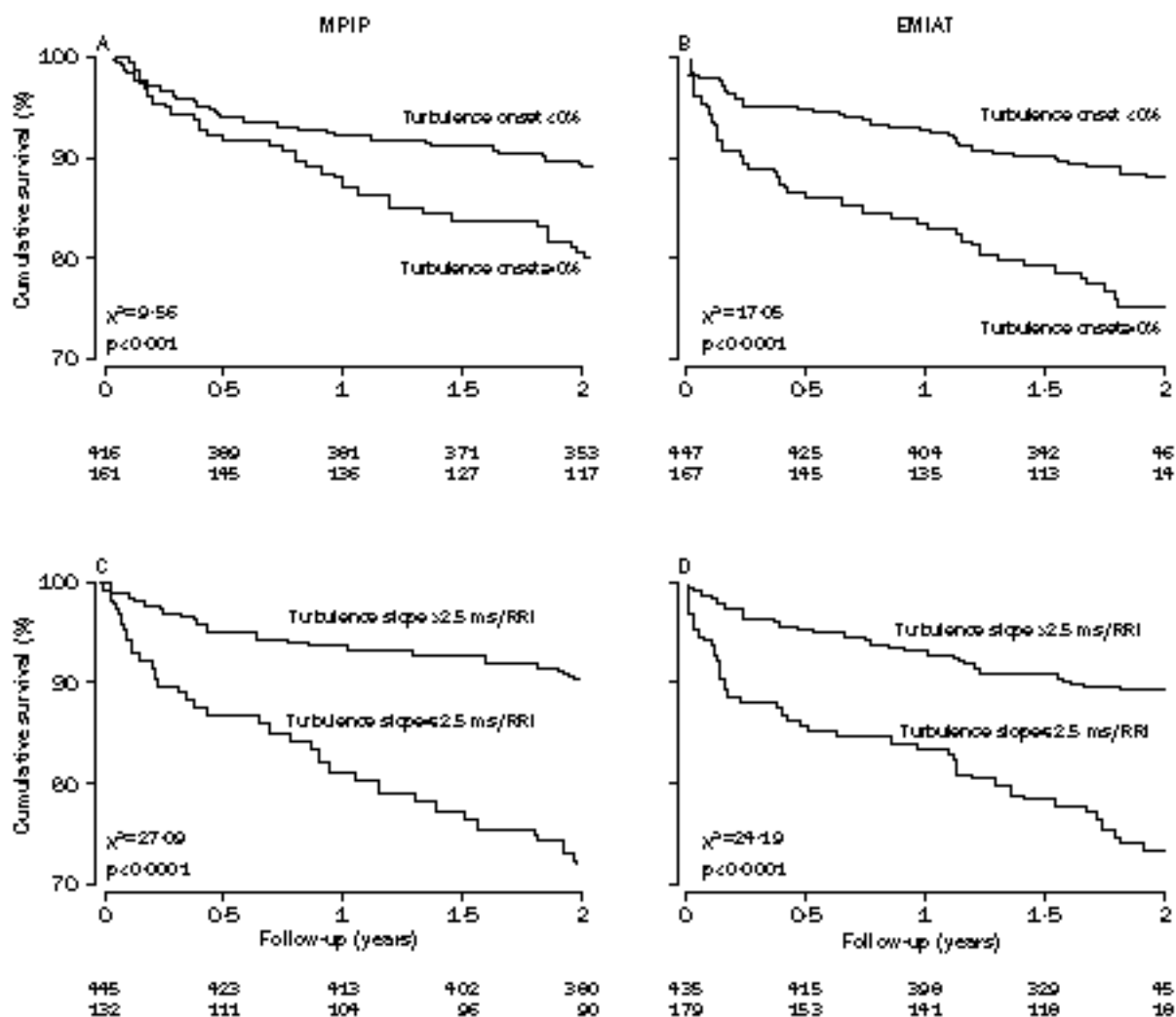


Figure 2: Kaplan-Meier survival curves in MPIP and EMIAT patients stratified to those with turbulence onset <0 and ≥ 0 (A, B) and stratified to those with turbulence slope >2.5 and ≤ 2.5 per RR interval (C, D)

The numbers of patients of the individual groups involved in the analysis at 0, 6, 12, 18, and 24 months are shown under each graph: the top and bottom row corresponds to the upper and bottom survival curve, respectively.

turbulence slope is expressed in ms per RR interval and for each recording, it was obtained from the tachogram $RR_1, RR_2, RR_3, \dots, RR_{20}$, where RR_i is the average of i -th sinus-rhythm RR interval after the compensatory pause of a singular VPB. The log-rank test statistics for all possible cut-off points revealed optimal dichotomies of 0 for turbulence onset and 2.5 ms per RR interval for turbulence slope. In the training sample, there were significant associations of turbulence onset and slope with mortality (tables 2 and 3).

MPIP and EMIAT

In univariate analyses of both MPIP and EMIAT populations, we noted a strong and significant association of turbulence onset and slope with total mortality both when used as continuous variables and when dichotomised at the predefined cut-off points. In MPIP data, the LVEF, HRV triangular index, and turbulence slope provided the most significant difference between numerical values in survivors and non-survivors; in EMIAT data, the differences in numerical values of turbulence slope were most significant (table 2). In EMIAT, the turbulence slope was the strongest univariate mortality predictor; in MPIP, it was the

second strongest univariate mortality predictor after low LVEF (table 3). Simultaneous use of turbulence onset and slope provided highest relative risks in both the MPIP population (5.0 [95% CI 2.8–8.8]) and the EMIAT population (4.4 [2.6–7.5], table 3).

Figure 2 shows Kaplan-Meier cumulative survival curves for turbulence onset and slope in MPIP and EMIAT patients. In the MPIP patients, those with turbulence onset of less than zero had a 2-year mortality of 11% versus 20% in patients with turbulence onset of zero or higher. In the EMIAT patients, the mortality rates were 11% and 24%, respectively. In the MPIP patients, those with turbulence slope greater than 2.5 ms had a 2-year mortality of 9% versus 27% in patients with turbulence slope of 2.5 ms or less. In the EMIAT, these mortalities were 9% and 26%, respectively. The differences in cumulative survival were highly significant.

Figure 3 shows Kaplan-Meier cumulative survival curves for the combinations of turbulence onset and slope in MPIP and EMIAT. In the MPIP population, the 2-year mortality rates were 9%, 15%, and 32% in patients with both factors normal, patients with either factor abnormal, and patients with both factors

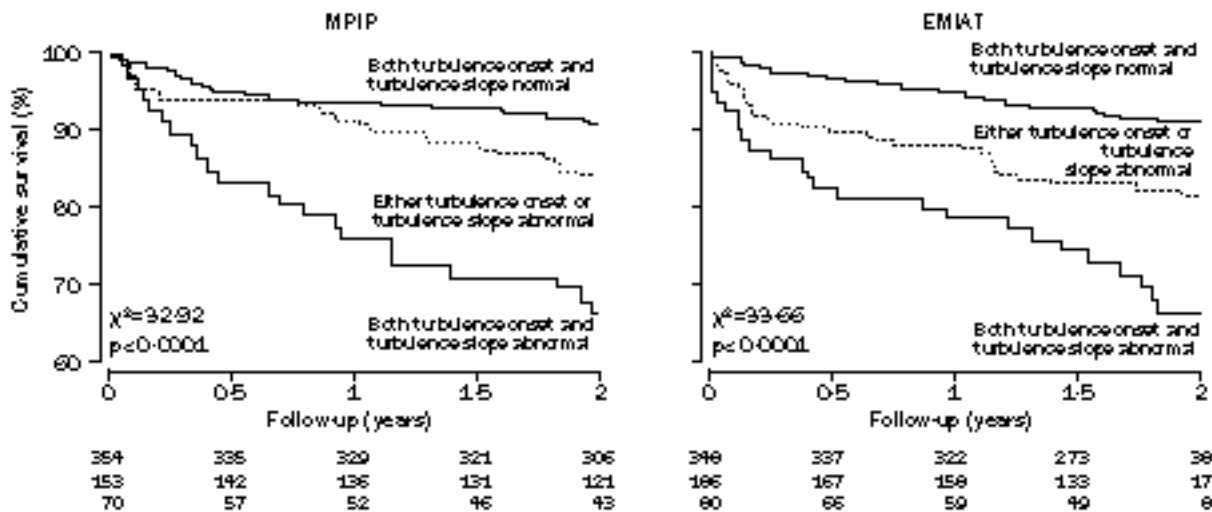


Figure 3: Kaplan-Meier survival curves in MPIP and EMIAT patients stratified to three groups

Turbulence onset <0 and turbulence slope >2.5 ms/RR interval (both factors normal); either turbulence onset ≥0 or turbulence slope ≤2.5 ms/RR interval (one of the factors abnormal); turbulence onset ≥0% and turbulence slope ≤2.5 ms/RR interval (both factors abnormal). The numbers of patients of the individual groups involved in the analysis at 0, 6, 12, 18, and 24 months are shown under each graph: the order of the rows corresponds to the order of the survival curves.

abnormal, respectively. In EMIAT, these figures were 9%, 18%, and 34%, respectively. Again, the differences in cumulative survival were highly significant.

In both MPIP and EMIAT, the combination of turbulence onset greater than zero and turbulence slope of 2.5 ms per RR interval or less yielded a positive predictive accuracy (33% and 31%, respectively), that was higher than the positive predictive accuracy of any conventional predictor while maintaining the same level of negative predictive accuracy around 90% (table 3).

Table 4 presents the results of the stepwise, multivariate, Cox regression analysis with turbulence onset and slope as separate variables. In the MPIP population, LVEF and turbulence slope were the only independent variables (p<0.001) and their relative hazards were almost identical (3.0 and 2.5). In EMIAT, five variables were independent predictors of mortality, namely turbulence onset and slope, history of previous myocardial infarction, LVEF, and mean heart rate.

Table 5 presents the results of the stepwise, multivariate, Cox-regression analysis on a combination of turbulence onset and slope. In both MPIP and EMIAT populations, the combination of abnormal turbulence onset (≥0) and an abnormal turbulence slope (≤2.5 ms per RR interval) was the strongest mortality predictor. In the MPIP population, LVEF and the combination of turbulence onset and slope were the only independent mortality predictors (p<0.001 and

p<0.0001, respectively). The relative hazard for LVEF (≥30% vs <30%) was 2.9; the relative hazard of the turbulence onset/slope combination (slope >2.5 and onset <0% vs slope ≤2.5 and onset ≥0) was 3.2. In EMIAT, four variables were independent predictors: the strongest predictor was the combination of turbulence onset and slope with a relative hazard of 3.2, while the other significant predictors were history of previous myocardial infarction, LVEF, and mean heart rate with relative hazards between 1.7 and 1.8. Patients with abnormal turbulence onset and abnormal turbulence slope are not infrequent; in the MPIP and EMIAT population, there were 70 (12.1%) and 80 (13.0%) such patients, respectively.

Discussion

The results of this study clearly show that heart-rate turbulence (ie, the acceleration and subsequent deceleration of sinus rhythm after a singular VPB) is a consistent phenomenon in low-risk patients with ischaemic heart disease. The absence of this phenomenon indicates a significantly increased risk of subsequent mortality. The two measures for quantifying heart-rate turbulence were developed in one population of patients with ischaemic heart disease, and prospectively tested with masking in two large and independent populations taken from multicentre postinfarction trials MPIP and EMIAT. Therefore, we believe that our analysis proves the clinical relevance of

	MPIP population		EMIAT population	
	Relative hazard (95% CI)	p	Relative hazard (95% CI)	p
Age ≥65 years
Previous myocardial infarction	1.8 (1.2-2.7)	0.01
Mean RR <800 ms	1.8 (1.1-2.9)	0.01
HRV index ≤20 units
Arrhythmia on Holter
LVEF <30%	3.0 (1.8-5.0)	<0.0001	1.7 (1.1-2.7)	0.03
Turbulence onset ≥0%	1.9 (1.2-2.9)	0.005
Turbulence slope <2.5 ms per RR interval	2.5 (1.5-4.1)	0.0002	1.7 (1.1-2.7)	0.02

Table 4: Relative hazards of significant and independent risk variables in a multivariate analysis

	MPIP population		EMIAT population	
	Relative hazard (95% CI)	p	Relative hazard (95% CI)	p
Age ≥65 years
Previous myocardial infarction	1.8 (1.2-2.7)	0.01
Mean RR <800 ms	1.8 (1.1-2.9)	0.01
HRV index ≤20 units
Arrhythmia on Holter
LVEF <30%	2.9 (1.8-4.9)	0.0001	1.7 (1.1-2.7)	0.03
Combined use of turbulence onset and slope	3.2 (1.7-6.0)	0.0002	3.2 (1.8-5.6)	<0.0001

Table 5: Relative hazards of individual variables in a multivariate analysis involving combination of turbulence onset and slope

the new phenomenon. Because of the treatment practice changes, more patients in EMIAT than in MPIP received thrombolysis β -blockers, and inhibitors of angiotensin-converting enzyme (ACE). These differences show that our finding is independent of modern management of postinfarction patients. The MPIP population was also an unselected population of postinfarction patients, whereas only patients with low LVEF were enrolled in the EMIAT trial. Consequently, the numbers of VPBs differed in these populations, but our results were not affected.

Turbulence onset and slope are both predictors of mortality containing information additional to each other and to other established risk factors. The combination of turbulence onset and slope was a very strong risk predictor in patients of the MPIP trial and of the placebo group of EMIAT, even when adjusted for other established mortality predictors, such as LVEF, arrhythmia count, heart-rate variability, mean heart rate, and history of previous myocardial infarction. Turbulence onset and slope in combination was by far the strongest Holter-based risk predictor.

It has long been known that a ventricular systole can influence the rate of sinus nodal discharge, even in the absence of retrograde atrioventricular conduction. As early as 1909, first observations of the so-called ventriculophasic sinus arrhythmia were made in experimental atrioventricular block.²¹ The first clinical description was made in 1914 by Hecht,²² who observed ventriculophasic sinus arrhythmia in a child with Adams-Stokes syndrome. Later on, ventriculophasic arrhythmia was observed in patients with ventricular-inhibited pacing.²³ To our knowledge, however, only one case report exists on ventriculophasic sinus arrhythmia triggered by VPBs.²⁴

Various pathophysiological mechanisms have been discussed to explain the ventriculophasic mechanisms, including changes in autonomic tone,^{12-14,25,26} traction on the atrium as well as atrial appendages, atrioventricular junction, and the sinus nodal region,^{12,23,27,28} and transient improvement of the blood supply to the sinus node.^{12,29,30} Some authors even speculated that the character of ventriculophasic phenomena will eventually gain an important clinical role.¹³

Although it is plausible to expect the cardiac autonomic status to influence heart-rate turbulence, it is also plausible to expect the physiological background of the turbulence to be different from that of heart-rate variability, which reflects, partly, the modulations of the cardiac autonomic status. Long-term, such as 24 h, heart-rate variability probably mostly reflects autonomic responses to environmental and external stimuli that activate a broad variety of physiological reflexes. By contrast heart-rate turbulence is a phenomenon triggered by a minimum endogenous stimulus to which the reflex responses are possibly more organised and systematic. This might also be the explanation why the risk-predictive power of heart-rate turbulence appears to be superior to that of heart-rate variability.

The mechanisms linking the absence of heart-rate turbulence to mortality are not obvious. Probably, the turbulence onset and slope assessment reflects specific aspects of cardiac autonomic status. The preserved vagal tone is known to be antiarrhythmic^{31,32} and probably constitutes autonomic antiarrhythmic protection. Thus, by measurement of the heart-rate turbulence, a direct

manifestation of this protection may be captured when responding to a potentially proarrhythmic VPB. If the erratic or absent response to VPBs in patients with high values of turbulence onset and low values of turbulence slope is a manifestation of lost antiarrhythmic protection, the chronotropic response to VPBs might be the mechanistic link between impaired autonomic balance and cardiac mortality.

The limitations of our approach have to be recognised. We have merely taken measures averaged over 24 h and not investigated the spontaneous variability of the chronotropic response. We have not made any detailed distinction between VPBs with and without retrograde conduction but, judging from the compensatory pauses with both present and absent heart-rate turbulence (figure 1), the phenomenon we describe is unlikely to be related solely to such a distinction. We have not investigated the effect of therapy on heart-rate turbulence, especially the effects of thrombolytic therapy, β -blockade, an ACE inhibition, which are currently frequent in patients surviving acute myocardial infarction. However, the observations made in the data of the MPIP study in which these therapeutic interventions were not used indicate that our observations are not merely a by-product of modern therapeutic interventions. Our method is clearly inapplicable to patients without any VPBs but, as such patients are generally at low risk, this limitation is of no practical consequence. We also do not know whether the response to several VPBs needs to be averaged, as was the case in this study, to obtain a sensible measure of heart-rate turbulence. Although the averaging process in recordings with multiple VPBs helps to overcome the difficulties with precision of RR-interval measurement, the assessment of turbulence onset and slope depends on the sampling frequency of long-term ECGs. Still, our results show that even the contemporary precision of Holter reading is sufficient for assessment of turbulence onset and slope, possibly because the precision issue concerns mainly patients with very few VPBs who are known to be at low risk.

Despite the limitations of our approach, the masked tests of this study prove clearly that the absence of the characteristic heart-rate patterns after VPBs is a very potent postinfarction risk stratifier that is independent of other known risk factors and is stronger than other presently available factors.

Contributors

G Schmidt did the conceptual design of heart-rate turbulence, designed the investigations of this study, supervised the testing sample and data analyses. M Malik designed the investigations of this study, had responsibility for the evaluation of the EMIAT data, data exchange between the centres, and supervision of the text of the manuscript. P Barthel and R Schneider did the computer implementation and maintenance of the heart-rate technology. K Ulm did statistical analyses. L Rolnitzky and J T Bigger had responsibility for the MPIP trial data and their evaluations. A J Camm had responsibility for the EMIAT data. A Schomig supervised the study overall.

Acknowledgments

This study was supported in part by grants from the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (13N7073/7, to G Schmidt), and the Bund der Freunde der Technischen Universität München (to G Schmidt).

References

- 1 Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia: Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**: 1933-40.

- 2 Guidelines for risk stratification after myocardial infarction. *Ann Intern Med* 1997; **126**: 556–60.
- 3 Sanz G, Castaner A, Betriu A, et al. Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. *N Engl J Med* 1982; **306**: 1065–70.
- 4 Multicenter Postinfarctions Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983; **309**: 331–36.
- 5 Bigger JJ, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984; **69**: 250–58.
- 6 Moss AJ, DeCamilla JJ, Davis HP, Bayer L. Clinical significance of ventricular ectopic beats in the early posthospital phase of myocardial infarction. *Am J Cardiol* 1977; **39**: 635–40.
- 7 Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 1981; **64**: 235–42.
- 8 Kleiger RE, Miller JP, Bigger JJ, Moss AJ. Decreased heart rate variability and its association with increase mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**: 256–62.
- 9 Copie X, Hnatkova K, Staunton A, Fei L, Camm AJ, Malik M. Predictive power of increased heart rate versus depressed left ventricular ejection fraction and heart rate variability for risk stratification after myocardial infarction: results of a two-year follow-up study. *J Am Coll Cardiol* 1996; **27**: 270–76.
- 10 Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991; **68**: 434–39.
- 11 Redwood SR, Odemuyiwa O, Hnatkova K, et al. Selection of dichotomy limits for multifactorial prediction of arrhythmic events and mortality in survivors of acute myocardial infarction. *Eur Heart J* 1997; **18**: 1278–87.
- 12 Parsonnet AE, Miller R. Heart block. The influence of ventricular systole upon the auricular rhythm in complete and incomplete heart block. *Am Heart J* 1944; **27**: 676–87.
- 13 Jedlicka J, Martin P. Time course of vagal effects studies in clinical electrocardiograms. *Eur Heart J* 1987; **8**: 762–72.
- 14 Skanes AC, Tang ASL. Ventriculophasic modulation of atrioventricular nodal conduction in humans. *Circulation* 1998; **97**: 2245–51.
- 15 Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997; **349**: 667–74.
- 16 Schmidt G, Morfill GE, Barthel P, et al. Variability of ventricular premature complexes and mortality risk. *Pacing Clin Electrophysiol* 1996; **19**: 976–80.
- 17 Breimann L, Friedman JH, Ohlsen RA, Stone CJ. Classification and regression trees (CART). Belmont, CA: Wadsworth International Group, 1984.
- 18 LeBlanc M, Crowley J. Relative risk trees for censored survival data. *Biometrics* 1993; **48**: 411–25.
- 19 Cox DR. Regression models and life-tables. *J R Stat Soc* 1972; **34**: 187–220.
- 20 Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; **93**: 1043–65.
- 21 Erlanger J, Blackman JR. Further studies in the physiology of heart block in mammals: chronic auriculo-ventricular heart-block in the dog. *Heart* 1909; **1**: 177.
- 22 Hecht AF. Das Morgani-Adams-Stokes Syndrome im Kindesalter und seine Behandlung. *Wien med Wch schr* 1914; **64**: 178.
- 23 Chung EK, Jewson DV. Ventriculophasic sinus arrhythmia in the presence of artificial pacemaker induced ventricular rhythm. *Cardiology* 1970; **55**: 65–68.
- 24 Döhlemann C, Murawski P, Theissen K, Haider M, Forster C, Poppl SJ. Ventriculophasische Sinusarrhythmie bei ventrikulärer Extrasystolie. *Z Kardiol* 1979; **68**: 557–65.
- 25 Roth IR, Kirsch B. The mechanism of irregular sinus rhythm in auriculoventricular heart block. *Am Heart J* 1948; **36**: 257–76.
- 26 Rosenbaum M, Lepeschkin E. The effect of ventricular systole on auricular rhythm in auriculoventricular block. *Circulation* 1955; **11**: 240–61.
- 27 Kappagoda CT, Linden RJ, Saunders DA. The effect on heart rate of distending the atrial appendages in the dog. *J Physiol Lond* 1972; **225**: 705–19.
- 28 Kappagoda CT, Linden RJ, Snow HM. A reflex increase in heart rate from distension of the junction between the superior vena cava and the right atrium. *J Physiol Lond* 1972; **220**: 177–97.
- 29 Wenckebach KF, Winterberg H. Die unregelmäßige Herztätigkeit. 1 edn. Leipzig: Verlag von Wilhelm Engelmann, 1927.
- 30 Hashimoto K, Tanaka S, Hirata M, Chiba S. Responses of the sinoatrial node to change in pressure in the sinus node artery. *Circ Res* 1967; **21**: 297–304.
- 31 Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med* 1976; **294**: 1165–70.
- 32 Corr PB, Yamada KA, Witkowski FX. Mechanisms controlling cardiac autonomic function and their relation to arrhythmogenesis. In: Fozzard HA, Haber E, Jennings RB, Katz AN, Morgan HE, eds. The heart and cardiovascular system. New York: Raven Press, 1986: 1343–403.