Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study

Axel Bauer, Jan W Kantelhardt, Petra Barthel, Raphael Schneider, Timo Mäkikallio, Kurt Ulm, Katerina Hnatkova, Albert Schömig, Heikki Huikuri, Armin Bunde, Marek Malik, Georg Schmidt

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Deutsches Herzzentrum München (A Bauer MD, P Barthel MD, Prof A Schömig MD), **Erste Medizinische Klinik** (R Schneider Dipl Ing, Prof G Schmidt MD), **Institut für Statistik und Epidemiologie** (Prof K Ulm PhD), **Klinikum rechts der Isar, Technische Universität München, Germany; Institut für Theoretische Physik III, Justus-Liebig-Universität Giessen, Germany** (Prof A Bunde PhD); **Fachbereich Physik, Martin-Luther Universität Halle, Germany** (J W Kantelhardt PhD); **Department of Medicine, University of Oulu, Finland** (T Mäkikallio MD, Prof H Huikuri MD); **and Cardiac and Vascular Sciences, St George's, University of London, UK** (H Hnatkova PhD, Prof M Malik MD)

Correspondence to:
Prof Georg Schmidt
gschmidt@tum.de

Summary

Background **Decreased vagal activity after myocardial infarction results in reduced heart-rate variability and increased risk of death. To distinguish between vagal and sympathetic factors that affect heart-rate variability, we used a signal-processing algorithm to separately characterise deceleration and acceleration of heart rate. We postulated that diminished deceleration-related modulation of heart rate is an important prognostic marker. Our prospective hypotheses were that deceleration capacity is a better predictor of risk than left-ventricular ejection fraction (LVEF) and standard deviation of normal-to-normal intervals (SDNN).**

Methods **We quantified heart rate deceleration capacity by assessing 24-h Holter recordings from a post-infarction cohort in Munich (n=1455). We blindly validated the prognostic power of deceleration capacity in post-infarction populations in London, UK (n=656), and Oulu, Finland (n=600). We tested our hypotheses by assessment of the area under the receiver-operator characteristics curve (AUC).**

Findings **During a median follow-up of 24 months, 70 people died in the Munich cohort and 66 in the London cohort. The Oulu cohort was followed-up for 38 months and 77 people died. In the London cohort, mean AUC of deceleration capacity was 0·80 (SD 0·03) compared with 0·67 (0·04) for LVEF and 0·69 (0·04) for SDNN. In the Oulu cohort, mean AUC of deceleration capacity was 0·74 (0·03) compared with 0·60 (0·04) for LVEF and 0·64 (0·03) for SDNN (p<0·0001 for all comparisons). Stratification by dichotomised deceleration capacity was especially powerful in patients with preserved LVEF (p<0·0001 in all cohorts).**

Interpretation **Impaired heart rate deceleration capacity is a powerful predictor of mortality after myocardial infarction and is more accurate than LVEF and the conventional measures of heart-rate variability.**

Introduction

Results of randomised trials[1,2] indicate that, in high-risk survivors of myocardial infarction, mortality can be greatly reduced by implantation of a cardioverter defibrillator. Extent of impairment of left-ventricular ejection fraction (LVEF) is generally used to predict risk.[3] However, in unselected post-infarction populations undergoing modern treatment, particularly treatment involving acute revascularisation procedures,[4] most deaths arise in patients with preserved LVEF. An alternative, more accurate method of risk prediction is, therefore, needed. One approach might be to measure LVEF—ie, a marker of myocardial viability—and a marker of cardiac autonomic responsiveness,[5] such as heart-rate variability. However, although there is evidence that decreased heart-rate variability is associated with a poor prognosis, the clinical usefulness of established measures is low.[5]

Heart-rate variability is affected by both vagal and sympathetic modulation of the sinus node. Evidence from experimental and clinical studies[6–8] indicates that a fall in vagal activity increases the risk of death. However, overall measures of heart-rate variability, such as the standard deviation of all normal-to-normal intervals (SDNN), do not distinguish between vagal and sympathetic effects.[9] Without directly recording neural activity, which is impractical in a clinical setting, exact assessment of the effect of these separate limbs of the autonomic nervous system is not possible. However, an approximate distinction of the effects might be made possible by separate assessment of deceleration-related and acceleration-related heart-rate variability.

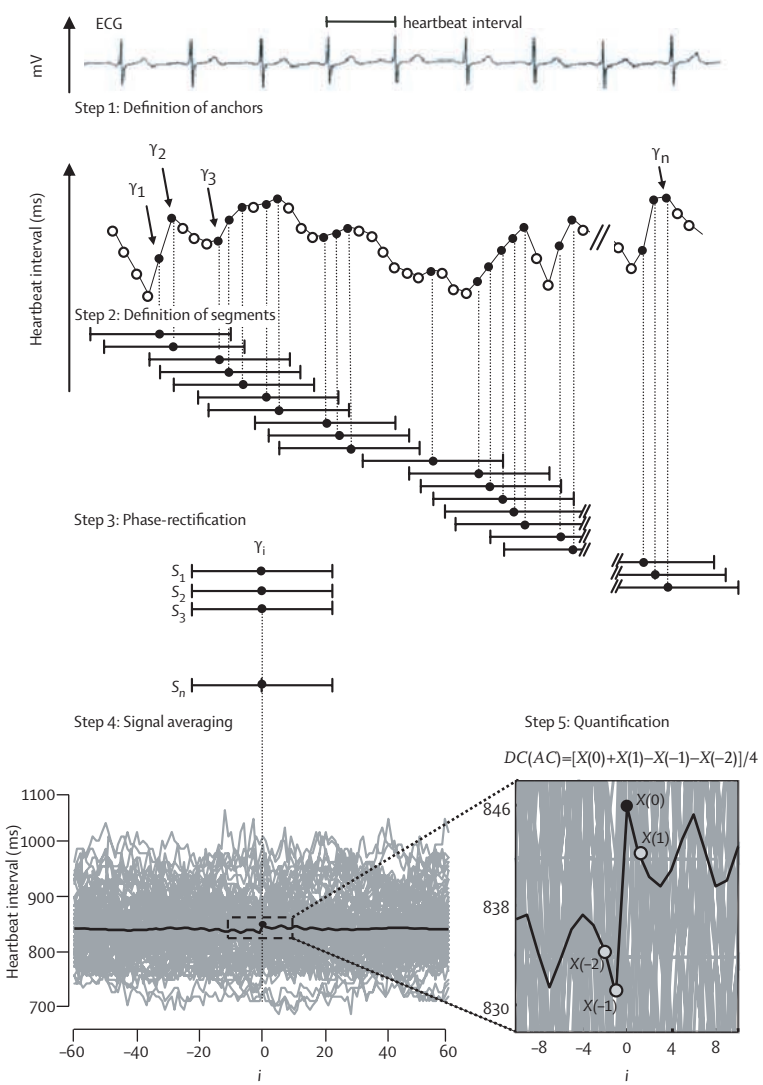
We propose a way to analyse heart-rate variability and use it to try to characterise rhythm modulations associated separately with deceleration and acceleration. We postulate that extent of deceleration-related heart-rate variability is, in terms of post-infarction risk prediction, better than the acceleration-related heart-rate variability, the established global heart-rate variability indices, and LVEF.

Methods

Participants

We derived our hypothesis from a set of patients who had had an acute myocardial infarction and were treated at the German Heart Centre or the Klinikum rechts der Isar, Munich, Germany.[4] We blindly validated the hypothesis in two independent post-infarction populations. The first was enrolled at St George's Hospital, London, UK,[10,11] and the second comprised survivors of acute myocardial infarction who participated in the prospective Multiple Risk Factor Analysis Trial (MRFAT) set in Oulu, Finland.[12]

Inclusion criteria for all patients were diagnosis of acute infarction, age 75 years or younger, and sinus rhythm. In every cohort, acute myocardial infarction was defined by



Step 1: Definition of anchors
For computation of deceleration capacity (DC), heartbeat intervals longer than the preceding interval are identified as anchors (black circles in figure; $\gamma_1, \gamma_2, \gamma_3, \ldots \gamma_n$). For computation of acceleration capacity (AC), heartbeat intervals shorter than the preceding interval are identified as anchors (white circles in figure). About 45 000 of 100 000 RR intervals become anchors in a typical 24-h Holter recording. To suppress errors due to artifacts, RR interval prolongations (or shortenings for AC computation) of more than 5% are excluded.

Step 2: Definition of segments ($S_1, S_2, S_3, \ldots S_n$)
Segments of interval data around the anchors (bars in figure) are selected. All segments have the same size (chosen according to the lowest frequency to be visualised[13]). Segments that surround adjacent anchors can overlap. For the sake of clarity, segments are truncated at 12 heartbeat intervals in this figure.

Step 3: Phase rectification
Segments are aligned at the anchors.

Step 4: Signal averaging
The PRSA signal *X(i)* is obtained by averaging the signals within the aligned segments—ie, *X*(0) is the average of the RR intervals at all anchors (grey lines), *X*(1) and *X*(–1) are the averages of the RR intervals (black line) immediately following and preceding the anchors, etc.

Step 5: Quantification of DC or AC
$DC\ (AC)=[X(0)+X(1)-X(-1)-X(-2)]/4$
Technically,[13] this method of quantification corresponds to a quantification of *X* by Haar wavelet analysis, where the scale of 2 is used. Although the technique for obtaining the PRSA curve requires computer processing of the heart period sequence, the curve itself can easily be interpreted visually. The centre deflection of the curve characterises the average capacity of the heart to decelerate the cardiac rhythm from one beat to the next. Distinction between deceleration-related and acceleration-related heart-rate variations constitutes the main advantage of PRSA over standard approaches used to measure heart-rate variability. Black circle=average of anchors—*X*(0). Grey circles=averages of adjacent intervals.

Figure 1: **Assessment of deceleration capacity by PRSA in a 24-h recording of heartbeat intervals**
i=index of PRSA signal X(*i*).

use of contemporary guidelines at the beginning of data collection.[4,10–12]

All three local ethics committees approved the collection of data and analysis of Holter recordings. Since the data obtained were non-invasive and did not exceed usual clinical management of the patients, the local ethics committees decided that signed informed consent was not needed. However, we did obtain oral informed consent.

Procedures

We recorded the median of the 24-h Holter recordings of individuals in all cohorts in the second week after index infarction (Munich 7–14 days, Oulu 5–14 days, London 5–11 days). The recordings were digitised at 128 Hz, automatically processed with an Oxford Excel Holter system (Oxford Instruments, Abingdon, UK; Munich, Oulu), a Pathfinder 700 system (Reynolds Medical, Hertford, UK; Munich), and a Marquette Holter 8000 scanner (Marquette Electronics, Milwaukee, USA; London). We visually verified and manually checked QRS classifications (normal, ventricular ectopic, and supraventricular ectopic) and corrected them if necessary.

We used a signal processing technique of phase-rectified signal averaging (PRSA)[13] to process sequences of RR intervals obtained from pre-discharge Holter

recordings. The technique provides separate characterisations of deceleration-related and acceleration-related modulations, quantified by deceleration capacity and acceleration capacity. We transferred the data of RR intervals and QRS beat types of individual patients from the London and Oulu cohorts to the centre in Munich for computation of deceleration. To eliminate possible bias, the centre in Munich did not receive individual clinical data (clinical variables or mortality) of the London and Oulu cohorts. The centres in London and Oulu were not aware of the PRSA quantification until all statistical analyses were complete.

PRSA extracts periodicities from complex time series that might include non-stationarities, noise, and artefacts, as well as periodic components. Non-periodic components are eliminated. Figure 1 shows the computation of PRSA in a 24-h recording of heart-beat intervals; the five steps of PRSA are briefly outlined (see also webpresentation).[13] Because non-periodic components are eliminated, the PRSA computation is robust against artefacts and ectopic beats, and no extensive editing of Holter recordings is required.

See Online for webpresentation

As well as PRSA, we assessed other risk predictors. In the Munich cohort we assessed LVEF by left ventriculography (n=1274) and by single-plane echocardiography (n=181), in the London cohort we used left ventriculography (n=367) and radionuclide ventriculography (n=289), and in the Oulu cohort we used single-plane echocardiography (all patients). We assessed LVEF 3–7 days after the index infarction in Finland, and after 5–10 days in the UK and 7–14 days in Germany. As proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology,[9] we calculated the following conventional risk predictors of heart-rate variability from the 24-h Holter recordings: mean heart rate, SDNN, heart-rate variability index, square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals, and the standard deviation of the average normal-to-normal interval for all 5-min segments. Other risk predictors included age, history of myocardial infarction, presence of diabetes mellitus, mean heart rate, and signs of arrhythmia on Holter recording. We prospectively defined cut-off points, which were identical to those used in our previous study:[4] age younger than 65 years versus 65 years or older; LVEF of 30% or less versus more than 30%, mean heart rate of 75 bpm or less versus more than 75 bpm; SDNN of 70 ms or less versus more than 70 ms; less than ten single ventricular premature complexes per h versus ten or more; and no episodes of non-sustained ventricular tachycardia in 24 h versus one or more. We used the latter two variables to form two arrhythmia categories: negative (less than ten single ventricular premature complexes per h and no non-sustained ventricular tachycardia) and positive (ten or more single ventricular premature complexes per h or one or more non-sustained ventricular tachycardia in 24 h).

Our primary endpoint was total mortality.

	Munich (n=1455)	London (n=656)	Oulu (n=600)
Study characteristics			
Follow-up (months), median (IQR)	24 (24–24)	24 (24–24)	38 (28–50)
Deaths	70 (5%)	66 (10%)	77 (13%)
Patients' characteristics			
Age (years), median (IQR)	59 (51–67)	57 (52–64)	64 (55–70)
Women	300 (21%)	126 (19%)	145 (24%)
Diabetes mellitus	242 (17%)	94 (14%)	131 (22%)
History of myocardial infarction	209 (14%)	117 (18%)	133 (22%)
LVEF (%), median (IQR)	56 (46–63)	47 (36–57)	48 (39–48)
Treatment			
β blockers	1357 (93%)	344 (52%)	584 (97%)
Angiotensin converting enzyme inhibitors	1304 (90%)	149 (23%)	239 (40%)
Aspirin	1439 (99%)	440 (67%)	518 (86%)
Thrombolysis	87 (6%)	386 (59%)	285 (48%)
Percutaneous coronary intervention	1314 (90%)	0	141 (24%)

Data are number (%) unless otherwise stated

Table 1: **Study and patients' characteristics and treatment, by cohort**

Statistical analyses

We calculated receiver-operator characteristic (ROC) curves for deceleration capacity, acceleration capacity, conventional risk indices of heart-rate variability, LVEF, and for their combinations. We quantified ROC curves by the integrals of the curves (area under the curve; AUC), plotting the dependency of specificity on sensitivity.[14] The AUC of a risk variable was prospectively defined as the statistical measure of the prognostic power of the variable. The technique for computation of ROC curves for pairs of risk variables has been described elsewhere.[15] To test the difference between two ROC curves, we used bootstrapping,[16] based on the creation of pseudoreplicate datasets by random resampling of the dataset N times for error estimation (N=1000 in this study). We tested differences between AUC values with non-parametric tests and judged a p value of less than 0·05 significant. We undertook non-parametric comparison of continuous variables with the Mann-Whitney U test.

We used the Munich cohort to define high-risk and low-risk patients. First, we identified cut-off values of deceleration capacity by searching for the maximum log-rank statistics. We used the Cox proportional hazard model to identify independent mortality predictors. We prospectively tested our definitions of low-risk and high-risk populations in the London and Oulu cohorts. We estimated survival curves by the Kaplan-Meier method and compared them with the log-rank test. Two-tailed Fisher exact test was used to compare sensitivities (proportion between true positive and false negative) and positive predictive accuracies (proportion between true positive and false positive) in different selections of high-risk groups.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Table 1 shows the patients' characteristics. In the Munich (n=1455) and London (n=656) cohorts, during a median follow-up of 24 months, 70 and 66 patients died from all causes, respectively. 77 patients died over a median of 38 months in the Oulu cohort (n=600).

Figure 2, A, shows the deceleration-related PRSA signal of a 24-h recording of heartbeat intervals in a patient who had a myocardial infarction and survived the follow-up period. In his case, the PRSA signal contains two periodicities with wavelengths of about 5 and 40 heartbeat intervals, respectively. At the anchor (*i*=0), all oscillations are in phase and their amplitudes compound to each other. Thus, deceleration capacity is an integral measure of all periodic deceleration-related oscillations noted over 24 h. Panel B of figure 2 shows the acceleration-related PRSA from the same patient. Acceleration capacity is an integral measure of all periodic acceleration-related oscillations. In this patient, deceleration capacity and acceleration capacity correspond in size. Panels C and D of figure 2 show the PRSA signals of a patient who died during follow-up. Both, deceleration capacity and acceleration capacity are substantially smaller than in the patient shown in panels A and B. Panels E and F show the PRSA signals of another patient who died during follow-up. In this case, deceleration-related and acceleration-related PRSA signals are asymmetric, with deceleration capacity being substantially smaller than acceleration capacity. We noted this pattern in about 15% of patients.

In the Munich cohort, we noted that low values of deceleration capacity were more strongly associated with mortality than low values of acceleration capacity. In patients who survived follow-up, mean deceleration capacity was 5·9 ms, whereas in those who died it was 2·8 ms (p<0·0001, table 2). For acceleration capacity, these figures were –8·0 ms and –7·4 ms, respectively (p=0·0005, table 2). Figure 3 shows the ROC curves for deceleration capacity, acceleration capacity, LVEF, and SDNN, which was the strongest conventional risk predictor of heart-rate variability in the Munich cohort. AUC of deceleration capacity (mean 0·77 [SD 0·03]) was significantly larger than that of LVEF (0·70 [0·03], p<0·0001) and of SDNN (0·68 [0·03], p<0·0001). Acceleration capacity yielded the lowest AUC (0·61 [0·04], p<0·0001). Based on these observations, we postulated that deceleration capacity yields a significantly larger AUC than LVEF (primary hypothesis) and SDNN (secondary hypothesis).

Our prospective hypotheses were consistently confirmed in both validation samples. In the London cohort, mean deceleration capacity was 5·9 ms in patients who survived follow-up and 3·3 ms in those who died (p<0·0001, table 2). In the Oulu cohort, these figures were 5·3 ms and 3·4 ms, respectively (p<0·0001, table 2). In the London and Oulu cohort, deceleration capacity provided significantly larger AUCs than LVEF and SDNN (table 3, figure 3). As well as providing proof for our prospective hypotheses, our data indicate that the predictive power of deceleration capacity alone is significantly better than that of the combination of SDNN and LVEF (table 3). The combination of deceleration

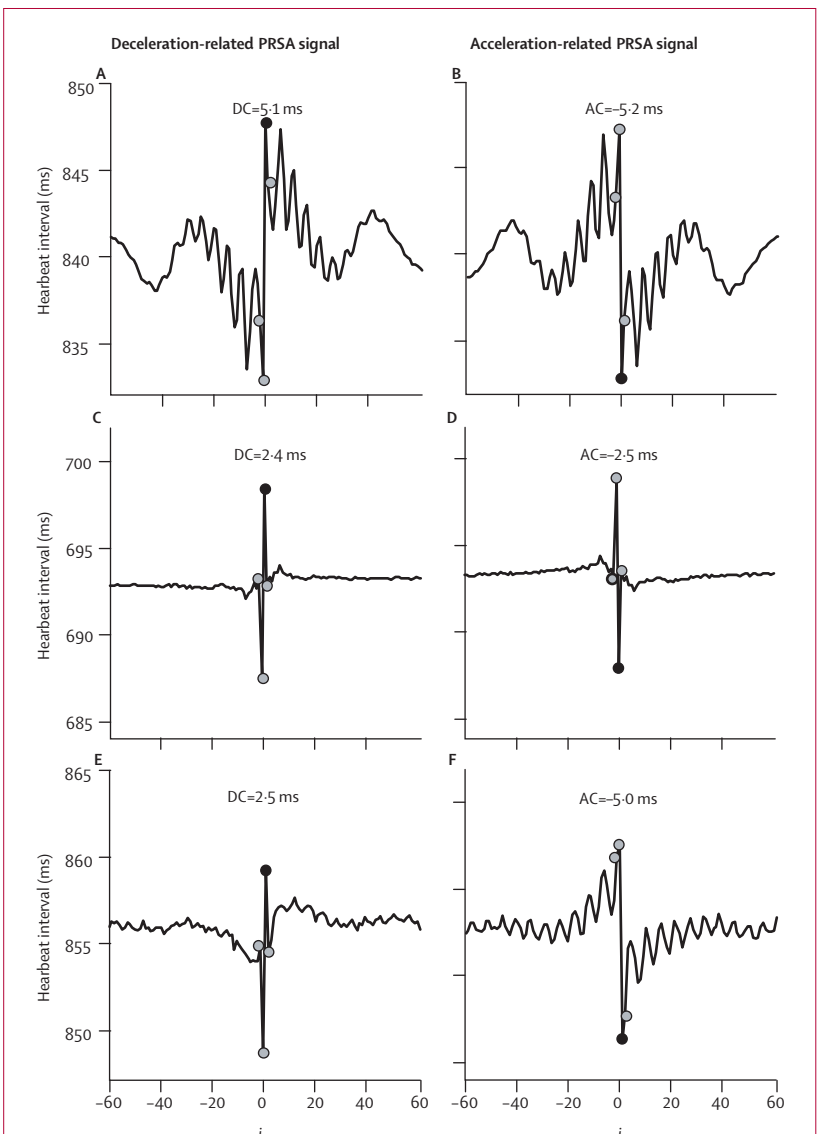


Figure 2: **Representative PRSA signals of 24-h recordings of heartbeat intervals in one patient who survived myocardial infarction for more than 2 years (A and B) and in two patients who died 3 months and 5 months after index infarction, respectively (C–F)**
i=index of PRSA signal *X*(*i*). Panels A, C, and E: deceleration-related PRSA signals (anchors defined as heartbeat prolongations). Panels B, D, and F: acceleration-related PRSA signals (anchors defined as heartbeat shortenings). Circles=values of PRSA signal used for computation of deceleration capacity (DC) and acceleration capacity (AC), respectively (see figure 1 step 5).

	Munich			London			Oulu		
	Survivors (n=1385)	Non-survivors (n=70)	p	Survivors (n=590)	Non-survivors (n=66)	p	Survivors (n=523)	Non-survivors (n=77)	p
DC (ms)	5·9 (4·0)	2·8 (4·6)	<0·0001	5·9 (2·9)	3·3 (3·1)	<0·0001	5·3 (2·6)	3·4 (2·3)	<0·0001
AC (ms)	−8·0 (4·5)	−7·4 (6·1)	0·0005	..	..	..	..	..	..
LVEF (%)	54·7 (12·5)	43·5 (16·0)	<0·0001	48·1 (14·2)	38·8 (18·1)	<0·0001	45·9 (8·8)	41·1 (11·0)	0·0002
SDNN (ms)	100 (16)	78 (32)	<0·0001	95 (35)	77 (44)	<0·0001	99 (32)	83 (27)	0·0001

Data are mean (SD) unless otherwise stated. AC=acceleration capacity. DC=deceleration capacity.

Table 2: **Statistical association of risk variables with mortality**

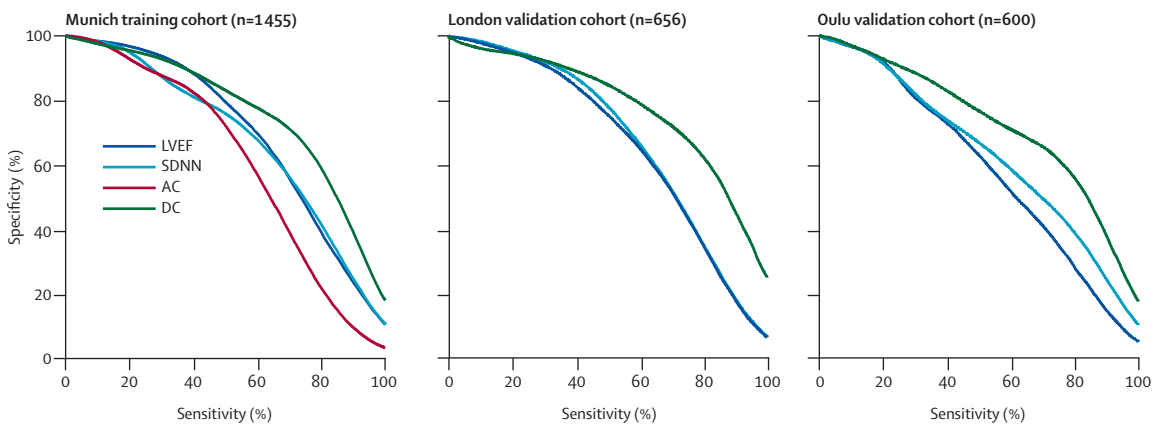


Figure 3: **ROC curves for prediction of total mortality by deceleration capacity (DC), acceleration capacity (AC), LVEF, and SDNN in Munich, London, and Oulu**
Sensitivity is proportion of non-survivors identified as high risk; specificity is proportion of survivors identified as low risk.

capacity and LVEF yielded the largest AUC tested (table 3).

In the Munich data, we noted two distinct maxima in the log-rank statistics that corresponded with deceleration capacity cut-off values of 4·5 ms and 2·5 ms. Thus, we proposed a deceleration capacity-based distinction between high-risk (deceleration capacity ≤2·5 ms), intermediate-risk (2·6 ms to ≤4·5 ms), and low-risk (>4·5 ms) patients, which we then prospectively tested in the London and Oulu cohorts. In all three cohorts, the mortality probabilities of the deceleration capacity categories were significantly different (p<0·0001). Figure 4 shows mortality probabilities in the combined population of all cohorts.

We tested the independence of deceleration-capacity categories from other established risk predictors and clinical covariates by multivariate Cox regression analysis. In all cohorts, deceleration capacity of 2·5 ms or less consistently indicated the highest relative risk (table 4). Since LVEF and deceleration capacity were the only independent predictors of mortality in the Munich cohort—ie, cohort used to identify deceleration capacity cut-off points—we merged the high-risk groups selected by these two stratifiers. Table 5 shows the sizes, sensitivities, and positive predictive accuracies of high-risk groups defined by an LVEF of 30% or less and by a combination of either an LVEF of 30% or less or a deceleration capacity of 2·5 ms or less. Risk stratification by deceleration capacity is especially useful in patients with preserved LVEF (figure 5). Merging of the high-risk groups defined by depressed LVEF and by reduced deceleration capacity therefore substantially and significantly increases sensitivity while positive predictive accuracy is practically unaffected (table 5). Deceleration capacity-based risk categories also separated the risk within patients with an LVEF of 30% or less (figure 5). Because of the small number of individuals in the

	Munich	London	Oulu
DC	0·77 (0·03)	0·80 (0·03)	0·74 (0·03)
AC	0·61 (0·04)	..	..
LVEF	0·70 (0·03)	0·67 (0·04)	0·60 (0·04)
SDNN	0·68 (0·03)	0·69 (0·04)	0·64 (0·03)
DC+LVEF	0·80 (0·03)	0·83 (0·02)	0·77 (0·03)
AC+LVEF	0·72 (0·03)	..	..
SDNN+LVEF	0·75 (0·03)	0·72 (0·03)	0·70 (0·03)

Data are mean (SD) of AUC of ROCs. In all cohorts, AUC of DC was significantly larger than that of LVEF, SDNN, and SDNN+LVEF; the AUC of DC+LVEF was significantly larger than that of DC, LVEF, SDNN, and of SDNN+LVEF. In Munich cohort, AUC of DC was significantly larger than that of AC and of AC+LVEF. p<0·0001 for all these comparisons.

Table 3: **AUC of ROC of deceleration capacity (DC), acceleration capacity (AC), LVEF, and SDNN, as well as of combinations of DC and LVEF, AC and LVEF, and SDNN and LVEF, by cohort**

deceleration capacity-based risk categories within the groups with LVEF of 30% or less, we noted a significant separation of the three strata only in the analysis of the data of all three cohorts combined.

Discussion

Our findings indicate that deceleration capacity is a strong predictor of mortality after myocardial infarction and is better than LVEF, conventional measures of heart-rate variability, and the combination of both. We confirmed our hypotheses—that deceleration capacity would yield a significantly larger AUC than LVEF and SDNN—in two large and independent post-infarction populations, proving the prognostic capabilities of the deceleration capacity index. We believe that deceleration capacity provides a measure of cardiac vagal modulations. The results of several clinical and experimental studies indicate a cardioprotective role of vagal activity.[17–19] Our findings are, hence, in agreement with available physiological observations.

The effects of vagal and sympathetic modulators on the heart are difficult to separate for analysis, and whether our method of distinguishing between deceleration capacity and acceleration capacity succeeds in doing so is uncertain. Nevertheless, our results clearly show that there are large differences in risk assessment derived from heart-rate acceleration and deceleration. Even without direct links to autonomic modulators, the physiological mechanisms responsible for acceleration and deceleration of heart rate are probably different. In this sense, our findings show that pathologies that slow the heart down are more clinically important than those that speed it up. We also noted that this difference in particular relates to sizeable groups of patients with poor outlook who have a preserved acceleration capacity, but lack deceleration capacity.

As previously noted,[13] the PRSA technique synchronises the phases of all periodic components of the signal

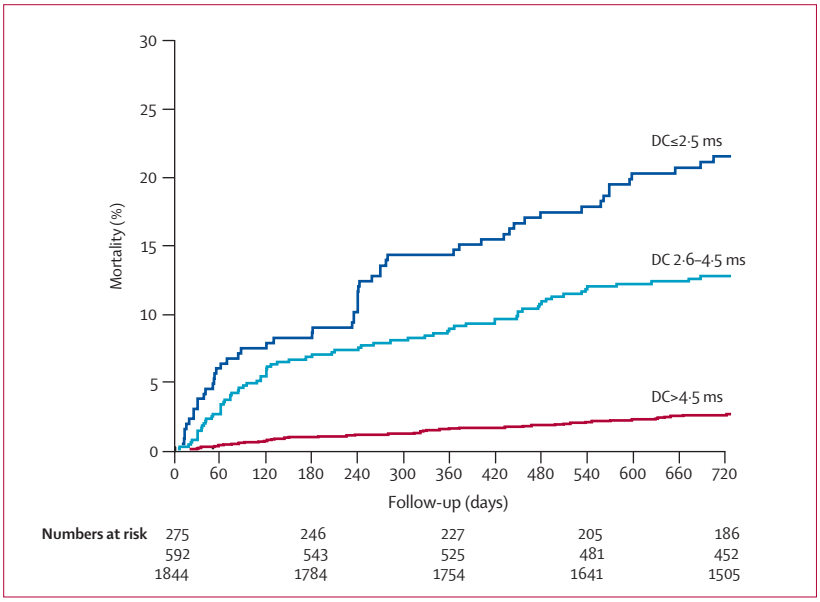


Figure 4: **Kaplan-Meier curves of mortality for patients in all three cohorts stratified by three risk groups**
DC=deceleration capacity. Mortality probabilities were significantly different (p<0·0001 in all cohorts).

	Munich		London		Oulu		Overall	
	Relative risk (95% CI)	p	Relative risk (95% CI)	p	Relative risk (95% CI)	p	Relative risk (95% CI)	p
Arrhythmia	..	..	..	..	..	..	..	..
Mean heart rate >75 bpm	..	..	2·0 (1·2–3·5)	0·0141	..	..	1·9 (1·4–2·7)	0·0001
SDNN ≤70 ms	..	..	..	..	..	..	..	..
LVEF ≤30%	3·9 (2·3–6·4)	<0·0001	1·8 (1·1–3·1)	0·0268	..	..	2·4 (1·7–3·3)	<0·0001
DC category 1 *vs* 0	3·0 (2·3–6·4)	<0·0001	2·9 (1·5–5·4)	0·0013	7·5 (2·5–22·3)	0·0003	2·9 (2·0–4·4)	<0·0001
DC category 2 *vs* 0	5·7 (3·1–10·4)	<0·0001	5·3 (2·7–10·6)	<0·0001	9·8 (3·0–32·0)	0·0001	5·0 (3·3–7·7)	<0·0001

Multivariate analysis adjusted for age, presence of diabetes mellitus, and history of myocardial infarction. DC=deceleration capacity. DC categories: 0=DC >4·5 ms, 1=DC 2·5 to ≤4·5 ms, 2=DC ≤2·5 ms.

Table 4: **Association of risk variables with total mortality in a multivariate analysis**

	Munich			London			Oulu			Overall		
	Number	Sensitivity	Positive predictive accuracy	Number	Sensitivity	Positive predictive accuracy	Number	Sensitivity	Positive predictive accuracy	Number	Sensitivity	Positive predictive accuracy
LVEF ≤30%	82	27·1	23·2	100	37·9	25·0	58	23·4	31·0	240	29·1	25·8
LVEF ≤30% or DC ≤2·5 ms	189	47·1	17·5	145	59·1	26·9	127	46·8	28·4	461	50·7	23·4
p	..	0·0024	0·36	..	0·0232	0·76	..	0·0039	0·73	..	<0·0001	0·54*

DC=deceleration capacity. *Because of large numbers comparison of positive predictive accuracy in the overall data group was not possible with Fisher's exact test, result of Yates corrected χ^2 test shown.

Table 5: **Sensitivity and positive predictive accuracy of high-risk groups**

irrespective of their frequencies or characteristic time scales. It thus integrates their contributions by accumulation of the corresponding amplitudes at the centre of the PRSA signal. Autonomic heart-rate modulations due to specific regulation processes—eg, respiratory, baroreflex mediated, circadian—occur on different timescales. Thus, deceleration capacity indicates the overall deceleration capacity of sinus rhythm, without being linked necessarily to one particular physiological process.

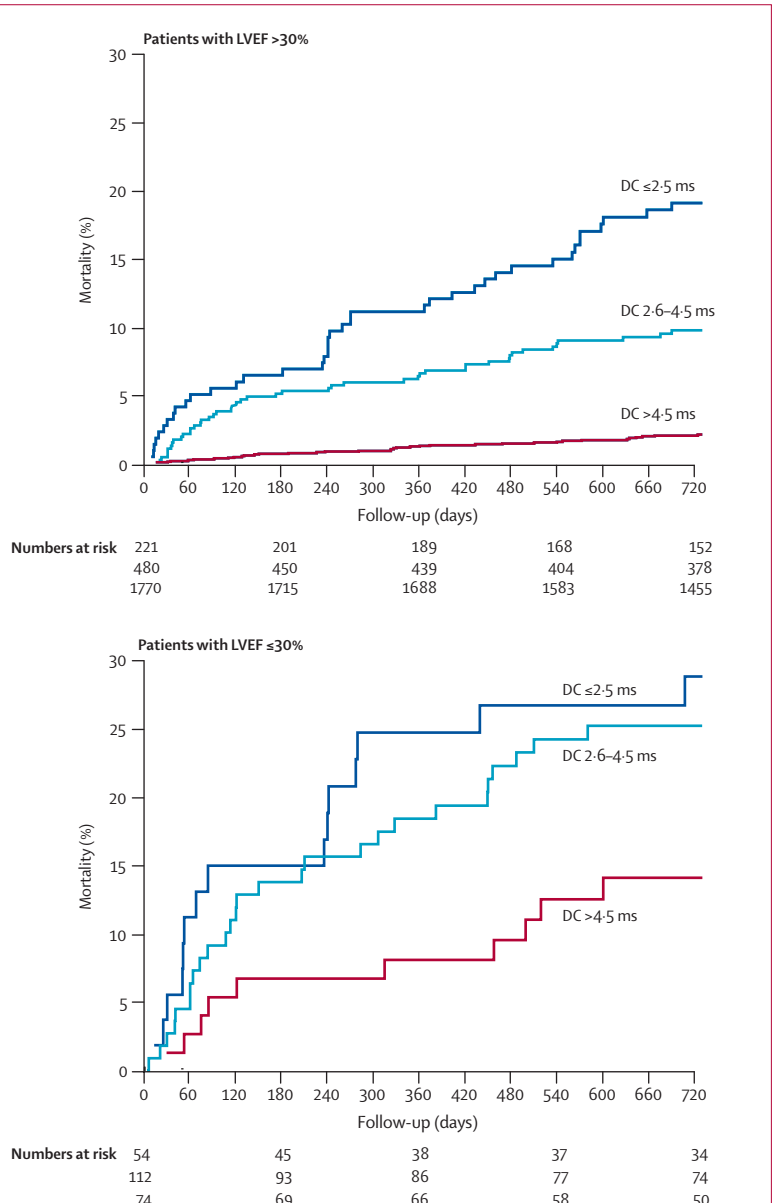


Figure 5: **Kaplan-Meier curves of mortality for patients of all three cohorts stratified by risk, according to deceleration capacity (DC)**
In subgroups with LVEF >30%, mortality probabilities of patients stratified by DC significantly different (p<0·0001 in all cohorts). In subgroups with LVEF ≤30%, differences between mortality probabilities p=0·166 in Munich cohort, p=0·180 in Oulu cohort, p=0·056 in London cohort, and p=0·025 overall.

Statistically, we assessed the differences between risk stratifiers with the AUC of the ROC curve. This method is unbiased and well established. Furthermore, AUC of an ROC curve is independent of specific cut-off values. In all three populations studied, the largest separations of ROC curves between deceleration capacity and LVEF or SDNN had sensitivity levels of about 80%. Thus, use of deceleration capacity with a threshold leading to this sensitivity correctly identifies four of five non-survivors as at high risk. At the same time, the corresponding specificity of deceleration capacity was consistently substantially higher than that of LVEF and of SDNN. Deceleration capacity-based risk assessment is hence especially suitable for a more accurate identification of low-risk patients in whom further interventions or potentially costly diagnostic workout are not warranted.

This notion was confirmed in our model of clinical usefulness, in which preserved deceleration capacity (>4·5 ms) indicated an extremely low risk of mortality, whereas poor deceleration capacity (≤2·5 ms) indicated high mortality risk even in the presence of preserved LVEF (and is therefore an ideal candidate for combination with impaired LVEF). When adding the criterion of reduced deceleration capacity to the criterion depressed LVEF, the size of the high-risk group almost doubles whereas the positive predictive accuracy is practically unaffected. Both the possibility of identifying high-risk patients who would be missed by present methods, as well as the possibility of identifying truly low-risk patients who do not need further investigations, are of obvious clinical use.

Our study had various limitations. First, we did not prospectively enrol patients. Second, in all cohorts, age was restricted to 75 years. The results cannot, therefore, be directly extrapolated to older patients. Third, we compared deceleration capacity with all established risk predictors of heart-rate variability recommended by the Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology.[9] However, we did not include other strong risk markers, such as baroreflex sensitivity[20] and heart-rate turbulence[21] in our analysis. Fourth, the three cohorts were compiled over different time periods[4,10–12] and thus differed somewhat in the contemporary clinical standards. Nevertheless, the consistency of the findings across the cohorts shows that the predictive power of deceleration capacity is independent of treatment standards. Fifth, use of total mortality as an endpoint has both advantages and disadvantages. Although the definition of death is without any ambiguity, the potential association with the risk of arrhythmic death might be lost. Nevertheless, the definitions of sudden death available in the databases of the cohorts are not only inconsistent each with the other but also only poorly reflect a category of antiarrhythmia-preventable death that might have been of interest. Furthermore, the incidence of unambiguous arrhythmic death in the individual cohorts is too low for any

meaningful comparisons. We did not, therefore, analyse the sudden-death endpoints, but did analyse the cardiac mortality endpoints and obtained findings similar to those presented here. Finally, although we have shown that deceleration capacity is a powerful risk predictor, we have no data to show that specific treatments provided based on use of this predictor will improve patients' outcome.

Deceleration capacity substantially improves risk prediction in survivors of acute myocardial infarction. The deceleration capacity-based risk stratification is significantly better than measurement of LVEF. The high consistency of the deceleration capacity-based tests, together with the simplicity of the computational algorithm, suggest that the deceleration capacity index is suitable as an inexpensive, easily obtainable, and non-invasive post-infarction screening method for use in the early identification of low-risk patients in whom further diagnostic workout is not warranted, and in the improved selection of those who are likely to benefit from prophylactic interventions.

Contributors

G Schmidt and A Bauer developed the technology, which P Barthel, R Schneider, and K Ulm then improved. J Kantelhardt and A Bunde undertook mathematical characterisation. A Schömig helped to design the study. M Malik, K Hnatkova, H Huikuri, and T Mäkikallio validated the technique. M Malik, A Bunde, and G Schmidt wrote the report with input from all other authors. A Bauer and J Kantelhardt contributed equally to this study.

Conflict of interest statement

G Schmidt has applied for a patent on the PRSA technology —10,535,921 (PCT/DE 2002/004349).

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