JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 19, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.03.484

Expiration-Triggered Sinus Arrhythmia Predicts Outcome in Survivors of Acute Myocardial Infarction

Daniel Sinnecker, MD,[a] Michael Dommasch, MD,[a] Alexander Steger, MD,[a] Anna Berkefeld, MD,[a] Petra Hoppmann, MD,[a] Alexander Müller, MSc,[a] Josef Gebhardt, MSc,[a] Petra Barthel, MD,[a] Katerina Hnatkova, PhD,[b] Katharina M. Huster, MD,[a] Karl-Ludwig Laugwitz, MD,[a,c] Marek Malik, MD, PhD,[b] Georg Schmidt, MD[a,c]

ABSTRACT

BACKGROUND Respiratory sinus arrhythmia (RSA), a measure of cardiac vagal modulation, provides cardiac risk stratification information. RSA can be quantified from Holter recordings as the high-frequency component of heart rate variability or as the variability of RR intervals in individual respiratory cycles. However, as a risk predictor, RSA is neither exceptionally sensitive nor specific.

OBJECTIVES This study aimed to improve RSA determination by quantifying the amount of sinus arrhythmia related to expiration (expiration-triggered sinus arrhythmia [ETA]) from short-term recordings of electrocardiogram and respiratory chest excursions, and investigated the predictive power of ETA in survivors of acute myocardial infarction.

METHODS Survivors of acute myocardial infarction (N = 941) underwent 30-min recordings of electrocardiogram and respiratory chest excursions. ETA was quantified as the RR interval change associated with expiration by phase-rectified signal averaging. Primary outcome was 5-year all-cause mortality. Univariable and multivariable Cox regression was used to investigate the association of ETA with mortality.

RESULTS ETA was a strong predictor of mortality, both in univariable and multivariable analysis. In a multivariable model including respiratory rate, left ventricular ejection fraction, diabetes mellitus, and GRACE score, ETA ≤0.19 ms was associated with a hazard ratio of 3.41 (95% confidence interval: 1.10 to 5.89, $p < 0.0001$). In patient subgroups defined by abnormal left ventricular ejection fraction, increased respiratory rate, high GRACE score, or presence of diabetes mellitus, patients were classified as high or low risk on the basis of ETA.

CONCLUSIONS Expiration-triggered sinus arrhythmia (ETA) is a potent and independent post-infarction risk marker. (J Am Coll Cardiol 2016;67:2213–20) © 2016 by the American College of Cardiology Foundation.

Respiratory sinus arrhythmia (RSA)—first described by Carl Ludwig more than 150 years ago (1)—is caused by phasic changes of vagal neural discharge directed to the sinus node. During inspiration, vagal activity is inhibited, causing a prompt heart rate increase. During expiration, the pattern of vagal discharge resumes, causing a prompt heart rate decrease (2,3). Thus, the extent of the corresponding heart rate changes is largely dependent on vagal modulation.

RSA is therefore a major determinant of heart rate variability (HRV), particularly when considering short-term HRV. RSA decrease is commonly observed in conditions characterized by altered sympathovagal balance with reduced vagal and increased sympathetic neural activity. In many clinical conditions

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]1. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [b]Saint Paul's Cardiac Electrophysiology, University of London and Imperial College, London, London, United Kingdom; and the [c]DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany. This work was supported by the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (13N/7073/7), by the Deutsche Forschungsgemeinschaft (Si 1747/1-1), and by the Else Kröner-Fresenius-Stiftung. The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Sinnecker and Dommasch contributed equally to this work.

Manuscript received February 3, 2016; revised manuscript received March 2, 2016, accepted March 7, 2016.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ECG = electrocardiogram

ETA = expiration-triggered sinus arrhythmia

HRV = heart rate variability

IQR = interquartile range

LVEF = left ventricular ejection fraction

MI = myocardial infarction

ROC = receiver-operating characteristic

RSA = respiratory sinus arrhythmia

(e.g., myocardial infarction [MI], heart failure), this autonomic pattern has been associated with a poor prognosis (4).

Various parameters have been proposed for RSA quantification and its use as a predictor for subsequent mortality in cardiac patients (5,6). Commonly, these markers quantify the HRV within entire respiratory cycles. We present a method that addresses heart rate changes mediated by the expiration-driven increase of vagal activity. For this purpose, we used bivariate phase-rectified signal averaging (7,8) technology to quantify fluctuations of heartbeat intervals triggered by expiration. We term such fluctuations expiration-triggered sinus arrhythmia (ETA). We also investigated the prognostic power of this parameter for risk stratification of survivors of acute MI.

SEE PAGE 2221

METHODS

STUDY COHORT. From May 2000 to March 2005, 941 consecutive survivors of acute MI were enrolled at 2 university hospitals (Deutsches Herzzentrum München and Klinikum Rechts der Isar, both in Munich, Germany). The study protocol was approved by the local ethics committee, and all participants gave written informed consent.

Patients were eligible for the study if they were ≤80 years of age, survived the acute MI phase, presented in sinus rhythm, and did not meet criteria for implantable cardioverter-defibrillator implantation for secondary prevention before hospital discharge. Mean follow-up was 4.9 years, with the last follow-up performed in August 2010. The primary endpoint of the study was all-cause mortality within 5 years after the index MI. Patients were followed up with clinical appointments every 6 months. If patients did not attend, they were contacted by letter, by telephone, or through their general practitioner. If this was not successful, the local population registry office was contacted to trace their new address or to identify those who died.

DATA RECORDINGS. Within 2 weeks of their index MI and during the initial hospitalization, patients underwent 30-min recordings of high-resolution electrocardiograms (ECGs) (1.6 kHz in orthogonal XYZ leads, TMS International, Enschede, the Netherlands) and respiratory activity (Pro-Tech piezoelectric thoracic sensor, signal acquired at 1.6 kHz, Porti system, TMS International). To avoid disturbing spontaneous respiration, patients were not reminded that a sensor was attached to monitor respiration (although they initially consented to their ECG, arterial pressure, and respiration being monitored). Recordings were made in the morning after administration of routine medications, in a supine resting position in a quiet surrounding. In analogy to the standards of Holter ECG analysis (9), raw signals were reviewed, artefacts were eliminated where needed, and QRS classifications were carefully reviewed and manually corrected when appropriate. This post-processing, which typically took <5 min, was performed by an experienced technician unaware of the clinical outcome data.

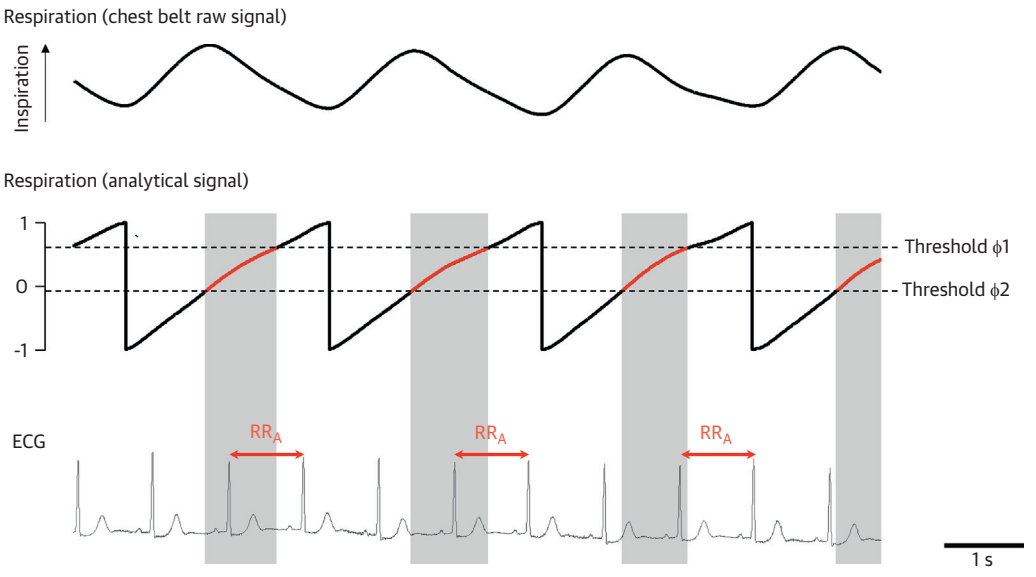
ASSESSMENT OF RSA. A mathematical representation of the respiratory signal (analytical respiratory signal) was constructed, ranging from −1 (beginning of inspiration) to +1 (end of expiration) (**Figure 1**). The expiratory phase was defined as the time interval between 2 threshold values: $\phi 1$ and $\phi 2$. For computation of ETA, heartbeat intervals starting between $\phi 1$ and $\phi 2$ were identified as anchors. About 700 of 2,000 RR intervals become anchors in a typical 30-min recording. RR interval segments around the anchors were selected and averaged. The average change in RR intervals was quantified by Haar wavelet analysis with a scale of 2 (8).

The numerical values of $\phi 1$ and $\phi 2$ (0.6 and −0.1, respectively) were optimized with respect to prediction of 5-year all-cause mortality, as assessed by receiver-operating characteristic (ROC) analysis (details are presented in the Online Appendix).

Figure 2A shows a typical phase-rectified and averaged RR interval tachogram centered on expiratory RR intervals in a long-term MI survivor. A positive central deflection is clearly visible, indicating that, on average, expiration leads to RR interval prolongation (i.e., heart rate decrease) (**Figure 2A**). By contrast, **Figure 2B** shows an averaged tachogram of a patient who died during follow-up. In nonsurvivors, the central deflection was typically less pronounced or even negative.

RSA was also assessed by 2 standard methods: a spectral analytic technique, that is, the high-frequency component of HRV—RSA_{HF}, and a peak-to-trough algorithm that estimates RSA from the variability of RR intervals in individual respiratory cycles—RSA_{PT}. For calculation of RSA_{HF}, the high-frequency (0.15 to 0.40 Hz) component of HRV was obtained by fast Fourier transformation in 5-min segments of the RR interval time series, and RSA_{HF} was calculated as the average of all segments (5). For the calculation of RSA_{PT}, inspiratory and expiratory phases of each respiratory cycle were analyzed separately,

FIGURE 1 Calculation of Expiration-Triggered Sinus Arrhythmia From ECG and Respiratory Signals

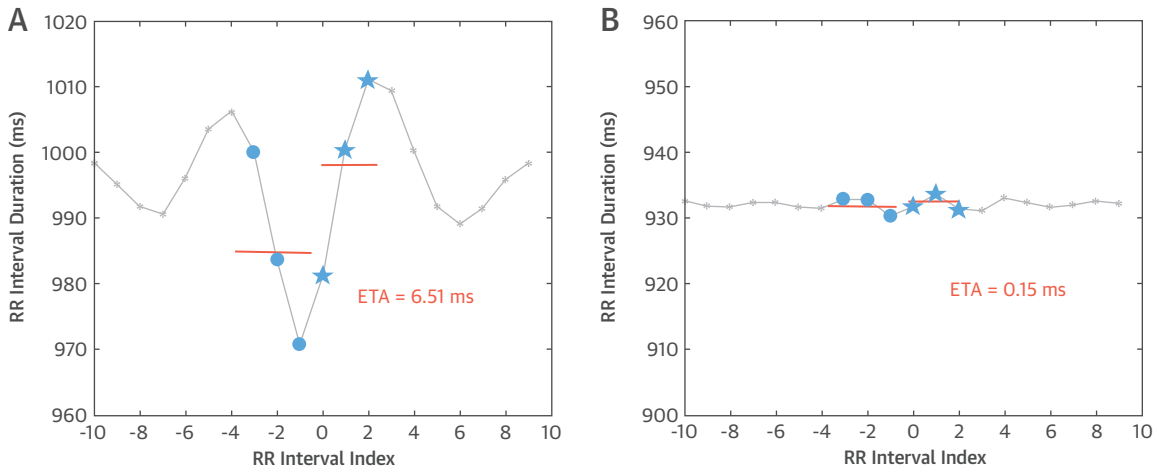


The respiratory signal is transformed into an analytical signal. All RR intervals that lie within the expiratory phase (i.e., between the threshold values ϕ1 and ϕ2 in the analytical signal) are used as anchor points for the subsequent phase-rectified signal averaging (PRSA). Electrocardiogram (ECG) segments around these anchor points are aligned by the anchors and subsequently averaged.

and the minimum RR interval during inspiration was subtracted from the maximum RR interval during expiration. RSA_{PT} was calculated as the average of these differences over all respiratory cycles (6).

DEFINITIONS AND CLINICAL VARIABLES. For the initial MI diagnosis, at least 2 of the following 3 criteria were required: typical chest pain for at least 20-min duration, creatine kinase above twice the

FIGURE 2 Phase-Rectified and Averaged RR Interval Tachograms Centered on Expiration



The anchor RR interval has index 0. Tachograms from a long-term myocardial infarction survivor **(A)** and a patient who died during follow-up **(B)** are shown. Expiration-triggered sinus arrhythmia (ETA) is quantified as: $1/6(\Sigma_{post}-\Sigma_{pre})$, where Σ_{pre} is the sum of the 3 RR intervals preceding the anchor (indicated as **filled circles**), and Σ_{post} is the sum of the anchor RR interval and the following 2 (indicated as **filled stars**). The averages of the pre- and post-anchor RR intervals are shown as **orange lines**.

upper normal limit, and ST-segment elevation ≥0.1 mV in at least 2 limb leads or ≥0.2 mV in at least 2 contiguous precordial leads at admission.

Diabetes mellitus was diagnosed if a patient was already receiving treatment (diet, tablets, or insulin) or if fasting blood glucose concentration repeatedly exceeded 11 mmol/l. GRACE score (a clinical score combining patient age, serum creatinine, past MI, past heart failure, in-hospital percutaneous coronary intervention, heart rate, systolic blood pressure, ST-segment deviation, and positive enzymes) was assessed as previously proposed for the prediction of long-term prognosis (10).

Left ventricular ejection fraction (LVEF) was assessed by angiography (n = 445; 47.3%) or biplane echocardiography according to Simpson's method (n = 496; 52.7%; Sonos 5500, Hewlett Packard, Palo Alto, California) within the first 2 weeks (median 7 days, interquartile range [IQR]: 5 to 9 days) after the index MI.

EVALUATION OF RISK PREDICTORS. In the primary analysis, ETA, respiration rate, LVEF, and GRACE score were treated as continuous variables. In the secondary analysis, ETA was dichotomized at the optimum cutoff according to Youden's index J (i.e., maximizing the sum of sensitivity and specificity) (11). Other variables were dichotomized prospectively: respiratory frequency at 18.6 breaths/min (12,13), LVEF at 35% (14), and the GRACE score at 120 points (15).

STATISTICS. Continuous variables are presented as median and IQR. Categorical data are expressed as absolute frequencies and percentages. Cox proportional hazards models were used with all variables entered simultaneously to assess the independence and prognostic value of mortality predictors. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. To assess the intradata reproducibility of the findings, Kaplan-Meier survival curves and areas under the ROC curves were calculated together with their confidence intervals (CIs) obtained by bootstrap with 10,000 repetitions. Differences were considered statistically significant if $p < 0.05$ (IBM SPSS Statistics 20.0, SPSS, Armonk, New York).

RESULTS

Table 1 shows clinical and demographic characteristics of the enrolled patients. Five years after the index MI, 72 patients (7.7%) had died.

ETA AS A CONTINUOUS VARIABLE. Median ETA in the cohort was 0.54 ms (IQR: −0.25 to 1.66 ms). In patients who died during follow-up, ETA was significantly smaller compared with that of the survivors: −0.35 (−1.33 to 0.30) ms versus 0.64 (−0.16 to 1.75) ms ($p < 0.0001$). The area under the ROC curve for all-cause mortality prediction by ETA was 0.72 (95% CI: 0.67 to 0.78).

In univariable Cox analysis, ETA was a significant predictor of outcome. An increase of ETA by 1 ms was associated with a hazard ratio of 0.94 (95% CI: 0.90 to 0.97; $p = 0.001$) (Table 2). Respiratory rate, LVEF, presence of diabetes mellitus, and GRACE score also were significant predictors of all-cause mortality (Table 2). In multivariable Cox analysis considering all the aforementioned risk predictors, the association of ETA with mortality remained statistically significant, with a hazard ratio of 0.95 (95% CI: 0.91 to 0.99; $p = 0.035$) (Table 2).

Performance of the standard methods for RSA assessment was much weaker, with areas under the ROC curve of 0.57 (95% CI: 0.49 to 0.64) and 0.62 (95% CI: 0.55 to 0.69) for RSA_{HF} and RSA_{PT}, respectively; neither parameter reached statistical significance in univariable Cox analysis.

TABLE 1 Clinical Characteristics of the Study Cohort (N = 941)

Age, yrs	61 (52–69)
Females	182 (19.3)
Diabetes mellitus	184 (19.6)
History of previous MI	90 (9.6)
Hypertension	682 (72.5)
Smoking	488 (51.9)
History of COPD	39 (4.1)
CK max, U/l	1,302 (647–2,465)
LVEF, %	53 (45–60)
Localization of AMI	
Anterior wall	391 (41.6)
Posterior wall	435 (46.2)
Lateral wall	102 (10.8)
Unclassified	12 (1.3)
BMI, kg/m^2	27 (24–29)
Serum creatinine, mg/dl	1.1 (0.9–1.3)
Cardiogenic shock/CPR	41 (4.4)
Intervention	
PCI	878 (93.3)
Thrombolysis	14 (1.5)
CABG	6 (0.6)
No revascularization possible	43 (4.6)
Aspirin	913 (97.0)
Clopidogrel	920 (97.8)
Beta-blockers	897 (95.3)
ACE inhibitors	885 (94.0)
Statins	879 (93.4)
Diuretics	415 (44.1)

Values are median (interquartile range) or n (%).

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CK = creatinine kinase; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Univariable and Multivariable Cox Regression Analysis (Continuous Variables)

	Univariable			Multivariable		
	HR (95% CI)	Chi-Square	p Value	HR (95% CI)	Chi-Square	p Value
ETA (per 1 ms)	0.94 (0.90–0.97)	11.56	0.001	0.95 (0.91–0.99)	4.47	0.035
LVEF (per 1%)	0.96 (0.94–0.97)	24.21	<0.0001	0.98 (0.96–0.99)	5.38	0.02
Diabetes mellitus present	2.78 (1.73–4.47)	17.89	<0.0001	1.86 (1.15–3.02)	6.34	0.012
Respiratory rate (per 1 breath/min)	1.19 (1.12–1.27)	30.36	<0.0001	1.14 (1.07–1.22)	14.82	<0.0001
GRACE score (per 1 point)	1.04 (1.03–1.05)	64.99	<0.0001	1.03 (1.02–1.04)	36.45	<0.0001

GRACE score: composite of age of the patient, serum creatinine, past myocardial infarction, past heart failure, in-hospital percutaneous coronary intervention, heart rate, systolic blood pressure, ST-segment deviation, and positive enzymes.

CI = confidence interval; ETA = expiration-triggered sinus arrhythmia; LVEF = left ventricular ejection fraction.

ETA AS A DICHOTOMOUS VARIABLE. According to Youden's index J, the optimum dichotomy for ETA was 0.19 ms. In univariable Cox analysis, the hazard ratio for ETA ≤0.19 ms versus >0.19 ms was 5.12 (95% CI: 3.00 to 8.73; $p < 0.001$). Kaplan-Meier survival probability curves of patients with ETA values above and below this threshold are shown in the **Central Illustration** together with their CIs. Five-year mortality rates in the high- and low-risk groups were 15% and 3%, respectively. In multivariable Cox analysis, ETA ≤0.19 ms remained a strong risk predictor (with a hazard ratio of 3.43; 95% CI: 1.10 to 5.89; $p < 0.0001$) (**Table 3**). Upon addition of ETA to a model comprising respiratory rate, LVEF, presence of diabetes mellitus, and GRACE score, the area under the ROC curve increased significantly from 0.79 to 0.82 ($p = 0.02$) (Online Figure 1).

Figure 3 shows Kaplan-Meier survival probability curves for combinations of dichotomized ETA with dichotomized LVEF, respiratory rate, GRACE score, and presence or absence of diabetes mellitus. In all cases, the addition of ETA led to strong separation of survival curves. Within patient subgroups defined by abnormal LVEF, respiratory rate, GRACE score, or presence of diabetes mellitus, ETA >0.19 ms was consistently associated with a considerably improved prognosis, and vice versa for ETA ≤0.19 ms (**Table 4**, **Central Illustration**).

DISCUSSION

This study demonstrates that ETA is a potent risk marker in post-infarction patients. ETA is particularly strong in patients with reduced LVEF (**Figure 3A**). This observation is of clinical importance, because risk stratification in patients with reduced LVEF has so far been very challenging. ETA allows for further risk stratification, not only in patients pre-stratified by LVEF, but also by other accepted risk predictors such as GRACE score, presence of diabetes mellitus, or respiratory rate, with hazard ratios between 3 and 5 (**Table 4**). Moreover, ETA is independent of a number of established risk markers, including late potentials in signal-averaged ECGs (16), heart rate turbulence (17), deceleration capacity (18), spontaneous baroreflex sensitivity (15,19), post-extrasystolic blood pressure potentiation (20), and periodic repolarization dynamics (21) (Online Appendix), and standard methods of RSA assessment, that is, RSA_{HF} and RSA_{PT}, were by far not as strong as ETA. The predictive power of ETA was independent from β-blocker use, as well as from infarct localization (Online Appendix).

We understand that ETA extracts the effects of the expiration-triggered vagal surge on the sinus node discharge rate. Because attenuated vagal function is apparent already at early stages of left ventricular dysfunction (22), ETA seems particularly suitable for risk stratification purposes. Also, the phase-rectified signal averaging method makes ETA assessment robust and practically independent of noise and nonstationarities. ETA is ideally assessed during spontaneous breathing, because controlled breathing may change the sympathovagal balance (23).

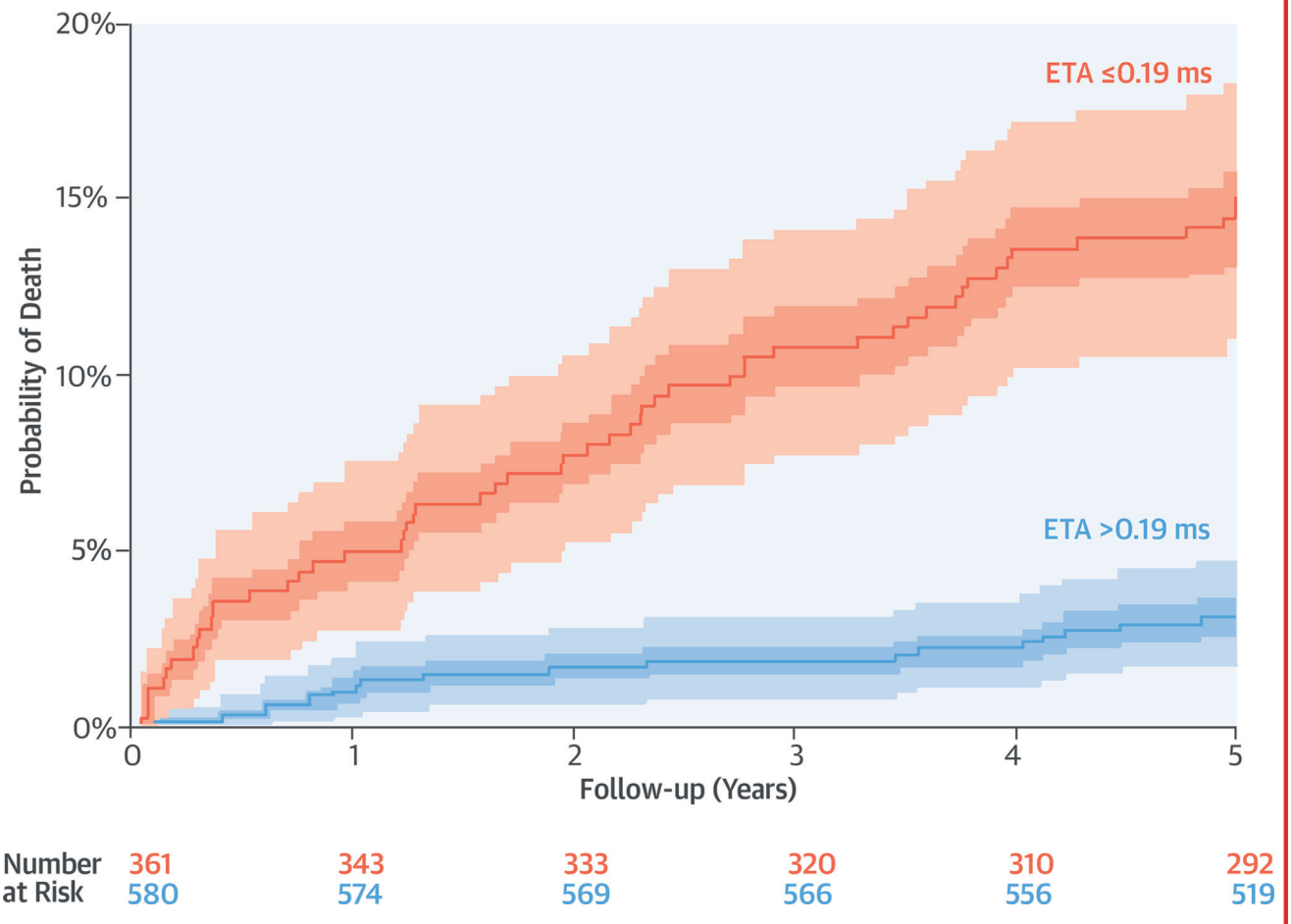
Inspiration-triggered sinus arrhythmia derived by an ETA-analogous parameter that uses inspiration segments for the selection of anchor RR intervals was also a significant mortality predictor, albeit at a lower statistical significance level as compared with ETA (data not shown).

STUDY LIMITATIONS. This study only included post-infarction patients age 80 years and younger. Our results might thus not translate to other patient populations.

The respiration signal was obtained using a chest belt, that is, by a method not regularly used in clinical routine. However, respiratory cycles and respiration phases can be identified in high-resolution ECG signals alone (24). Broad applications of ETA are thus technically feasible.

Although the ETA assessment method was optimized to achieve large areas under the ROC curve of mortality prediction, the dependency of the areas

CENTRAL ILLUSTRATION **Expiration-Triggered Sinus Arrhythmia: Probability of Mortality Over 5 Years in Patients Stratified by ETA**



Sinnecker, D. et al. J Am Coll Cardiol. 2016;67(19):2213–20.

Mortality curves in patients with expiration-triggered sinus arrhythmia (ETA) ≤0.19 ms **(orange line)** and ETA >0.19 ms **(blue line)** are shown, together with interquartile ranges **(dark shaded area)** and 95% confidence intervals **(light shaded areas)**. The number of patients at risk in the individual groups at 0, 1, 2, 3, 4, and 5 years is shown below the graph in the same color coding.

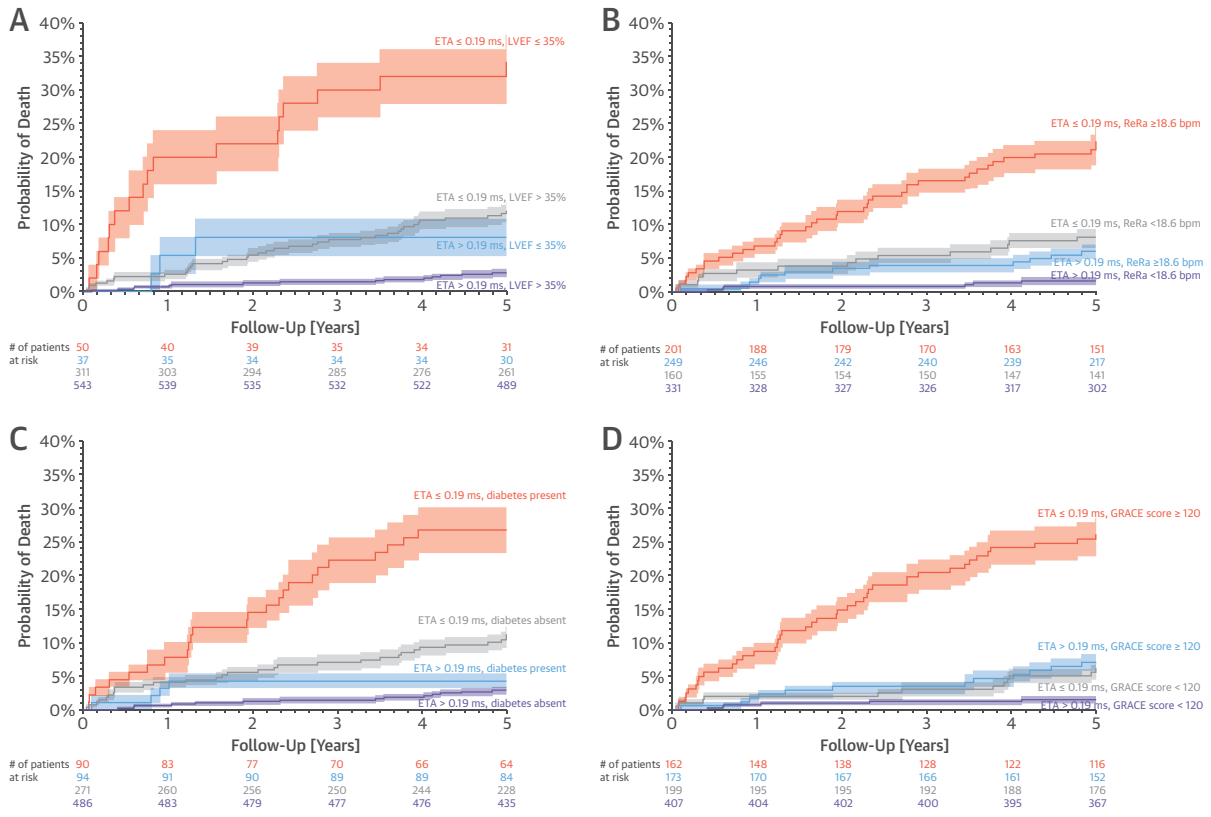
TABLE 3 **Univariable and Multivariable Cox Regression Analysis (Dichotomized Variables)**

	Univariable			Multivariable		
	HR (95% CI)	Chi-Square	p Value	HR (95% CI)	Chi-Square	p Value
ETA ≤0.19 ms	5.12 (3.00–8.73)	36.00	<0.0001	3.43 (1.10–5.89)	19.88	<0.0001
LVEF ≤35%	4.29 (2.56–7.19)	30.64	<0.0001	2.25 (1.32–3.82)	8.92	0.003
Diabetes mellitus	2.78 (1.73–4.47)	17.89	<0.0001	1.82 (1.13–2.95)	5.94	0.015
Respiratory rate ≥18.6 breaths/min	3.78 (2.28–6.29)	26.32	<0.0001	2.47 (1.47–4.15)	11.71	0.001
GRACE score ≥120 points	5.82 (3.41–9.92)	41.87	<0.0001	3.90 (2.26–6.73)	23.90	<0.0001

GRACE score: composite of age of the patient, serum creatinine, past myocardial infarction, past heart failure, in-hospital percutaneous coronary intervention, heart rate, systolic blood pressure, ST-segment deviation, and positive enzymes.

Abbreviations as in Table 2.

FIGURE 3 Risk Stratification by ETA in Combination With Other Risk Predictors



Mortality probabilities (shown together with their interquartile ranges) over 5 years in patients stratified according to expiration-triggered sinus arrhythmia (ETA) in combination with left-ventricular ejection fraction (LVEF) **(A)**, respiratory rate **(B)**, presence of diabetes mellitus **(C)**, and GRACE score **(D)**. The number of patients at risk in the individual groups at 0, 1, 2, 3, 4, and 5 years is shown below the graph in the same color coding. ReRa = respiratory rate.

under the ROC curve on the values of $\phi 1$ and $\phi 2$ was rather shallow (Online Figure 2).

The primary endpoint of the study was all-cause mortality. With respect to cardiac mortality, we obtained similar results as with all-cause mortality, albeit at a lower statistical significance level. The number of sudden cardiac deaths in our study was too small to perform multivariable analyses considering multiple risk factors in addition to ETA (25,26). However, in pairwise multivariable analyses, ETA appeared to also predict sudden cardiac death independently of other risk predictors (Online Appendix, Online Figure 3).

TABLE 4 5-Year Mortality in Subgroups Defined by Expiration-Triggered Sinus Arrhythmia and Other Risk Predictors

	All Patients	ETA ≤0.19 ms	ETA >0.19 ms
LVEF ≤35%	20/87 (23.0)	17/50 (34.0)	3/37 (8.1)
Respiratory rate ≥18.6 breaths/min	51/379 (13.5)	39/176 (22.2)	12/203 (5.9)
Diabetes mellitus present	28/184 (15.2)	24/90 (26.7)	4/94 (4.3)
GRACE score ≥120 points	54/335 (16.1)	42/162 (25.9)	12/173 (6.9)

Values are n dead/total n (%). GRACE score: composite of age of the patient, serum creatinine, past myocardial infarction, past heart failure, in-hospital percutaneous coronary intervention, heart rate, systolic blood pressure, ST-segment deviation, and positive enzymes.

Abbreviations as in Table 2.

CONCLUSIONS

ETA appears to be a potent risk marker in post-infarction patients. The association of ETA and mortality is independent of other established risk factors, indicating that inclusion of ETA in risk stratification models will significantly improve the predictive power of these models.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Georg Schmidt, 1. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, 81675 München, Germany. E-mail: gschmidt@tum.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ETA, determined by signal-averaged ECG-derived RR interval tachograms gated to the respiratory cycle, reflects the influence of vagal tone on heart rate. Attenuation of ETA, reflecting less respiratory variation in heart rate, is a strong, independent predictor of mortality in survivors of MI.

TRANSLATIONAL OUTLOOK: Future investigations should address the mechanisms relating ETA to clinical outcomes among MI survivors and explore interventions that might reduce mortality in those with impaired reflex activity.

REFERENCES

1. Ludwig C. On the influence of respiratory movements on blood flow in the aortic system [in German]. Arch Anat Physiol Leipzig 1847;13:242–302.

2. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol 1975;39:801–5.

3. Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol Respir Environ Exerc Physiol 1983;54:961–6.

4. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.

5. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354–81.

6. Grossman P, van Beek J. A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. Psychophysiology 1990;27:702–14.

7. Schumann AY, Kantelhardt JW, Bauer A, et al. Bivariate phase-rectified signal averaging. Physica A 2008;387:5091–100.

8. Bauer A, Kantelhardt JW, Bunde A, et al. Phase-rectified signal averaging detects quasi-periodicities in non-stationary data. Physica A 2006;364:423–34.

9. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA guidelines for ambulatory electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). J Am Coll Cardiol 1999;34:912–48.

10. Eagle KA, Lim MJ, Dabbous OH, et al., for the GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month post discharge death in an international registry. JAMA 2004;291:2727–33.

11. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.

12. Dommasch M, Sinnecker D, Barthel P, et al. Nocturnal respiratory rate predicts non-sudden cardiac death in survivors of acute myocardial infarction. J Am Coll Cardiol 2014;63:2432–3.

13. Sinnecker D, Dommasch M, Barthel P, et al. Assessment of mean respiratory rate from ECG recordings for risk stratification after myocardial infarction. J Electrocardiol 2014;47:700–4.

14. Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? Eur Heart J 2013;34:1967–71.

15. Barthel P, Bauer A, Müller A, et al. Spontaneous baroreflex sensitivity: prospective validation trial of a novel technique in survivors of acute myocardial infarction. Heart Rhythm 2012;8:1288–94.

16. Bauer A, Guzik P, Barthel P, et al. Reduced prognostic power of ventricular late potentials in post-infarction patients of the reperfusion era. Eur Heart J 2005;26:755–61.

17. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353:1390–6.

18. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367:1674–81.

19. Bauer A, Morley-Davies A, Barthel P, et al. Bivariate phase-rectified signal averaging for assessment of spontaneous baroreflex sensitivity: pilot study of the technology. J Electrocardiol 2010;43:649–53.

20. Sinnecker D, Dirschinger R, Barthel P, et al. Post-extrasystolic blood pressure potentiation predicts poor outcome of cardiac patients. J Am Heart Assoc 2014;3:e000857.

21. Rizas KD, Nieminen T, Barthel P, et al. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. J Clin Invest 2014;124:1770–80.

22. Kinugawa T, Dibner-Dunlap ME. Altered vagal and sympathetic control of heart rate in left ventricular dysfunction and heart failure. Am J Physiol 1995;268:R310–6.

23. Howorka K, Pumprla J, Tamm J, et al. Effects of guided breathing on blood pressure and heart rate variability in hypertensive diabetic patients. Auton Neurosci 2013;179:131–7.

24. Helfenbein E, Firoozabadi R, Chien S, Carlson E, Babaeizadeh S. Development of three methods for extracting respiration from the surface ECG: a review. J Electrocardiol 2014;47:819–25.

25. Peduzzi P, Concato J, Feinstein AR, Hoford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–10.

26. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–8.

KEY WORDS heart rate variability, phase-rectified signal averaging, respiratory sinus arrhythmia, risk stratification

APPENDIX For expanded Methods and Results sections as well as supplemental figures, please see the online version of this article.