Respiratory rate predicts outcome after acute myocardial infarction: a prospective cohort study

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Aims
Risk stratification after acute myocardial infarction (MI) remains imperfect and new indices are sought that might improve the post-MI risk assessment. In a contemporarily-treated cohort of acute MI patients, we tested whether the respiratory rate provides prognostic information and how this information compares to that of established risk assessment.

Methods and results
A total of 941 consecutive patients (mean age 61 years, 19% female) presenting with acute MI were enrolled between May 2000 and March 2005. The last follow-up was performed May 2010. Main outcome measure was total mortality during a follow-up period of 5 years. Patients underwent 10-min resting recordings of the respiratory rate within 2 weeks after MI in addition to the measurement of the left ventricular ejection fraction (LVEF) and standard clinical assessment including the GRACE score. During the follow-up, 72 patients died. The respiratory rate was a significant predictor of death in univariable analysis (hazard ratio 1.19 per 1/min, 95% confidence interval: 1.12–1.27) as was the GRACE score [1.04 (1.03–1.05) per point], LVEF [0.96 (0.94–0.97) per 1%], and the diagnosis of diabetes mellitus [2.78 (1.73–4.47)], all \( P \), 0.0001. On multivariate analysis, the GRACE score (\( P \), 0.0001), respiratory rate (\( P \), 0.0001), LVEF (\( P \), 0.013), and diabetes (\( P \), 0.016) were independent prognostic markers.

Conclusion
The respiratory rate provides powerful prognostic information which is independent and complementary to that of existing risk assessment. Simple and inexpensive assessment of the respiratory rate should be considered a complementary variable for the assessment of risk after acute MI.

Keywords
Myocardial infarction • Respiration rate • Risk assessment • GRACE score • Left ventricular ejection fraction

Introduction
After acute myocardial infarction (MI), mortality risk of an individual patient can be estimated at the point of care by clinical risk scores that include variables showing evidence of MI, e.g. ST-segment deviation and elevated cardiac enzymes, co-morbidities, e.g. renal impairment, or abnormal physiology, e.g. systolic blood pressure and heart rate.1–3 The degree of left ventricular impairment by the measurement of the left ventricular ejection fraction (LVEF) is used to select patients suitable for ICD implantation.4,5 Although LVEF measurement involves a substantial investment of specialist time and care, it is neither sensitive nor specific.6–8

Prognostic evaluation is far from perfect, and therefore a search is ongoing for risk markers complementary to currently applied risk scores and LVEF, preferably not imposing undue demands on equipment and/or specialist time.9

Changes in respiratory control due to cardiovascular dysfunction are known to indicate worsened prognosis. For example, chemoreflex hypersensitivity or enhanced ventilatory responses to exercise indicate failure of the auto-regulatory processes of...
the cardiopulmonary system and may serve diagnosis in chronic heart failure. However, the quantification of these reflex abnormalities requires complex equipment, trained staff, and patient co-operation. It is thus unlikely suitable for widespread application.

The most elementary measure of respiratory reaction to cardiovascular disturbance is the elevation in the respiratory rate, which is very easy to measure. An association between respiratory rate and post-MI prognosis has been described well before the contemporary treatment of acute MI. However, this observation is not in routinely used in clinical practice and its validity in modern practice is unknown.

In this study, we examined whether an increased respiratory rate, measured under standardized conditions before hospital discharge, still contains clinically useful prognostic information in MI patients. The study was a prospective observational evaluation of the Autonomic Regulation Trial (ART).

Methods

Study cohort

This study was conducted at two University hospitals of the Technische Universität München, the German Heart Centre, and the Klinikum Rechts der Isar, both in Munich, Germany. Subjects were prospectively enrolled between March 2000 and May 2005, the last follow-up was performed on May 2010. Eligible acute MI patients were aged ≤80 years, presented in sinus rhythm, survived till hospital discharge, and did not meet criteria for immediate implantation of a cardioverter-defibrillator. Acute myocardial infarction was diagnosed if a patient had at least two of the following findings: chest pain for ≥20 min, creatine kinase ≥twice the upper limit of normal, and ST-elevation ≥0.1 mV in two or more contiguous precordial leads on admission. The study protocol was approved by the local ethics committee and written consent was obtained.

Measurements

Respiratory rate

Within the first 2 weeks after index MI, all patients underwent three series of 10-min measurement of the respiratory rate under standardized conditions. Patients were studied in the morning in supine position without interruption of their normal medication regimen. A piezoelectric thoracic sensor (Pro-Tech) was attached, and the signal acquired at 1.6 kHz was analysed automatically (Porti, TMS International, The Netherlands). To avoid disturbing the spontaneous pattern of breathing, patients were not instructed that the sensor was attached to monitor respiration (although they initially gave informed consent to monitoring of ECG, arterial pressure, and respiratory rate as part of the protocol). The last of the repeated 10-min recordings of the respiration rate were used for the measurements used in the study.

Left ventricular ejection fraction

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

Clinical variables

In addition to the respiratory rate and the LVEF, we also assessed the diagnosis of diabetes mellitus and a point-of-care clinical evaluation. Diabetes was considered present if a patient was already diagnosed and was receiving treatment (diet, tablets, or insulin) or if fasting blood glucose concentration repeatedly exceeded 11 mmol/L.

Of the previously suggested clinical assessment scores, we selected the GRACE score proposed for the prediction of long-term prognosis. This includes nine elements (age of the patient, a history of past heart failure, a history of past MI, serum creatinine at admission, the cardiac biomarker status at admission, systolic blood pressure at admission, pulse at admission, ST-deviation at admission, and in-hospital percutaneous coronary intervention).

The presence of chronic obstructive pulmonary disease was defined as the necessity of chronic treatment with bronchodilators and/or inhalation glucocorticoids.

Endpoints

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 that they had died. The endpoint of the study was total mortality during 5 years of the index MI.

Evaluation of risk predictors

In the primary analysis, the respiratory rate, LVEF, and GRACE score were treated as continuous variables. In secondary analysis, the respiratory rate was prospectively dichotomized at 20 cycles per minute, and the LVEF was prospectively dichotomized at 35%. The GRACE score’s dichotomy was set at 120, optimizing the separation between high and low-risk cases (log-rank optimization) as an independent guidance for prospective dichotomy is available.

Statistics

The study was planned and powered to evaluate the influence of clinical variables on mortality. Applying the recommendation by Peduzzi et al. that at least 10 events are needed per variable, the study was continued until 70 events were observed. This also allowed considering some elements of the GRACE score separately (analysis not presented here).

Continuous variables are presented as median and IQR. Categorical data are expressed as absolute frequencies and percentages. A Cox proportional hazard model was used that included all variables at one time (enter procedure) to assess independence of prognostic capability of mortality predictors. The proportional hazards assumption was investigated using Schoenfeld residuals. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated together with the change of the area under the receiver operator characteristic (AUC ROC) for the addition of the respiratory rate to the other variables considered. Differences in the AUC were tested using bootstrap methods. Differences were considered statistically significant if P < 0.05. Reproducibility of measurements of the respiratory rate was assessed by calculating the intra-class correlation coefficient of the three measurements. The regression analysis results were validated by internal bootstrap.

IBM SPSS Statistics 19.0, SPSS, Inc. statistical package and R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) were used in the calculations.
Results

During the recruitment period, a total of 1937 patients hospitalized for acute MI were screened. The inclusion criteria were met by 1511 patients. Out of these, 542 patients declined to participate. In 28 patients who initially consented, the protocol was not carried out for various reasons (e.g. withdrawal of consent, technical defects, early discharge, or transfer to another hospital). The remaining 941 patients constituted the study cohort (Figure 1). Their clinical and demographic characteristics are shown in Table 1 (for further details, see Supplementary material online). Most patients received percutaneous coronary intervention as acute MI therapy and were treated with beta-blockers, angiotensin-converting enzyme inhibitors, statins, and aspirin. Eleven of the 941 patients (1.2%) were lost to follow-up and were censored at the time of last contact. At 5 years of follow-up, 72 (7.7%) patients had died.

Comparison of continuous variables

On both, univariable and multivariable analyses, the respiratory rate, the GRACE score, LVEF, chronic obstructive pulmonary disease, and diabetic status were all statistically associated with the outcome (Table 2 and Supplementary material online). The internal bootstrap validation provided statistically significant results ($P < 0.001$).

An increased respiratory rate was continuously related to worsening prognosis, with a doubling of mortality for every four-breath increment in the respiratory rate (Figure 2). Intra-class correlation coefficient of the three serial measurements of the respiratory rate was 0.9, indicating a high degree of reproducibility.

Analyses by ROC AUC, NRI, and IDI showed increases in the predictive ability of the respiratory rate: IDI increased by 2.12% ($P = 0.004$) for non-surviving patients, and by 0.24% ($P = 0.081$) for survivors. Net reclassification improvement improved in 50.8% of the cases: in 25.1% of patients who died, and in 25.7% of survivors. The ROC AUC increased from 0.79 to 0.82 ($P = 0.12$).

Subgroup analysis

Of the total population, 335 patients (36%) had the GRACE score $>120$, 233 (25%) patients had the respiration rate $>20$ cycles per minute, and 87 patients (9%) had the LVEF $<35%$.

The left panel of Figure 3 shows that in patients with GRACE $<120$, no meaningful risk stratification is provided by the LVEF, respiratory rate, or their combination. All the survival curves in this panel of Figure 3 show 5-year mortality $<5\%$ and are not statistically different from each other ($P = 0.936$).

On the contrary, the right panel of Figure 3 shows that in patients with the GRACE score $\geq 120$; both the LVEF and the respiratory rate provide further meaningful risk prediction. The differences between the survival curves shown in the panel are highly statistically significant ($P < 0.0001$). Among these patients, those with both, LVEF $\leq 35\%$ and respiration rate $\geq 20$ breaths/min, are at the greatest risk with 5-year mortality exceeding 50%. Patients with either LVEF $\leq 35\%$ or respiration rate $\geq 20$ breaths/min have practically the same intermediate risk of 5-year mortality $\sim 25\%$ although the survival profile over the observation period is different. Interestingly, patients with the GRACE score $\geq 120$ but both LVEF $>35\%$ and respiration rate $<20$ breaths/min (who constitute $\sim 65\%$ of all patients with the
Table 1  Clinical characteristics of the study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study population (n = 941)</th>
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<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>61 (52–69)</td>
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<tr>
<td>Females, n (%)</td>
<td>182 (19.3)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>184 (19.6)</td>
</tr>
<tr>
<td>History of previous MI, n (%)</td>
<td>90 (9.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>682 (72.5)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>488 (51.9)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>39 (4.1)</td>
</tr>
<tr>
<td>CK max (U/l), median (IQR)</td>
<td>1302 (647–2465)</td>
</tr>
<tr>
<td>LVEF (%), median (IQR)</td>
<td>53 (45–60)</td>
</tr>
</tbody>
</table>

MI localization

| Anterior, n (%)                         | 391 (41.6)                 |
| Posterior, n (%)                        | 435 (46.2)                 |
| Lateral, n (%)                          | 102 (10.8)                 |
| Unclassified, n (%)                     | 12 (1.3)                   |

BMI (kg/m²), median (IQR)

| 27 (24–29)                              |

Serum creatinine (mg/dL), median (IQR)

| 1.1 (0.9–1.3)                           |

Cardiogenic shock/CPR, n (%)

| 41 (4.4)                                |

Intervention

| PCI, n (%)                              | 878 (93.3)                 |
| Thrombolysis, n (%)                     | 14 (1.5)                   |
| CABG, n (%)                             | 6 (0.6)                    |
| No revascularization possible, n (%)    | 43 (4.6)                   |

Aspirin, n (%)

| 913 (97.0)                              |

Clopidogrel, n (%)

| 920 (97.8)                              |

Beta-blockers, n (%)

| 897 (95.3)                              |

ACE-inhibitors, n (%)

| 885 (94.0)                              |

Statins, n (%)

| 879 (93.4)                              |

Diuretics, n (%)

| 415 (44.1)                              |

GRACE score ≥120) are only at relatively low risk not very different from those with the GRACE score <120, with 5-year mortality <10%. The tests for interaction in the Cox model were both significant (interaction respiration rate and LVEF: P = 0.013, respiration rate and GRACE: P = 0.014). Kaplan–Meier curves of patients with a GRACE score ≥120 stratified by a combination of the left ventricular function ≤35% and the respiratory rate ≥20 breaths/min are shown in the Supplementary material online.

Analyses by ROC AUC, NRI, and IDI showed all significant increases in the predictive ability of the respiratory rate: IDI increased by 4.26% (P = 0.007) for non-surviving patients and by 1.25% (P = 0.012) for survivors. Net reclassification improvement improved in 58.4% of the cases: in 25.9% of patients who died, and in 32.4% of survivors. The ROC AUC increased from 0.71 to 0.78 (P = 0.004).

Discussion

The study shows that the measurement of resting respiratory rate under standardized conditions provides important prognostic information in patients with contemporary post-MI treatment. This prognostic information is independent of and complementary to that of established risk assessment including left ventricular ejection fraction and point-of-care-risk assessment.

The respiratory rate is easy and inexpensive to measure and—if performed under controlled conditions—highly reproducible. There are no technical barriers to its incorporation as part of immediate point-of-care-risk assessment.

The study measured the respiratory rate shortly prior to hospital discharge. The protocol was designed in this way since earlier measurement (e.g. after admission) might have interfered with clinical care in the acute MI phase. In designing the protocol, we also hypothesized that the measurement of the respiratory rate under controlled conditions just before hospital discharge would be most predictive of future risk.

Respiratory responses in heart disease

There is a body of evidence that an abnormal respiratory response in heart disease is an indicator of adverse prognosis. The respiratory response can be quantified using a variety of stimuli. Patients with the most abnormal ventilatory responses during exercise stress testing have a poor prognosis, even when limiting the analysis to those with preserved exercise capacity. Abnormal responses can also be elicited without physical exercise by the stimulation of the chemoreflexes that raise ventilation when carbon dioxide levels rise or oxygen levels fall. However, despite clear evidence from these reflex measurements, these tests are unlikely to become clinical routine in post-MI patients because they require significant specialist involvement and equipment, as well as substantial patient co-operation.

Our prospective data collection protocol did not include serum creatinine assessment on the same day as the respiratory frequency was measured (this was available in slightly less than two-thirds of the patients). When using serum creatinine data...
from up to ±3 days of respiration measurement, we were able to add the estimated glomerular filtration rate to the Cox regression model. This weakened the multivariable contribution of the GRACE score (χ² statistics was lowered to 22.7) but the contribution of the respiratory rate remained unchanged. Adding medication to the model had no further effect (for details, see supplementary material online).

**Pathophysiology of abnormal respiratory responses**

Circulatory failure can affect the physiology of respiration by altering both ventilatory control and pulmonary perfusion. An increase in left ventricular filling pressure (and hence in pulmonary capillary pressure) affects—among others—pulmonary compliance and alveolocapillary membrane conductance. These alterations raise the respiratory rate (rather than tidal volume), which can be detected using any of a wide spectrum of monitoring systems. This simple count of the respiratory rate was first identified to be a prognostic marker after MI before the advent of routine echocardiography, and of modern medical and interventional therapy.13 Our data show that the prognostic value of the respiratory rate remains undiminished in the era of modern acute treatment.

It is well established that frank pulmonary oedema is a poor prognostic sign in acute MI.23 In this study, however, only eight patients had clinically overt pulmonary congestion. Repeating the analyses after exclusion of these patients revealed essentially identical results (data not shown).

Subclinical pulmonary congestion, and abnormally enhanced physiological responses to it, may well be a *forme fruste* of pulmonary oedema. There may also be a contribution from the profound disturbance of cardiac autonomic control seen in acute MI, with increased sympathetic activity and vagal withdrawal which could further interfere with ventilatory control. Observations from

<table>
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<th>Table 2 Univariable and multivariable Cox regression analysis</th>
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<tr>
<td><strong>Variable</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Respiratory rate (per 1/min)</td>
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<tr>
<td>LVEF (per 1%)</td>
</tr>
<tr>
<td>Diabetes mellitus (n/y)</td>
</tr>
<tr>
<td>GRACE score (per 1 point)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (n/y)</td>
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All χ² values are distributed with 1 degree of freedom. LVEF, left ventricular ejection fraction; GRACE score, composite of age of the patient, serum creatinine, history of a past MI, history of past congestive heart failure, in-hospital percutaneous coronary intervention, pulse, systolic blood pressure, ST-segment deviation and positive enzymes; COPD, chronic obstructive pulmonary disease.

**Figure 3** Cumulative rates of deaths, in patients with a GRACE score of <120 (left panel) and ≥120 (right panel) stratified according to left ventricular function (LVEF ≤35% vs. LVEF >35%), and respiratory rate (≥20 breaths/min vs. <20 breaths/min). The numbers of patients of the individual groups involved in the analysis at 0, 1, 2, 3, 4, and 5 years are shown below each graph; the order of the rows corresponds to the order of the mortality curves. Test by log-rank statistics.
patients with chronic heart failure show increased ventilation as a result of increased che-morreflex gain and peripheral stimuli,24,25 which signify poor prognosis.11,12 These changes are linked to cardiac autonomic control and it is conceivable that similar changes might occur acutely after MI. Increase in the respiratory rate might therefore also be a reflection of disturbed autonomic control.

Nevertheless, regardless of the precise mechanism, the respiratory rate is arguably the simplest physiological variable of all to measure, requiring only standard medical equipment.

Clinical implications

The prognostic strengths combined with simplicity of measurement make the respiratory rate a strong candidate to include in risk-assessment algorithms. The subgroup analysis of our data suggests that the respiratory rate can complement the LVEF, for prognostic assessment especially in patients with abnormal clinical scores. In our data, the patients with an abnormal GRACE score represented ~35% of all post-MI patients of whom ~30% presented with an increased respiratory rate. On the contrary, in our patients with a low to moderate GRACE score (65% of the population), the mortality risk was very low and no meaningful improvement in risk prediction was achieved by considering respiration rate, LVEF, or their combination.

Results of single risk stratification studies might serve as a starting point of randomized interventional studies which are needed to prove the appropriateness of any general proposal of changes in clinical practice. At the same time, risk assessment on its own can and should contribute to individualized medicine. Thus, while the standard clinical procedures should presently be used in patients with an elevated respiratory rate, their scheduling, combination, and intensity should be tailored to the increased risk. These patients should receive closer clinical attention with more densely scheduled diagnostic procedures, more frequent follow-up assessments, and increased intensity of therapy control.

Study limitations

This study only evaluated the respiratory rate and not ventilation or tidal volume. The rationale for this restriction was three-fold. First, ventilation it primarily altered by the respiratory rate and not tidal volume in heart disease.22 Secondly, the measurement of tidal volume requires some element of specialized equipment which may be difficult to provide and therefore limit universal applicability in routine clinical settings. Thirdly, although our patients were generally aware that their physiology including respiration was monitored, they were put to no significant inconvenience by that measurement and did not have specific attention drawn to the time window when the quantification of the respiratory rate was made. This would not be possible with tidal volume assessment, possibly influencing the natural character of measured data.

As detailed lung function measurements were not prospectively collected, we were unable to classify lung disease beyond the distinction of patients with chronic obstructive pulmonary disease. Also, we have not collected comparable data of the respiratory rate on admission since the detailed protocol on measuring the respiration rate during undisturbed supine rest would be difficult if not impossible to include with the admission tests. We are thus unable to comment on the development of the respiration rate during hospital stay and of its prognostic strength.

Our study cannot confirm the precise mechanism by which the increase in mortality is associated with higher respiratory rates. Nevertheless the effect is large: indeed comparing well in magnitude to the effects of the GRACE score and of low ejection fraction.

Finally, per study protocol, the age of investigated patients was not exceeding 80 years. We are unable to comment on any extrapolation of the results to older patients especially since pulmonary disease might be more prevalent in this age group.

Conclusion

After MI, patients with an elevated respiratory rate have a significantly worse survival. A four-breath-per-minute increase in the respiratory rate indicates a doubling of risk. The prognostic information of the respiratory rate is independent to those of established risk assessments models. In patients with high-point-of-care-risk scores (e.g. such as the GRACE score), the respiratory rate allows further risk stratification.

As one of the simplest, quickest and most inexpensive of physiological variables to measure, the independent prognostic power of the respiratory rate commends it for consideration for incorporation within established risk-assessment strategies for patients after MI even in the era of modern investigations and treatment strategies. In conjunction with clinical assessment and LVEF, it allows identifying patients with truly benign prognosis as well as those at substantial risk of death.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: none declared.

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