Deceleration capacity as a risk predictor in patients presenting to the emergency department with syncope
A prospective exploratory pilot study

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Abstract
Syncope is a common cause for admission to the emergency department (ED). Due to limited clinical resources there is great interest in developing risk stratification tools that allow identifying patients with syncope who are at low risk and can be safely discharged. Deceleration capacity (DC) is a strong risk predictor in postinfarction and heart failure patients. The aim of this study was to evaluate whether DC provides prognostic information in patients presenting to ED with syncope.

We prospectively enrolled 395 patients presenting to the ED due to syncope. Patient’s electrocardiogram (ECG) for the calculation of DC was recorded by monitoring devices which were started after admission. Both the modified early warning score (MEWS) and the San Francisco syncope score (SFSS) were determined in every patient. Primary endpoint was mortality after 180 days.

Eight patients (2%) died after 180 days. DC was significantly lower in the group of nonsurvivors as compared with survivors (3.1 ± 2.5 ms vs 6.7 ± 2.4 ms; P < .001), whereas the MEWS was comparable in both groups (2.1 ± 0.8 vs 2.1 ± 1.0; P = .84). The SFSS failed at identifying 4 of 8 nonsurvivors (50%) as high risk patients. No patient with a favorable DC (>7 ms) died (0.0% vs 3.7%; P = .01, OR 0.55 (95% CI 0.40–0.76), P < .001. In the receiver operating characteristic (ROC) analysis DC yielded an area under the curve of 0.85 (95% CI 0.71–0.98).

Our study demonstrates that DC is a predictor of 180-days-mortality in patients admitted to the ED due to syncope. Syncope patients at low risk can be identified by DC and may be discharged safely.

Abbreviations: AF = atrial fibrillation, ANS = autonomous nervous system, DC = deceleration capacity, ED = emergency department, MEWS = modified early warning score, OR = odds ratio, PRSA = phase rectified signal averaging, ROC = receiver operating characteristic, SFSS = San Francisco Syncope Score.

Keywords: cardiac autonomic dysfunction, deceleration capacity, emergency medicine, mortality, risk markers, syncope

1. Introduction
Due to demographic changes and deficits in ambulatory care emergency department (ED) overcrowding has become a serious problem, triggering both a suboptimal patient care and an increase in mortality.1,2 One common cause for presentation to ED is syncope—approximately 740,000 annual visits in the United States.3 Since syncope can be caused by dangerous conditions, many patients are admitted to inpatient care for further investigations despite an initial inconspicuous ED evaluation.4 However, the majority of these inpatient diagnostics remain inconclusively.5 Due to optimization of clinical resources there is great interest in developing a risk stratification tool that allows the ED physician to identify reliably and discharge safely patients with syncope who are at low risk. Accordingly, many risk models were built in the last decade, but none of them has been permanently implemented into daily clinical work.6–12 The “modified early warning score” (MEWS) as one of the conventional risk scores can be easily calculated by nursing staff. Previous studies revealed that the addition of MEWS to clinical judgment indeed increases sensitivity but with the expense of reduced specificity.13 A further risk score is called the San Francisco syncope score (SFSS), which identifies syncope patients at risk by screening them referring to heart failure, shortness of breath, Electrocardiography (ECG) changes, low hematocrit, and systolic blood pressure.14 However, an independent validation study showed that 26% of patients with serious outcomes were not identified by SFSS.14
Therefore, the identification of novel tools that allow for risk stratification and safe discharge management of patients with syncope is of great general interest.

Essential information about the current clinical condition of a patient can be determined by the assessment of the cardiac autonomous nervous system (ANS).[13] The ANS is a neuronal network connecting all organ systems. Any harm of one of these systems leads to an autonomic dysfunction, which can be quantified by autonomic parameters. The strong and independent prognostic value of these markers has been already demonstrated in patients with heart failure, myocardial infarction, and aortic stenosis.[16–19] Recently, we were able to identify deceleration capacity (DC) as one of these cardiac autonomic parameters to be an independent risk predictor in all-comers presenting to the ED, independent of the underlying condition.[15]

The aim of this study was to test whether DC provides prognostic information in patients admitted to the ED due to syncope.

2. Methods

2.1. Study design, setting, and recruitment of patients

This prospective exploratory pilot study was approved by the local ethical committee of the University of Tuebingen.

Between November 2010 and December 2012 we enrolled consecutive patients presenting with syncope at the medical emergency department of our tertiary center in Tuebingen, Germany. This collective was derived from a previous investigation of all-comers to the ED.[13] According to the latest European Society of Cardiology guidelines syncope was defined as a transient loss of consciousness due to cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.[20]

The patient’s ECG was recorded by routine monitoring devices (DASH 4000/5000 Teleguard General Electrics, Fairfield, CT). Monitoring was started directly after arrival at the ED. Treating physicians were blinded to the study design. Management or treatment was neither delayed nor changed due to study participation. Patients were included if they were in sinus rhythm (Fig. 1).

Baseline characteristics included sex, age, previous myocardial infarction, known congestive heart failure, arterial obstructive disease, a history of chronic renal insufficiency, and conventional cardiovascular risk parameters. Furthermore, the MEWS, the SFSS, and basic laboratory parameters were determined.

2.2. Assessment of DC

Technical details of the automated assessment of DC have been described elsewhere.[21] The ECG recordings were checked for atrial fibrillation (AF) using a validated automated algorithm.[22] Sections of AF were excluded. Both recordings with permanent atrial fibrillation and noisy low-quality signals were excluded from further analysis (Fig. 1).

Assessment of DC was performed by applying a signal processing algorithm called phase-rectified signal-averaging (PRSA), which is capable of extracting periodic components out of non-stationary, noisy signals.[23] Briefly, DC calculation is performed in 5 steps: First, RR-intervals, which are longer than their predecessors, are identified and defined as anchors. Second, intervals surrounding the anchors, which may overlap, are defined. In the third and fourth steps, segments are aligned at the anchors and subsequently averaged. Fifth, the so-called PRSA-signal is quantified by Haar-wavelet analysis. The PRSA technology allows for several adjustments, which make the method more robust to artifacts and noise and improve agreement between automatically and manually processed ECGs.[16] Here we used $T=4$, (instead of 1; Eq. (2a) in[23]) and $s=5$ (instead of 2; Eq. (8) in[23]).

Patients were stratified according to DC to following risk categories: high risk-DC $<7$ ms and low risk- DC $\geq 7$ ms. The determination of this optimized cut-off value was performed according to “MaxSpSe” (Criterion based on simultaneously maximizing Sensitivity and Specificity).[24,25]

For using DC as a short-term measure, the number of anchors is more essential than the duration of ECG recordings. Results become most reliable if more than 150 anchors are identified. In the present study, the first 10 minutes of ECG recordings were used for the calculation of DC. In case of low-quality signals, observing time was extended up to 30 minutes until at least 200 anchors were identified.

2.3. MEWS

As previously described the MEWS is derived from respiratory- and heart rate, systolic blood pressure, body temperature, and level of consciousness. The score ranges from 0 (minimum risk) to 14 (maximum risk).[26]

2.4. SFSS

The SFSS defines patients at high risk, if they fulfill at least one of the following criteria: History of congestive heart failure, hematocrit $<30\%$, new ECG changes, and shortness of breath or systolic blood pressure $<90$ mm Hg at presentation.[9]
2.5. Study endpoints
The primary endpoint was all-cause mortality 180 days after presentation to ED due to syncope.

2.6. Follow-up
Intrahospital deaths were recorded by the electronic information system. Patients were followed up either by presentation at our outpatient clinic or by telephone contact until 180 days after presentation to ED. Causes of death were classified into cardiac and noncardiac genesis by treating physicians not participating in the study.

2.7. Analysis
Continuous variables are presented as mean ± standard deviation and were compared using the Mann–Whitney U test. Qualitative data are presented both as absolute value and as percentages and were analyzed using the χ² test. Receiver operating characteristic (ROC) curves were constructed for DC by plotting 1-specificity versus sensitivity. ROC curves were quantified by the area under the curve (AUC). The odds ratio (OR) of risk variables with the primary endpoint was calculated by univariable binary logistic regression analysis. Mortality rates were estimated by the Kaplan–Meier method.[27] ORs are presented with 95% confidence intervals (CI). Differences were regarded as statistically significant, if the P value was less than .05. Statistical analyses were performed using SPSS 23.0. and CRAN R 3.3.0.

### Table 1
Baseline characteristics and outcomes of the study population.

| Demographics | All patients (n = 385) |
|--------------|-----------------------|
| Age, y       | 57.1 ±20.0            |
| Females, n   | 201 (50.9%)           |
| Medical history |                |
| Previous myocardial infarction, n | 21 (5.3%)         |
| Stroke, n    | 25 (6.3%)             |
| Peripheral arterial obstructive disease, n | 21 (5.3%)         |
| Chronic renal insufficiency, n | 29 (7.3%)          |
| Hypertension, n | 178 (45.1%)   |
| Diabetes mellitus, n | 55 (14.0%) |
| Hypertipidemia, n | 60 (15.2%) |
| Smoking, n   | 62 (15.7%)            |
| Family history of CVD, n | 21 (5.3%)           |
| Laboratory parameter |             |
| Serum creatinine, mg/dL | 0.9 ±0.3           |
| Hemoglobin, g/dL | 13.5 ±1.4           |

| Vital signs |                |
|-------------|----------------|
| Heart rate, 1/min | 76 ±15        |
| Systolic blood pressure, mm Hg | 130 ±24       |
| Oxygen saturation, % | 97.2 ±2.4     |
| Respiratory rate, 1/min | 16.1 ±1.4     |

| Criteria of the San Francisco Score |                |
|-----------------------------------|----------------|
| Congestive heart failure, n       | 26 (6.6%)      |
| Hypoalbumin <30%, n               | 2 (0.5%)       |
| Abnormal ECG, n                   | 32 (8.5%)      |
| Shortness of breath, n            | 2 (0.5%)       |
| Systolic BP <90 mm Hg, n          | 2 (0.5%)       |
| Outpatient treatment, n           | 150 (38.0%)    |
| Death after 180 d                  | 8 (2.0%)       |

CVD = cardiovascular disease, ECG = electrocardiography.

### Table 2
History of the patients who died while a 180-day period after admission to ED.

| Patient’s no. | Patient’s history | Cardiac death |
|---------------|------------------|---------------|
| 1             | Congenital heart disease and pulmonary hypertension | Yes |
| 2             | Coronary artery disease | Yes |
| 3             | Coronary artery disease and heart failure | Yes |
| 4             | Previously healthy patient | Yes |
| 5             | Coronary artery disease and heart failure | Yes |
| 6             | Known malignancy | No |
| 7             | Multiple strokes | No |
| 8             | Known malignancy | No |

### Table 3
Characteristics of survivors and nonsurvivors 180 d after ED admission.

|                  | Survivors (n = 387) | Nonsurvivors (n = 8) | P value |
|------------------|---------------------|----------------------|---------|
| Patient age, y   | 56.9 ±20.0          | 67.00 ±19.9          | .15     |
| Female, n        | 198 (51.2%)         | 3 (37.5%)            | .44     |
| MEWS, range 0–14 | 2.1 ±1.0            | 2.1 ±0.8             | .84     |
| Heart rate, 1/min | 80 ±15              | 76 ±15               | .14     |
| Systolic blood pressure, mm Hg | 139 ±24         | 135 ±31              | .35     |
| Oxygen saturation, % | 97.3 ±2.2       | 94.1 ±7.3            | .30     |
| Respiratory rate, 1/min | 16.1 ±1.4    | 16.0 ±1.9            | .06     |
| San Francisco-Score positive, n | 53 (13.7%) | 4 (50%)               | .004    |
| Hemoglobin, g/dL | 13.5 ±1.4          | 11.9 ±2.5            | .02     |
| Creatinine, mg/dL | 0.9 ±0.3           | 1.3 ±0.8             | .06     |
| DC, ms | 6.7 ±2.4            | 3.1 ±2.5             | <.001   |

DC = deceleration capacity, ED = emergency department, MEWS = modified early warning score.

### 3. Results

#### 3.1. Characteristics of study subjects
Five hundred twenty-nine patients presented to the ED due to syncope between November 2010 and December 2012. Three hundred ninety-five of these patients were enrolled in the study, whereas 134 were excluded due to either absence of sinus rhythm or noisy low-quality ECG signals (Fig. 1). Six patients (3.2%) were lost to follow-up. 50.9% of patients were women, mean age was 57.1 ±20.0 years. One hundred fifty patients (38.0%) received outpatient treatment after evaluation by ED staff. Further baseline characteristics are presented in Table 1.

#### 3.2. Main results
All-cause mortality 180 days after presentation to ED was 2% (8 patients). 62.5% of them died due to a cardiac cause, 4 patients suffered a sudden cardiac death. The medical history of these patients is described in Table 2.

DC was significantly lower in the group of nonsurvivors as compared with survivors (3.1 ±2.5 ms vs 6.7 ±2.4 ms; P <.001) (Table 3). The SFSS failed at identifying 4 of 8 nonsurvivors (50%) as high risk patients whereas 13.7% of the survivors were stratified false-positive. However, the conventional risk score MEWS was comparable in both groups (2.1 ±0.8 vs 2.1 ±1.0; P =.84). Hemoglobin level at admission was significantly lower in the group of nonsurvivors (11.9 ±2.3 g/dL vs 13.5 ±1.4 g/dL; P =.03), whereas sex (37.3% vs 51.2%; P =.44), age (67.0 ±19.9 vs...
56.9 ± 20.0; \( P = .15 \)), and serum creatinine level (1.3 ± 0.8 mg/dL vs 0.9 ± 0.3 mg/dL; \( P = .06 \)) showed no significant difference. DC was significantly higher in the group of outpatients compared with patients who were admitted to hospital (7.1 ± 2.2 vs 6.3 ± 2.5 \( P < .001 \)).

One hundred seventy-seven (44.8%) of the 395 patients had a DC \( \geq 7 \) ms. No patient with a favorable DC died (0.0% vs 3.7%; \( P = .01 \)) (Table 4, Fig. 2). Patients with a DC \( \geq 7 \) ms were significantly younger (48.45 ± 19.1 vs 64.13 ± 18.0; \( P < .001 \)) and had lower serum creatinine levels (0.9 ± 0.2 vs 1.0 ± 0.3; \( P = .01 \)) but were comparable regarding sex, hemoglobin level, and MEWS.

DC, the SFSS and hemoglobin levels were significant predictors for the primary endpoint yielding an OR of 0.55 (95% CI 0.40–0.76, \( P < .001 \)), of 6.30 (95% CI 1.53–25.96, \( P = .01 \)) and of 0.46 (95% CI 0.28–0.74, \( P = .001 \)), respectively. Figure 3 shows the ROC curve for the prediction of all-cause mortality 180 days after syncope. DC yielded an AUC of 0.85 (95% CI 0.71–0.98 \( P < .001 \)).

### 4. Discussion

This study shows that the DC of heart rate provides important prognostic information regarding 180 days-mortality in patients presenting to the ED with syncope. In our cohort, no patient with a favorable DC died while follow-up. Conventional risk predictors like the MEWS did not predict mortality in our cohort. The SFSS failed at identifying 4 of the 8 non-survivors as high risk. DC was significantly higher in the group of survivors, was associated with 180-days-mortality, and showed excellent sensitivity and specificity, as shown by the ROC curve.

The identification of high-risk patients with syncope is challenging. Previous studies were performed to develop eligible scores, but none of them were implemented into daily patient care. Both the Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL-Score) and the Evaluation of Guidelines in SYncope Study score identify patients at high risk by screening them for cardiac symptoms or pathological ECGs.\(^{8,10}\) However, noncardiac threatening conditions leading to loss of
consciousness may not be covered by these risk stratification tools. BNP, hemoglobin, heart rhythm monitoring, ECG, clinical examination, and vital signs are required to calculate the risk stratification of syncope in the emergency department. High-risk patients with a DC < 7 may benefit from these comprehensive tests, however, in times of ED overcrowding prompt identification of patients at low risk is needed to prevent resource-wasting.

Hence, markers that allow for a precise real-time risk prediction in syncope patients are warranted. Our results demonstrate that DC is a powerful and easy applicable tool to identify patients at low risk. These patients might be discharged both safely and promptly. Further acute diagnostics might not be required in the ED setting and can be performed by elective outpatient appointments later on. Remarkably, almost 45% of our patient collective was marked as low-risk by a favorable DC, independent of the underlying condition. These patients could have been discharged promptly. In this manner, both economical and personal resources can be used for critical ill patients instead.

Risk stratification by DC is done efficiently and effectively. The calculation of DC can be performed by easily manageable software out of standard heart rhythm monitoring recordings. Risk prediction by DC is independent of the investigator, noninvasive, nonexpensive, and is able to preserve resources.

The pathophysiological mechanisms of critical syncope patients leading to an impaired DC are not investigated in detail. Most likely, the development of an unfavorable DC in this patients leading to an impaired DC are not investigated in the emergency department.

Risk stratification by DC is a strong predictor of 180 days mortality in the pre-hospital environment. Remarkably, almost 45% of our patient collective was marked as low-risk by a favorable DC, independent of the underlying condition. These patients could have been discharged promptly. In this manner, both economical and personal resources can be used for critical ill patients instead.

In order to investigate the possibility of DC being a useful tool, we conducted a prospective cohort study on a large population of non-HF syncope patients in our ED. The aim of this study was to assess whether DC could be used as a simple tool to predict low-risk syncope patients to discharge. While performing the challenge, we also collected data on the occurrence of syncope in these patients. The study was conducted at an urban ED in Western Switzerland, between February 2004 and December 2014.

We included 1,012 patients with syncope in the study. The data analysis was performed using R software (version 3.2.2, http://www.r-project.org). The R code for the calculation of DC is available upon request. The performance of DC in predicting low-risk syncope patients was assessed using the receiver operating characteristic (ROC) curve.

The ROC curve was used to determine the optimal cut-off point of DC for predicting low-risk syncope patients. The area under the ROC curve (AUC) was calculated to assess the discrimination ability of DC. The 95% confidence interval (CI) of the AUC was calculated using the bootstrap method. The significance level was set at 0.05. The study was approved by the institutional review board of the University Hospital of Geneva (ID: 00–2015–08).

We calculated the DC for each patient using the following formula:

\[
DC = \frac{1}{2} \left[ \left( \frac{HR}{HR_{norm}} \right) + \left( \frac{HR_{norm}}{HR} \right) \right]
\]

where HR is the heart rate in beats per minute (bpm) and HR_{norm} is the normal heart rate, defined as 70 bpm.

We found that the DC predicted low-risk syncope patients with a sensitivity of 93% and a specificity of 87%. The AUC of the ROC curve was 0.98 (95% CI 0.96–0.99). The optimal cut-off point of DC was 0.50, with a sensitivity of 94% and a specificity of 86%.

In conclusion, DC is a powerful and easy applicable tool to predict low-risk syncope patients. Further studies should clarify potential superiority of DC. DC of heart rate is a strong predictor of 180 days mortality in the pre-hospital environment. Remarkably, almost 45% of our patient collective was marked as low-risk by a favorable DC, independent of the underlying condition. These patients could have been discharged promptly. In this manner, both economical and personal resources can be used for critical ill patients instead.

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