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Deceleration capacity for rapid risk stratification in patients suffering from acute ischemic stroke

A prospective exploratory pilot study

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Abstract

Deceleration capacitiy for rapid risk stratification in stroke patients

Cerebral ischemia is a major cause of neurologic deficit and patients suffering from ischemic stroke bear a relevant risk of mortality. Identifying stroke patients at high mortality risk is of crucial clinical relevance. Deceleration capacity of heart rate (DC) as a parameter of cardiac autonomic function is an excellent predictor of mortality in myocardial infarction and heart failure patients.

The aim of our study was to evaluate whether DC provides prognostic information regarding mortality risk in patients with acute ischemic stroke.

From September 2015 to March 2018 we prospectively enrolled consecutive patients presenting at the Stroke Unit of our university hospital with acute ischemic stroke who were in sinus rhythm. In these patients 24 hours-Holter-ECG recordings and evaluation of National Institute of Health Stroke Scale (NIHSS) were performed. DC was calculated according to a previously published algorithm. Primary endpoint was intrahospital mortality.

Eight hundred seventy eight stroke patients were included in the study. Intrahospital mortality was 2.8% (25 patients). Both DC and NIHSS were significantly different between non-survivors and survivors (Mean ± SD: DC: 4.1 ± 2.8 ms vs 6.3 ± 3.3 ms, $P < .001$) (NIHSS: 7.6 ± 7.1 vs 4.3 ± 5.5, $P = .02$). DC achieved an area under the curve value (AUC) of 0.708 for predicting intrahospital mortality, while the AUC value of NIHSS was 0.641. In a binary logistic regression analysis, DC, NIHSS and age were independent predictors for intrahospital mortality (DC: HR CI 95%: 0.88 (0.79–0.97); $P = .01$; NIHSS: HR CI 95%: 1.08 (1.02–1.15); $P = .01$; Age: HR CI 95%: 1.07 (1.02–1.11); $P = .004$. The combination of NIHSS, age and DC in a prediction model led to a significant improvement of the AUC, which was 0.757 ($P < .001$, incremental development index [IDI] 95% CI: 0.037 (0.018–0.057)), compared to the individual risk parameters.

Our study demonstrated that DC is suitable for both objective and independent risk stratification in patients suffering from ischemic stroke. The application of a prediction model combining NIHSS, age and DC is superior to the single markers in identifying patients at high mortality risk.

Abbreviations: ANS = autonomous nervous system, DC = deceleration capacity, IDI = incremental development index, NIHSS = National Institute of Health Stroke Scale, ROC = receiver-operator characteristic, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

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

Editor: Ovidiu Constantin Baltatu.

This study was supported by the Geschwister-Kessel-Stiftung, Langenenslingen, Germany.

This study was approved by the local ethical committee of the University of Tuebingen. The committee reference number is 522/2012BO2.

The authors do not have any affiliation to one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this article.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Duckheim M, Gaebler M, Mizera L, Schreieck J, Poli S, Ziemann U, Gawaz M, Meyer-Zuern CS, Eick C. Deceleration capacity for rapid risk stratification in patients suffering from acute ischemic stroke: A prospective exploratory pilot study. Medicine 2021;100:13(e25333).

Received: 30 October 2020 / Received in final form: 6 February 2021 / Accepted: 23 February 2021

http://dx.doi.org/10.1097/MD.0000000000025333

1. Introduction

Acute ischemic stroke is a major cause of neurologic deficit. About 800.000 patients in the United States and nearly 300.000 patients in Germany suffer from this fatal event every year.[1,2] Although incidence has decreased the last decade, stroke is still the fifth most common cause of death.[3] Several scores as the National Institute of Health Stroke Scale (NIHSS) were developed to assess both the neurologic impact and disability.[4,5] However, a tool, which is capable to identify high risk stroke patients quickly and reliably, is of essential clinical relevance. Predicting unfavorable courses of stroke patients enables the physician both to react and treat appropriately, which might be life-saving and prognosis-improving.

The assessment of the cardiac autonomic system (ANS) provides crucial information about current clinical condition of a patient.[6,7] The integrity of any organ system is reflected by the ANS. Consecutively, any damage leads to an autonomic dysfunction, which can be measured and quantified by autonomic parameters derived from standard ECGs. Previously, the excellent prognostic value of these markers has been demonstrated in numerous disease entities.[8–13] Based on the results of a small scale study correlation between changes in ANS and mortality in patients with acute ischemic stroke could be assumed.[14] However, data from larger, prospective trials are still missing.

Deceleration capacity (DC) as one of these parameters mirrors the ability to decelerate the heart rate which reflects the vagal tone. DC is calculated by the mean altitude of all decreasing-associated undulations of the heart rate.[10] Alterations of DC in patients with acute ischemic stroke have been demonstrated in a small investigation with 63 participants.[15] However, the prognostic value of this parameter has never been examined and, therefore, remains unclear.

The aim of this study was to test whether DC provides prognostic information with regard to intrahospital mortality in acute ischemic stroke patients.

2. Methods

2.1. Study design, setting and recruitment of patients

This prospective explorative pilot study (ClinicalTrials.gov Identifier: NCT04352790) was approved by the local ethical committee of the University of Tuebingen. (522/2012BO2). Informed consent was waived by the ethical committee. Data are available on request from the corresponding author.

Data were collected between September 2015 and March 2018. All Patients, who presented with acute ischemic stroke at the Stroke Unit of our tertiary center in Tübingen, Germany, were enrolled in the study.

All patients received 24 hours-Holter ECGs (Getemed CardioMem CM 3000SM 24 hours Holter ECG Recorder) to detect previously unknown atrial fibrillation during their stay in the hospital. These ECG recordings were routinely assessed by a cardiologist. Neither he nor the treating neurologists were informed about the results of DC calculation. For that reason, they were not able to change patient management, purely due to the value of DC, and participation in this prospective, observational study did not delay or change treatment.

Baseline characteristics included sex, age, medical history, cardiovascular risk factors, laboratory markers sensitive Troponin I and NT-pro-BNP were evaluated. Ultrasound diagnostics, including transthoracic and transesophageal echocardiography as well as Doppler sonography of the carotid arteries were performed. Furthermore TOAST-Classification (Trial of Org 10172 in Acute Stroke Treatment) and NIHSS were determined.[5,16]

The primary endpoint was intrahospital all-cause mortality. Intrahospital deaths were enrolled via the hospital electronic information system (SAP ERP 6.0).

2.2. Assessment of DC

The assessment of DC was performed automatically out of Holter ECG recordings. Technical details have been reported before.[17] Briefly, these ECG recordings were screened for episodes of atrial fibrillation using a validated algorithm.[18] Those episodes were cut out. ECGs from patients with either permanent atrial fibrillation or noisy and diminished-quality ECG signals where DC cannot be calculated were excluded.

Calculation of DC was executed by applying a signal processing algorithm called phase-rectified signal-averaging, which is able to identify periodic components out of non-stationary, noisy signals.[19] DC was assessed in 5 steps: Firstly, RR-intervals were identified which are longer than their precursors. These RR-intervals were defined as so-called anchors. Secondly, segments surrounding the anchors were defined. Thirdly, these segments, which may overlap, were aligned at the anchors and averaged in a fourth step. Fifth, these phase-rectified and averaged signals were quantified by Haar-wavelet analysis. Several adoptions of the Phase rectified signal averaging technology led to an improvement regarding vulnerability to both signal noise and artefacts, but also to an increased concordance between automatically and manually processed ECG's.[8,10] Here we used $T=4$, (instead of 1; Eq. (2a) in[19]) and $S=5$ (instead of 2; Eq. (8) in[19]).

Signal processing for calculation of DC was performed out of the first 10 minutes of ECG recordings. In case of noisy or diminished-quality signals, evaluation time was prolonged up to 30 minutes until 200 anchors were identified. With this short duration measurement, the number of anchors is more essential, producing reliable results, than the pure duration of ECG recordings. Results become most robust, if more than 150 anchors are observed.[6]

2.3. NIHSS

The NIHSS was determined by evaluation of complete neurological function including level of consciousness, horizontal eye movement, visual field test, facial palsy, motoric function of arms and legs, ataxia, somatosensory function, language and level of attention. The score ranges from 0 to 42 points (0 means no, and 42 means maximal neurological deficit).[5]

2.4. Analysis

Continuous variables are shown as mean ± standard deviation. Continuous parameters were compared by using the Mann–Whitney *U* Test. Qualitative variables are presented both as absolute value and as percentages and were compared by using the Chi-Squared test. Receiver-operator characteristic (ROC) curves were plotted for DC, NIHSS and a combined model. ROC curves were quantified by the area under the curve (AUC). The hazard ratios (HR) of DC, age and NIHSS were calculated by

binary logistic regression analysis and are presented with 95% confidence intervals. Differences were defined as statistically significant, if the *P* value was less than .05. The incremental prognostic value of DC added to age and NIHSS was implemented by c-statistics and integrated discrimination improvement (IDI). Statistical analyses were performed using SPSS 23.0. and CRAN R 3.3.0.

3. Results

One thousand five hundred twenty one patients presented to the stroke unit with any neurologic deficit between September 2015 and March 2018. One thousand one hundred twenty two of these patients were diagnosed to suffer from an ischemic stroke and underwent 24-hour Holter ECG recording. Two hundred forty four Patients with ECG recordings revealing either noisy low-quality ECG signals or persistent/permanent atrial fibrillation were excluded. Hence, 878 patients were enrolled in the study (Fig. 1). Mean age was 69.6 ± 13.5 48 years and 43.2% of the patients were women. Intrahospital mortality was 2.8% (25 patients). Further baseline characteristics can be seen in Table 1.

DC was significantly lower in the non-survivors compared to survivors (4.10 ± 2.82ms vs 6.27 ± 3.27 ms; $P < .001$). NIHSS was higher in the group of patients, who died (7.6 ± 7.1 vs 4.26 ± 5.53; $P = .02$) and patients were significantly older in the non-surviving group (78.7 ± 10.8 vs 69.5 ± 13.5 47 years; $P < .001$). Sensitive Troponin I and NT-pro-BNP were increased in patients, achieving the primary endpoint (Troponin 0.28 ± 0.61 pg/ml vs 0.13 ± 1.8 pg/ml; $P = .01$) and NT-pro-BNP 2282.78 ± 3964.35 ng/l vs 729.05 ± 2210.62 ng/l; $P < .001$). Further differences of the 2 groups are summarized in Table 2.

In a binary logistic regression analysis, DC, NIHSS and age were independent predictors for intra hospital mortality [DC: HR CI 95%: 0.88 (0.79–0.97); $P = .01$; NIHSS: HR CI 95%: 1.08 (1.02–1.15); $P = .01$; Age: HR CI 95%: 1.07 (1.02–1.11); $P = .004$] (Table 3). DC yielded an AUC value of 0.708, whereas the AUC value of NIHSS was 0.641. Age achieved an AUC of 0.700. The combination of NIHSS, age and DC in a prediction model yielded an AUC of 0.757, which is a significant improvement compared to every individual parameter [$P < .001$, IDI 95% CI: 0.037 (0.018–0.057)] (Fig. 2).

4. Discussion

This trial reveals that DC of heart rate provides important prognostic information regarding intrahospital mortality in ischemic stroke patients. First, DC was significantly lower in the group of patients who died. Second, DC was an independent predictor of intrahospital mortality shown by the binary logistic regression analysis and third, DC revealed both best specificity

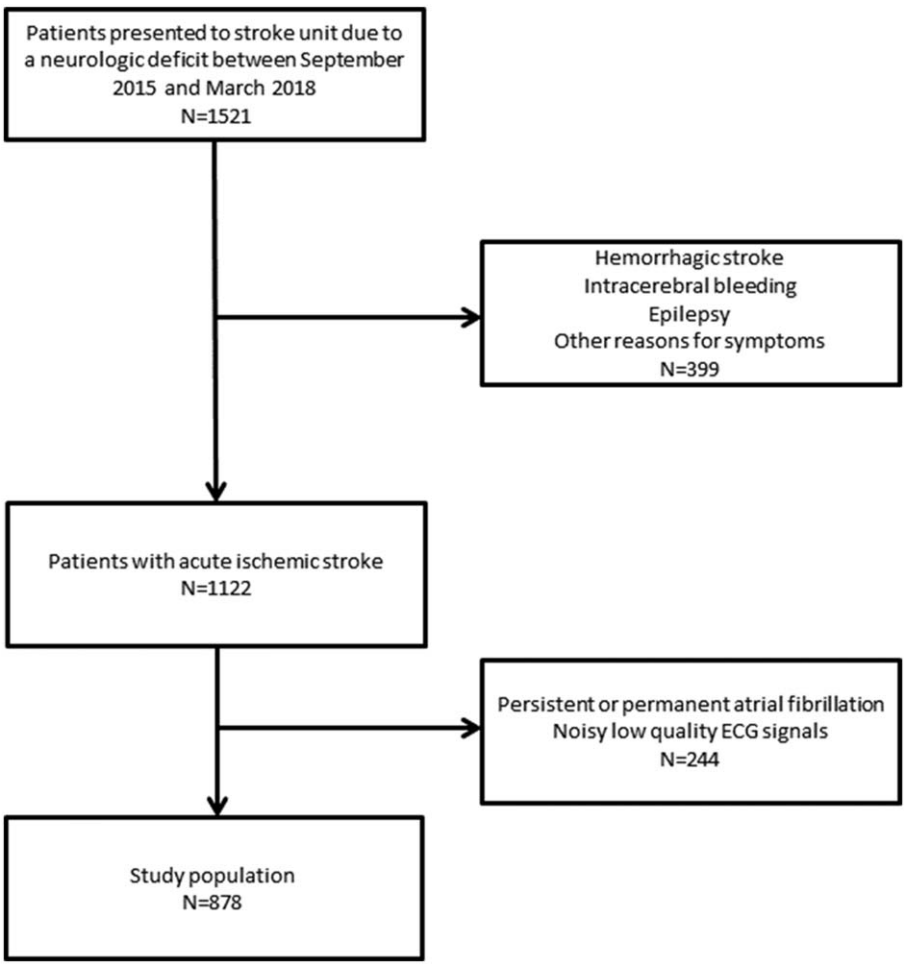

Figure 1. Flowchart of patient recruitment.

Table 1

Baseline characteristics of the study population.

Demographics	All patients (n = 878)
Age (Yr)	69.7 ± 13.5
Females (n)	379 (43.2%)
NIHSS Score at admission:	4.4 ± 5.6
Deceleration Capacity (ms)	6.2 ± 3.3
Medical history:	
Known coronary heart disease (n)	119 (13.6%)
Previous stroke (n)	186 (21.2%)
Peripheral arterial disease (n)	34 (3.9%)
Arterial hypertension (n)	641 (73%)
Diabetes mellitus (n)	187 (21.3%)
Hyperlipidemia (n)	257 (29.3%)
Smoking or ex-smoker (n)	172 (19.6%)
Obesity (n)	111 (12.6%)
Family history of CVD	54 (6.2%)
Laboratory Marker	
Sensitive Troponin (pg/ml)	0.1 ± 1.8
NT-pro-BNP (ng/l)	773 ± 2288.3
TOAST Classification:	
1	204 (23.2%)
2	219 (24.9%)
3	151 (17.2%)
4	31 (3.5%)
5	273 (31.1%)
Treatment	
Intracerebral mechanical recanalisation	102 (11.6%)
Intravenous thrombolysis	237 (27%)
TEA of any internal carotid artery	39 (4.4%)
Ultrasound Diagnostic	
PFO	169 (19.2%)
Left atrial thrombus	3 (0.3%)
Stenosis of the carotid artery (>50% NASCET)	155 (17.7%)
Severely impaired LVEF (EF < 35%)	12 (1.4%)
Intrahospital Mortality	25 (2.8%)

CVD = Cardiovascular Disease, LVEF = left ventricular ejection fraction, NASCET = North American Symptomatic Carotid Endarterectomy Trial, NIHSS = National Institute of Health Stroke Scale, PFO = patent foramen ovale, TEA = thrombendarteriectomy.

Table 2

Characteristics of patients stratified by intra hospital survival.

	Survivors (n = 853))	Non-survivors (n = 25)	*P* value
Patient age (yr)	69.5 ± 13.5	78.7 ± 10.8	.001
Females (n)	368 (43.1%)	11 (44.0%)	.93
NIHSS Score	4.3 ± 5.5	7.6 ± 7.1	.02
DC (ms)	6.3 ± 3.3	4.1 ± 2.8	<.001
Medical History:			
Known coronary heart disease (n)	111 (13%)	8 (32%)	.01
Previous stroke (n)	127 (14.9%)	7 (28%)	.16
Peripheral arterial disease (n)	31 (3.6%)	3 (12%)	.03
Hypertension (n)	619 (72.6%)	22 (88%)	.09
Diabetes mellitus (n)	179 (21%)	8 (32%)	.19
Hyperlipidemia (n)	254 (29.8%)	3 (12%)	.05
Smoking or ex-smoker (n)	169 (19.8%)	3 (12%)	.61
Obesity (n)	109 (12.8%)	2 (8%)	.48
Family history of CVD (n)	52 (6.1%)	2 (8%)	.7
Laboratory Marker:			
Sensitive Troponin (pg/ml)	0.13 ± 1.8	0.28 ± 0.61	.01
NT-proBNP ng/l	729.05 ± 2210.62	2282.78 ± 3964.35	<.001
Treatment:			
Intracerebral mechanical recanalization	97 (11.4%)	5 (20%)	.19
Intravenous thrombolysis	229 (26.9%)	8 (32%)	.57
TEA of any internal carotid artery	36 (4.2%)	3 (12%)	.06
Ultrasound Diagnostic			
PFO	168 (19.7%)	1 (4%)	.05
Left atrial thrombus	2 (0.2%)	1 (4%)	.001
Stenosis of the carotid artery (>50% NASCET)	147 (17.2%)	8 (32%)	.06
Severely impaired LVEF (EF<35%)	140 (16.4%)	2 (8%)	.26

CVD = Cardiovascular Disease, DC = Deceleration capacity, NASCET = North American Symptomatic Carotid Endarterectomy Trial, NIHSS = National Institute of Health Stroke Scale, PFO = Patent foramen ovale, TEA = thrombendarteriectomy. Differences were defined as statistically significant, if the *P* value was less than .05 (Mann–Whitney *U* test for continuous variables and Chi-Squared test for categorical variables).

Table 3

Binary logistic regression analysis for prediction of intra hospital mortality in patients with ischemic stroke.

Variables	HR (CI 95%)	*Z*	*P* value
Patient age (yr)	1.07 (1.02–1.11)	8.21	.004
NIHSS	1.08 (1.02–1.15)	7.53	.006
DC (ms)	0.88 (0.79–0.97)	6.19	.013

CI = confidence interval, DC = deceleration capacity of heart rate, HR = hazard ratio, ms = milliseconds, NIHSS = National Institute of Health Stroke Scale.

and sensitivity compared to the other independent parameters (age, NIHSS), as indicated by the ROC-Curve. Incorporation of the other tested independent risk factors age and NIHSS in a combined model even increased its predictive value.

Predicting mortality in patients suffering from ischemic stroke is of crucial importance. The ability to identify high risk patients may improve outcome after ischemic stroke by bundling personal and material resources. Astonishingly, no known predictor of mortality has been established into every day clinical work. The NIHSS was developed to evaluate the severity of neurological deficit after ischemic stroke, but not to predict mortality.[4,5] In our patient cohort, the NIHSS was also an independent predictor of intrahospital mortality. Recently, a score combining the clinical parameters NIHSS, modified Rankin Scale, Glasgow-Coma-Scale, glucose level at admission and High sensitive C-reactive Protein was presented to evaluate mortality risk in these patients.[20] However, prompt identification of an unfavorable course is essential. Hence, these comprehensive tests in a first contact setting might be both debilitating and lead to delayed decision-making.

Previous studies identified cardiac Troponin to be highly associated with mortality in acute ischemic stroke patients.[21–23] This might be due to concomitant cardiac disease or, as concluded in another trial, based on elevated sympathoadrenal activation in a setting of acute ischemic stroke.[24] This imbalance between sympathetic and vagal influences is quantified by DC, which therefore might be such a strong risk predictor. The pathophysiological mechanisms of decreased DC are not understood in detail. Most likely, an increased sympathetic overshoot disables the ANS to react with vagal activation. Our results are in line with earlier studies evaluating the prognostic power of DC in heart failure or Acute Coronary Syndrome patients.[10,25] These findings lead to the conclusion, that an impaired DC predicts serious complications, independent of the underlying disease. It can be used as a stand-alone prediction tool, combined with other risk markers, as also shown in our trial or as

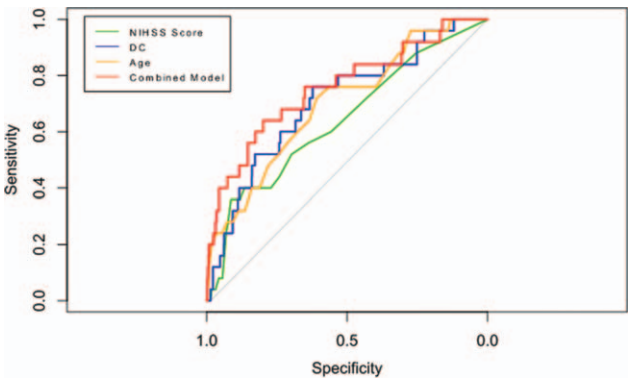

Figure 2. ROC curve of deceleration capacity (DC), National Institute of Health Stroke Scale (NIHSS), age and the prediction model combining the individual risk parameters for prediction of intra hospital mortality after admission to the stroke unit due to ischemic stroke.

an additional tool facilitating diagnosis and treatment of acutely diseased patients.

Risk stratification by DC is effective and efficient. It can be calculated by fully-automated software either out of 24 hours Holter ECGs or, as shown in recent trials, out of standard heart rhythm monitoring.[6,12] Determination of DC is non-invasive, independent of the investigator and non-expensive.

The limitations of our study need to be mentioned: First, the calculation of DC can only be performed in patients with an adequate period of sinus rhythm. Unfortunately, a relevant portion of strokes are associated with atrial fibrillation.[26] However, the detection of atrial arrhythmia is a risk marker itself in this patient collective.[27] Second, the NIHSS was not developed to predict mortality in ischemic stroke patients. Hence, this score might not be the appropriate comparator. Third, the design of our study is both purely observational and hypothesis-generating. We did not define any cut-off value of DC in this trial. So, further studies need to investigate the optimal cut-off value to use DC as decision guidance in daily clinical business.

In Conclusion, DC of heart rate is a strong and independent predictor of intrahospital mortality in stroke patients. The integration of this tool might enable the physician to identify patients suffering from ischemic stroke at risk for an unfavorable outcome.

Author contributions

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