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Deceleration capacity is associated with acute respiratory distress syndrome in COVID-19

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ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) is considered the main cause of COVID-19 associated morbidity and mortality. Early and reliable risk stratification is of crucial clinical importance in order to identify persons at risk for developing a severe course of disease. Deceleration capacity (DC) of heart rate as a marker of cardiac autonomic function predicts outcome in persons with myocardial infarction and heart failure. We hypothesized that reduced modulation of heart rate may be helpful in identifying persons with COVID-19 at risk for developing ARDS.

Methods: We prospectively enrolled 60 consecutive COVID-19 positive persons presenting at the University Hospital of Tuebingen. Arterial blood gas analysis and 24 h-Holter ECG recordings were performed and analyzed at admission. The primary end point was defined as development of ARDS with regards to the Berlin classification.

Results: 61.7% (37 of 60 persons) developed an ARDS. In persons with ARDS DC was significantly reduced when compared to persons with milder course of infection (3.2 ms vs. 6.6 ms, $p < 0.001$). DC achieved a good discrimination performance (AUC = 0.76) for ARDS in COVID-19 persons. In a multivariate analysis, decreased DC was associated with the development of ARDS.

Conclusion: Our data suggest a promising role of DC to risk stratification in COVID-19.

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Introduction

The current worldwide pandemic of the 2019 coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) poses a significant threat to global health and economy. The clinical presentation varies widely among individuals from mild afebrile respiratory symptoms to severe illness causing acute respiratory distress syndrome (ARDS).¹ Approximately 5% of infected persons require admission to an intensive care unit and approximately 12% of hospitalized COVID-19 persons receive mechanical ventilation.^{2,3} Prediction models for both prognosis and clinical course of COVID-19 are urgently required to identify persons at high risk of developing severe ARDS requiring mechanical ventilation. The quick COVID-19 severity index has been recently postulated as a risk score for short-term respiratory deterioration by assessing respiratory rate, oxygen saturation and oxygen flow rate.⁴ Current data suggest, however, that reliable prediction models are missing.⁵

Therefore, further tools to support medical decision making are of great interest, especially in the setting of an emergency department or in an outpatient area. Heart rate variability analysis is a non-invasive, objective method assessing the sympathetic and vagal balance of the autonomic nervous system. Reduced heart rate deceleration capacity (DC) indicates impaired cardiac vagal modulations.⁶ DC has already been proved to be a powerful predictor of mortality in persons with myocardial infarction, heart failure, cancer, aortic stenosis, syncope, stroke and pneumonia.^{6–13} Recently, a retrospective, observational case series emphasized direct and indirect affection of the central nervous system in COVID-19 persons with respiratory insufficiency.¹⁴ In the current study, we postulate that impaired DC provides prognostic information in persons with COVID-19.

Methods

Study design, setting and participants

This prospective study was conducted in the Department of Cardiology, Angiology and Cardiovascular Medicine at the University

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Hospital of Tuebingen, Germany. 60 consecutive COVID-19 positive persons were enrolled between March and April 2020. Inclusion criteria consisted of diagnosis of COVID-19 infection and sinus rhythm. During the first pandemic wave, a plethora of patients with mild to severe symptoms was hospitalized. SARS-CoV-2 was isolated from nasal and pharyngeal specimens by real-time reverse transcriptase polymerase chain reaction. The study was approved by the local Ethics Committee (238/2018BO2) and complies with the declaration of Helsinki and the Good Clinical Practice Guidelines.^{15–17} Written informed consent was obtained from all persons or their legal representatives.

Measurements

Oxygen saturation and routine blood samples were obtained at hospital admission. If progressive dyspnea, oxygen requirement or reduced oxygen saturation <97% occurred, arterial blood gas analysis was performed. Additional arterial blood gas analysis was completed when persons showed relevant clinical worsening of their symptoms or oxygen insufflation was required. We determined ARDS by the ratio of partial pressure of oxygen in blood to fraction of inhaled oxygen ($\text{PaO}_2/\text{FiO}_2$). In this sense, ARDS was classified as mild ($\text{PaO}_2/\text{FiO}_2 >200$ mmHg, but ≤ 300 mmHg), moderate ($\text{PaO}_2/\text{FiO}_2 >100$ mmHg, but ≤ 200 mmHg) and severe ($\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg) according to the Berlin Definition of ARDS.¹⁸ Oxygen delivery devices such as nasal cannulas or venturi masks were used in non-ventilated persons to increase the FiO_2 up to 60% based on known equipment standards. With a nasal cannula, the FiO_2 increases by approximately 4% for every additional liter of oxygen flow provided. For example, a flow rate at 1L/min is able to increase the FiO_2 to 24%, 3L/min to 32% and 6L/min up to 44%.¹⁹

Persons received a 24 h-ECG Holter recording within 24 h after admission to the isolation ward. DC was automatically assessed from a 24 h-ECG Holter (Getemed CardioMem CM 3000SM 24 h Holter ECG Recorder) according to validated technologies.²⁰ Briefly, sequences of RR intervals were processed by a signal processing algorithm called phase-rectified signal averaging (PRSA). RR intervals longer than their precursors are identified as so-called anchors. Segments with certain length surrounding the anchors are aligned and averaged to obtain the PRSA signal. The DC is acquired by quantifying the central amplitude of the PRSA signal by Haar-wavelet analysis. The DC can be considered as integral of all deceleration-related fluctuations during the selected period of observation.^{6,21} We only used the first 10 min of the ECG recordings for analysis of at least 200 anchors. In case of low signal quality, the observation period was extended to a maximum of 30 min until 200 anchors were identified. ECG recordings with noisy, low-quality signals were excluded using a validated algorithm.²² According to Bauer et al., a DC ≤ 4.5 ms might be associated with high risk of mortality.⁶

Outcomes

We defined a composite of mild, moderate and/or severe ARDS during hospitalization as the primary endpoint.

Analysis

All statistical analyses were performed using SPSS version 26.0 2019 (SPSS Inc., Chicago IL). Non-normally distributed data was compared using Mann-Whitney *U*-Test. Chi-squared cross-tabulations were used to analyze qualitative data. Data was presented as mean \pm standard deviation. Univariate and multivariate binary logistic regression analyses were used to evaluate associations between patient characteristics, laboratory results at admission and DC in terms of development of ARDS. The confidence interval was set to 95% and a *p*-value of ≤ 0.05 was considered significant. Receiver

operating characteristic (ROC) curves were used to assess the sensitivity and specificity of DC for prediction of ARDS after admission to ED due to COVID-19. The overall discriminatory capacity of the test is estimated by the area under the ROC curve. Values of 1.0 indicate excellent and values of 0.5 imply missing discrimination. Values ranging from 0.7 to 0.8 represent good discrimination.

Results

Characteristics of study participants

60 persons with COVID-19 infection requiring hospitalization underwent 24 h-ECG Holter recording. Baseline characteristics, medical history and outcome of the overall cohort are presented in Table 1.

Main results

The incidence of ARDS was 61.7% (37 of 60 persons), with an intrahospital mortality of 5.0% (3 of 60 persons). Persons with ARDS matched by age (69.1 years vs. 63.3 years, *p* = 0.058), sex (21 males vs 15 males, *p* = 0.515) and body mass index (29.6 kg/m² vs. 27.6 kg/m², *p* = 0.412) when compared to the non-ARDS group. Hypertension as a comorbidity was more frequent in the ARDS group (*p* = 0.007). ARDS persons had a mean (\pm SD) $\text{PaO}_2/\text{FiO}_2$ of 178 ± 58 mmHg. 24 persons (64.9%) developed moderate to severe ARDS and 17 out of 37 ARDS persons (45.9%) required intubation. The mean timespan between DC measurement at isolation ward and admission to the ICU was 3.6 ± 4.6 days. Table 2 compares ARDS and non-ARDS persons in detail. There were no differences with regard to medication with possible impact on DC, such as beta-blockers or prevalence of diabetes between the two groups. Further characteristics comparing ARDS and non-ARDS persons are presented in Table 2. One person suffered from congestive heart failure (CHF).

We found DC to be significantly lower in persons with ARDS compared to non-ARDS persons (3.2 ± 2.2 ms vs. 6.6 ± 6.1 ms; *p* < 0.001, OR=0.7; 95% CI, 0.5–0.9; *p* = 0.005). Persons with ARDS were more likely to show a reduced DC <4.5 ms (ARDS 75.7% vs. non-ARDS 34.8%, *p* = 0.003). Furthermore, in ARDS persons, levels of troponin I, D-dimers, C-reactive protein and LDH levels were significantly higher and lymphocytes significantly lower when compared to non-ARDS persons.

COVID-19 persons with hypertension as a comorbidity had a increased risk of developing ARDS (OR=4.7; 95% CI, 1.5–14.9; *p* = 0.009). Additionally, univariate analysis indicated an association with ARDS in COVID-19 persons for the following factors: DC (OR=0.7; 95% CI, 0.5–0.9; *p* = 0.005), troponin I (OR=1.1; 95% CI, 1.0–1.2; *p* = 0.047) and LDH levels (OR=1.0; 95% CI, 1.0–1.01;

Table 1
Baseline characteristics and outcomes of the study population (*n* = 60).

Age, years (mean \pm SD)	66.9 (\pm 13.4)
Male, <i>n</i> (%)	36 (60.0)
Body mass index (mean \pm SD)	28.9 (5.7)
Medical history, <i>n</i> (%)	
Known coronary artery disease	14 (23.3)
Congestive heart failure	1 (1.7)
Chronic kidney disease	6 (10.0)
Hypertension	41 (68.3)
Diabetes mellitus	11 (18.3)
Chronic obstructive pulmonary disease	5 (8.3)
Immunosuppression	6 (10.0)
Active Smoker	1 (1.7)
Obesity	14 (23.3)
Outcome, <i>n</i> (%)	
Admission to ICU	19 (31.7)
Mechanical Ventilation	17 (28.3)
Death	2 (3.3)

Table 2
Baseline characteristics stratified according to the primary endpoint.

	Non-ARDS (n = 23)	ARDS (n = 37)	p value
Age, years (mean ± SD)	63.3 (±13.9)	69.1 (± 12.8)	0.058
Male, n (%)	15 (65.2)	21 (56.8)	0.515
Body mass index (mean ± SD)	27.6 (5.5)	29.6 (5.8)	0.412
Medical History, n (%)			
Coronary artery disease	3 (13.0)	11 (29.7)	0.137
Congestive heart failure	0 (0.0)	1 (3.3)	0.387
Chronic kidney disease	3 (13.0)	3 (8.1)	0.536
Hypertension	11 (47.8)	30 (81.1)	0.007
Diabetes mellitus	5 (21.7)	6 (16.7)	0.656
Chronic obstructive pulmonary disease	0 (0.0)	5 (13.5)	0.066
Immunosuppression	3 (13.0)	3 (8.1)	0.536
Active smoker	1 (4.3)	0 (0.0)	0.213
Obesity	5 (22.7)	9 (24.3)	0.889
Laboratory values at admission, mean ± SD			
Leucocytes (1000/ μ l)	5.2 (± 2.6)	6.5 (± 2.4)	0.102
Lymphocytes (1000/ μ l)	0.9 (± 0.3)	0.6 (± 0.3)	0.015
Creatinine (mg/dl)	1.7 (± 2.2)	1.1 (± 0.7)	0.570
D-dimers (μ g/ml)	0.9 (± 1.0)	3.2 (± 6.7)	0.001
C-reactive protein (mg/dl)	5.4 (± 6.8)	8.8 (± 6.1)	0.007
Troponin I (ng/l)	7.7 (± 6.4)	33.3 (± 65.6)	0.007
NT-pro-BNP (ng/l)	532 (± 1312)	2444 (± 6267)	0.088
LDH (U/l)	257 (± 86)	354 (± 149)	0.003
Medication at admission, n (%)			
Oral anticoagulation	1 (4.5)	1 (4.0)	0.926
ACEi/ARB	9 (40.9)	18 (64.3)	0.100
Calcium channel blockers	7 (31.8)	7 (23.3)	0.496
Beta-blockers	9 (40.0)	12 (40.9)	0.947
Statins	9 (40.9)	14 (46.7)	0.680
ASS	5 (22.7)	10 (33.3)	0.404
P2Y12 inhibitors	1 (4.5)	0 (0.0)	0.238
Severity of ARDS, n (%)			
Mild		13 (21.7)	
Moderate		19 (31.7)	
Severe		5 (8.3)	
Main study parameter			
Nadir PaO ₂ /FiO ₂ (mmHg)	411 ± 72	178 ± 58	< 0.001
Intrahospital days	7.6 ± 8.6	16.0 ± 10.9	0.003
Deceleration capacity (ms, mean ± SD)	6.6 ± 6.1	3.2 ± 2.2	< 0.001
Deceleration capacity <4.5 ms, n (%)	8 (34.8%)	28 (75.7%)	0.003
Deceleration capacity <2.5 ms, n (%)	2 (8.7%)	17 (45.9%)	0.003

$p = 0.009$) (Table 3). In the multivariate logistic regression analysis, decreased DC was associated with increased risk for ARDS (OR=0.7; 95% CI, 0.6–1.0; $p = 0.043$). DC yielded an AUC of 0.76 in the ROC curve indicating a good discriminatory capacity of predicting COVID-19 persons at risk of developing ARDS (Fig. 1).

Discussion

The major findings of the current study are¹: Compromised DC was associated with an increased risk of developing ARDS in persons

with COVID-19 infection.² DC may be helpful to characterize persons in a more advanced disease stage of COVID-19 and therefore may be used as a marker of advanced disease.

Severe respiratory failure with development of ARDS is a potential complication of COVID-19 infection. Previous reports also consider severe ARDS to be responsible for the majority of COVID-19 associated morbidity and mortality.^{1,23} Prognostic markers that help to distinguish persons at risk for severe ARDS are urgently needed to establish proper treatment strategies. Coagulation abnormalities and myocardial injury were found to be prevalent in COVID-19 positive persons and to be predictive of adverse outcomes.^{24–28} These studies identified higher levels of the myocardial distress marker troponin I, as well as higher levels of D-dimers, C-reactive protein and LDH on admission being highly predictive for respiratory insufficiency during the course of the COVID-19 disease. In line with these papers, we also found higher levels of troponin I and LDH in the ARDS group. Interestingly, persons in the ARDS group were more likely to suffer from hypertension.

As an early marker for progressive disease, we propose calculation of the DC. DC provides information regarding the cardiac autonomic function. The mechanisms of compromised DC are various and related to altered sympathetic vascular tone, reduced neuro-humoral organ interaction and cardiac injury due to myocardial inflammation.²⁹ Since DC reflects cardiac vagal modulation, decreased DC may be used to estimate disease severity, independent of the underlying cause. It is certainly not specific to COVID-19. However, as risk predictor DC may aid to identify persons at risk of a severe course of disease including COVID-19. In an emergency setting with patients presenting at different stages of disease, risk stratification can be challenging. Besides respiratory rate, heart rate or blood pressure, DC may allow a quick assessment by evaluation of ECG signals. In a previous study, the prognostic value of DC was demonstrated in emergency patients with pneumonia.¹¹

The calculation of DC is efficient, user independent and can be performed fully-automated either from of heart rhythm monitoring or, as carried out in our study, from of 24 h-Holter ECGs. According to our findings, DC as well as previously postulated risk factors (troponin I, D-dimers, LDH, hypertension) may be associated with ARDS.^{25,30,31} Furthermore, DC may be considered a suitable screening method to identify persons at low risk for developing severe ARDS. In times of the COVID-19 pandemic with scenarios of overcrowded emergency departments, this might be of crucial importance.

Since the DC can be determined both easily and non-invasively with the help of software algorithms, its use is also conceivable in an outpatient setting. Due to advancement of technologies, the requirements of a proper ECG recording with wrist-worn heart rate monitors, such as the Apple Watch (Apple, Cupertino, California) are already in place. The accuracy of variables was proven in various studies.^{32,33} This novel technology provides adequate signal quality of ECG recordings and could be used for automated assessment of DC within 10 min.³⁴ Thus, the DC might be a useful tool for risk prediction in COVID-19 persons and therefore could support decision-

Table 3
Univariate and multivariate binary logistic regression analysis for prediction of the primary endpoint.

Variable	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio (95% CI)	Wald	p-value	Hazard Ratio (95% CI)	Wald	p-value
DC	0.7 (0.5–0.9)	8.0	0.005	0.7 (0.6–1.0)	4.1	0.043
Hypertension	4.7 (1.5–14.9)	6.8	0.009	2.7 (0.6–12.3)	1.7	0.196
D-dimers	1.9 (0.9–3.7)	3.0	0.810			
C-reactive protein	1.1 (1.0–1.2)	3.4	0.640			
Troponin I	1.1 (1.0–1.2)	3.9	0.047	1.0 (1.0–1.1)	1.7	0.300
LDH	1.0 (1.0–1.01)	6.9	0.009	1.0 (1.0–1.01)	1.8	0.175

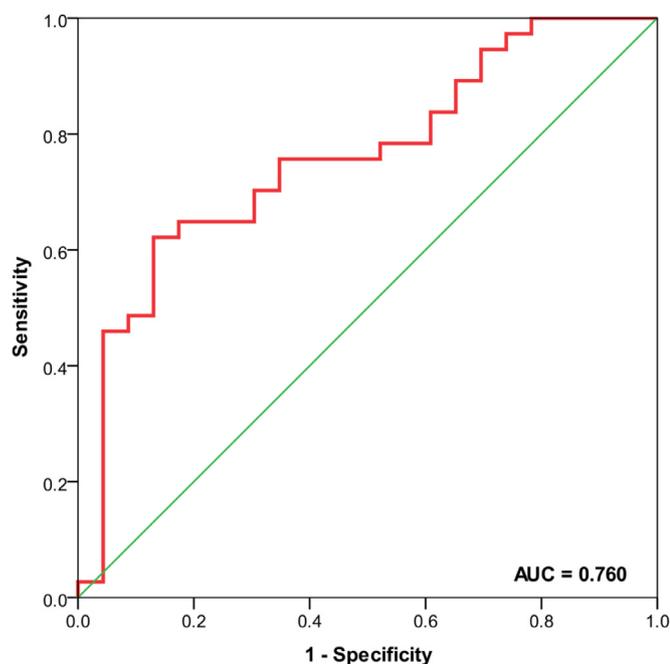


Fig. 1. ROC curve of DC for prediction of ARDS after hospital admission due to COVID-19 infection. DC, deceleration capacity, ROC, receiver operating characteristic.

making in the outpatient area, help to establish treatment strategies and avoid unnecessary hospitalization for low-risk persons. In this sense, both material and personal resources might be preserved and exposition of health care personal can be reduced.

Various limitations of our study need to be mentioned. First, due to the small cohort of COVID-19 infected persons in this study, the present data should be considered hypothesis generating and multivariate analysis needs cautious interpretation. Further verification in prospective control studies is required. Second, the proportion of persons who developed ARDS in this study population is high compared to previous investigations. This might be due to the fact, that only hospitalized persons were included. A continuous rhythm monitoring providing data for real-time analysis of DC would be desirable. This could improve the ability for risk prediction of this patient collective. Third, calculation of DC can only be performed in the presence of sinus rhythm. Persons with either atrial fibrillation or permanent stimulation by a pacemaker need to be excluded. It should further be noted that ARDS has cofounders such as CHF which is a risk factor for a severe course of COVID-19 itself.³⁵ DC may serve as an indicator of poor prognosis in persons with both COVID-19 as well as CHF.

To conclude, this is the first study of biosignal analysis in hospitalized persons with ARDS secondary to COVID-19. DC seems to be a convenient and promising prognostic tool that may identify persons with advanced COVID-19 that could develop ARDS.

Declaration of Competing Interest

Previously, we submitted an interim analysis of impaired cardiac function in COVID-19 positive persons to a different journal, which has been accepted for publication on May 28th (Rath D, Petersen-Urbe Á, Avdiu A, et al. Impaired cardiac function is associated with mortality in persons with acute COVID-19 infection. *Clin Res Cardiol.* 2020;1-9). However, the endpoint in this subanalysis differed and fewer persons were enrolled. Furthermore, additional biosignal analyses from 24 h ECG Holter recordings were performed in the current manuscript.

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Ethics approval and consent to participate

The study was approved by the local Ethics Committee (238/2018BO2) and complies with the declaration of Helsinki and the Good Clinical Practice Guidelines. Written informed consent was obtained from all persons or their legal representatives.

Consent for publication

The authors declare that they agree to the publication of this article.

Availability of data and material

The datasets analyzed during the present study are available from the corresponding author on reasonable request.

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