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Cardiac arrhythmias in patients with COVID-19: Lessons from 2300 telemetric monitoring days on the intensive care unit

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Abstract

Background: Patients with COVID-19 seem to be prone to the development of arrhythmias. The objective of this trial was to determine the characteristics, clinical significance and therapeutic consequences of these arrhythmias in COVID-19 patients requiring intensive care unit (ICU) treatment.

Methods and results: A total of 113 consecutive patients (mean age 64.1 ± 14.3 years, 30 (26.5%) female) with positive PCR testing for SARS-CoV2 as well as radiographically confirmed pulmonary involvement admitted to the ICU from March to May 2020 were included and observed for a cumulative time of 2321 days. Fifty episodes of sustained atrial tachycardias, five episodes of sustained ventricular arrhythmias and thirty bradycardic events were documented. Sustained new onset atrial arrhythmias were associated with hemodynamic deterioration in 13 cases (35.1%). Patients with new onset atrial arrhythmias were older, showed higher levels of Hs-Troponin and NT-proBNP, and a more severe course of disease.

Conclusion: Relevant arrhythmias are common in severely ill ICU patients with COVID-19. They are associated with worse courses of disease and require specific treatment. This makes daily close monitoring of telemetric data mandatory in this patient group.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus first detected in Wuhan, China, that causes coronavirus disease 2019 (COVID-19). The SARS-CoV-2 outbreak has rapidly spread and developed to a pandemic, leading to significant morbidity and mortality. Cardiac injury is a common condition among hospitalized patients with COVID-19 and is associated with a higher risk of fatal outcome of COVID-19 [1,2]. Emerging data also indicate that the incidence of cardiac arrhythmias is increased in patients with COVID-19 infection and a considerable number of patients with worse outcome presented with cardiovascular comorbidities (up to 15%) [3]. Guan et al. reported nonspecific heart palpitations in 7.3% of patients admitted due to COVID-19 [3]. Among patients hospitalized with COVID-19 the reported incidence of cardiac arrhythmias ranged between 15 and 40% [1,4,5]. Guo et al. showed that patients with COVID-19 and elevated troponin T levels had an increased risk for malignant ventricular tachycardia with an incidence of 11.5% [1]. Suspected sudden cardiac death was also reported in Italian patients quarantined with mild COVID-19 [6]. In addition, clinical reports indicate that critically ill COVID-19 patients develop sepsis and acute respiratory distress syndrome (ARDS), which is paralleled by a surge of cytokines and might represent the culprit for cardiac injury and consecutive atrial and/or ventricular arrhythmias in these patients [7]. This data suggest that cardiac arrhythmias in patients with COVID-19 significantly contribute to morbidity and mortality and are relevant for the disease pathophysiology. However, specifics about the types of arrhythmias that occur in COVID-19 patients are lacking. The aim of this study was to describe the incidence and type of cardiac arrhythmias and to identify potential associations with comorbidities as well as severity and course of COVID-19.

Material and methods

In this prospective, observational trial, adult patients admitted to an ICU at one of the three sites of the university hospital center at the Charité Berlin from March to May 2020 were included in the analysis. Patients were only included if ICU treatment was primarily due to respiratory deterioration of COVID-19. All patients had positive PCR testing for SARS-CoV-2 as well as radiographically confirmed pulmonary involvement. The end of the observation period was 14 days after the last included patient.

On admission, as part of a routine, patient demographics and medical history including history of cardiac arrhythmias and long-term medications, were recorded. Specific data including oxygenation index, vasopressor support, antibiotic therapy, ventilation mode, need for transfusion and validated mortality prediction scores including Acute Physiology and Chronic Health Evaluation II (APACHE II), Sepsis-related Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score (SAPS-2) were documented. The laboratory values on admission were considered as baseline. To account for disease progression and dynamics, the maximal or minimal values of laboratory parameters and mortality prediction score corresponding to a worsening of the clinical condition during the course of the ICU stay were noted at the end of the study period.

Continuous telemetric 3-lead electrocardiogram (ECG) data was available for all patients. Interpretation was conducted by 4 experienced electrophysiologists blinded for patient name and history. Standard 12-lead ECGs were recorded when deemed necessary to differentiate or confirm arrhythmias. Atrial fibrillation (AF) was defined according to ESC guidelines with a minimum duration of more than 30 s [8]. New onset sustained atrial tachycardias (AT)/AF episodes were defined as tachycardias that were not present at the time of ICU admission. The cut-off for a significant number of premature ventricular beats (PVC) was set to more than 30 per hour, as more than 30 PVCs may be associated with worse outcomes in ICU [9]. Non-sustained ventricular tachycardia (VT) was defined as three or more consecutive ventricular beats (>100 beats/min), lasting longer than 30 s [10]. Arrhythmias were defined as hemodynamically relevant if they led to a systolic blood pressure reduction below a mean arterial pressure of 65 mmHg, if vasopressors had to be initiated or increased or if a cardioversion was carried out immediately. All arrhythmias occurring in a one-hour time window before death not directly related to a malignant arrhythmia were excluded. This study was approved by the institutional ethical committee.

Statistical analysis

Descriptive methods were used for analysis of all clinical and demographic parameters. For continuous variables, the arithmetic average ± standard deviation or median with 25% and 75% percentiles were calculated, for categorical values absolute and relative frequencies are indicated. To analyze potential associations between clinical parameters such as scores indicating severity of illness and arrhythmia events we used Mann-Whitney U tests in case of skewed data, independent sample t-tests was used for normally distributed variables and chi-squared tests for categorical variables. As this study is explorative, no adjusting for multiple testing was performed. All analyses were explorative, p-values are interpreted as such. Statistical analysis was performed with SPSS version 25 (IBM, Armonk, USA).

Results

Patient characteristics

A total of 113 patients (mean age 64.1 ± 14.3 years, 30 (26.5%) female) with COVID-19 requiring ICU treatment were included in the analysis. The cumulative observation time was 2321 days. The median observation time was 18.1 (7–29.1) days. At the time of final data analysis 51 (45.1%) of the included patients had been discharged, 27 (23.9%) died and 35 (31.0%) remained hospitalized. Detailed patient characteristics are shown in Table 1.

The mean APACHE II score at admission was 24.5 ± 10.1, the SOFA score at admission was 8.0 (4.0–11.0). hs- Troponin and NT-proBNP were both markedly elevated at the time of the admission to the ICU ((33.5 (11.0–73.253) ng/l and 1279.0 (289.5–3457.5) pg/ml). 90 of the 113 patients (79.6%) required mechanical ventilation and catecholamine treatment while they were hospitalized.

18 patients (15.9%) had a history of prior arrhythmia, the most common being atrial fibrillation/flutter (N = 16, 14.2%).

Patients with bradyarrhythmic or tachycardic arrhythmias

Sustained atrial arrhythmias were observed in 50 patients (44.2%) while 38 patients (33.6%) had non-sustained atrial arrhythmia. 37 of the sustained atrial arrhythmias were classified as new onset atrial arrhythmia. The most common atrial arrhythmia, found in 40 patients (35.4%) was AF.

Sustained ventricular arrhythmias (ventricular fibrillation, VT or torsade de pointes tachycardia) were observed in 4 patients (3.5%), non-sustained VT in 31 patients (27.4%), and frequent PVCs in 28 patients (24.8%).

Out of 113 patients, 30 patient (26.5%) had relevant bradycardic events. Of those, 15 patients (13.3%) had sinus bradycardia (defined as heart rate < 40 bpm), 5 patients (4.4%) showed atrial fibrillation (AF) with slow conduction to the ventricle (defined as heart rate < 40 bpm) and in 10 patients (8.9%), a second-degree or third-degree AV block was detected (Table 2). Noteworthy, the predominant subtype of AV conduction disorders was a third-degree AV block (8 out of 10 patients). With the exception of one patient, the AV block was intermittent and lasted only for a few seconds with a narrow complex escape rhythm. In one case, a patient with a third-degree AV block presented
Baseline characteristics; COPD = chronic obstructive pulmonary disease, PVC = premature ventricular contraction, CIED = cardiovascular implantable electronic device, ACEI = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensin-Receptor-Blocker, ARNI = Angiotensin-Receptor-Nephrilysine-Inhibitor, MRA = mineralocorticoid receptor antagonist, AAD = antiarrhythmic drugs, SOFA = Sepsis-related organ failure assessment, APACHE = Acute Physiology And Chronic Health Evaluation, SAPS = Simplified Acute Physiology Score, ECMO = extracorporeal membrane oxygenation, NT proBNP = N-terminal pro-brain natriuretic peptide, WBC = White blood cells, GFR = glomerular filtration rate, CRP = C-reactive protein, ALT = Alanine Aminotransferase, AST = Aspartate-Aminotransferase.

Table 1

| Characteristic                  | Baseline | Worst |
|---------------------------------|----------|-------|
| Total number of patients        | N = 113  |       |
| **Age (years)**                 | Mean ± sd| 64.1 ± 14.3 |
| **Female**                      | N (%)    | 30 (26.5) |
| **BMI (kg/m²)**                 | Mean ± sd| 29.5 ± 6.6 |
| **Arterial hypertension**       | N (%)    | 69 (61.1) |
| **Coronary artery disease**     | N (%)    | 21 (18.6) |
| **COPD**                        | N (%)    | 13 (11.5) |
| **Current smoker**              | N (%)    | 19 (16.8) |
| **Anemia**                      | N (%)    | 7 (6.2) |
| **Congestive heart failure**    | N (%)    | 13 (11.5) |
| **LVF (%)**                     | Median (25–75%) | 60 (57.5–60) |
| **Chronic kidney disease**      | N (%)    | 17 (15.0) |
| **Malignancy**                  | N (%)    | 9 (8.0) |
| **Any prior Arrhythmias**       | N (%)    | 18 (15.9) |
| **Prior atrial fibrillation/−flutter** | N (%) | 16 (14.2) |
| **Prior ventricular tachycardia** | N (%) | 1 (0.9) |
| **Prior frequent PVCs**         | N (%)    | 2 (1.8) |
| **CIED**                        | N (%)    | 6 (5.3) |
| **Baseline medication**         |          |       |
| **Beta Blockers**               | N (%)    | 31 (27.4) |
| **Calcium Antagonists**         | N (%)    | 18 (15.9) |
| **ACEI/ARB/ARNI**               | N (%)    | 39 (34.5) |
| **Platelet Inhibitors**         | N (%)    | 27 (23.9) |
| **MRA**                         | N (%)    | 6 (5.3) |
| **NOAC/OAC**                    | N (%)    | 13 (11.5) |
| **Class LRI AAD**               | N (%)    | 1 (0.9) |
| **Severity of illness**         |          |       |
| **SOFa**                        | Median (25–75%) | 8.0 (4.0–11.0) |
| **APACHE II**                   | Mean ± sd| 24.5 ± 10.1 |
| **Horowitz Index (mmHg)**       | Median   | 158.0 |
| **SAPS**                        | Mean ± sd| 42.7 ± 14.1 |
| **Dialysis during ICU treatment** | N (%) | 66 (58.4) |
| **Total days in hospital**      | Median (25–75%) | 30.0 (20.0–41.0) |
| **Total days ICU treatment**    | Median (25–75%) | 23.0 (11.0–37.5) |
| **ECMO treatment**              | N (%)    | 25 (22.1) |
| **Total days ECMO**             | Median (25–75%) | 12.0 (6.8–31.3) |
| **Mechanical ventilation**      | N (%)    | 90 (79.6) |
| **Total days mechanical ventilation** | Median | 24.0 (13.0–38.0) |
| **Catecholamine use**           | N (%)    | 90 (79.6) |
| **Antibiotic treatment**        | N (%)    | 102 (90.3) |
| **Red blood cell transfusion**  | N (%)    | 70 (61.9) |
| **Death**                       | N (%)    | 27 (23.9) |
| **Discharged**                  | N (%)    | 51 (45.1) |
| **Under treatment**             | N (%)    | 35 (31.0) |

**Laboratory findings**

| Laboratory findings | Baseline | Worst |
|---------------------|----------|-------|
| **HS Troponin (ng/l)** | Median (25–75%) | 33.5 (11.0–73.3) | 60.0 (28.5–171.0) |
| **NT proBNP (pg/ml)** | Median (25–75%) | 1279.0 | 3390.0 |
| **Haemoglobin, g/l** | Mean ± sd | 11.3 ± 2.2 |
| **Creatinine** | Median (25–75%) | 1.10 (0.8–1.7) | 1.8 (1.2–2.9) |
| **GFR** | Median (25–75%) | 66.0 (36.0–90.0) | 33.0 (21.5–60.0) |

with an asystole lasting 30 s. After cardiopulmonary resuscitation (CPR) and medical therapy with atropine and epinephrine, a stable sinus rhythm was established. Interestingly, all patients with a second-degree or third-degree AV block showed evidence of myocardial injury, defined as elevated high-sensitivity Troponin (hs-TnT) levels above the 99th percentile (> 16 ng/l). However, it must be said that cardiac arrhythmias can also cause biomarker elevation [11,12].

In addition, the reservation must be made that hs-TnT levels were not determined in one patient with a second-degree AV block and in one patient with a third-degree AV block.

In our study population, 93% of the patients with atrial or ventricular arrhythmias had elevated hs-TnT levels (> 16 ng/l) compared to 58% of the patients without arrhythmias (p < 0.01).

**Characteristics and treatment of patients with sustained new onset atrial arrhythmias**

For this analysis, patients with new onset atrial arrhythmias were compared to patients with no atrial arrhythmias. Patients that showed...

| Laboratory findings | Baseline | Worst |
|---------------------|----------|-------|
| **Lactate, mmol/l** | Median (25–75%) | 11.0 (8.3–16.0) | 24.0 (18.0–42.0) |
| **Potassium (mmol/l)** | Mean ± sd | 4.2 ± 0.8 |
| **Sodium (mmol/l)** | Mean ± sd | 140.2 ± 6.5 |
| **Procalcitonin, ng/ml** | Median (25–75%) | 0.5 (0.2–1.7) |
| **CRP, ng/m** | Median (25–75%) | 163.0 (85.0–282.5) |
| **ALT, U/l** | Median (25–75%) | 40.0 (27.0–70.5) |
| **Bilirubin, g/l** | Median (25–75%) | 0.6 (0.4–0.8) |

Table 2

| Arrhythmia details | FAT = focal atrial tachycardia; AV-block = atrioventricular block |
|--------------------|------------------------------------------------------------------|
| Total number of patients | N = 113 |
| **Atrial arrhythmias** |          |
| Non-sustained atrial tachycardia, N (%) | 38 (33.6) |
| Sustained atrial tachycardia (atrial fibrillation or regular atrial tachycardia), N (%) | 50 (44.2) |
| New onset atrial tachycardia, N (%) | 37 (32.7) |
| Atrial fibrillation, N (%) | 40 (35.4) |
| New onset atrial fibrillation N (%) | 27 (23.9) |
| Time in atrial fibrillation/Total ICU time (% of days) | 35.1 ± 40.3 |
| Sustained regular atrial tachycardia (FAT or atrial flutter), N (%) | 22 (19.5) |
| New onset regular atrial tachycardia, N (%) | 21 (18.6) |
| **Ventricular arrhythmias** |          |
| Premature ventricular beats, N (%) | 28 (24.8) |
| Non-sustained ventricular tachycardia, N (%) | 31 (27.4) |
| Sustained ventricular tachycardia or fibrillation or Torsade de pointes, N (%) | 5 (4.4) |
| Sustained ventricular fibrillation, N (%) | 2 (1.8) |
| Sustained ventricular tachycardia, N (%) | 2 (1.8) |
| Torsade de pointes tachycardia, N (%) | 1 (0.9) |
| **Bradyarrhythmia** |          |
| Total number of patients with bradycardia, N (%) | 30 (26.5) |
| AV block II, N (%) | 2 (1.8) |
| AV block III, N (%) | 8 (7.1) |
| Sinus node dysfunction, N (%) | 15 (13.3) |
| Bradycardiac atrial fibrillation, N (%) | 5 (4.4) |
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Table 3
Characteristics of patients with new onset sustained atrial arrhythmias. COPD = chronic obstructive pulmonary disease, ACEI = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensin Receptor-Blocker, ARNI = Angiotensin-Receptor-Nephrilysine-Inhibitor, MRA = mineralocorticoid receptor antagonist, AAD = antiarrhythmic drugs, SOFA = Sepsis-related organ failure assessment; APACHE = Acute Physiology And Chronic Health Evaluation, SAPS = Simplified Acute Physiology Score, ICU = Intensive Care Unit, ECMO = extracorporeal membrane oxygenation, NT proBNP = N-terminal pro-brain natriuretic peptide, WBC = White blood cells, GFR = glomerular filtration rate, CRP=C-reactive protein. Statistical test used: I = T-Test, x = chi-square, * = Mann-Whitney-U Test.

| Parameter                              | New onset sustained atrial arrhythmias | No sustained atrial arrhythmias | p-value          |
|----------------------------------------|----------------------------------------|---------------------------------|-----------------|
| Age (years)                            | 68.1 ± 11.4                           | 59.8 ± 15.3                    | p = 0.005 (†)    |
| Female                                 | 20 (31.7)                              | 20 (31.7)                      | p = 0.276 (x)   |
| BMI (kg/m²)                            | 28.9 ± 3.9                             | 30.4 ± 7.7                     | p = 0.210 (†)   |
| Arterial hypertension                  | 24 (64.9)                              | 34 (54.0)                      | p = 0.286 (x)   |
| Coronary artery disease                | 8 (21.6)                               | 8 (21.6)                       | p = 0.240 (x)   |
| LVEF (%) (baseline)                    | 60 (57.5–60.0)                        | 60 (60.0–60.0)                 | p = 0.522 (*)    |
| COPD                                   | 4 (10.8)                               | 7 (11.1)                       | p = 0.963 (x)   |
| Baseline medication                    |                                       |                                 |                 |
| Beta Blockers                          | 11 (29.7)                              | 12 (19.0)                      | p = 0.220 (x)   |
| Calcium Antagonists                    | 8 (21.6)                               | 6 (9.5)                        | p = 0.092 (x)   |
| ACE/ARB/ARNI                           | 16 (43.2)                              | 15 (39.8)                      | p = 0.042 (x)   |
| MRA                                    | 1 (2.7)                                | 1 (1.6)                        | p = 0.700 (x)   |
| NOAC/OAC                               | 3 (8.1)                                | 2 (3.2)                        | p = 0.274 (x)   |
| Class LII AAD                           | 0 (0.0)                                | 0 (0.0)                        |                 |
| Severity of illness                    |                                       |                                 |                 |
| SOFA (baseline)                        | 9.0 (5.0–11.5)                         | 7.0 (4.0–11.0)                 | p = 0.461 (*)    |
| SOFA (worst)                           | 14.0 (11.0–16.0)                       | 12.0 (9.0–15.0)                | p = 0.006 (*)    |
| APACHE II (baseline)                   | 27.1 ± 9.5                             | 22.4 ± 10.1                    | p = 0.024 (I)    |
| APACHE II (worst)                      | 31.8 ± 9.3                             | 26.2 ± 11.0                    | p = 0.012 (I)    |
| Horowitz Index (worst)                 | 93.75 (660–1418)                       | 105.0 (760–1356)               | p = 0.302 (*)    |
| SAPS (baseline)                        | 46.3 ± 14.3                            | 39.8 ± 14.1                    | p = 0.031 (I)    |
| SAPS (worst)                           | 62.9 ± 14.1                            | 53.5 ± 16.3                    | p = 0.004 (I)    |
| Dialysis during ICU treatment          | 28 (75.7)                              | 33 (52.4)                      | p = 0.021 (x)    |
| Total days ICU treatment               | 33.0 (19.5–44.5)                       | 17.0 (8.0–29.0)                | p = 0.001 (*)    |
| ECMO treatment                         | 8 (21.6)                               | 14 (22.2)                      | p = 0.944 (x)    |
| Mechanical ventilation                 | 35 (94.6)                              | 47 (74.6)                      | p = 0.012 (x)    |
| Catecholamine use                      | 35 (94.6)                              | 47 (74.6)                      | p = 0.012 (x)    |
| Antibiotic use                         | 33 (89.2)                              | 57 (90.5)                      | p = 0.836 (x)    |
| Red blood cell transfusion             | 27 (73.0)                              | 33 (52.4)                      | p = 0.042 (x)    |
| Death                                  | 10 (27.0)                              | 17 (27.0)                      | p = 0.996 (x)    |
| Laboratory findings                   |                                       |                                 |                 |
| Hs-Troponin (ng/l) (baseline)          | 35.0 (19.0–171.3)                      | 19.0 (9.0–62.5)                | p = 0.054 (†)    |
| Hs-Troponin (ng/l) (worst)             | 180.0 (603–2533)                       | 390.0 (150–960)                | p = 0.001 (†)    |
| NT proBNP (pg/ml) (baseline)           | 1711.5 (335.3–3848.25)                 | 767.0 (182.5–3056.5)           | p = 0.102 (I)    |
| NT proBNP (pg/ml) (worst)              | 6826.0 (1851.0–16974.0)                | 1651.0 (442.0–6500.0)          | p = 0.002 (I)    |
| GFR (baseline)                         | 44.0 (30.0–82.0)                       | 71.0 (19.0–90.0)               | p = 0.048 (†)    |
| GFR (worst)                            | 28.0 (19.0–43.5)                       | 39.0 (22.0–81.0)               | p = 0.031 (I)    |
| CRP, ng/ml (baseline)                  | 152.0 (55.1–290.6)                     | 176.0 (105.0–282.0)            | p = 0.453 (†)    |
| Lactate, mmol/l (baseline)            | 110.0 (9.0–17.5)                       | 105.0 (8.0–14.0)               | p = 0.320 (I)    |

At atrial arrhythmias at the time of ICU admission were not included, as the duration of the current episode was unknown. Patients with new onset atrial arrhythmias were older (68.1 ± 1.9 vs. 59.8 ± 1.9 years, p = 0.005), had a more frequent use of ACE-Inhibitors, ARB or ARNI and higher baseline SAPS and APACHE II scores. They developed higher levels of Hs-Troponin (264.3 ± 69.9 vs.70.2 ± 10.6 ng/l, p < 0.001 and NT- proBNP (10,792.4 ± 2058.5 vs. 5907.2 ± 1423.3 pg/ml, p = 0.002). Atrial arrhythmias also were associated with a more severe course of disease, reflected by a higher percentage of the requirement of mechanical ventilation or the use of catecholamines (35/37 vs. 47/63, p = 0.012 and 35/37 vs.47/63, p = 0.012) as well as the development of higher SOFA, APACHE II and SAPS scores (14.0 (11.0–16.0) vs. 12.0 (9.0–15.0)), p = 0.006; 31.8 ± 9.3 vs. 26.2 ± 11.0, p = 0.015; 62.9 ± 14.1 vs. 53.5 ± 16.3, p = 0.004) (see Table 3). Total time in the ICU was longer for patients with new onset atrial arrhythmias (33.0 (19.0–44.5) vs. 17.0 (8.0–29.0)). Out of the 22 patients treated with antiarrhythmic drugs, 12 patients were treated with amiodarone only, 6 patients with amiodarone and beta-blocker / digitalis glycosides, and 4 patients with betablocker / digitalis glycoside only.

One new onset sustained atrial arrhythmia led to hemodynamic deterioration in 13 of the 37 patients (35.1%). Electrical cardioversion was performed in 4 of the 37 patients (10.8%) and antiarrhythmic drug treatment was initiated in 17 of the 37 patients (46.0%) (see Table 4).

One ischemic stroke potentially associated with the new onset AF was observed.

**Patients with sustained ventricular arrhythmias**

Five sustained ventricular arrhythmias (two VTs, two episodes of ventricular fibrillation, one torsade de pointes tachycardia) were observed in 4 patients. All episodes could be terminated by immediate defibrillation/cardioversion. Two of the patients died during ICU treatment with antiarrhythmic drugs, one of them from a presumed ischemic attack.

**Table 4**
New onset sustained atrial arrhythmias: treatment and consequences. TIA = transient ischemic attack.

| Total number of patients | N = 37 |
|--------------------------|--------|
| Treatment with electrical cardioversion, N (%) | 4 (10.8) |
| Treatment with antiarrhythmic drugs, N (%) | 17 (46.0) |
| Associated hemodynamic deterioration, N (%) | 13 (35.1) |
| Associated stroke/TIA, N (%) | 1 (2.7) |
treatment, however deaths were not directly related to ventricular arrhythmia events. Clinical characteristics and outcome of the four patients are depicted in Table 5.

Patients with bradycardia

No relevant differences were identified between patients with and without bradycardic events (Supplemental table 1). In case of the 30 bradycardic events potentially precipitating factors could be identified in 19 of 30 episodes (63.3%). However, neither temporary cardiac pacing nor pacemaker implantation was required in any patient. Table 6 shows potentially precipitating factors and treatment of bradycardic events.

Discussion

Involvement of the cardiovascular system, which is observed in up to 20% of total patients with COVID 19, plays an important role for the course and prognosis of the disease [2]. Early reports from Wuhan, China identified relevant arrhythmias in up to 44.4% of COVID-19 patients, depending on the severity of the disease [5]. However further differentiation of the type of arrhythmia was not provided. A recently published case series by Kochav et al. reported potentially COVID-19-associated arrhythmias ranging from third degree AV-Block to polymorphic ventricular tachycardia [13].

To shed further light on this issue, we analyzed the incidence and significance of arrhythmias in severely ill COVID-19 patients under continuous ECG monitoring on ICU.

Atrial arrhythmias

In our study cohort of 113 patients non-sustained atrial arrhythmias occurred in 38 (33.6%), while new onset sustained atrial arrhythmias were observed in 37 patients (44.2%). Not surprisingly, AF was the most common sustained arrhythmia.

In comparison with previous studies investigating AF incidence in critically ill patients, the incidence in our study population was higher when compared to ARDS patients (10%) [14] or patients with severe sepsis (weighted incidence 10% (4 to 23%)) and similar compared to patients with septic shock (weighted incidence 23% (6 to 46%)) [15,16]. Up to now, two studies investigated the incidence of atrial arrhythmias in COVID-19 patients. Colon et al. [17] found atrial tachyarrhythmias in 19 of 69 patients (27.5%) admitted to the medical ICU, whereas Bhatla et al. reported an incidence of only 14 out of 79 patients (17.7%) [17,18].

This makes sustained atrial arrhythmias the most frequently clinically relevant arrhythmia in the available reports investigating arrhythmias in COVID-19 patients treated on an ICU. In our analysis, in about one third of the patients, the arrhythmia was associated with hemodynamic deterioration and about half of the patients with sustained atrial arrhythmias received treatment with AAD or underwent electrical cardioversion.

However, our therapy regimen of cardiac arrhythmias did not change because of COVID-19 infection. In case of hemodynamic instability due to an atrial arrhythmia, an electrical cardioversion was performed. In hemodynamically stable patients, atrial arrhythmias were treated with antiarrhythmic drugs to slow the ventricular rate.

New-onset AF has been associated with higher short- and long-term mortality in patients with sepsis and ARDS hospitalized on ICUs [19]. We found that new onset atrial arrhythmias were associated with a more severe course of disease, higher levels of biomarkers indicating cardiac involvement, a higher likelihood for the requirement of mechanical ventilation or the use of catecholamines, the development of higher SOFA, APACHE II and SAPS scores and a longer total time on the ICU.

The causes of this additional morbidity of patients with AF in this setting remains unclear. AF may be regarded as a marker for cardiac involvement of COVID-19 (either direct or indirect), alternatively AF itself may cause clinical deterioration e.g., by inducing heart failure or thromboembolic complications.

With regard to recent data showing that COVID-19 patients demonstrate a high incidence of thrombotic complications [20], the observed high rate of AF may be part of the increased risk for arterial thromboses. However, the acute anticoagulation management in COVID-19 patients remains unclear. Additionally, the need for long term anticoagulation for patients with new onset sustained atrial arrhythmias that recovered from the COVID-19 infection has to be determined. In a similar setting with critical ill patients with new onset atrial arrhythmias during septic shock, long-term thromboembolic risk seems to remain relatively high after recovery [21]. Long term surveillance data of patients having recovered from a severe COVID-19 infection is needed to solve this issue in the future.

Ventricular arrhythmias

While non-sustained VTs occurred in 31 patients (27.4%), sustained VT, ventricular fibrillation or torsade de pointes tachycardias were only observed in 4 patients (3.5%).

Except for the study by Bhatla et al. [18] there is currently no published data available on the amount of non-sustained VTs in this patient group. In their study non-sustained VTs were found only in 6 of 79 COVID-19 patients (8.7%) requiring ICU treatment.

Rates of sustained ventricular arrhythmias in COVID-19 patients requiring ICU treatment show considerable variation. In a retrospective

### Table 5

| Characteristics of patients with ventricular arrhythmias. CAD = coronary artery disease, PEA = pulseless electrical activity, ROSC = return of spontaneous circulation. |
|---------------------------------------------------------------|
| Type of ventricular arrhythmia                               | Precipitating factor                                              | Treatment                                  | Outcome |
| 81 y/o male known CAD, baseline EF 20%                       | Torsade de pointes tachycardia                                    | QT prolongation under fluoroquinolone      | Defibrillation | ROSC |
| 76 y/o male with ischemic heart disease                       | Ventricular tachycardia                                           | Volume depletion/tachy-cardial atrial fibrillation | Amiodaron + electrical cardioversion | ROSC |
| 57 y/o male with progressive pulmonary infiltration and acute right ventricular failure | Ventricular tachycardia and ventricular fibrillation               | Hypoxia, ventricular tachycardia and ventricular fibrillation following PEA | Defibrillation | ROSC |
| 74 y/o male with acute left heart failure and septic shock   | Ventricular fibrillation                                           | Hypoxia, ventricular fibrillation following PEA | Defibrillation | ROSC |

### Table 6

| Total number of patients with bradycardia | N = 30 |
|------------------------------------------|-------|
| Potentially precipitating factors identified, N (%) | 19 (63.3) |
| Vagal reaction, N (%)                    | 7 (23.3) |
| Medication side effect, N (%)            | 12 (40.0) |
| Associated hemodynamic deterioration, N (%) | 5 (16.7) |
| Temporary or permanent cardiac pacing, N (%) | 0 (0.0) |
analysis from Wuhan, China 11 of 187 (5.8%) hospitalized patients with COVID-19 had either sustained VT or ventricular fibrillation, while Bhatla et al. observed only one case of shockable sustained arrhythmia (torsade de pointes tachycardia) [1,18].

Not surprisingly both trials found an association of ventricular arrhythmias with the disease severity, the amount of myocardial injury and underlying cardiovascular disease.

Detailed analysis of the 4 patients in our study with sustained ventricular arrhythmias lead to identification of precipitating factors in all cases. Two cases were associated with severe hypoxia and ventricular fibrillation only occurred during cardiopulmonary resuscitation. One torsade de pointes tachycardia was seen with QT prolongation under fluoroquinolone treatment and one regular ventricular tachycardia occurred during volume depletion and atrial fibrillation with fast conduction to the ventricle in a patient with a history of ischemic heart disease. In summary, in our study we found no signs for an increased risk of sustained ventricular arrhythmias in the absence of severe precipitating factors.

Bradydysrhythmias

About one fourth of the observed patients experienced relevant bradydysrhythmias during ICU treatment. All bradydysrhythmia episodes were transient and did not require permanent pacemaker implantation. Bradydysrhythmia episodes associated with hemodynamic deterioration were found in 5 of 113 patients (4.4%), which is similar to the 6.3% reported by Bhatla et al. [18].

There are several situations that may cause transient bradydysrhythmia or even asystole in critically ill COVID-19 patients. These include increased vagal tone during intubation, trachea suction or patient turning for prone ventilation as well as hypoxemia [22]. In our study population, we found a correlation of bradydysrhythmia events with the above-mentioned conditions in 23% of the cases.

A variety of drugs commonly administered in critically ill patients represent another common cause for sinus node dysfunction (SND) or AV-Block. These include non-dihydropyridine Ca-channel or beta-blockers, digoxin, beta-adrenolytic drugs, and sympatholytic or parasympathomimetic agents. A dose change or new administration of such an agent was found in 12 of 30 the observed bradydysrhythmia events (40%).

Comparison of the characteristics of patients with or without bradydysrhythmia episodes revealed no significant differences regarding comorbidities, age or course of disease. This makes a direct link between cardiac involvement of COVID-19 (direct or indirect) and the onset of bradydysrhythmia episode unlikely.

Conclusion

Relevant arrhythmias are common in severely ill ICU patients with COVID-19. The most common arrhythmias are sustained atrial arrhythmias, which are also associated with worse courses of disease. Sustained ventricular arrhythmias occurred less frequently and only in specific triggering situations. Most bradydysrhythmia events observed could be related to vagal responses or medication side effects. All bradydysrhythmia episodes could be managed without temporary or permanent cardiac pacing.

Because of the frequency and potential clinical implications of these arrhythmias daily close monitoring of telemetric data is mandatory in this patient group.

Limitations

No information is available on the clinical course of the patients after discharge. Thus, the effect of the observed arrhythmias on long-term outcome cannot be determined.

At the time of data analysis, one third of our study patients still received ICU treatment. This may lead to an underestimation of the observed incidence of arrhythmias and mortality rate.

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