BRIEF REPORT

Cardiac arrhythmias in patients hospitalized with COVID-19: The ACOVID study

Bochra Zareini, MD, PhD,* Deepthi Rajan, BMSc,* Mohammed El-Sheikh, BMSc,* Mads Hashiba Jensen, BMSc,* Mats Christian Højbjerg Lassen, MD,* Kristoffer Skaarup, BMSc,* Morten Lock Hansen, MD, PhD,* Tor Biering-Sørensen, MD, PhD, MPH,*§§ Reza Jabbari, MD, PhD,† Ole Kirk, MD, DMSc,‡ Jakob Tfelt-Hansen, MD, DMSc,† Olav Wendelboe Nielsen, MD, PhD, DMSc,§ Birgitte Lindegaard, MD, PhD,‖ Niels Tønder, MD, DMSc,¶ Lars Kliesch Pedersen, MD, PhD,# Charlotte Suppli Ulrik, MD, DMSc,** Peter Ellekvist, MD,†† Jens Ulrik Stæhr Jensen, MD, PhD,†† Morten Schou, MD, PhD,* Gunnar Gislason, MD, PhD,*‡‡ Morten Lamberts, MD, PhD*

*From the *Department of Cardiology, Herlev and Gentofte Hospital, Herlev, Denmark, †Department of Cardiology, Rigshospitalet, Copenhagen, Denmark, ‡Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark, §Department of Cardiology, Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark, ‖Department of Pulmonary and Infectious Diseases, North Zealand Hospital, Hillerød, Denmark, ¶Department of Cardiology, North Zealand Hospital, Hillerød, Denmark, #Department of Respiratory Medicine, Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark, **Department of Clinical Medicine, Hvidovre Hospital, Hvidovre, Denmark, ††Department of Internal Medicine, Herlev and Gentofte Hospital, Copenhagen, Denmark, ‡‡Danish Heart Association, Copenhagen, Denmark, and §§Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.*

Introduction

First reports from the initial epicenter of the coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China included case series of rapid clinical deterioration of seemingly healthy individuals.[1,2] Based on a cohort of 138 Chinese patients, 16.7% of patients with COVID-19 suffered from unspecified arrhythmias despite cardiac biomarkers being within normal range. In patients admitted to the intensive care unit (ICU), arrhythmias was reported in 44.4% of the patients. But how diagnosis of arrhythmias were made was not clearly specified.[1,3] Regardless of pathophysiological pathways for deterioration, of which proposed mechanisms include myocarditis, depressed cardiac function, worsening of prior cardiovascular disease, or cytokine storm syndrome, 1 phenotypic presentation may be sudden death and arrhythmias.[2,4,5] Our main aim was to estimate the type of arrhythmias with continuous electrocardiogram (ECG) in patients hospitalized with COVID-19, as well as to describe the following clinical episodes according to arrhythmia presentation: (1) initiation of continuous positive airway pressure and noninvasive ventilation treatment, (2) acute respiratory distress syndrome based on a diagnosis in the patients' medical records, (3) transfer to ICU, (4) in-hospital death, (5) computed tomography scan–verified pulmonary embolism (PE) /deep venous thrombosis (DVT), and (6) discharged alive.

Methods

The ACOVID (Arrhythmias in hospitalized patients with COVID-19) study is a multicenter prospective cohort study recruiting patients hospitalized with COVID-19 at 6 hospitals in the Greater Copenhagen area. Inclusion criteria were patients hospitalized with laboratory-confirmed test of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and age above 18 years. The exclusion criteria were pregnancy, inability to give informed consent, not willing to participate, and recordings with very high levels of noise (>95%). The study period ran from April 27, 2020 to July 30, 2020. All participants gave written informed consent. The study was conducted in accordance with the second Declaration of Helsinki and approved by the regional ethics committee (registration number: H-20021500) and the Danish Data Protection Agency (registration number: P-2020-384). The study is registered at Clinicaltrials.gov (registration number: NCT04395664).

Address reprint requests and correspondence: Dr Bochra Zareini, Department of Cardiology, Herlev Gentofte, University of Copenhagen, Niels Andersens vej 65, 2900 Hellerup, Denmark. E-mail address: bochra.zareini.03@regionh.dk.

https://doi.org/10.1016/j.hroo.2021.03.008

KEY FINDINGS

- In a population of 54 hospitalized COVID-19 patients, major arrhythmias developed in 15 (28%) patients and consisted mostly of supraventricular tachycardia (22%) and new-onset atrial fibrillation/atrial flutter (4%).
- Patients with major arrhythmias were more likely to develop pulmonary embolus/deep vein thrombosis, transfer to the intensive care unit, and death.
- Nonsustained ventricular tachycardia was observed in 1 patient.

Information on patient characteristics was obtained at the day of inclusion. We systematically evaluated all clinical records to obtain demographic characteristics and medical comorbidities. A Cortrium 3^{+} ECG Holter device was used for monitoring (cortrium.com). The device was placed upon day of admission or as earliest as possible during hospital stay. The device remained on until discharge, transfer to the ICU, or death. The final classification of arrhythmias was done according to current guideline definitions.[6,7] The major arrhythmia group was defined as at least 1 episode of supraventricular tachycardia (SVT) (defined as any SVT lasting longer than 7 consecutive beats), new-onset atrial fibrillation (AF) / atrial flutter (AFL) lasting longer than 30 seconds, sinus pauses lasting longer than 2 seconds, second- or third-degree atrioventricular block, ventricular tachycardia, and/or ventricular fibrillation. Nonmajor arrhythmias were defined as absence of major arrhythmia, but presence of sinus tachycardia or premature atrial or ventricular complexes. Further details on monitoring device and validation are included in the Supplemental Material.

Statistics

Baseline characteristics were described by use of proportions for categorical variables and means and standard deviations or medians and interquartile ranges for non-normally distributed continuous variables. Differences between groups were computed with Student t test for normally distributed continuous variables and Wilcoxon rank test for continuous but non-normally distributed variables. Differences between categorical variables were estimated by the χ^2 test. Median duration of admission was estimated as the number of days from admission until discharge, death, or end of study date (July 30, 2020), for patients still admitted at the end of the study period. When estimating the difference in percentage discharged alive, the 1 patient still admitted at time of study end was not included in the analysis. Significance level was set to $P < .05$. Analyses were performed using R Version 4.0.1; R Core Team (2019).[8]

Results

Study population

Of 117 screened candidates with confirmed COVID-19, 54 patients accepted to participate in the study (Figure 1). The majority of patients were excluded owing to refusal to participate when approached or inability to give informed consent. A total of 4 recordings were excluded owing to a high level of noise (>95%). Patient characteristics according to the total population and arrhythmia are shown in Table 1.

Cardiac arrhythmias and clinical course during hospitalization

Patients with major arrhythmias were older (mean age 76 years vs 67 years) and were more likely to have ischemic heart disease (47% vs 8%), chronic heart failure (33% vs 8%), active cancer (27% vs 15%), and pacemaker and implantable cardioverter-defibrillator (13% vs 0%) and require higher levels of supplemental oxygen therapy (6 L/min vs 2 L/min). There was no difference in percentage of patients presenting with elevated levels of C-reactive protein, procalcitonin, or troponin T at inclusion (Table 1). Type of arrhythmia found during the study is shown in Figure 2. Supplemental Figures S3–S17 include further details. One patient was still hospitalized at the end of the observation period. A total of 9 patients (17%) were at the time of admission classified as not being candidates for intensive care treatment, in case of acute respiratory failure, or

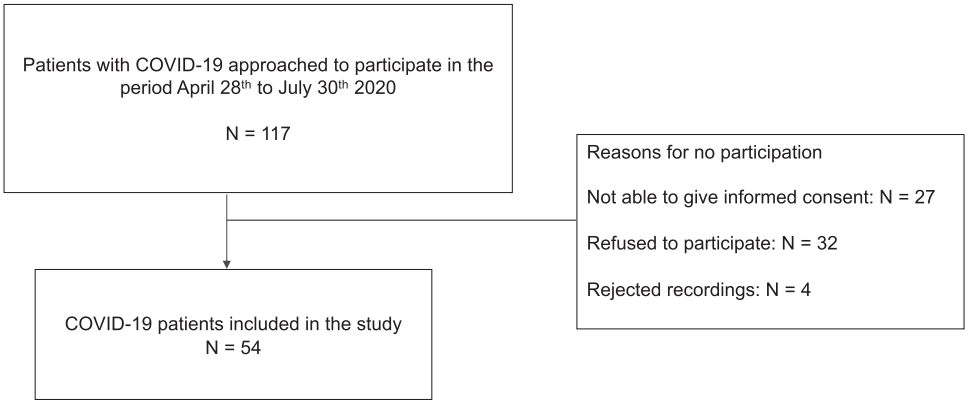

Figure 1 Flowchart of study population.

Table 1 Characteristics of patients hospitalized with COVID-19

	Nonmajor arrhythmia	Major arrhythmia	Total
N	39	15	54
Age (years),† median (IQR)	67.3 (52.7, 78.7)	75.5 (66.0, 81.2)	69.5 (61.1, 79.7)
Male sex, n (%)	20 (51.3)	11 (73.3)	31 (57.4)
Known comorbidities at inclusion, n (%)			
Stroke/TIA	6 (15.4)	2 (13.3)	8 (14.8)
IHD	3 (7.7)	7 (46.7)	10 (18.5)
PAD	1 (2.6)	1 (6.7)	2 (3.7)
Hypertension	19 (48.7)	5 (33.3)	24 (44.4)
Diabetes	10 (25.6)	4 (26.7)	14 (25.9)
Chronic heart failure	3 (7.7)	5 (33.3)	8 (14.8)
Asthma	3 (7.7)	1 (6.7)	4 (7.4)
COPD	7 (17.9)	2 (13.3)	9 (16.7)
History of DVT/PE	4 (10.3)	2 (13.3)	6 (11.1)
Any cardiac valve disease	6 (15.4)	2 (13.3)	8 (14.8)
CKD	5 (12.8)	2 (13.3)	7 (13.0)
Rheumatic disease†	1 (2.6)	4 (26.7)	5 (9.3)
Active cancer	6 (15.4)	4 (26.7)	10 (18.5)
Previous cancer	5 (12.8)	4 (26.7)	9 (16.7)
Atrial fibrillation	5 (12.8)	1 (6.7)	6 (11.1)
Pacemaker/ICD	0 (0.0)	2 (13.3)	2 (3.7)
Concomitant medication at inclusion, n (%)			
ACEi/ARB	10 (25.6)	5 (33.3)	15 (27.8)
Beta-blockers	10 (25.6)	4 (26.7)	14 (25.9)
Calcium channel blockers	14 (35.9)	1 (6.7)	15 (27.8)
Aldosterone antagonists	4 (10.3)	0 (0.0)	4 (7.4)
Diuretics	12 (30.8)	3 (20.0)	15 (27.8)
NSAID	5 (12.8)	7 (46.7)	12 (22.2)
Clinical parameters at inclusion			
Systolic blood pressure (mm Hg), mean (SD)	125.3 (18.2)	122.7 (16.1)	124.6 (17.6)
Diastolic blood pressure (mm Hg), mean (SD)	70.8 (9)	71.7 (9.4)	71.1 (9)
Heart rate (beats/min), mean (SD)	82.1 (13.3)	80.7 (12.6)	81.7 (13.1)
Respiration frequency (breaths/min), mean (SD)	19.1 (2.6)	18.5 (3)	18.9 (2.7)
Temperature (°C), mean (SD)	37.1 (1.1)	37.1 (0.6)	37.1 (0.9)
Saturation (%), mean (SD)	95.1 (3)	93.9 (3.1)	94.8 (3)
Supplemental oxygen therapy (L/min), mean (SD)	2.3 (4.4)	6.1 (8)	3.3 (5.8)
LVEF <50%	2 (5.1)	3 (20.0)	5 (9.3)
Increased CRP >10 mg/L	30 (76.9)	14 (93.3)	44 (81.5)
Procalcitonin >0.5 μg/L†	19 (48.7)	10 (66.7)	29 (53.7)
Troponin T >14 ng/L	8 (20.5)	5 (33.3)	13 (24.1)
Troponin I >59 ng/L	0	0	0
Lactate >2.1 mmol/L†	1 (2.6)	1 (6.7)	2(3.7)

Values are counts (column percentages) unless stated otherwise. Major arrhythmias were defined as supraventricular tachycardia, new-onset atrial fibrillation/flutter, ventricular tachycardia/fibrillation, second- or third-degree atrioventricular block, or sinus pauses >2 seconds. Nonmajor arrhythmias were defined as sinus tachycardia, premature atrial beats, and premature ventricular beats.

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; DVT = deep vein thrombosis; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PE = pulmonary embolism.

†Significant *P* value; *P* values indicate differences between patients with nonmajor and major arrhythmias, normal ranges for clinical parameters are included in footnotes.

resuscitation, in case of cardiac arrest. Clinical course during the observation period is shown in Table 2.

Discussion

In 54 patients hospitalized with COVID-19, our primary finding was that 28% of patients experienced primarily SVT, of which 4% were incident AF/AFL. Ventricular arrhythmias were rare. PE/DVT, transfer to the ICU, or death were more likely to occur in patients with major arrhythmia.

Our cohort differed from other reported cohorts admitted to non-ICU hospital wards. Our cohort was older and had higher proportions of comorbidities, especially ischemic heart disease, heart failure, and chronic obstructive pulmonary disorder.[1,9,10] The small sample size of an older, more frail population in this study could have underestimated the number and type of arrhythmia detected. In a large cohort of 700 hospitalized patients with COVID-19 with a mean age of 50 years, of which 621 patients were admitted to general wards with cardiac telemetry, incident AF was found among 25 patients and was the most common arrhythmia found

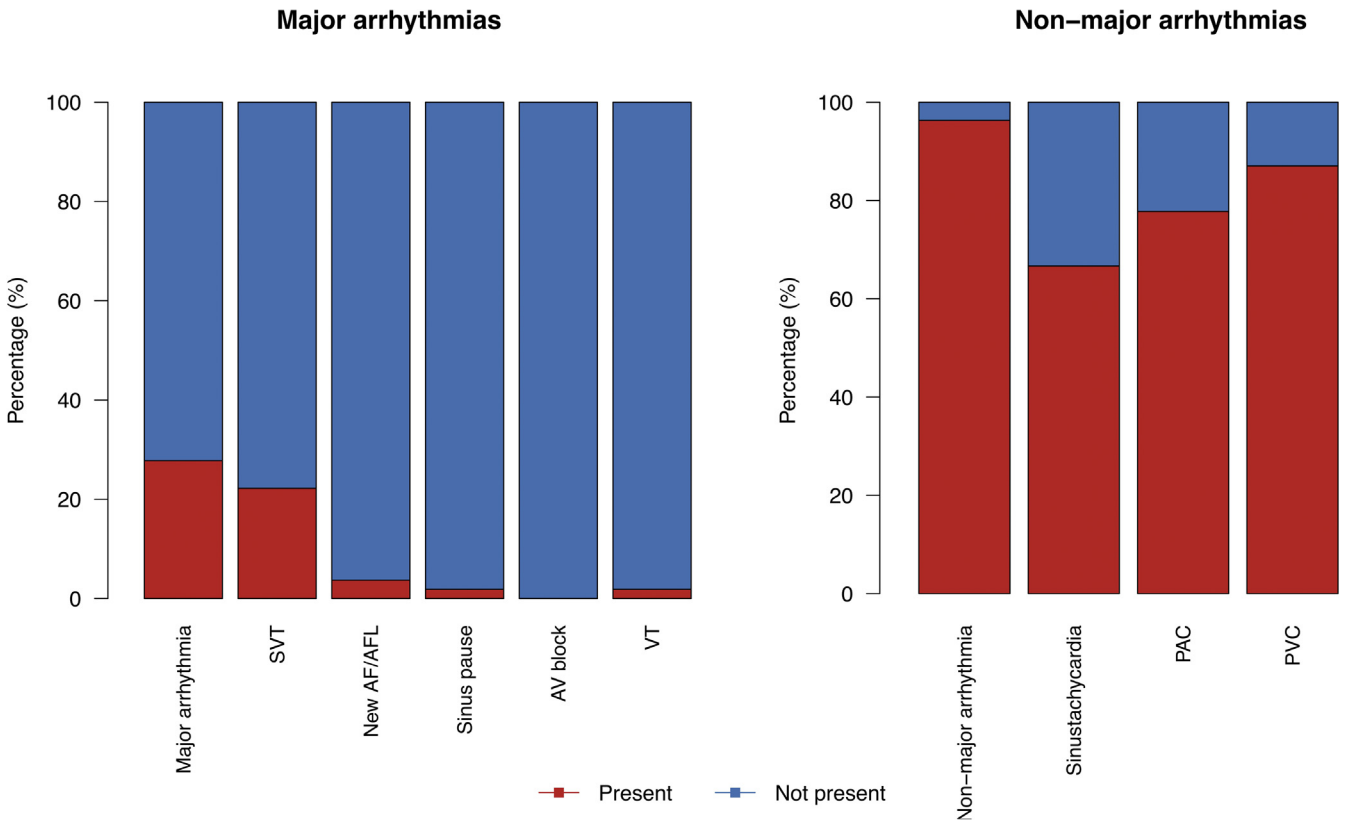

Figure 2 Distribution of major and nonmajor arrhythmias. AF = atrial fibrillation; AFL = atrial flutter; AV = second- or third-degree atrioventricular; PAC = premature atrial complexes; PVC = premature ventricular complexes; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

during the observation period. No cases of ventricular tachycardia or ventricular fibrillation were observed, nor did they report on prevalence of SVT.[11] Despite the differences in baseline characteristics, the distribution and type of arrhythmia detected were similar to our findings.

The majority of arrhythmias detected in our population were mainly SVT; only 4% of the patients developed incident AF/AFL. The clinical significance of SVT on prognosis can be argued; however, patients with SVT were more likely to experience respiratory deterioration and admission to the ICU and could be regarded as a marker of increased systemic distress. In the previously mentioned cohort study of 700 patients, admission to the ICU was significantly associated with the development of incident AF and nonsustained ventricular tachycardia.[11] Whether the arrhythmias detected in our study were the cause or effect of respiratory deterioration remain unanswered. Finally, 17% of the population was evaluated during hospitalization not to benefit from transfer to ICU or cardiac resuscitation, indicative of an older, frail study population; thus our patient population could have underestimated the association we have found.

There was no difference in troponin levels between patients with major or nonmajor arrhythmias upon inclusion. We collected information on biochemical parameters from routine clinical blood work taken upon admission. At inclusion, we suspect that the systemic inflammatory response was not strong enough to elicit a troponin release. We cannot dismiss subsequently increased cardiac biomarker levels,

Table 2 Clinical course in patients hospitalized with COVID-19 according to major and nonmajor arrhythmias

	Nonmajor arrhythmias (n = 39)	Major arrhythmias (n = 15)	Total (n = 54)	*P* value
Death, n (%)	1 (2.6)	4 (26.7)	5 (9.3)	.03[†]
Admission to ICU, n (%)	3 (7.7)	5 (33.3)[‡]	8 (14.8)	.05
CPAP/NIV treatment, n (%)	9 (23.1)	8 (53.3)	17 (31.5)	.07
ARDS, n (%)	6 (15.4)	3 (20.0)	9 (16.7)	.4
PE/DVT, n (%)	2 (5.1)	5 (33.3)	7 (13.0)	.02[†]
Discharged,[†] n (%)	38 (97.4)	10 (71.4)	48 (90.6)	.02[†]

ARDS = acute respiratory distress syndrome; CPAP = continuous positive airway pressure; DVT = deep vein thrombosis; ICU = intensive care unit; NIV = noninvasive ventilation; PE = pulmonary embolus.

[†]Only including patients who were discharged during the study period, a total of 53 patients. The 1 patient not included in the analysis was still admitted in the hospital.

[‡]Three of the 5 patients received treatment with respirator.

since no serial blood work was planned owing to the pragmatic nature of the study.

The strengths and novelty of our study include the prospective nature with continuous ECG recordings during hospitalization of non-ICU COVID-19 patients. Second, we used a validated device with manual adjudication of all arrhythmias found. The main limitation of the study is the small sample size, which was limited by the decrease in hospital admission during the inclusion period. The age distribution and the relative mild disease presentation (total mean oxygen saturation 95% and total supplemental oxygen therapy 3.3 L/min) upon inclusion could also have affected the type of arrhythmia detected. Fortunately, the effects of the national lockdown and social distancing in Denmark were in full effect during our inclusion period, causing a marked drop in the number of hospitalized patients with COVID-19.[12]

In conclusion, in 54 non-ICU hospitalized patients with COVID-19, 28% developed SVT, of which 4% developed incident AF/AFL, although critical arrhythmias were rare. PE/DVT, transfer to the ICU, and death were more likely to occur in patients with major arrhythmia.

Acknowledgments

We would like to thank all the nurses, staff, and doctors working at the COVID-19 wards for their patience and help with recruiting of patients, and also Ambu A/S Denmark for providing ECG electrodes. We also would like to thank Morten Roth at HESSEL HiRE for providing us with a car to transport equipment between hospitals in the greater Copenhagen area.

Funding Sources

This research is supported by a COVID-19 specific grant from Innovation Fund Denmark (grant no. 0208-00014B).

Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All participants gave written informed consent.

Ethics Statement

This study was conducted in accordance with the second Declaration of Helsinki and approved by the regional ethics committee (registration number: H-20021500) and the Danish Data Protection Agency (registration number: P-2020-384). The study is registered at Clinicaltrials.gov (registration number: NCT04395664).

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.03.008.

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