# CLINICAL INVESTIGATION

#### 

# Cardiac arrhythmias in critically ill patients with coronavirus disease 2019: A retrospective population-based cohort study

Mik Wetterslev<sup>1</sup> | Peter Karl Jacobsen<sup>2</sup> | Christian Hassager<sup>2</sup> | Christian Jøns<sup>2</sup> | Niels Risum<sup>2</sup> | Steen Pehrson<sup>2</sup> | Anders Bastiansen<sup>4</sup> | Anne Sofie Andreasen<sup>5</sup> | Klaus Tjelle Kristiansen<sup>6</sup> | Morten H. Bestle<sup>7</sup> | Thomas Mohr<sup>8</sup> | Hasse Møller-Sørensen<sup>3</sup> | Anders Perner<sup>1</sup>

<sup>1</sup>Department of Intensive Care, Rigshospitalet University of Copenhagen, Copenhagen, Denmark

<sup>2</sup>Department of Cardiology, Rigshospitalet University of Copenhagen, Copenhagen, Denmark

<sup>3</sup>Department of Cardiothoracic Anaesthesiology, Rigshospitalet University of Copenhagen, Copenhagen, Denmark

<sup>4</sup>Department of Anaesthesia and Intensive Care, Bispebjerg Hospital and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

<sup>5</sup>Department of Anaesthesia and Intensive Care, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark

<sup>6</sup>Department of Anaesthesia and Intensive Care, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

<sup>7</sup>Department of Anaesthesia and Intensive Care, Nordsjællands Hospital, University of Copenhagen, Copenhagen, Denmark

<sup>8</sup>Department of Anaesthesia and Intensive Care, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

#### Correspondence

Mik Wetterslev, Department of Intensive Care, 4131, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark.

Email: mik.wetterslev.02@regionh.dk

#### **Funding information**

MW's salary is paid by the Research Council of Rigshospitalet.

#### Abstract

**Background:** Coronavirus disease 2019 (COVID-19) may be associated with cardiac arrhythmias in hospitalized patients, but data from the ICU setting are limited. We aimed to describe the epidemiology of cardiac arrhythmias in ICU patients with COVID-19.

**Methods:** We conducted a multicenter, retrospective cohort study including all ICU patients with an airway sample positive for severe acute respiratory syndrome corona-virus 2 from March 1st to June 1st in the Capital Region of Denmark (1.8 million inhabitants). We registered cardiac arrhythmias in ICU, potential risk factors, interventions used in ICU and outcomes.

**Results:** From the seven ICUs we included 155 patients with COVID-19. The incidence of cardiac arrhythmias in the ICU was 57/155 (37%, 95% confidence interval 30-45), and 39/57 (68%) of these patients had this as new-onset arrhythmia. Previous history of tachyarrhythmias and higher disease severity at ICU admission were associated with cardiac arrhythmias in the adjusted analysis. Fifty-four of the 57 (95%) patients had supraventricular origin of the arrhythmia, 39/57 (68%) received at least one intervention against arrhythmia (eg amiodarone, IV fluid or magnesium) and 38/57 (67%) had recurrent episodes of arrhythmia in ICU. Patients with arrhythmias in ICU had higher 60-day mortality (63%) as compared to those without arrhythmias (39%).

**Conclusion:** New-onset supraventricular arrhythmias were frequent in ICU patients with COVID-19 and were related to previous history of tachyarrhythmias and severity of the acute disease. The mortality was high in these patients despite the frequent use of interventions against arrhythmias.

#### **Editorial Comment**

In this multi-centre retrospective cohort study of COVID-19 patients admitted to the ICU, supraventricular arrhythmias were common, frequently resulted in therapeutic interventions. These were associated with a worse 60-day survival. It is unclear whether tachyarrhythmias

© 2021 The Acta Anaesthesiologica Scandinavica Foundation. Published by John Wiley & Sons Ltd

action Anaesthesion

naesthesiologica

are equally common in other patient cohorts treated in the ICU for respiratory failure not due to COVID-19 disease. The results demonstrate the multi-organ effect of COVID-19, and high-light the complex treatment and monitoring required for those with the most severe form of the disease.

# 1 | INTRODUCTION

In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in the Hubei Province of China.<sup>1</sup> SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), the burden of which has challenged healthcare systems and ICUs globally.

The clinical presentation and severity of COVID-19 varies from mild upper respiratory tract symptoms to severe pneumonia, acute respiratory distress syndrome, septic shock and multiorgan failure.<sup>2-5</sup> Moreover, studies have shown different cardiovascular manifestations in hospitalized patients with COVID-19, including cardiac arrhythmias, myocardial injury and thromboembolic events.<sup>6-8</sup> Recently published studies conducted in different populations with COVID-19 have reported occurrence of cardiac arrhythmias, bradycardia and atrioventricular blocks with varying frequencies.<sup>9</sup>Taken together, these findings suggest that cardiovascular-related manifestations, especially cardiac arrhythmias may be an important aspect of COVID-19 and may affect the management and outcome of these patients. However, epidemiological data are still limited regarding cardiac arrhythmias in ICU patients with COVID-19.

In this study, we aimed to describe the incidence of and risk factors for clinically-detected cardiac arrhythmias, the management strategies used against the arrhythmias and the clinical outcomes for ICU patients with COVID-19 and cardiac arrhythmias.

# 2 | METHODS

We conducted a multicentre, retrospective cohort study of all patients admitted to the ICUs in the Capital Region of Denmark after approval from the Danish Patient Safety Authority (ref. no. 31-1522-55) and Knowledge Centre on Data Protection Compliance (ref. no. 31-1522-55). Ethical committee approval or consent was not required due to the observational design as per Danish law. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>10</sup>

# 2.1 | Setting and patients

All seven ICUs (in six public hospitals) serving the 1.8 million inhabitants in the Capital Region of Denmark participated in the study. One ICUs also provided extracorporeal membrane oxygenation (ECMO) service for an additional 0.8 million inhabitants of Region Zealand. We assessed all patients admitted to one of the seven ICUs in the period from March 1st to June 1st 2020 for eligibility and included all patients who had at least one positive SARS-CoV-2 PCR-sample from the upper or lower airways during the index hospitalization. The study population was followed for a maximum of 60 days after the date of the index ICU admission.

# 2.2 | Data

Data were retrospectively obtained from the electronic medical record system (Epic Systems healthcare software, US) and entered into a RedCap database.

We obtained data on patient demographics, pre-existing comorbidity and cardiovascular risk factors, outpatient medication, and the duration of COVID-19 symptoms before hospital admission. We registered the following data at ICU admission and during the ICU stay: use of mechanical ventilation, vasopressor therapy, renal replacement therapy (RRT), prophylactic anticoagulant, and EMCO and documented episodes of cardiac arrhythmias (ESM, Table S8).

All the participating ICUs used continuous 3-lead monitoring in all patients during the study period. It was not possible to retrospectively obtain prints or digital reports from the 3-lead monitoring. Therefore, it was not possible to estimate the duration and timing of detected arrhythmias.

All notes for each enrolled patient were manually screened for the full ICU stay to assess key words indicating detected episodes of cardiac arrhythmia. All episodes of arrhythmia during the ICU stay were considered as a clinically relevant arrhythmia if it was documented in doctor's notes. Episodes where doctor's or ICU nursing notes only reported sinus tachycardia or rapid ventricular rate without any further description were not considered as an arrhythmia episode.

The diagnostic methods and management strategies for the cardiac arrhythmia were registered, including the total number of described arrhythmia episodes. The arrhythmias were classified as supraventricular tachyarrhythmias (SVAs), heart blocks or ventricular arrhythmias based on description in medical records or available ECGs. Additionally, SVAs were further divided as atrial fibrillation/flutter (AF), atrioventricular reentry tachycardia and other atrial tachyarrhythmias.

Available ECGs were independently validated by two cardiologists (among PKJ, STP, CJ and NR) to assess the diagnostic accuracy while blinded to all demographic and clinical data except for gender.

	Overall (n = 155)	No arrhythmias (n = 98)	Arrhythmias (n = 57)	P-value
Age, years, median (IQR)	66 (55-74)	64 (53-71.75)	71 (63-76)	<.001
Male	113 (73)	71 (72)	42 (74)	1.00
Time from COVID-19 symptoms to hospital admission, days, median (IQR)	7 (5-10)	7 (6-10)	7 (4-10)	.08
Pre-existing conditions				
Active smoker	20 (13)	11 (11)	9 (16)	.56
COPD	14 (9)	7 (7)	7 (12)	.43
Arterial hypertension	68 (44)	41 (42)	27 (47)	.61
Diabetes mellitus	32 (21)	21 (21)	11 (19)	.91
Haematological malignancy or metastatic cancer	13 (8)	7 (7)	6 (11)	.55
Chronic kidney disease	6 (4)	2 (2)	4 (7)	.19
Cardiovascular disease				
Tachyarrhythmia	22 (14)	5 (5)	17 (30)	<.001
Bradyarrhythmia	2 (1)	1 (1)	1 (2)	1.00
Ischemic heart disease	15 (10)	9 (9)	6 (11)	1.00
Thromboembolic episodes or vascular disease	12 (8)	3 (3)	9 (16)	.009
Cardiac surgery	1 (0.6)	0	1 (2)	.36
Cardiac valve disease	5 (3)	1 (1)	4 (7)	.06
Electronic cardiac devices	3 (2)	1 (1)	2 (4)	.55
Medication before hospital a	admission			
Beta blockers	30 (19)	11 (11)	19 (33)	.001
Calcium-channel blockers	25 (16)	17 (17)	8 (14)	.75
Digoxin	2 (1)	1 (1)	1 (2)	1.00
Amiodarone	1 (0.6)	0	1 (2)	.36
Propafenone	1 (0.6)	0	1 (2)	1.00
ACE, ARB or renin inhibitors	49 (32)	28 (29)	21 (37)	.37
Anticoagulants	13 (8)	3 (3)	10 (18)	.004
Antiplatelet agents	33 (21)	17 (17)	16 (28)	.17

**TABLE 1** Characteristics athospitalization in ICU patients withCOVID-19 stratified by the occurrence ofcardiac arrhythmias in ICU

Abbreviations: ACE, angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; N, number.

<sup>a</sup>Values are numbers (percentages) unless stated otherwise

In the case of disagreement, consensus was attained in conference among three cardiologists.

Outcome measures in the 60 days follow-up period included vital status, ICU and hospital length of stay, thromboembolic events, myocardial infarction, myocarditis (as diagnosed by a cardiologist) and echocardiographic evidence of newly acquired cardiac dysfunction (ESM, Table S8).

# 3 | STATISTICS

As we planned to include all ICU patients with COVID-19 during the study period, no sample size estimation was performed.

The population was stratified according to the occurrence of one or more episodes of cardiac arrhythmias vs no episodes during the ICU stay. We expressed continuous variables as medians with interquartile range

772

Anaesthesiologica Scandinavica

				Scandinavica	
<b>TABLE 2</b> Characteristics in hospital, atICU admission and during the ICU stay in patients with COVID-19 stratified by the		Overall (n = 155)	No arrhythmias (n = 98)	Arrhythmias (n = 57)	P-value
occurrence of cardiac arrhythmias in ICU	Hospital admission				
	Days from hospital to ICU admission, median (IQR)	3 (1-5)	3 (1-4)	2 (0-5)	.66
	Use of hydroxychloroquine before ICU admission	0	0	0	
	Use of macrolides before ICU admission, n (%)	33 (21)	16 (16)	17 (30)	.07
	Localization before ICU admission, n (%)				
	Emergency department	39 (25)	23 (23)	16 (28)	-
	Hospital ward	106 (68)	71 (72)	35 (61)	-
	Operation room	2 (1)	2 (2)	0	-
	Intermediate care unit	8 (5)	2 (2)	6 (11)	-
	The first 24 h of ICU admission				
	SMS-ICU score, median (IQR)	22 (16-25)	20 (13-25)	25 (22-26)	<.001
	Initiation of prophylactic anticoagulant	143 (92)	88 (90)	55 (96)	.21
	Use of vasopressor/inotropes	108 (70)	59 (60)	49 (86)	.001
	Use of mechanical ventilation	118 (76)	66 (67)	52 (91)	.001
	Use of renal replacement therapy	3 (2)	0	3 (5)	.04
	Septic shock within the first 24 h	24 (15)	14 (14)	10 (18)	.75
	During the whole ICU stay				
	Use of vasopressor/inotropes	125 (81)	70 (71)	55 (96)	<.001
	Use of mechanical ventilation	131 (85)	74 (76)	57 (100)	<.001
	Duration of ventilation, days, median (IQR)	12 (3.5-21)	9 (1-18)	16 (7-22)	.002
	Use of RRT	52 (34)	27 (28)	25 (44)	.05

Use of EMCO

Abbreviations: EMCO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation; N, number; RRT, renal replacement therapy; SMS-ICU, simplified mortality score for the intensive care unit. <sup>a</sup>Values are numbers (percentages) unless stated otherwise

19 (12)

(IQR) and categorical variables as numbers with corresponding percentages. We report the incidence with 95% CIs as the number of patients with at least one detected episode of cardiac arrhythmia in ICU among those at risk, ie all ICU patients with COVID-19 in the study period.

WETTERSLEV ET AL

We evaluated any baseline or outcome differences between the groups using two-tailed X<sup>2</sup> test, Fisher's exact test or Mann-Whitney U test, as appropriate. In addition, Kaplan-Meier curve was performed to assess the survival times during the 60 days follow-up period in the two groups.

We used uni-and multivariable logistic regression analysis to assess baseline risk factors for cardiac arrhythmias in ICU. The following covariables were considered as potentially important risk factors and included into the multivariable logistic regression model: gender, history of tachyarrhythmias, history of diabetes mellitus, history of arterial hypertension and the SMS-ICU (ESM, Table S9) score and the presence of septic shock at ICU admission.

Missing data were reported without any further analysis. All statistical analyses were performed using R (version 4.0.2) and Pvalues  $\leq$  0.05 were considered statistically significant.

12 (12)

7 (12)

1.00

#### RESULTS 4

We included all 155 patients with COVID-19 admitted to one of the ICUs in the period from March 1st to June 1st 2020. A small number of variables had missing data (Electronic Supplementary Material (ESM, Table S1-4).

For the total population the median age was 66 years (IQR 55-74) and most were men (Table 1). Frequent comorbidities included arterial hypertension (44%), diabetes mellitus (21%), previous history of tachycardia (14%), ischemic heart disease (10%) and chronic obstructive pulmonary disease (9%).

#### CICLCI Scandinavica

# 4.1 | Cardiac arrhythmia

The incidence of arrhythmia in the ICU was 57/155 (37% (95% CI 30-45)) of whom 68% had new-onset arrhythmia episode (defined as patients without previously known arrhythmia) (Table 3). Sixty-three percent of the patients had sinus rhythm at ICU admission. SVAs were the most frequent type of arrhythmia (95%), mainly atrial fibrillation/flutter; few had ventricular arrhythmias (3%) or heart blocks (2%).

The cardiac arrhythmia diagnosis was confirmed by 12-lead ECG in 22/57 (39%) of the patients (Table 3). The diagnostic accuracy was 82% for patients with available 12-lead ECGs (ESM, Table S7).

# 4.2 | Risk factors

The severity score SMS-ICU was higher in patients with cardiac arrhythmia in ICU than in those without. Also, the use of vasopressor therapy and mechanical ventilation were common for patients with arrhythmia including the number of days on mechanical ventilation (Table 2).

Baseline variables associated with arrhythmias in ICU included previous history of tachyarrhythmias and higher SMS-ICU at ICU admission in the adjusted analysis (ESM, Table S5).

## 4.3 | Management of the arrhythmia

Different management strategies were used for the arrhythmias (Table 3). Administration of one or more pharmacological agent was used in 47/57 (82%), correction of modifiable factors in 32/57 (56%) and a combined strategy in 29/57 (51%) of the patients. Direct current (DC) cardioversion was applied in 7/57 (12%) and 11/57 (6%) did not receive any type of intervention to manage the arrhythmia.

The most used interventions were amiodarone, IV fluid, magnesium infusion and digoxin (Table 3). Approximately 80% of the detected cardiac arrhythmias resolved at some time point during the ICU stay, but recurrence was frequently reported (Table 3).

# 4.4 | Outcomes

The overall mortality for the whole population was 48% at day 60 and those with cardiac arrhythmias had higher mortality (63% vs 39% in those without arrhythmias, corresponding to a RR of 1.63 (95% Cl 1.19-2.24; P = .005).

A total of 81 patients had an echocardiographic evaluation (81/155) during the index hospitalization and abnormal echocardiographic findings were documented in 35% of the patients. Reduced left ventricular ejection fraction was frequent in those with arrhythmia (Table 4).

The majority of patients received anticoagulant prophylaxis in the ICU within the first 24 hours of ICU admission. Sixteen percent 
 TABLE 3
 Arrhythmia subtype and management strategies used

 in ICU patients with COVID-19 and cardiac arrhythmias

Number of patients with arrhythmias	57	
Incidence of arrhythmias based on the total study population (n = 155)	37% (95% Cl: 30;45)	
Arrhythmia characteristics (n $=$ 57)		
Potassium level, mmol/L, median (IQR)	4.0 (3.7-4.3)	
Diagnosis only based on 3-lead monitoring	35 (61)	
Combined 3-lead monitoring and 12-lead electrocardiogram	22 (39)	
Subtype of arrhythmias ( $n = 57$ )		
Supraventricular tachyarrhythmia	54 (95)	
Atrial fibrillation/flutter	52 (96)	
Other atrial tachycardia	0 (0)	
Atrioventricular reentry tachycardia	2 (4)	
Heart block	1 (2)	
Ventricular arrhythmia	2 (3)	
Management strategies used (n = $57$ )		
None	6 (11)	
Interventions to correct modifiable factors	32 (56)	
Fluid therapy	23 (40)	
Magnesium	20 (35)	
Red blood cell transfusion	3 (5)	
Potassium	2 (4)	
Electrical Cardioversion	7 (12)	
Pharmacological interventions	47 (82)	
Amiodarone	44 (77)	
Digoxin	9 (16)	
Beta-blockers	4 (7)	
Course of detected arrhythmia episode ( $n = 57$ )		
Resolvement of first detected arrhythmia	47 (82)	
No other episodes detected	19 (33)	
Between 1-3 additional episodes detected	25 (44)	
Between 4-7 additional episodes detected	9 (16)	
≥8 additional episodes detected	4 (7)	
In-hospital course in patients with arrhythmias (n =	57)	
Death in the ICU	35 (61)	
Discharged from the ICU	20 (35)	
Arrhythmia during the post-ICU hospitalisation period	8 (40)	
Still in ICU at 60 day follow-up	2 (4)	

Abbreviations: CI, confidence interval; DC-cardioversion, direct current cardioversion; HR, heart rate; ICU, intensive care unit; IQR, interquartile range; mmol/L, milimoles per liter.

<sup>a</sup> Values are numbers (percentages) unless stated otherwise

of the population had reported thromboembolic event or venous thrombosis at some time point during the study period, mainly pulmonary embolism (52%) and deep venous thrombosis (24%),

#### TABLE 4 Clinical outcomes in ICU patients with COVID-19

7	7	5

Outcome measure	Overall (n = 155)	No arrhythmias (n = 98)	Arrhythmias (n = 57)	RR (95% CI)	RD (95% CI)	P-value	
Death at day 60	74 (48)	38 (39)	36 (63)	1.63 (1.19;2.24)	24.4% (8.6;40.2)	0.005	
Hospital LOS, days, median (IQR)	24 (13-35)	23.5 (12.25-35.75)	24 (13-33)	-	-	0.84	
ICU LOS, days, median (IQR)	14 (5-24)	11 (3.25-24)	17 (9-23)	-	-	0.04	
Cardiovascular events within 60 days							
AMI episodes	2 (1)	1 (1)	1 (2)	1.72 (0.11;26.96)	0.7% (-3.2;4.7)	1.00	
Deep venous thrombosis or thromboembolic events	25 (16)	14 (14)	11 (19)	1.35 (0.66;2.77)	5.0% (7.4;17.4)	0.55	
Myocarditis episodes	0	0	0	-	-	-	
Echocardiography	Overall (n = 81)	No arrhythmias (n = 46)	Arrhythmias (n = 35)				
Abnormal TTE or TEE	29 (36)	12 (26)	17 (49)	1.86 (1.03;3.37)	22.5% (1.6;43.3)	0.06	
LVEF ≤ 60%	17 (59)	4 (9)	13 (37)	4.27 (1.52;11.97)	28.4% (10.5;46.4)	0.02	
Valve abnormality	4 (14)	2 (4)	2 (6)	1.31 (0.20-8.88)	1.4% (-8.3;11.1)	1.00	
Right-sided dysfunction	11 (38)	7 (15)	4 (11)	0.75 (0.24;2.367)	-3.8% (-18.6;11.0)	0.74	
Abnormal pericardium	0	0	0	-	-	-	

Abbreviations: AMI, acute myocardial infarction; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LVEF, left ventricular ejection fraction; N, number; RD, risk difference; RR, risk ratio; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. <sup>a</sup>Values are numbers (percentages) unless stated otherwise

ischemic stroke (16%) or other events (8%). Moreover, we observed a trend towards worse outcomes for patients with additional detected episodes of cardiac arrhythmias (ESM, Table S6).

# 5 | DISCUSSION

In this population-based cohort study of ICU patients with COVID-19, we found that one-third had cardiac arrhythmias in ICU and most occurred in patients without previously known cardiac arrhythmia as a new-onset atrial fibrillation/flutter. Risk factors were previous tachyarrhythmia and higher acute disease severity. Most of the patients had at least one intervention against the arrhythmia; despite this the mortality was high.

Previous studies assessing tachyarrhythmias in ICU patients in general have reported considerably varying incidences from 1% to 45%.<sup>11-13</sup> The high incidence of cardiac arrhythmias identified in our population may in part be explained by the high disease severity and the presence of several proarrhythmic risk factors. Clinicians did intervene in most cases suggesting these arrhythmia events were clinically relevant, and it may be that access to raw data from the monitors would have revealed an even higher incidence of arrhythmia.

In general, factors such as cardiovascular comorbidities, multiorgan failure and use of life-support have been associated with increased risk of cardiac arrhythmias, especially atrial fibrillation during critical illness.<sup>12,14,15</sup> In our cohort, patients who developed cardiac arrhythmias were older, had higher acute disease severity and higher use of ventilation, vasopressors and RRT, all factors that contribute to higher SMS severity score, which was associated with cardiac arrhythmias in the adjusted analysis together with previous history of tachyarrhythmias. This suggests that ICU patients with COVID-19 are at risk of developing cardiac arrhythmias due to the presence of predisposing and critical illness-related proarrhythmogenic risk factors as it has been observed in other cohorts of critically ill patients. Moreover, the reported incidence in our study population is similar to other studies assessing the arrhythmia incidence in critically ill patients without COVID-19.<sup>10,11</sup>

COVID-19 may contribute as an arrhythmogenic mediator and thus increase the risk of developing arrhythmia during critical illness in addition to heart failure, myocarditis and acute coronary syndrome.<sup>9,16-18</sup> The combination of systemic and local myocardial inflammation may lead to direct cardiomyocyte damage. Subsequently, electrophysiological and structural changes induced by the acute viral infection may lead to abnormalities in the cardiac conduction system, thereby lowering the threshold for developing arrhythmias.<sup>9,19</sup> Thus, it seems reasonable that these COVID-related mechanisms combined with the well-established proarrhythmic risk factor (eg hypoxemia, metabolic disturbance, advanced age) explains, at least in part, the high frequency of arrhythmias in these patients.<sup>9,19</sup> However, COVID-19 may not be an independent risk factor for arrhythmia in ICU patients, but we cannot assess this further, because we did not include non-COVID-19 controls in our study.

Anaesthesiologic Scandinavica

Recently published studies suggest that the SARS-Cov-2 infection may cause regional inflammation and thrombotic microangiopathy of the myocardium.<sup>6,18,20,21</sup> This may lead to increased biomarker levels such as troponins, brain natriuretic peptide and D-dimer and may explain some of the observed cardiovascular complications including cardiac arrhythmias, acute myocardial infarction, myocarditis and thromboembolic events observed in COVID-19. However, we only identified two patients diagnosed with myocardial infarction and none with myocarditis, but both these conditions may be difficult to identity in ICU patients. Cardiac markers such as troponins, BNP or D-dimer were not recorded in this study, which makes it difficult to assess the extent of myocardial damage for the whole study population and specifically for those with arrhythmias.

We found that abnormal echocardiographic findings were frequent in the patients with cardiac arrhythmia including reduced left ventricular ejection fraction and right-sided dysfunction of the heart. Previous studies have reported similar findings, but the general understanding of the pathophysiology is still limited.<sup>22,23</sup> Notably, 16% of the population developed a thromboembolic event during the 60days follow-up period, despite the fact that most patients received anticoagulant prophylaxis at the ICU admission. This may be due to the hypercoagulable state and increased thromboembolic risk that this population may have.<sup>8,24</sup>

In our study population, amiodarone was the most frequently used pharmaceutical intervention against arrhythmias. Clinicians possibly prefer amiodarone due to its antiarrhythmic efficacy against a broad range of arrhythmias and limited negative inotropic effect.<sup>25</sup> However, amiodarone has well-known adverse effects such as lung toxicity, liver impairment and proarrhythmic effect.<sup>25</sup> Moreover, the use of amiodarone in ICU patients is not supported by trial data and the evidence is mainly derived from non-critically ill populations. Thus, the overall balance between benefit and harm of amiodarone and other interventions is still unknown in ICU patients with cardiac arrhythmia.<sup>12</sup>

We found high mortality in the patients with arrhythmias. It may be that cardiac arrhythmias reflects disease severity directly (eg cardiac involvement and/or endogenous catecholamines) or indirectly (eg consequences of the life-supportive interventions) or increases mortality in itself or that the interventions used against arrhythmias cause serious adverse events. The potential causalities around this, if any, are still debated in critically ill patients in general.<sup>26-32</sup>

Our study has several limitations. First, the observational and retrospective design makes it prone to different types of bias and risk of residual confounding. We only assessed ICU patients with COVID-19. Thus, the lack of a non-COVID-19 control group makes it difficult to make any interference about the potential causality link between cardiac arrhythmias and worse outcomes for this specific ICU population. Moreover, it was not possible to assess whether COVID-19 independently contributes as a risk factor for developing cardiac arrhythmias in this population. Second, our sample size was relatively small and data only derived from one region in Denmark. This resulted in some uncertainty for some estimates, it reduced the number of risk factors included in the model and reduced the external validity. Third, cardiac arrhythmias were retrospectively assessed by medical records and fewer patients had the arrhythmia confirmed by 12-lead ECG, which may underestimate the incidence and increase the risk of misclassification. Additionally, it was not possible to distinguish and assess the prognostic impact of sustained arrhythmias as compared with transient episodes due to the lack of digital reports in the electronic record system. Also, the lack of cardiac biomarkers did not allow us to assess the level of myocardial damage.

# 6 | CONCLUSIONS

In this population-based, retrospective cohort study, the incidence of detected cardiac arrhythmias was 37% in ICU patients with COVID-19 and atrial fibrillation/flutter was the most common arrhythmia. Risk factors were a history of tachyarrhythmias and higher acute disease severity. Most patients received at least one intervention against arrhythmia, but these patients had a high mortality. Therefore, further research is needed to assess whether arrhythmias are drivers of worse outcome or a bystander phenomenon in ICU patients with COVID-19 and to assess the optimal management strategies in these patients.

#### CONFLICTS OF INTERESTS

None of the authors have any conflicts of interest or financial ties to disclose.

#### AUTHORS' CONTRIBUTIONS

MW, PKJ, CH, CJ, NR, SP and AP contributed to the study design. All the authors contributed to patient identification and the revision of the manuscript.

### ORCID

Mik Wetterslev b https://orcid.org/0000-0002-8798-1133 Anders Perner b https://orcid.org/0000-0002-4668-0123

#### REFERENCES

- Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199-1207.
- 2. Lai CC, Liu YH, Wang CY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. *J Microbiol Immunol Infect*. 2020;53:404-412.
- 3. Xu J, Yang X, Yang L, et al. Clinical course and predictors of 60day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care*. 2020;24:394.

- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a singlecentered, retrospective, observational study. *Lancet Respir Med.* 2020;8:475-481.
- 5. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.
- Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802-810.
- 7. Bhatla A, Mayer MM, Adusumalli S, et al. COVID-19 and cardiac arrhythmias. *Heart Rhythm*. 2020;17:1439-1444.
- Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46:1089-1098.
- Babapoor-Farrokhran S, Rasekhi RT, Gill D, Babapoor S, Amanullah A. Arrhythmia in COVID-19. SN Compr Clin Med. 2020;14:1-6. https://doi.org/10.1007/s42399-020-00454-2
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-349.
- 11. McIntyre WF, Um KJ, Cheung CC, et al. Atrial fibrillation detected initially during acute medical illness: a systematic review. *Eur Heart J Acute Cardiovasc Care*. 2019;8:130-141.
- Wetterslev M, Haase N, Hassager C, et al. New-onset atrial fibrillation in adult critically ill patients: a scoping review. *Intensive Care Med.* 2019;45:928-938.
- Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. Crit Care Med. 1990;18:1383-1388.
- Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. J Intensive Care. 2015;3(1):19. https://doi. org/10.1186/s40560-015-0085-4
- Bedford JP, Harford M, Petrinic T, Young JD, Watkinson PJ. Risk factors for new-onset atrial fibrillation on the general adult ICU: a systematic review. J Crit Care. 2019;53:169-175.
- Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Euro Heart J. 2006;27:136-149.
- 17. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130:2620-2629.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.
- Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: THE possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17:1463-1471.
- Han H, Xie L, Liu R, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol. 2020;92:819-823.

- Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:811-818.
- 22. Szekely Y, Lichter Y, Taieb P, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. *Circulation*. 2020;142:342-353.
- Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2019;2020:e203557. https://doi.org/10.1001/jamacardio -2020.3557
- 24. Shi W, Lv J, Lin L. Coagulopathy in COVID-19: focus on vascular thrombotic events. *J Mol Cell Cardiol*. 2020;146:32-40.
- 25. Hughes M, Binning A. Intravenous amiodarone in intensive care. Time for a reappraisal? *Intensive Care Med.* 2000;26:1730-1739.
- Seguin P, Laviolle B, Maurice A, Leclercq C, Mallédant Y. Atrial fibrillation in trauma patients requiring intensive care. *Intensive Care Med.* 2006;32:398-404.
- Carrera P, Thongprayoon C, Cheungpasitporn W, Iyer VN, Moua T. Epidemiology and outcome of new-onset atrial fibrillation in the medical intensive care unit. J Crit Care. 2016;36:102-106.
- Chen AY, Sokol SS, Kress JP, Lat I. New-onset atrial fibrillation is an independent predictor of mortality in medical intensive care unit patients. *Ann Pharmacother*. 2015;49:523-527.
- Yoshida T, Uchino S, Yokota T, Fujii T, Uezono S, Takinami M. The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: a retrospective cohort study. J Crit Care. 2018;44:267-272.
- Klein Klouwenberg PM, Frencken JF, Kuipers S, et al. Predictors, and outcomes of new-onset atrial fibrillation in critically III patients with sepsis. A cohort study. Am J Respir Crit Care Med. 2017;195:205-211.
- Yoshida T, Uchino S, Sasabuchi Y, Hagiwara Y. Prognostic impact of sustained new-onset atrial fibrillation in critically ill patients. *Intensive Care Med*. 2020;46:27-35.
- Shaver CM, Chen W, Janz DR, et al. Atrial fibrillation is an independent predictor of mortality in critically III patients. *Crit Care Med*. 2015;43:2104-2111.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

#### How to cite this article: Wetterslev M, Jacobsen PK,

Hassager C, et al. Cardiac arrhythmias in critically ill patients with coronavirus disease 2019: A retrospective populationbased cohort study. *Acta Anaesthesiol Scand*. 2021;65:770– 777. https://doi.org/10.1111/aas.13806

Anaesthesiologic Scandinavica