Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Cardiology 80 (2022) 298–302

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original Article

Incidence and predictors of cardiac arrhythmias in patients with COVID-19 induced ARDS

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ARTICLE INFO

Article history:
Received 23 March 2022
Received in revised form 12 April 2022
Accepted 18 April 2022
Available online 16 May 2022

Keywords:
Arrhythmia
Ventricular tachycardia
Atrioventricular block
Coronavirus disease 2019
Acute respiratory distress syndrome

ABSTRACT

Introduction: Recent studies suggest cardiac involvement with an increased incidence of arrhythmias in the setting of coronavirus disease 2019 (COVID-19). The aim of this study was to evaluate the risk of potentially lethal arrhythmias and atrial fibrillation in patients with COVID-19-induced acute respiratory distress syndrome (ARDS) and to elicit possible predictors of arrhythmia occurrence.

Methods and results: A total of 107 patients (82 male, mean age 60 ± 12 years, median body mass index 28 kg/m^2) treated for COVID-19-induced ARDS in a large tertiary university hospital intensive care unit between March 2020 and February 2021 were retrospectively analyzed. Eighty-four patients (79%) had at least moderate ARDS, 88 patients (83%) were mechanically ventilated, 35 patients (33%) received vvECMO. Forty-three patients (40%) died during their hospital stay. Twelve patients (11%) showed potentially lethal arrhythmias (six ventricular tachycardia, six significant bradycardia). Atrial fibrillation occurred in 27 patients (25%). In a multivariate logistic regression analysis, duration of hospitalization was associated with the occurrence of potentially lethal arrhythmias ($p = 0.006$). There was no association between possible predictive factors and the occurrence of atrial fibrillation. Invasive ventilation, antipsychotics, and the QT_c interval were independently associated with acute in-hospital mortality, but this was not arrhythmia-driven as there was no association between the occurrence of arrhythmias and mortality.

Conclusion: In this relatively young population with COVID-19-induced ARDS, the incidence of potentially lethal arrhythmias was low. While overall mortality was high in these severely affected patients, cardiac involvement and arrhythmia occurrence was not a significant driver of mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a pandemic with more than 245 million infections and approximately 5 million cases of death worldwide as of late October 2021 and a far-reaching impact on the world's health and economic sectors [1]. Approximately a quarter of hospitalized patients require intensive care treatment [2]. These seem to be at higher risk for developing cardiac arrhythmias, with a previously suggested prevalence of up to 44% [3], whereas the risk for arrhythmias in clinically stable patients seems to be low [4].

Recent studies suggest that COVID-19 can be associated with myocardial damage, defined as an elevation of high-sensitivity troponin I above the 99th percentile, possibly caused by direct and indirect viral effects. Troponin elevation has been observed in 20–30% of hospitalized patients and was associated with higher in-hospital mortality [5,6]. In a recent observational study, cardiac involvement was shown in 78% of patients who recovered from COVID-19 using magnetic resonance imaging. After a median follow-up duration of 71 days, there was ongoing inflammation in 60% of the patients, independent of severity or course of illness [7]. In a systematic review of 1601 articles, pericardial or myocardial late gadolinium enhancement was observed in 4–100% of COVID-19 survivors [8]. In view of these data, cardiac arrhythmias driven by myocardial damage due to direct viral effects seem to be

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https://doi.org/10.1016/j.jjcc.2022.04.010
0914-5087/

possible. The present study was therefore conducted to elicit the incidence and possible predictive factors of cardiac arrhythmias in a patient population severely affected by COVID-19 by analyzing all consecutive patients admitted to a tertiary university hospital intensive care unit (ICU) for COVID-19-induced acute respiratory distress syndrome (ARDS).

Methods

The study was conducted in accordance with the declaration of Helsinki and was designed as a retrospective analysis including all patients admitted to the internal medicine intensive care unit of a large tertiary university hospital for COVID-19-induced ARDS between 03/2020 and 02/2021. All patients admitted during this time were analyzed concerning the occurrence of cardiac arrhythmias during their stay on the ICU and possible predictors were recorded.

Therapy of COVID-19-induced ARDS

All included patients had at least moderate ARDS at the time of ICU admission. Patients were treated according to the state of evidence at the time of admission, especially concerning the status of noninvasive ventilation, the time of intubation, and the use of dexamethasone, which was administered according to the RECOVERY or DEXA-ARDS protocols as appropriate [9,10]. In all patients with a $p_aO2/F_iO2 < 1.5$, prone ventilation was attempted for 5 cycles of 16 h each [11]. If patients were not mechanically ventilated, this was done as awake proning [12]. Patients with a $p_aO2/F_iO2 < 1.0$ were evaluated for veno-venous extracorporeal membrane oxygenation (vv-ECMO) therapy, which was administered either with the Maquet Rotaflow (Maquet, Rastatt, Germany) or Getinge Cardiohelp (Getinge, Göteborg, Sweden) systems. Antiviral agents such as remdesivir were not routinely administered during intensive care treatment as there was no evidence of benefit in this severely affected population [13]. All patients received a transthoracic echocardiography and a control of cardiac laboratory parameters on admission and when clinically indicated.

Statistical analysis

Data were stored using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) while SPSS Version 27 (IBM Corporation, Somers, NY, USA) and MedCalc Version 19.6.4 (MedCalc Software Ltd., Ostend, Belgium) were used for statistical analysis. Univariate analyses were conducted using Mann-Whitney U, chi-square, or Fisher exact tests as appropriate. A multivariate logistic regression model was used for multivariate analysis. Statistical significance was defined as a two-sided alpha level of 0.05 or less.

Results

One-hundred and seven patients were included. Patient characteristics are shown in Table 1 and relevant previous medical history is listed in Online Table 1. The patient population included 82 male patients (77%), mean age was 60 ± 12 years, and the median duration of ICU stay was 11 days (interquartile range: 5–16 days). Eighty-four patients (79%) had at least moderate ARDS, 59 patients (55%) received at least one proning session with a median of 4 proning sessions per patient, and 35 patients (33%) received a vvECMO during their course of treatment. Online Table 2 displays relevant medication use in the patient population during the ICU treatment. Forty-three patients (40%) died during their hospital stay.

Table 1
Clinical characteristics of the included patient population.

Number of patients	107
Gender (male/female)	82 (77%)/25 (23%)
Age in years (mean ± SD)	60 ± 12
Time from first diagnosis to ICU admission in days (IQR)	8 (3−12)
Length of ICU stay in days (IQR)	11 (5–16)
BMI in kg/m^2 (IQR)	28 (25–33)
Severity of ARDS	
- Mild	23 (21%)
- Moderate	38 (36%)
- Severe	46 (43%)
Mechanical ventilation	88 (82%)
vv-ECMO	35 (33%)
Number of patients with proning	59 (55%)
- Median number of proning sessions (IQR)	4 (3–5)
Bacterial/fungal superinfection	44 (41%)
Number of patients on hemodialysis	31 (29%)
ECG on admission	
- PQ (IQR)	149 (130–160)
- QRS (IQR)	82 (80–90)
- QT_c (IQR)	440 (420–460)
Arrhythmias	
- Ventricular tachycardia	6 (6%)
- Bradyarrhythmias (AVB, sinus arrest, asystole)	6 (6%)
- Atrial fibrillation	27 (25%)
Death during hospital stay	43 (40%)

AVB, atrioventricular block; BMI, body mass index; ECG, electrocardiogram; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; vv-ECMO, veno-venous extracorporeal membrane oxygenation.

Ventricular tachycardias

Six patients (6%) developed ventricular tachycardia (VT) during their intensive care treatment. Median age was 64 years and median body mass index 30 kg/m^2. In all of these patients, a monomorphic VT was documented (see Fig. 1). Five of six patients were male, all were mechanically ventilated and four of six patients received a vvECMO during their treatment course. Only two patients had previously known coronary artery disease. In two patients cardiopulmonary resuscitation (CPR) was needed but all patients survived their episode(s) of VT. However, three of the six patients later died due to end-stage pulmonary COVID-19 involvement and, in one case, fungal superinfection.

Two of the patients with ventricular tachycardia exhibited increased serum troponin and reduced left ventricular function on echocardiography. In one of these patients the most likely cause of the cardiac involvement was deemed to be a septic cardiomyopathy caused by *Candida* sepsis and left ventricular ejection fraction (LVEF) improved after antifungal treatment. The other patient had COVID-induced myocarditis with a regeneration of LVEF after resolution of COVID-induced ARDS. A cardiac magnetic resonance imaging conducted six months after first diagnosis was able to document a reduced cardiac perfusion reserve in this patient.

Bradyarrhythmias

Six patients (6%) developed relevant bradyarrhythmias during ICU treatment necessitating medical or interventional treatment. Two patients had one episode of asystole which were clinically determined to be of vagal origin and neither patient needed CPR nor developed another episode of relevant bradyarrhythmias. One further patient developed bradycardia of unknown etiology, received CPR for 5 min but recovered and did not show any further bradycardia. The remaining three patients developed complete atrioventricular (AV)-nodal block (see Fig. 1) during their ICU stay with two patients needing a permanent pacemaker and one patient with recovering AV-nodal conduction after implantation of a temporary pacemaker. All six patients recovered from their severe COVID-19 illness and were able to be discharged from the ICU.

Atrial fibrillation

Twenty-seven patients (25%) developed at least one episode of atrial fibrillation (AF) during their intensive care treatment. AF was previously

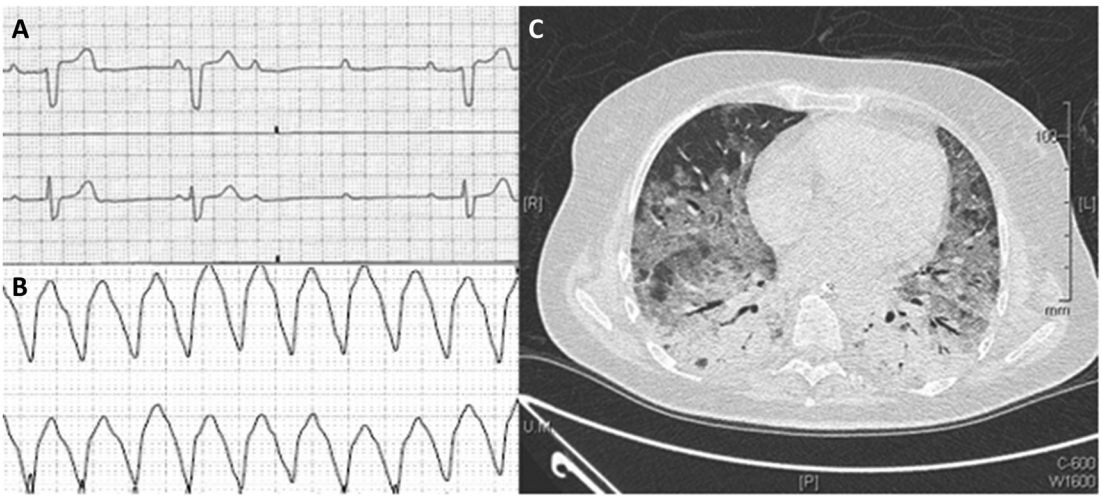

Fig. 1. Representative depictions of complete atrioventricular-nodal block (A), monomorphic ventricular tachycardia (B) and typical computed tomographic imaging findings in a 50-year-old female patient with coronavirus disease 2019-induced acute respiratory distress syndrome (C).

known in three of these twenty-seven patients (11%). Nineteen patients (70%) were male with a mean age of 62 ± 9 years. Twenty-one patients (78%) received betablockers, 18 patients (66%) were treated with amiodarone, and 5 patients (19%) received cardiac glycosides. Twelve patients (44%) were electrically cardioverted during their treatment course.

Predictors of cardiac arrhythmias

Possible predictors of cardiac arrhythmias were recorded in all patients and analyzed in a univariate analysis and a multivariate logistic regression model. Table 2 displays the relevant results. Because of the substantially different impact for affected patients, we decided to analyze predictors of potentially lethal arrhythmias (ventricular tachycardia and relevant bradyarrhythmias) separately from predictors of AF.

On univariate analysis, duration of ICU treatment and the use of antipsychotics showed a significant association with the occurrence of lethal arrhythmias. In the multivariate logistic regression model, only duration of ICU treatment remained as an independently associated factor (see Table 2). None of the recorded possible predictors showed a significant association with the development of AF. Not surprisingly, betablockers and amiodarone were used more often in patients with AF.

Predictors of mortality

Recorded parameters were analyzed for an association with mortality in a univariate analysis and a logistic regression model. On univariate analysis, QT_c, invasive ventilation, proning, vv-ECMO, and the use of catecholamines, amiodarone, antipsychotics, and sedatives showed a significant association with mortality. In the multivariate model, QT_c,

Table 2
Results of univariate and multivariate analyses for possible predictors of lethal arrhythmias, atrial fibrillation and mortality.

	Clinical characteristic	*p*-Value (univariate)	*p*-Value (multivariate)	Odds ratio* (CI)
Lethal arrhythmias	Duration of treatment	0.04	**0.006**	1.08 (1.02–1.14)
	Antipsychotics	0.02		
	Non-significant: PQ, QRS, QTc, age, time from first diagnosis to ICU admission, height, weight, BMI, proning, mortality, vv-ECMO, invasive ventilation, dialysis, gender, ARDS, superinfection; PMH: CHD, diabetes, hypertension, CKD, PAD, liver cirrhosis, AF, asthma, COPD, status post transplantation, smoking, IBD, autoimmune disease, stroke, DVT, PE; Medication: betablockers, catecholamines, amiodarone, antibiotics, sedatives, anticonvulsives, sympathomimetics, alpha-2 agonists, virostatics, cardiac glycosides			
Atrial fibrillation	Betablockers	0.006	**0.02**	4.2 (1.3–13.7)
	Amiodarone	<0.001	**<0.001**	26.7 (7.7–92.8)
	Cardiac glycosides	0.001		
	Non-significant: PQ, QRS, QTc, age, time from first diagnosis to ICU admission, duration of treatment, height, weight, BMI, proning, mortality, vv-ECMO, invasive ventilation, dialysis, gender, ARDS, superinfection; PMH: CHD, diabetes, hypertension, CKD, PAD, liver cirrhosis, AF, asthma, COPD, status post transplantation, smoking, IBD, autoimmune disease, stroke, DVT, PE; Medication: catecholamines, antibiotics, sedatives, anticonvulsives, sympathomimetics, alpha-2 agonists, virostatics, antipsychotics			
Mortality	QT_c	0.02	**0.003**	1.03 (1.01–1.04)
	Invasive ventilation	0.004	**<0.001**	28.8 (4.7–175.7)
	Proning	0.001		
	vv-ECMO	0.006		
	Catecholamines	0.01		
	Amiodarone	0.02		
	Antipsychotics	0.001	**<0.001**	0.05 (0.01–0.24)
	Sedatives	0.007		
	Non-significant: PQ, QRS, age, time from first diagnosis to ICU admission, duration of treatment, height, weight, BMI, mortality, dialysis, gender, ARDS, superinfection; PMH: CHD, diabetes, hypertension, CKD, PAD, liver cirrhosis, AF, asthma, COPD, status post transplantation, smoking, IBD, autoimmune disease, stroke, DVT, PE; Medication: betablockers, antibiotics, anticonvulsives, sympathomimetics, alpha-2 agonists, virostatics, cardiac glycosides			

Significance was defined as a *p*-value <0.05.
AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; PAD, peripheral arterial disease; PE, pulmonary embolism; vv-ECMO, veno-venous extracorporeal membrane oxygenation. Note that the odds ratio for continuous variables is per unit (i.e. days for duration of treatment and ms for QT_c).

invasive ventilation, and the use of antipsychotics remained independently associated with mortality. The association between the QT_c interval and mortality was not arrhythmia-driven, as there was neither an association of QT_c with potentially lethal arrhythmias nor an association of potentially lethal arrhythmias to mortality in our population. Nevertheless, the association of QT_c with mortality remained statistically significant in the multivariate regression model even when corrected for QRS duration [14]. Additionally, sensitivity analyses with clinically relevant QT_c cutoff values of 450 ms ($p = 0.003$) and 470 ms ($p = 0.007$) also showed a statistically significant association with mortality. Antipsychotics showed an inverse relationship to mortality, possibly indicating patients who survived a prolonged treatment course and became delirious during the weaning period.

Discussion

The present study including 107 patients suffering from COVID-19 with at least moderate ARDS documents an overall low incidence of life-threatening arrhythmias. While mortality was high in this previously healthy and comparatively young patient population, our analyses suggest that this was not primarily driven by arrhythmia occurrence.

Concerning AF, our reported incidence in this patient population is comparable to the results of a recent study analyzing the incidence of AF in a large general intensive care cohort [15], indicating that the occurrence of AF corresponds to the overall severity of disease and not to SARS-CoV-2 infection specifically. The reported association between the occurrence of AF and amiodarone or betablockers is most likely a reverse causality, as patients received the medication as treatment for AF. Our findings support the idea that despite possible myocardial involvement, arrhythmia occurrence mainly corresponds to the severity of illness including hypoxia and systemic inflammation rather than viral infection. After multivariate adjustment, only duration of intensive care treatment was associated with the occurrence of ventricular tachycardias and significant bradycardia, indicating a higher incidence in patients requiring prolonged treatment due to their critical course of illness. Importantly, mortality was not associated with the occurrence of arrhythmias and all patients survived their acute arrhythmic events. While recent studies suggest the possibility of myocardial involvement due to direct SARS-CoV-2 effects including elevated troponin levels and pericardial and myocardial late enhancement in magnetic resonance imaging, our analyses were unable to show a corresponding increased risk of cardiac arrhythmias despite our severely affected patients. It is therefore questionable whether cardiac arrhythmias represent a significant factor in COVID-19 mortality, with previous studies likely reporting imaging abnormalities with little clinical impact [16]. Additionally, tissue damage related to COVID-19 might not only be the result of local inflammatory mechanisms but also possibly the result of vascular-related damage, such as capillary leakage and vessel thrombosis [17].

We found a significant association between a slightly increased QT_c interval at the time of admission and in-hospital mortality on multivariate analysis, which was not arrhythmia-driven. The QT_c interval could therefore be a marker for subclinical cardiac injury and reduced cardiac reserve respectively. Correspondingly, QT_c prolongation was previously shown to be a predictor of cardiovascular mortality and morbidity in patients with known cardiovascular disease [18]. In our center, patients were not routinely treated with azithromycin or other QT_c-prolonging medications for COVID-19. Therefore a systemic effect of the COVID-19 specific medical therapy on QT_c interval seems unlikely. While invasive ventilation is likely a surrogate for disease severity in general and lung involvement in particular, the use of antipsychotics displayed an inverse relationship to mortality in our data. This is most likely explained by many COVID-19 patients exhibiting a prolonged weaning phase with a high incidence of delirium after having survived the most life-threatening phase of their illness.

Limitations

The presented results may be limited because of the relatively short inclusion period and our study's single center design. Since we present a relatively young population with few previously known comorbidities, findings may not be generalizable to a general population with COVID-19, especially in the absence of ARDS. In addition, there was no long-term follow-up to evaluate possible future health effects of arrhythmia occurrence. However, few data are available concerning the impact of arrhythmia on overall COVID-19 mortality with no long-term follow-up available because of the novelty of the disease.

Conclusion

In a relatively young and previously healthy population with COVID-19-induced ARDS, the incidence of potentially lethal arrhythmias during intensive care treatment was low. Only duration of ICU stay was found to be independently associated with the occurrence of lethal arrhythmias in a multivariate logistic regression analysis. While the overall mortality was high in these severely affected patients, arrhythmias did not seem to be a significant driver of mortality. In addition to invasive ventilation, a prolonged QT_c on admission electrocardiogram was associated with increased mortality, potentially indicating subclinical myocardial injury or reduced cardiac reserve.

Funding

No funding was used for this study.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.04.010.

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