MULTIMEDIA REPORT

COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies

Rakesh Gopinathannair [1,2] · Faisal M. Merchant [3] · Dhanunjaya R. Lakkireddy [1,2] · Susan P. Etheridge [4] · Suzy Feigofsky [5] · Janet K. Han [6] · Rajesh Kabra [7] · Andrea Natale [8] · Stacy Poe [9] · Sandeep A. Saha [10] · Andrea M. Russo [11]

Abstract

Background Cardiovascular and arrhythmic events have been reported in hospitalized COVID-19 patients. However, arrhythmia manifestations and treatment strategies used in these patients have not been well-described. We sought to better understand the cardiac arrhythmic manifestations and treatment strategies in hospitalized COVID-19 patients through a worldwide cross-sectional survey.

Methods The Heart Rhythm Society (HRS) sent an online survey (via SurveyMonkey) to electrophysiology (EP) professionals (physicians, scientists, and allied professionals) across the globe. The survey was active from March 27 to April 13, 2020.

Results A total of 1197 respondents completed the survey with 50% of respondents from outside the USA, representing 76 countries and 6 continents. Of respondents, 905 (76%) reported having COVID-19-positive patients in their hospital. Atrial fibrillation was the most commonly reported tachyarrhythmia whereas severe sinus bradycardia and complete heart block were the most common bradyarrhythmias. Ventricular tachycardia/ventricular fibrillation arrest and pulseless electrical activity were reported by 4.8% and 5.6% of respondents, respectively. There were 140 of 631 (22.2%) respondents who reported using anticoagulation therapy in all COVID-19-positive patients who did not otherwise have an indication. One hundred fifty-five of 498 (31%) reported regular use of hydroxychloroquine/chloroquine (HCQ) + azithromycin (AZM); concomitant use of AZM was more common in the USA. Sixty of 489 respondents (12.3%) reported having to discontinue therapy with HCQ + AZM due to significant QTc prolongation and 20 (4.1%) reported cases of Torsade de Pointes in patients on HCQ/chloroquine and AZM. Amiodarone was the most common antiarrhythmic drug used for ventricular arrhythmia management.

Conclusions In this global survey of > 1100 EP professionals regarding hospitalized COVID-19 patients, a variety of arrhythmic manifestations were observed, ranging from benign to potentially life-threatening. Observed adverse events related to use of HCQ + AZM included prolonged QTc requiring drug discontinuation as well as Torsade de Pointes. Large prospective studies to better define arrhythmic manifestations as well as the safety of treatment strategies in COVID-19 patients are warranted.

Keywords COVID-19 · SARS-CoV-2 · Arrhythmia · Cardiac arrhythmia · QTc

✉ Rakesh Gopinathannair
drrakeshg@yahoo.com; rakesh.gopinathannair@hcahealthcare.com

1 The Kansas City Heart Rhythm Institute & Research Foundation, 5100 W 110th St, Ste 200, Overland Park, KS 66211, USA

2 University of Missouri-Columbia, Columbia, USA

3 Emory University School of Medicine, Atlanta, GA, USA

4 University of Utah, Salt Lake City, UT, USA

5 Iowa Heart Center, Des Moines, IA, USA

6 Cardiac Arrhythmia Center, University of California at Los Angeles and VA Greater Los Healthcare Center, Los Angeles, CA, USA

7 University of Tennessee Health Science Center, Memphis, TN, USA

8 Texas Cardiac Arrhythmia Institute, Austin, TX, USA

9 Cleveland Clinic, Cleveland, OH, USA

10 Oregon Heart Center, Salem, OR, USA

11 Cooper University Hospital, Camden, NJ, USA

Abbreviations

HRS   Heart Rhythm Society
EP   Electrophysiology
LV   Left ventricular
TnT   Troponin T
VT   Ventricular tachycardia
VF   Ventricular fibrillation
ACE   Angiotensin-converting enzyme inhibitor
ARB   Angiotensin receptor blocker
HCQ   Hydroxychloroquine
AZM   Azithromycin

1 Introduction

The novel coronavirus (SARS-CoV-2) and the resulting respiratory tract infection (coronavirus disease 2019 or COVID-19) is a pandemic with over 5,800,000 cases globally, resulting in 362,000 deaths at the time of this writing [1, 2]. Following initial reports in Wuhan, China, viral progression culminated in over 80,000 cases in China during January/February 2020 [3, 4]. The subsequent global spread has involved more than 210 countries [1]. The USA has reported > 1.7 million confirmed cases and over 103,000 deaths, the highest in the world [1]. As this global pandemic continues to rage, cardiovascular, especially arrhythmic, manifestations associated with COVID-19 have become evident [5–7]. A recent report from Wuhan, China, noted that 16.7% of hospitalized and 44.4% of ICU patients with COVID-19 had arrhythmias [6]. Although arrhythmias appear to be common in hospitalized COVID-19 patients, arrhythmia mechanisms and characteristics as well as antiarrhythmic therapies and their outcomes have not been well-defined.

2 Objective

To better understand the cardiac arrhythmic manifestations and treatment strategies employed in hospitalized COVID-19 patients through a worldwide cross-sectional survey of arrhythmia professionals.

3 Methods

The Heart Rhythm Society (HRS) conducted a global survey that was developed by the HRS Communications Committee with input from the HRS COVID-19 Rapid Response Task Force. The survey was active from March 27, 2020, to April 13, 2020. The audience for the survey was electrophysiology (EP) professionals (physicians, nurse practitioners, physician assistants, nurses, EP lab technicians, scientists, and other allied professionals) across the globe. The survey consisted of 25 questions (Supplemental Appendix). Demographic questions included primary occupation, practice setting, and practice location (state/province and country). The goal of the survey was to understand the cumulative experience as well as the variability in incidence and management strategies of arrhythmias associated with COVID-19. The survey was administered using SurveyMonkey (SurveyMonkey, Palo Alto, CA, USA), and the survey link was disseminated to the HRS membership through a dedicated email, *Keeping Pace* weekly email, and also through the COVID-19 webpage on the HRS website and HRS member open forum. Additionally, it was disseminated to other arrhythmia societies across the world through email to their leadership and to the larger arrhythmia community through social media (Twitter, Facebook, and LinkedIn). The first 557 respondents were all HRS members who received the survey link through a dedicated email. The subsequent 640 respondents represented a combination of HRS members as well as self-identified respondents who received the survey link either from their respective arrhythmia societies or through social media channels.

3.1 Statistical analysis

Continuous variables are reported as mean ± standard deviation or median (interquartile range). Categorical variables are reported as frequency and percentages. Student's *t* test, or Mann-Whitney *U* test, was used to compare continuous variables, and categorical variables were analyzed using χ^2 tests. All tests are two-tailed and a *p* value < 0.05 indicates statistical significance. Statistical analysis of the responses was performed using Statistica 13.2 (TIBCO Software, Palo Alto, CA).

4 Results

A total of 1197 respondents completed the survey. Seventy-four percent of the respondents were physicians and 17% were allied professionals. Twenty-six percent were in academic practice, whereas 18% and 43% were in private and hospital-based practices, respectively. Fifty percent of respondents were from outside the USA and represented 76 countries and six continents. Practice locations of US respondents represented 44 states. Demographic characteristics are detailed in Table 1.

Of the 1197 respondents, 905 (76%) reported having COVID-19-positive patients in their hospital. For those who reported hospitalized COVID-19, the reported total number of hospitalized COVID patients at the time of the survey was 41,422, with a mean and median number of patients of 61.4 ± 366.2 and 16 (interquartile range, 6–40), respectively. Of the respondents who reported at least one COVID-19 patient in

Table 1 Demographic characteristics of survey participants

Demographic variable	N (%) of respondents (n = 1197)	Outside USA (n = 577)	USA (n = 567)	p value
Primary role				
Electrophysiologist	883 (73.8%)	482 (83.5%)	384 (67.7%)	0.0030
Physician assistant	14 (1.2%)	2 (0.3%)	11 (1.9%)	
Nurse practitioner	55 (4.6%)	5 (0.9%)	48 (8.5%)	
Nurse (RN)	49 (4.1%)	11 (1.9%)	38 (6.7%)	
EP technician	86 (7.2%)	42 (7.3%)	32 (5.6%)	
Other	110 (9.2%)	31 (5.4%)	54 (9.5%)	
Practice setting	n = 1150	n = 584	n = 566	
Academic practice	299 (26.0%)	121 (20.7%)	178 (31.4%)	0.0004
Private practice	205 (17.8%)	96 (16.4%)	109 (19.3%)	
Hospital-based practice	496 (43.1%)	314 (53.8%)	182 (32.2%)	
Outpatient clinic	65 (5.7%)	21 (3.5%)	44 (7.8%)	
Pediatric EP	17 (1.5%)	9 (1.5%)	8 (1.4%)	
Other	68 (5.9%)	23 (3.9%)	45 (8%)	
Practice location				
USA	567 (49.6%)			
Outside the USA	577 (50.4%)			
Number of US states represented	44			
Number of countries by continent				
Asia	23			
Africa	12			
Australia/Oceania	2			
Europe	23			
North America (other than USA)	8			
South America	8			

their hospital, 30.9% had < 10 patients, 21% had 10–19 patients, 24.6% had 20–49 patients, 10.6% had 50–99 patients, and 12.9% had ≥ 100 patients.

4.1 Tachyarrhythmias

A variety of supraventricular and ventricular arrhythmias were reported in COVID-19 patients. Of the 683 respondents, 142 (21%) reported cases of atrial fibrillation, 37 (5.4%) reported atrial flutter, 24 (3.5%) reported sustained atrial tachycardia, and 39 (5.7%) reported paroxysmal supraventricular tachycardia. Among ventricular arrhythmias, frequent monomorphic premature ventricular contractions were reported by 36 (5.3%) respondents, multimorphic premature ventricular contractions by 24 (3.5%), and non-sustained ventricular tachycardia (VT) by 43 (6.3%). Sustained monomorphic VT was reported by 26 (3.8%), polymorphic VT/Torsade de Pointes by 24 (3.5%), VT/ventricular fibrillation (VF) arrest by 33 (4.8%), and pulseless electrical activity by 38 (5.6%) respondents respectively (Fig. 1 and Table 2).

4.2 Bradyarrhythmias

Of 663 respondents, 51 (8%) reported significant sinus bradycardia, 51 (8%) reported complete heart block, 39 (5.9%) reported first- or second-degree AV block, and 26 (3.9%) reported bundle branch block or intraventricular conduction delay in COVID-19 patients (Fig. 2 and Table 2).

4.3 Anticoagulation

One hundred and forty of 645 (21.7%) respondents reported using empiric anticoagulation therapy in all COVID-19-positive patients who did not have an indication otherwise. Of those who used empiric anticoagulation, 88 of 140 (63%) reported using intravenous heparin or subcutaneous low molecular weight heparin, 43 (31%) reported using novel oral anticoagulants, and 9 (6%) reported using warfarin. Reported use of empiric intravenous heparin or subcutaneous low molecular weight heparin was more common outside the USA (21.1% vs 6.6%, p = 0.0001).
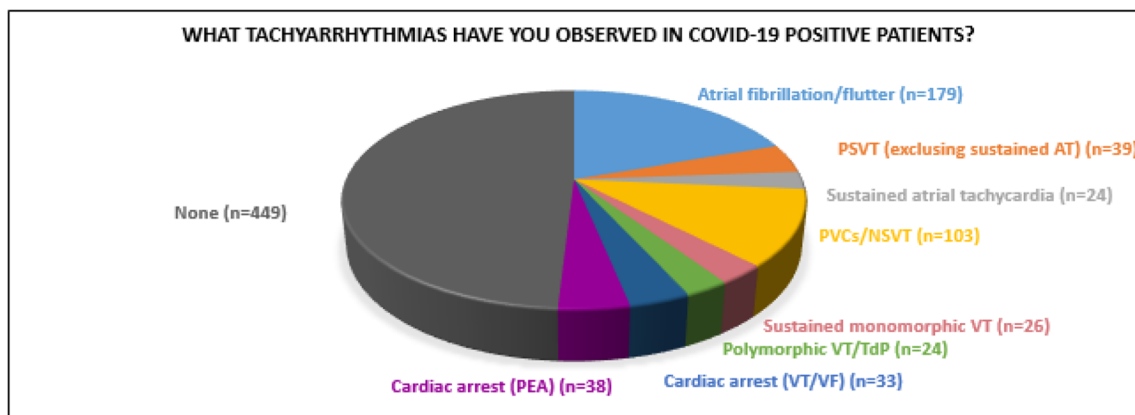
Fig. 1 Characteristics of tachyarrhythmias observed in hospitalized COVID-19 patients

4.4 Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use

Of a total of 643 respondents, 208 (32.3%) reported having patients on angiotensin-converting enzyme inhibitor (ACE)/angiotensin receptor blocker (ARB) at time of COVID-19 diagnosis, with 37 (5.8%) reporting ACE/ARB use in 1–10% of patients whereas 15 (2.3%) reported ACE/ARB use in 90–100% of their patients. Fifty-six (8.7%) reported having no patients on ACE/ARB and 379 (59%) answered that they did not know that information.

4.5 Myocarditis, left ventricular dysfunction, and need for mechanical circulatory support

One hundred and sixty-nine of 628 respondents reported seeing cases of severe left ventricular (LV) dysfunction (ejection fraction < 35%) in COVID-19 patients, but most respondents (68%) reported that ≤ 1 in every 5 patients at their institution had LV dysfunction. One hundred and forty-five (24%) of 610 respondents reported using hemodynamic support (intraaortic balloon pump, percutaneous left ventricular assist device, or extracorporeal membrane oxygenation), of which the majority (73%) of respondents noted that it was required only for a small proportion (1–10%) of their patients. Respondents noted that < 10% of the patients had signs and symptoms consistent with myocarditis. A total of 470 patients with COVID-19 were reported to have manifestations suggestive of ST-elevation acute coronary syndromes.

4.6 Elevated troponins and invasive coronary angiography in COVID-19 patients

Of 564 respondents, 215 (38.1%) reported having patients with elevated troponins, of which 63 (11.2%) reported elevated troponins in 1–10% of patients whereas 12 (2.1%) reported elevated troponins in 90–100% of patients. Fifty-seven

(10.1%) reported not having any patients with troponin elevation and 292 (51.8%) answered that they did not know that information.

Among 543 respondents, 147 (27.1%) reported that none of their troponin-positive COVID-19 patients underwent invasive angiography whereas 104 (19.1%) reported having a patient who underwent coronary angiography for elevated troponins. Of these, the majority (77/104, 74%) reported that ≤ 20% of the patients with elevated troponins underwent invasive coronary angiography.

4.7 Pericardial disease

Of 568 respondents, 37 (6.5%) reported acute pericarditis; small pericardial effusion was reported by 59 (10.4%), whereas moderate and large pericardial effusions were reported by 9 (1.6%) and 8 (1.4%) of respondents, respectively.

4.8 Use of hydroxychloroquine/chloroquine ± azithromycin

Of 511 respondents, 171 (33.5%) reported having patients on hydroxychloroquine (HCQ)/chloroquine. Twenty-seven (5.3%) reported using it only in 1–10% of patients, whereas 44 (8.6%) reported using it in 91–100% of COVID-19 patients. Of 498 respondents, 155 (31%) respondents reported using HCQ/chloroquine in combination with azithromycin (AZM). Thirty-six (7.2%) reported using the combination only in 1–10% of patients, whereas 27 (5.4%) reported using it in 91–100% of COVID-19 patients. For HCQ monotherapy, in the USA, 33% responded that they had not used HCQ in any patients, 49% had used it in some, but not all, patients, and 18% reported using it in essentially all patients. Outside the USA, 49% had not used it at all, 39% had used in some patients, and 12% reported using HCQ in essentially all patients ($p = 0.005$). For HCQ/AZM combination therapy, in the USA, 33%

**Table 2** Responses to selected questions regarding arrhythmia manifestations in hospitalized COVD-19 patients

Question	Answer choices	Responses	Response percentage
What tachyarrhythmic manifestations of COVID-19 have you seen? Please check all that apply.	Atrial fibrillation	142	20.79%
	Atrial flutter	37	5.42%
	Sustained atrial tachycardia	24	3.51%
	Paroxysmal SVT	39	5.71%
	Frequent monomorphic PVCs	36	5.27%
	Frequent multimorphic PVCs	24	3.51%
	Non-sustained VT	43	6.3%
	Sustained monomorphic VT	26	3.81%
	Polymorphic VT/Torsade de Pointes	24	3.51%
	Cardiac arrest, VT/VF	33	4.83%
	Cardiac arrest, PEA	38	5.56%
	I have not seen any yet	449	65.74%
	Answered	683	
	Skipped	521	
What bradyarrhythmic manifestations of COVID-19 have you seen? Please check all that apply.	Severe sinus bradycardia	51	7.69%
	AV block, first degree	18	2.71%
	AV block, Mobitz 1	9	1.36%
	AV block, Mobitz 2	12	1.81%
	AV block, complete heart block	51	7.69%
	Left bundle branch block	9	1.36%
	Right bundle branch block	7	1.06%
	Intraventricular conduction delay	10	1.51%
	I have not seen any yet	550	82.96%
	Answered	663	
	Skipped	541	
What percentage of COVID-19-positive patients have had QTc prolongation (> 500 ms or > 550 ms with bundle branch block)?	0	95	19.92%
	1–10%	50	10.48%
	11–20%	17	3.56%
	21–30%	8	1.68%
	31–40%	2	0.42%
	41–50%	3	0.63%
	51–60%	0	0.0%
	61–70%	0	0.0%
	71–80%	0	0.0%
	81–90%	0	0.0%
	91–100%	0	0.0%
	Not sure/do not know	302	63.31%
	Answered	477	
	Skipped	727	

SVT, supraventricular tachycardia; *PVCs*, premature ventricular contractions; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation; *PEA*, pulseless electrical activity

reported not using at all, 55% in some, and 12% in essentially all patients. Outside the USA, 50% of respondents had not used combination therapy at all, 41% had used in some patients, and only 9% responded using in essentially

Fig. 2 Characteristics of bradyarrhythmias observed in hospitalized COVID-19 patients
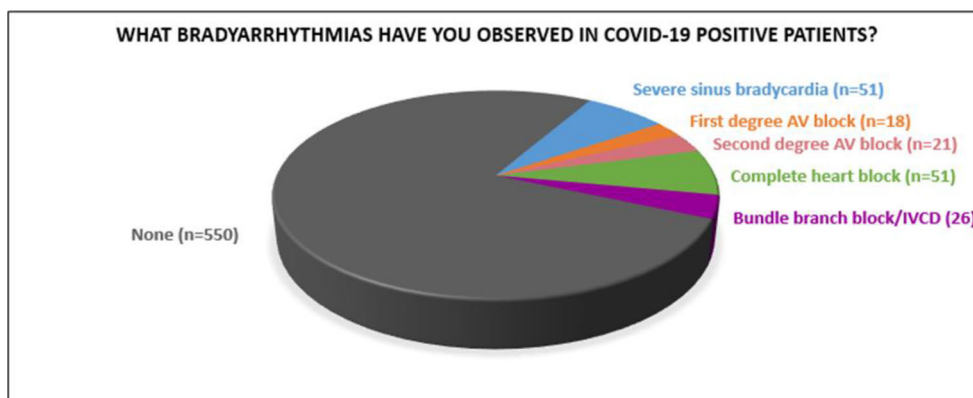
all patients ($p = 0.003$). Based on these results, use of either HCQ or HCQ in combination with AZM appears to be more common in the USA (Fig. 3).

Of 508 respondents, 254 (50%) reported using a QTc monitoring protocol for patients on HCQ/chloroquine, with no significant difference between those from the USA versus outside the USA (49% vs 51%, $p = 0.59$). Among individuals using a QTc monitoring protocol in the USA, 36% were in academic practice whereas outside the USA, only 21% of those using a QTc monitoring protocol were in academic practice ($p = 0.01$).

Twenty percent of respondents reported using magnesium supplementation in all patients on HCQ/chloroquine. QTc prolongation ≥ 500 ms (≥ 550 ms with QRS duration > 120 ms) was reported by 80 of 477 respondents (17%) (Table 2). Sixty (12.3%) of 489 respondents reported having to discontinue combination therapy with HCQ/chloroquine and AZM due to significant QTc prolongation. Twenty (4.1%) respondents reported cases of Torsade de Pointes in patients on HCQ/chloroquine and AZM.

4.9 Antiarrhythmic drug use

Prophylactic amiodarone use was rare (reported by only 8 (1.7%) of 477 respondents). In COVID-19 patients with ventricular arrhythmias, 250 (57%) of the 441 respondents reported not using any class I, II, or III antiarrhythmic agents whereas 150 (34%) used amiodarone and 64 (14.5%) used lidocaine/mexiletine. Sotalol and dofetilide use was infrequent, reported by 35 (8%) and 10 (2.3%) of survey respondents, respectively.

5 Discussion

The major findings of this global survey include the following: (a) In hospitalized COVID-19 patients, EP professionals across the globe reported a wide variety of arrhythmic manifestations, with several reporting potentially life-threatening ventricular arrhythmias (sustained monomorphic VT, polymorphic VT/Torsade de Pointes, VT/VF arrest) as well as

Fig. 3 Difference between US and non-US respondents regarding the percentage of hospitalized COVID-19 patients being treated with HCQ/chloroquine + azithromycin
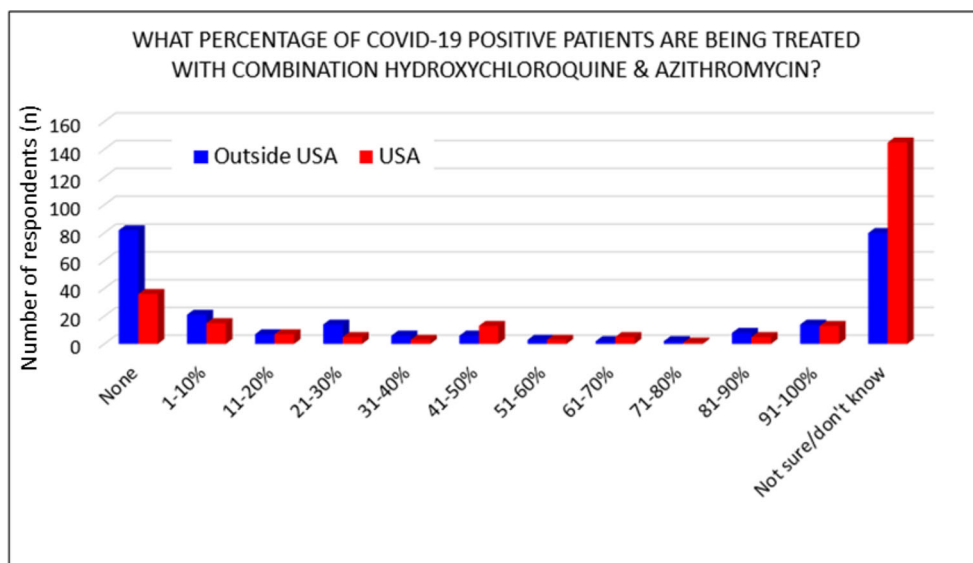
pulseless electrical activity. (b) Atrial fibrillation was the most common cardiac arrhythmia noted in these patients. Severe sinus bradycardia and complete heart block were the most common bradyarrhythmias. (c) Twenty-two percent of respondents used therapeutic anticoagulation in COVID-19 patients without established indications, with use of intravenous heparin/low molecular weight heparin more prevalent outside the USA. (d) There was wide variation in use of HCQ/chloroquine and AZM, with concomitant use of AZM more common in the USA. Discontinuation of HCQ/chloroquine + AZM due to QTc prolongation and Torsade de Pointes was reported by 12.3% and 4.1% of respondents, respectively. (e) Amiodarone was the most common antiarrhythmic drug used for managing ventricular arrhythmias.

Currently, limited information is available regarding arrhythmic manifestations associated with COVID-19. In one study of 137 patients, 7.3% reported palpitations at presentation [8]. Wang et al., in a single-center retrospective analysis of 138 consecutive patients admitted with COVID-19 in Wuhan, China, reported arrhythmias in 16.7% of hospitalized patients, with a much higher incidence (44.1%) in those needing intensive care. However, no definition as to what constituted an arrhythmia was provided [6]. Guo et al., in another single-center retrospective study of 187 patients from Wuhan, China, evaluated the association of underlying cardiovascular disease and myocardial injury on fatal outcomes in patients with COVID-19. They noted that 28% of patients had myocardial injury as evidenced by elevated troponin T (TnT) levels. Incidence of VT/VF was 5.9% and increased to 17.3% in patients with elevated TnT [9]. The reported percentage of VT/VF in our survey is comparable with the data from Guo et al. Moreover, our survey also provides additional information on pulseless electrical activity (reported by 5.6% respondents), underscoring the potential influence of COVID-19 on life-threatening cardiac arrhythmias and likely pump failure.

Atrial fibrillation was the most common reported arrhythmia in COVID-19 patients. Although we do not have demographic details of patients and do not know how many had *de novo* versus pre-existing atrial fibrillation, this is not surprising as the majority of sicker COVID-19 patients are older and have underlying comorbidities, predisposing to atrial fibrillation [10]. Multiple mechanisms could lead to the increased incidence of brady- and tachyarrhythmias associated with COVD-19 infection. Arrhythmic manifestations could be secondary to direct myocardial inflammation and injury. Severe hypoxic lung disease from COVID-19 can trigger atrial arrhythmias. Viral infection and associated increased metabolic demand and cytokine activation can trigger atrial and ventricular arrhythmias in patients who develop acute myocarditis or inflammatory response and in those with underlying coronary or other structural heart diseases.

Our data show that 22% of respondents are using anticoagulation, either oral, subcutaneous, or intravenous, in patients who did not otherwise have an indication for anticoagulation. This highlights the concern regarding the prothrombotic potential of COVID-19. The relatively common presence of atrial fibrillation further raises the need to address anticoagulation. These aspects as well as duration of anticoagulation following recovery from COVID-19 require further study.

At the time of this writing, except for the emergency use authorization of remdesivir, no other FDA-approved treatments are available for COVID-19. There has been great interest in HCQ/chloroquine ± AZM, for inpatient treatment of COVID-19; however, available data have been conflicting and randomized studies are lacking [11–13]. The combination, however, poses a significant risk of QTc prolongation and Torsade de Pointes [14]. A randomized, double-blind, currently non-peer-reviewed study from Brazil assigned 81 patients to a low- and high-dose chloroquine regimen; all patients received ceftriaxone and AZM. At 13-day follow-up, 15.1% had a QTc > 500 ms (11.1% in low-dose and 18.9% in high-dose arm ($p = 0.5$)). Two out of 73 patients (2.7%) had VT from QTc prolongation [14]. In a retrospective study of 84 patients given HCQ + AZM, 11% had a QTc > 500 ms [15]. Information from this survey closely mirrors data from these 2 recent studies [14, 15] and shows that the risk for arrhythmic adverse events is not inconsequential, and suggests a cautious approach and close monitoring of QTc when using these, yet to be proven, therapies.

6 Limitations

This study has several limitations. The findings represent cross-sectional data from a survey completed by arrhythmia professionals. Given that the survey was disseminated to the global arrhythmia community, it is difficult to assess a response rate. The opinions of the survey respondents may not fully represent the entire EP community and may not represent all practitioners who care for COVID-19 patients. The survey findings are subject to recall bias as respondents may tend to remember the sicker patients. Reports of arrhythmias are from EP professionals, likely representing selection bias for sicker COVID-19 patients at a higher risk for developing arrhythmias. Since the survey was disseminated to EP professionals and not to institutions, it is possible that respondents working in the same institution may be referencing the same patient or group of patients. Although a thorough review of the data did not reveal any duplicate responses, the fact that the survey was also disseminated through social media, it is not possible for us to be absolutely sure that only one response was obtained per respondent. The information on various arrhythmias presented here may not represent the accurate incidence of

arrhythmias in the COVID-19 population, but simply serve to provide a broad overview of arrhythmic manifestations and therapeutic strategies employed by EP professionals across the globe. The way the survey questions were worded, it was not possible to determine whether a reported brady- or tachyarrhythmia was *de novo* or pre-existing. This survey did not assess for comorbid conditions or the level of medical care the COVID-19 patients were receiving (regular ward vs intensive care, ventilator use); hence, no association could be made between underlying conditions or severity of illness and arrhythmic manifestations. With regard to empiric subcutaneous or intravenous anticoagulation, although the intent was to assess the use of therapeutic doses, the wording of the survey question may not distinguish between prophylactic and therapeutic use. These results should be confirmed by future prospective studies or registries.

7 Conclusions

In this global survey of data from > 1100 EP professionals regarding hospitalized COVID-19 patients, a variety of arrhythmic manifestations were observed, ranging from benign to life-threatening. Observed adverse events related to use of HCQ + AZM included prolonged QTc requiring drug discontinuation as well as Torsade de Pointes. These findings underscore the need for large, prospective studies to better define arrhythmic manifestations as well as the safety and efficacy of treatment strategies in COVID-19 patients.

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