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INTRODUCTION

At the time of writing the present article, SARS-CoV-2, aka COVID-19, has reportedly hit almost 180 million people globally in less than 18 months since its official identification and disclosure as pandemic. Initially announced as a severe acute respiratory syndrome due to a novel strain of coronavirus, after the acronym SARS-CoV-2, the first pandemic of the third millennium was unexpectedly far from being an isolated respiratory condition. Instead, a multitude of signs and symptoms, sometimes representing the only atypical manifestation of the disease, have been described with alacrity, making the COVID-19 indeed configuring as a systemic disease requiring a multidisciplinary care.

Pertaining to the cardiovascular complications or manifestations of the SARS-CoV-2, in the present article, we offer an overview of the ventricular arrhythmias related to acute COVID-19 infections, discussing the prevalence, the possible mechanisms due to direct or indirect virus involvement, and the currently proposed therapeutic options.
EPIDEMIOLOGY AND CLINICAL OUTCOMES

Prevalence and Nature of VAs

Mitacchione and colleagues described the first case of ventricular storm (12 episodes of sustained ventricular tachycardias [VTs]) with concomitant COVID-19 infection in a patient with defibrillator (ICD) and ischemic cardiomyopathy (ejection fraction = 34%) admitted to an Italian hospital for respiratory distress. ICD interrogation showed sustained and nonsustained monomorphic VTs since days before the admission. The authors excluded iatrogenic causes because the systemic use of QT-prolonging immunomodulators and antimicrobials was not recommended at that time, and the VT was probably due to other mechanisms (see paragraph 4). This insightful report suggests that VAs could be the first sign of latent infection in susceptible patients with structural heart disease.

In addition, two descriptions of polymorphic ventricular tachycardia (PMVT) in the settings of prolonged and normal QT, respectively, were also reported. Of interest, two separate cases of newly diagnosed Brugada syndrome were reported, one presenting as an asymptomatic coved-type pattern during febrile peak, and the other as PMVT due to fever and drug-induced bradycardia.

The overall prevalence of VAs in COVID-19 patients ranges between 0.15% and 8% (Table 1). Such a discrepancy stems from the definition of VAs and subpopulations analyzed. The first series by Guo showed that malignant arrhythmias were relatively more common in patients with cardiac injury—defined as troponin T elevation—(11% vs 5% over a total of 187 individuals). A retrospective study of 700 patients differentiated the prevalence between patients admitted to intensive care unit (ICU) compared with nonintensive care settings. In total, only one patient had a life-threatening torsade de pointes (TdP) in ICU (1.4% vs none in the comparison group). Similarly, nonsustained episodes were more common in critical patients (8% vs 0.6%). In line with this analysis, a Scandinavian group observed that incidence of VAs in ICU patients was about 3% (n = 2/155), yet, according to a larger cohort of 1053 hospitalized patients, nonsustained episodes are far less prevalent than malignant VAs (0.7% vs 3%).

Lastly, no data are currently available in regard to VAs incidence in COVID-19 patients with implanted cardiac devices treated conservatively at home. In this regard, it is worth carrying out such analysis, as experienced in different settings.

Clinical Value and Outcomes

Despite the slight numerical divergence, it is worth noting that the occurrence of VAs consistently clustered with complicated hospitalizations, suggesting that ventricular arrhythmias are a marker of severe systemic disease. Indeed, besides anecdotic cases of VA survivors, the mortality at 1 month is substantially higher in patients experiencing arrhythmias of ventricular nature (VT or ventricular fibrillation [VF], 59% vs 16% in controls; P < .001, respectively). On the contrary, nonsustained episodes of VAs do not seem to predict mortality within a year.

Furthermore, another detailed breakdown of the relationship between VAs and clinical outcomes argues against the role of malignant VTs as the primary/initial cause of death. For instance, as reported by two different groups, a nonshockable rhythm was the predominant cause of cardiac arrest/death (90% in both studies). Correspondingly, in a series of 140 patients admitted on telemetry monitor, fatal VAs were noted in only 12% of deceased patients (6/52). All the events were represented by VF, 1 patient survived, and 2 autopsy examinations suggested that the initial cause of death was pulmonary rather than cardiac.

The prevalence and clinical significance of premature ventricular contractions (PVCs) in the setting of acute infection were less investigated; although subjects with SARS-CoV-2 infection can initially complain of palpitations (7%), dedicated analysis is scarce. An Italian study showed that 4% (n = 13/324) of COVID-19 positive subjects admitted to the emergency department presented ventricular ectopy, compared to 13% of 1053 hospitalized patients (n = 137). Despite the evidence that PVCs are seen in cases of novel coronavirus-related myocarditis, the positive predictive value for cardiac involvement is poor, and likewise the association with mortality is borderline (HR = 2.79; 95% CI, 1.00–7.79; P = 0.051).

MECHANISMS AND PREDICTORS OF VAs IN THE SETTING OF ACUTE COVID-19 INFECTION

A broad number of articles discuss the possible causes of VAs during acute COVID-19. For the sake of simplification, herein we distinguish between intrinsic and extrinsic causes, depending on the direct or indirect role of the pathogenic agent. The former can be divided into 2 types: primary intrinsic (directly due to the interaction between the virus and the cardiomyocyte) and secondary intrinsic (after the immune response to the systemic infection; Fig. 1). Overall, rarely a
| Author and Date | Sample | Number and Type of VA | QT/QT-Prolonging Agents | Underlying Cardiac Disease | Primary Cause Hypothesized | Management | Outcome |
|----------------|--------|-----------------------|-------------------------|--------------------------|----------------------------|------------|---------|
| Mitacchione et al, 2020 | 1 | VT storm | • NS  
• none | ICM | • Systemic inflammation  
• Pre-existing cardiac disease | VT ablation with remote navigation control | Discharged |
| Elsad et al, 2020 | 1 | Bradycardia-induced TdP; VF | • 650 ms  
• none | None | Multiorgan failure | Lidocaine Magnesium Dopamine Transcutaneous pacing | Discharged |
| O’Brien et al, 2020 | 1 | PMVT | • 460 ms  
• Hydroxymorphone  
• Amiodarone  
• Trazodone | None | Multiorgan failure | Discontinuation of amiodarone Lidocaine Metoprolol | Demise |
| Chang et al, 2020 | 1 | NS | NS  
Brugada | None | Multiorgan failure | Supportive care | Demise |
| Tsimpoulis et al, 2020 | 1 | PMVT | • 422 ms  
• HCQ  
• AZT  
• Propofol  
• Dexmedetomidine | Brugada | Systemic inflammation  
• Fever  
• Congenital channelopathy | Supportive care | Demise |
| Bathla et al, 2020 | 700  
1 TdP  
10 NSVT | • NS  
• NS | De novo left ventricular dysfunction  
• NS | Multiorgan failure | NS  
10 survived  
1 demise |
| Guo et al, 2020 | 187  
11 VT/VF | • NS  
• NS | NS | Systemic inflammation  
• Cardiac injury | NS  
NS |

(continued on next page)
| Author and Date         | Sample | Number and Type of VA | QT/QT-Prolonging Agents | Underlying Cardiac Disease | Primary Cause Hypothesized | Management | Outcome                  |
|-------------------------|--------|-----------------------|-------------------------|----------------------------|----------------------------|------------|--------------------------|
| Wetterslev et al,9 2021 | 155    | 2 NS                  | • NS                    | NS                         | • Multiorgan failure       | NS         | NS                       |
|                         |        |                       | • NS                    | NS                         | • Pressors                 |            |                          |
| Peltzer et al,10 2020   | 1053   | 137 PVC, 7 NSVT, 13 VT, 9 PMVT, 8 VF | • NS/ 4 of the 745 using HCQ+ had PMVT | NS                         | • Multiorgan failure       | NS         | 59% of patients with VA died |
|                         |        |                       |                         | NS                         | • Pressors                 |            |                          |
| Turagam et al,11 2020   | 140    | 6 VF, 1 VT            | • NS                    | NS                         | • Multiorgan failure/ pressors (5/7) | NS         | 6 demises (VF group)      |
|                         |        |                       | • NS                    | NS                         | • NS in one VF patient     |            | 1 survived (VT patient)   |
| |                     |        |                       | • 107/140 used HCQ; - 62/140 used HCQ + AZT | Pre-existing cardiac disease (VT patient) |
| Mesquita D,12 2021      | 692    | 2 VT                  | Prolonged in both       | NS                         | • Multiorgan failure       | NS         | Demise in both b          |
|                         |        |                       |                         | NS                         | • QT prolongation          |            |                          |
|                         |        |                       |                         | NS                         | • Pre-existing cardiac condition |            |                          |
| Lanza et al,14 2021     | 324    | 13 PVC                | • NS                    | NS                         | NS                         | NS         | 4 demises                 |
|                         |        |                       | • NS                    | NS                         |                           |            |                          |
| Perretto et al,15 2021  | 7      | 2 PVC/NSVT, 1 VT, 1 VF | Normal; HCQ/AZT in 3/4 pts with VAs | CAD                        | • Myocarditis              | Amiodarone | Discharged (ICD in pt with VF and in 1 with NSVT). All alive at 6 months |
|                         |        |                       |                         |                            | • Pre-existing cardiac disease |            |                          |
|                         |        |                       |                         |                            | • Pressors                 | Metoprolol/ Bisoprolol in the others |                          |
|                         |        |                       |                         |                            |                           |            |                          |
| D’Ascenzo et al,30 2021 | 779    | 38 VT/VF              | • NS                    | CAD                        | ACS                        | NS         | NS                       |
|                         |        |                       | • NS                    |                            | Multifactorial             |            |                          |
| Author(s) | Year | No. | NSVT | NS | VT | Number treated | HCQ | Other treatments | Demises | Other complications |
|-----------|------|-----|------|----|----|----------------|-----|------------------|--------|--------------------|
| Saleh M,  | 2020 | 201 | 7    | NS | 1  | No             | 119 | AZT              | 2      | VT                 |
|           |      |     |      |    |    |                |     |                  |        |                    |
|           |      |     |      |    |    |                |     |                  |        |                    |
| Gasparetti A, | 2020 | 649 | 3    | NS | 4  | 6              | 119 | AZT              | 1      | VF                 |
|           |      |     |      |    |    |                |     |                  |        |                    |
|           |      |     |      |    |    |                |     |                  |        |                    |

**Abbreviations:** ACS, acute coronary syndrome; AZT, azithromycin; CAD, coronary artery disease; HCQ, hydroxychloroquine; ICM, ischemic cardiomyopathy; NS, nonspecified; NSVT, nonsustained VT; PMVT, polymorphic ventricular tachycardia; pts, patients; PVC, premature ventricular contraction; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

*For atrial fibrillation with rapid ventricular response.*

*Due to respiratory failure.*

Prevalence of VAs with Acute COVID-19 Infection
single factor can be pointed as the source of VA; instead, plural elements could affect the electrical vulnerability of the ventricles.18

**Intrinsic Factors**

A brilliant in vitro model showed that infected cardiomyocytes derived from a human pluripotent staminal cell exhibit a significant reduction of the contractile activity measured as beats per minute (4 vs 9 in controls) and a greater extent of contraction dis-synchrony compared with mock SARS-CoV-2 negative cultures.19 Such effect became even more prominent after 48 hours of treatment with interleukin-6. In fact, even though the presence of the virus in cardiac tissue or evidence of myocarditis have been inconsistently detected,20–22 cytokines surge from the systemic immune response are alone sufficient to dysregulate calcium handling, modulate ion channels expression, increase fibrosis, and exert a negative inotropic effect, ultimately enhancing the susceptibility to VAs.23–27 For example, late VAs and epicardial fibrosis at the magnetic resonance were documented in one case months after the resolution of the acute illness.28

**Extrinsic Factors and Predictors of VAs**

VAs can also be iatrogenic. Based on the evidence that hydroxychloroquine and chloroquine inhibit lysosome turnover, and consequently the antigen presentation initiating the immune response,38 there has been a large empirical use of antimalarial drugs at the beginning of the pandemic with the purpose to damper the adverse events and the hospitalization duration. However, the most concerning side effects of hydroxychloroquine are QT prolongation and TdP, especially if combined with antimicrobial prophylaxis with azithromycin or lopinavir/ritonavir.39,40 Indeed, the duration of phase 2 of the action potential is prolonged through hydroxychloroquine inhibition of the hERG channels, slowing the potassium rapid inward currents (iKr), and by means of sodium current enhancement exerted by azithromycin on SC5NA.41–43 Repolarization prolongation by 10 to 50 ms is relatively frequent (5%–50%),10,34,35,44 and in one series of 201 patients treated with empirical prophylaxis, 18 (11%) developed QTc prolongation greater than 500 ms, albeit only one patient had sustained VT (0.5%), and no TdP was recorded.34 In another series, no difference in VAs incidence was seen between patients treated with antimalarial agents versus controls,10 whereas Gasparetti and colleagues concluded that the 3 VF observed in 28 patients admitted in ICU (10%) were due to ongoing ACS and not hydroxychloroquine-induced QT.37
Therefore, QT prolongation inconsistently predicts VAs in COVID-19 patients, whereas hydroxychloroquine is rarely associated with malignant arrhythmias (<1%). ST-T wave changes seemingly are not related to VAs; however, elevated markers of cardiac injury (troponin, natriuretic peptide) and systemic inflammation (i.e., C-reactive protein, interleukin-6) are significantly higher in patients presenting life-threatening arrhythmias. Nonetheless it is not universally acknowledged. Differently, a high dose of pressors seems to correlate with VAs incidence, both due to adrenergic stimulation and also for an implication of severe cardiogenic shock, whereas the value of admission left ventricular ejection fraction is controversial.

**THERAPEUTIC OPTIONS**

If supportive management, including correction of electrolyte and acid/base derangement, fluid repletion, blood transfusion, coronary or pulmonary reperfusion, is not adequate, rationale antiarrhythmic strategies should be adopted. Sedatives and anesthetics should be titrated down or discontinued when identified as the cause of bradycardia or QT prolongation, and standard dose of beta blockers is certainly useful compatibly with the cardiac output.

Thirty-four percent of the 447 respondents (n = 150) to a global survey (March-April 2020) admitted to using amiodarone for VAs treatment, whereas 15% (n = 64) disclosed having used lidocaine or mexiletine for the same purpose. Other class III agents (sotalol and dofetilide) were rarely reported. Pulmonary and hepatic toxicity probably restrained most physicians from adopting amiodarone in secondary prevention in patients with a concomitant viral respiratory syndrome often complicated by liver dysfunction.

According to some authors, lung toxicity is more likely to occur in ICU patients in which the oxidative damage of high oxygen partial pressure potentiates the free radicals derived from the iodine accumulated in the alveoli. However, it is worth highlighting that acute lung toxicity is an adverse event reported anecdotally; rather, a cumulative dose of 150 g, equivalent to 400 mg daily for 3 months, or 200 mg for more than 18 months are associated with pulmonary injury.

On the contrary, liver toxicity requires as high as 300 g of cumulative dose, but according to some German scholars, one-third of the SARS-CoV-2 patients admitted in ICU has shock liver, which may compromise amiodarone metabolism.

In our opinion, the vast experience in daily practice and the existing literature in non-COVID scenarios is more than sufficient to state that amiodarone is efficacious for malignant arrhythmias in COVID-19 patients. Despite isolated warning reports about lung and hepatic toxicity in some subjects with new coronavirus infection, the legitimate concern should be the risk of liver injury and of QT prolongation secondary to drug-drug interaction with antimicrobials; thus, we think that amiodarone should be cautiously dosed in patients with extreme transaminosis, but still be preferred to other more torsadogenic class III agents. Furthermore, in the case of long QT (>550 ms), the treatment should switch to Ib agents, which can shorten the repolarization.

Interestingly, amiodarone exhibits pleiotropic effects that can interfere with SARS-CoV-2 infection, by altering the ion channels of the endosomal vesicles. Also, it prevents cytokines production supposedly through the same mechanism in lymphocytes in vivo, and additionally presents scavenging effects of oxygen free radicals in vitro. In light of such anti-inflammatory antioxidant properties, amiodarone has been proposed for the treatment of symptomatic patients; besides a single case report, a randomized trial in comparison with verapamil is currently on recruiting (ReCOVery-SIRIO, ClinicalTrials.gov identifier: NCT04351763).

ICDs and endocardial ablation should be recommended in agreement with the international guidelines, and when available, a remote navigation system should be used for the ablation to minimize the exposure of the medical staff.

**SUMMARY**

SARS-CoV-2 is a systemic disease that can also impair the electrical stability of the ventricles. Although a direct cardiac infection by the virus is plausible, the host’s systemic neuroinflammatory response in addition to metabolic disorders are the main triggers of VAs. The physician should be aware that subjects with pre-existing cardiac disease, admitted to ICU, requiring pressor support are more at risk of developing malignant arrhythmias. Therefore, strict monitoring of drugs interactions and precipitating factors (such as hypoxemia, hypokalemia, acidosis) is essential for primary prevention. Amiodarone is generally safe for the secondary prophylaxis of sustained events, and also might show unexplored antiviral/anti-inflammatory effects in human. Intravenous procaïnamide, lidocaine, or oral mexiletine are alternatives, albeit the evidence is limited. Contrarily, sotalol and dofetilide should be discouraged, because the more significant torsadogenic effect can be detrimental in such a delicate scenario. Lastly, substrate ablation is

*Prevalence of VAs with Acute COVID-19 Infection*
recommended in case of refractory episodes, possibly by using a remote navigation system to minimize the contact with the providers.

**CLINICS CARE POINTS**

- Ventricular arrhythmias prevail in less than 10% (<1–8%) of the patients with acute COVID-19 infection, including premature ventricular contractions and life-threatening events.
- The cause is multifactorial and includes direct virus interaction with cardiomyocytes, the effect of interleukins, neurohormonal output, pre-existing cardiac disease, metabolic disorders, iatrogenic toxicity, and latent congenital arrhythmic disorders precipitated by the systemic illness.
- Although VAs are associated with increased mortality, it does not imply that they are the primary cause of death. In contrast, they express the terminal event of a severe systemic metabolic and inflammatory catastrophe.
- In absence of reversible causes (ie, QT-prolonging agents, hypoxemia, hypokalemia), amiodarone is generally safe if other parameters are monitored (ie, liver function) and could theoretically exhibit pleiotropic beneficial effects on the infection itself. Class I agents represent valid alternatives, and ablation should be performed following the international guidelines, possibly with the help of a robotic navigation system to maximize contact isolation.

**DISCLOSURE**

Dr A. Natale has received speaker honoraria from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik, and Medtronic; and is a consultant for Biosense Webster, St. Jude Medical, and Janssen. Dr L. Di Biase is a consultant for Biosense Webster, RMG, Stereotaxis, Boston Scientific, and Abbott. Dr L. Di Biase received speaker honoraria/travel from Medtronic, Atricure, and Biotronik. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

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