Clinical Characteristics of Shocks in Patients with implanted cardioverter defibrillator Following COVID-19 Infection

Jianying sun[1], Juan Ma[1], Feiyu Wei[1], Yazhe Ma[1], Xi Zhang[1], Xiaolong Gao[1], Tao Ma[1], Jia Guo[1], Xiuhua Li[1], and Jie Fan[1]

[1]First People's Hospital of Yunnan

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Abstract

Background and Aims: The relationship between SARS-CoV-2 infection and ICD shock remains unclear. We analyzed the characteristics of patients received shocks after SARS-CoV-2 infection to explore causes of these shocks to provide information for subsequent treatment. **Methods:** We retrospectively analyzed data from seven patients who hospitalized the First People's Hospital of Yunnan Province between December 2022 and January 2023 after experiencing ICD shock or ventricular arrhythmias following SARS-CoV-2 infection. We collected baseline information i.e., age and sex, device type, arrhythmia type, comorbidities, etc to analyze the causes of electrical shocks. **Results:** All patients' devices were implanted in our hospital. The patients' mean age was 67±10 years. Four underwent implantation for primary prevention, and three for secondary prevention. These patients received 80 ICD shocks after SARS-CoV-2 infection, 71 (88.75%) nine (11.25%) of which were treatment for ventricular tachycardia and atrial fibrillation, respectively. There were 54 antitachycardia pacing(ATP) treatments, which forty-eight arrhythmic events were terminated through antitachycardia pacing and six not. Laboratory tests conducted upon admission revealed that six patients had blood potassium levels below 4.0 mmol/L. Five patients had blood calcium levels below 2.11 mmol/L. Four of seven patients had elevated troponin concentrations (0.030–0.297 ng/mL). All patients had significantly elevated N-terminal pro-B-type natriuretic peptide levels (608.8–25,758 pg/mL). Six patients had a QT interval of $>$ 440 ms and a mean QT interval of 460±46 ms. **Conclusion:** SARS-CoV-2 infection may be associated with ICD shock. Clinicians should pay close attention to patients with implanted devices after SARS-CoV-2 infection and actively eliminate arrhythmogenic triggers to minimize the likelihood of ICD shock.

Introduction

On February 11, 2020, the World Health Organization officially named the novel coronavirus-induced illness as coronavirus disease 2019 (COVID-19). Two days later, the International Committee on Taxonomy of Viruses (ICTV) officially named the organism severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the official website of the Chinese Center for Disease Control and Prevention, the number of novel coronavirus infections in China was expected to peak on December 22, 2022. Previous evidence indicates that novel coronavirus infections increase the risk of cardiovascular diseases,[1] and arrhythmias are a common cardiovascular manifestation, with high incidence rates reported in patients with COVID-19.[2,3]

Therefore, sudden cardiac death (SCD) is increasingly becoming a major clinical and public health concern. Implantable cardioverter defibrillators (ICDs) improve survival outcomes[4–7]and are currently the most effective treatment option for the prevention of SCD; however, ICD shock therapy is associated with higher mortality rates.[8–10] It is estimated that 20–35% of patients with an ICD will require ICD shock therapy to treat future arrhythmic events.[9,11] Large clinical trials, such as the Antiarrythmics Versus Implantable Defibrillators (AVID) trial, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have reported even higher shock rates. Reducing the

frequency of ICD shocks and avoiding inappropriate shocks are the main goals of long-term follow-up among patients with ICDs.

Recent studies indicate a significant increase in the number of ICD shocks delivered to patients with COVID-19 infection compared to the rates in the same period in previous years.[12] Our center has also observed a significant increase in the frequency of ICD shocks experienced in patients hospitalized after SARS-CoV-2 infection since the peak of the epidemic in China in December 2022; however, the relationship between COVID-19 and these events has not been well-explored.

Therefore, this study aimed to analyze the characteristics of treatment in patients with ICDs following SARS-CoV-2 infection, to explore the causes of the ICD shocks, and to provide clinical management references for the treatment of patients with ICDs during future periods involving similar infectious diseases.

Methods

Study design

This study involved a retrospective analysis of data from seven patients who were admitted to our treatment center between December 2022 and January 2023 for ICD shock or ventricular arrhythmias after SARS-CoV-2 infection. All patients signed an informed consent form, and the study complied with the Declaration of Helsinki.

Data collection

The enrolled patients' clinical data were collected and recorded, including primary data such as age and sex, device type and model, underlying disease, New York Heart Association (NYHA) cardiac function classification, and presence of comorbid diseases. Data related to device parameters and events, such as the ICD parameter settings, treatment type and frequency, arrhythmia type, and termination mode were also collected. Ancillary examination data were also obtained, including data from electrocardiograms and cardiac ultrasounds, as well as concentrations of electrolytes, markers of myocardial injury, and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Definitions related to ICD treatment of the study

Appropriate ICD treatment was defined as the correct treatment selection and delivery for persistent ventricular and hemodynamically unstable arrhythmias.

Inappropriate ICD treatment was defined as an inappropriate response to any signals other than those related to sustained ventricular and hemodynamically unstable arrhythmias.

The default event termination criteria of the ICDs were defined as eight consecutive intervals greater than or equal to the programmed diagnostic tachycardia circumference after antitachycardia pacing (ATP) or shock therapy.

The clinically recognized criteria for ICD treatment success were defined as the successful conversion of arrhythmia to sinus rhythm and its maintenance.

Ventricular electrical storm was defined as three or more sustained ventricular arrhythmic episodes occurring at least 5 min apart within a 24-h period, with each episode requiring termination by the intervention.[13]

Determination of the cause of inappropriate electroshock treatment

Following ICD treatment, two skilled deputy chief physicians with experience in electrophysiology ascertained the appropriateness of the electroshock treatment by examining the simulated body surface and intracavitary electrograms obtained through the program controls in conjunction with the patient's clinical condition. If the two deputy chief physicians' assessments were in disagreement, consensus was based on the chief physician's assessment. This methodology was crucial for identifying the causes of any inappropriate electroshock treatments.

Results

The baseline characteristics of the patients are shown in Table 1. The mean age was 67±10 years (range: 51–78 years). Six patients were male and one was female patient. Six of the seven patients had an ICD implanted for the treatment of ischemic cardiomyopathy; the other had an ICD implanted for the treatment of long QT syndrome. Two patients had implanted CRT-Ds (Medtronic, DTBC2QQ), whereas the remaining five had ICDs (Medtronic, BVAC). Four patients received ICDs for primary prevention for the treatment of ischemic cardiomyopathy with a low left ventricular ejection fraction (LVEF). One patient received ICDs for the secondary prevention of long QT syndrome with frequent torsades de pointes. Two patients received ICDs for the secondary prevention of ischemic cardiomyopathy with VT. The mean time since device implantation was 40±18 months.

The patient implant device settings are shown in Table 2. In one patient with atrial fibrillation (AF) at the time of implantation, the VF diagnostic interval was set to 270 ms to avoid inappropriate shock of the CRT-D due to AF, with as rapid a ventricular rate as possible. In another patient, the VT diagnostic interval was set to 390 ms based on the ventricular rate measured during previous VT episodes to optimize the device's ability to recognize VT as much as possible and provide treatment as early as possible to terminate the event.

The types of arrhythmias and the characteristics of the treatments administered by the devices for each of the seven patients are shown in Table 3. In seven patients, the average time between the initial onset of symptoms of COVID-19 infection and device shock was 9±5 days (range: 3–20 days). The average QT interval was 460±46 ms (range: 386–536 ms) in the seven patients; however, six patients exhibited QT intervals exceeding 440 ms. Five patients exhibited a significant prolongation of the QT interval after COVID-19 infection compared with the QT interval measured at the time of device implantation.

Review of the program control data from the patients' records revealed that seven patients received a combined total of 54 ATP treatments, all of which satisfied the default ICD criteria for event termination, including one case that fulfilled the clinically determined criteria for successful treatment. Additionally, four patients briefly exhibited evidence of sinus rhythm recovery following ATP treatment, with the event ultimately terminated by shock delivery. Another patient with a low ventricular rate during a VT episode resulting from long-term β-blocker use did not undergo ATP treatment or receive a shock; that patient was placed on a programmed ICD for *in vivo*defibrillation, which briefly restored the rhythm before recurrence, with the VT episode eventually being terminated via external defibrillation (see Case 2 for details). In total, the seven patients experienced 80 ICD shocks post-infection, 71 (88.75%) of which were administered for VT and nine (11.25%) of which were administered for AF; overall, this resulted in 66 successful terminations of arrhythmic events (82.5% effective). In total, ATP therapy was administered 54 times, resulting in the successful termination of 48 of these arrhythmic events. Five of the seven patients received appropriate treatment; two patients received inappropriate treatment. Three of the seven patients experienced ventricular electrical storms, with a single patient receiving shocks and ATP treatment with the greatest frequency (at 53 and 35, respectively; see Case 1 for details). The remaining four patients did not meet the diagnostic criteria for ventricular electrical storms, although they did receive shocks or ATP treatment multiple times within a single day.

The laboratory examination results are presented in Table 4. All patients exhibited symptoms of SARS-CoV-2 infection and tested positive for nucleic acids before admission. All patients demonstrated leukocyte and creatinine levels either within the normal range or only slightly elevated; with the exception of Case 2, who exhibited significantly elevated levels of both leukocytes and creatinine. Seven patients presented with varying degrees of electrolyte imbalance, which was primarily characterized by low blood concentrations of potassium and calcium. Six patients exhibited potassium levels below 4.0 mmol/L (range: 3.5–3.9 mmol/L), and five of the seven patients had blood calcium levels lower than 2.11 mmol/L. Troponin levels were elevated in five of the seven patients (range: 0.023–0.297 ng/mL). Additionally, all patients exhibited significantly elevated NT-proBNP concentrations at the time of admission (range: 608.8–25,758 pg/mL). The characteristics of two cases are described in more detail.

Case 1: A 78-year-old male with ischemic cardiomyopathy underwent CRT-D implantation for primary prevention four years previously. One week prior, he became infected with SARS-CoV-2 and was referred to our institution due to experiencing recurrent shocks from the device. Upon admission, the program control data revealed recurrent VT, with 35 and 53 episodes of ATP treatment and shock, respectively. His blood pressure and heart rate were unstable, with a maximum heart rate of 202 beats/min. The program control data revealed that each ATP treatment could terminate the tachycardia; however, sinus rhythm could not be maintained continuously. While monitored by an external defibrillator, his device underwent programming to augment the number of ATP treatments and abbreviate the VF diagnostic interval to mitigate shock administration. After ATP treatment, the patient received intravenous antiarrhythmic medications, including amiodarone, lidocaine, and esmolol. His blood pressure returned to normal after one day and remained stable.

Case 2: A 55-year-old male with ischemic cardiomyopathy and paroxysmal VT received an ICD for secondary prevention three years ago. The patient became infected with SARS-CoV-2 11 days before presentation and developed fever, palpitations, and muscle weakness. Two days before presentation, these symptoms worsened and were accompanied by dyspnea and an inability to lie down; therefore, he visited our institution. Upon admission, his physical condition was characterized by a temperature of 36.0 , blood pressure of 81/67 mmHg, and oxygen saturation of 85% in a non-oxygenated state, with wet rales in both lungs. The program suggested that he was experiencing sustained VT, with a heart rate fluctuating between 145 and 157 beats/min. No ATP or shock therapy was administered because the ventricular rate had not entered the VT/VF diagnostic interval of the program. He was administered intravenous amiodarone and received active anti-heart failure (HF) treatment. Arterial blood gas analysis indicated metabolic acidosis and type I respiratory failure, and chest computed tomography indicated diffuse, exudative lung changes, suggesting the possibility of viral pneumonia. He received ventilator-assisted respiration, antiviral drugs, antibiotic treatment with meropenem, and anti-inflammatory treatment with methylprednisolone. However, his condition did not improve, multiorgan failure developed, and he died eight days after admission.

Discussion

ICD shock negatively affects patients' quality of life, causes adverse outcomes, is associated with higher mortality rates,[9]and is the most critical cause of rehospitalization in patients with ICDs. This study revealed a significant increase in hospitalizations due to ICD shock during the peak period of SARS-CoV-2 infection compared with the rates in the same period in the past, suggesting a possible correlation between SARS-CoV-2 infection and ICD shock. Therefore, it is essential to understand the causes of ICD shock in patients with ICDs following SARS-CoV-2 infection to provide targeted treatment and prevent adverse events upon admission.

With the increase in the number of SARS-CoV-2-infected patients and the accumulation of clinical data, the development of significant cardiovascular complications after infection has become more apparent.[3,14–19] The current view is that SARS-CoV-2 infection triggers a range of cardiovascular manifestations through multiple mechanisms.[16,20–24] However, owing to the lack of related reports, the mechanism through which patients with ICDs become more susceptible to shocks following SARS-CoV-2 infection remains unknown. A previous multicenter study reported a significant increase in ICD shock among those with such devices during the COVID-19 outbreak in the United States.[12] Two other single-center studies reported no increase in ventricular arrhythmic events, although deaths were observed in patients with ICDs during the peak of the pandemic in Italy in 2020.[25,26] However, these studies evaluated ICD shocks using continuous remote monitoring systems and did not determine whether patients experiencing them were infected with SARS-CoV-2; therefore, the correlation between ICD shock and SARS-CoV-2 infection requires further investigation.

In this study, we analyzed data from seven patients who were admitted to our hospital for ventricular arrhythmias or ICD shocks within 3–20 days after SARS-CoV-2 infection. We analyzed their program and clinical data and observed that they shared specific characteristics that may have driven the development of ventricular arrhythmias or ICD shocks after SARS-CoV-2 infection. Most patients exhibited elevated troponin levels, suggesting the development of myocardial damage post-infection, which has been suggested

to be a cause of ICD-induced shocks.[14,27] A higher incidence of malignant ventricular arrhythmias has been reported in patients with severe left ventricular dysfunction and coronary artery disease.[28,29] Among these seven patients, six were implanted with ICDs or CRT-Ds for ischemic cardiomyopathy and were prone to malignant arrhythmias. SARS-CoV-2 infection can disrupt the oxygen supply equilibrium and cause a cytokine storm, further damaging cardiomyocytes, and the development of malignant arrhythmias increases the likelihood of ICD shock. In addition, SARS-CoV-2 can directly damage cardiomyocytes by downregulating angiotensin-converting enzyme 2 (ACE2) receptors and interfering with ACE2-associated signaling pathways.[30] It should be noted that these six patients had not experienced sustained VT or recurrent ICD shocks prior to infection, suggesting that SARS-CoV-2 infection may play a role in ICD shock as a potential arrhythmia trigger.

Decreased potassium and calcium concentrations may represent another mechanism underlying ICD shock development after SARS-CoV-2 infection. Most of the patients developed electrolyte imbalances post-infection, mainly in the form of reduced potassium and calcium ion levels, possibly due to a fever-induced increase in sweating post-infection, or insufficient potassium and calcium ion intake due to decreased appetite. Decreased calcium ion concentrations can induce arrhythmias by affecting ion channel functions and the difference in potential between the interior and exterior of myocardial cells.[31]Clinically, hypokalemia is a common cause of arrhythmogenesis, and severe hypokalemia can lead to life-threatening ventricular arrhythmias. In addition, hypokalemia and hypocalcemia can prolong the QT interval, inducing the development of malignant arrhythmias. In this study, six patients exhibited QT interval prolongation ($>$ 440 ms) (mean QT interval: 460 $\pm$ 46 ms; range: 386–536 ms). All patients exhibited varying degrees of HF symptom exacerbation after SARS-CoV-2 infection, and NT-proBNP levels significantly exceeded the normal range upon admission. We speculate that the exacerbation of HF due to SARS-CoV-2 infection may be another important factor leading to ICD shock. The current view is that an acute increase in cardiac load can cause cardiomyocyte stretching, altering myocardial electrical activity and leading to the development of various types of arrhythmias.[32] We believe that myocardial injury and electrolyte imbalances caused by infection are the leading causes of HF exacerbation in these patients. Furthermore, most patients did not continue to take their anti-HF medications regularly after the infection, out of concern for Safety, which may be another cause of the acute exacerbation of HF in these patients.

Previous studies have shown that secondary prevention and ICD implantation are risk factors for the development of malignant arrhythmias.[33] However, the total number of shocks administered was significantly higher in the patients who received ICDs for primary prevention than in those who received them for secondary prevention (68 vs. 12, respectively). This suggests that SARS-CoV-2 infection plays a dominant role in the induction of ICD shock. AF is a predictor of inappropriate shocks,[34,35] and patients with SARS-CoV-2 infection are more susceptible to AF during the acute and late recovery phases.[36,37] It can be hypothesized that SARS-CoV-2 infection increases the AF load, serving as another possible factor contributing to inappropriate shocks in these patients.

Three of the seven patients in this study experienced ventricular electrical storms post-infection, and these patients did not experience the reoccurrence of arrhythmias following the administration of antiarrhythmic drugs and the removal of the triggers. We suggest that SARS-CoV-2 infection can cause malignant arrhythmias through various mechanisms such as myocardial damage, electrolyte disturbances, QT interval prolongation, HF aggravation, and AF induction of AF; most of these malignant arrhythmias can be terminated by ICD shock, preventing mortality and demonstrating the value of ICDs in preventing SCD. Simultaneously, because ICD shock is associated with higher mortality,[9] the frequency of programmed follow-up should be increased during the COVID-19 pandemic. Post-infection, follow-up of patients can be conducted by telephone for timely clinical evaluation and guidance on medications. If necessary, patients should be admitted to the hospital as early as possible to eliminate the triggers of arrhythmia and minimize the likelihood of ICD shock. In the present study, none of the patients experienced further ICD shock after the removal of the aforementioned triggers.

It is important to note, however, that this study included only seven patients; therefore, more extensive

clinical studies are needed to confirm these findings.

Conclusion

This study indicate that SARS-CoV-2 infection can cause malignant arrhythmia episodes through various mechanisms, including myocardial damage, electrolyte disturbances, QT interval prolongation, HF aggravation, and AF induction, resulting in a significant increase in the number of ICD treatments administered. Patients with ICDs should be treated cautiously following SARS-CoV-2 infection. Early intervention and more active follow-up should be provided to minimize the likelihood of ICD shock and improve patients' prognosis. Ultimately, this study provides a basis for the future diagnosis and treatment of patients with such devices following similar infectious disease outbreaks.

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Disclosure

Conflict of interest: none declared.

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Tables Table 1 Patient baseline data

Patient	Sex	Sex	Age	Device type	Device type	Primary disease	Primary disease	EF, %	EF, %	Level of prevention	Level of prevention	NYHA classification	Unit type (Mec
Case 1	Male	Male	78	CRT-D	CRT-D	ICM	ICM	27%	27%	primary	primary	III	DTE
Case 2	Male	Male	55	ICD	ICD	ICM	ICM	20%	20%	secondary	secondary	III	DVA
Case 3	Female	Female	78	ICD	ICD	LQTS	LQTS	65%	65%	secondary	secondary	II	DVE
Case 4	Male	Male	51	CRT-D	CRT-D	ICM	ICM	26%	26%	primary	primary	III	DTE
Case 5	Male	Male	75	ICD	ICD	ICM	ICM	28%	28%	primary	primary	III	DVE
Case 6	Male	Male	70	ICD	ICD	ICM	ICM	36%	36%	secondary	secondary	III	DVE
Case 7	Male	Male	63	ICD	ICD	ICM	ICM	31%	31%	primary	primary	III	DDE

EF, ejection fraction; NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implanted cardioverter defibrillators; ICM, ischemic cardiomyopathy; LQTS, long Q-T syndrome; CHD, coronary heart disease; HT, hypertension; DM, diabetes mel-

Table 2	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Table 2**	**Tab**
Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter settings	Device parameter setti
Patient	Patient	Patient	Case 1	Case 1	Case 2	Case 2	Case 3	Case 3	Case 4	Case 4	Case 5	Case 6	Case
VT[a]	VT[a]	VT[a]	360 ms	360 ms	360 ms	360 ms	390 ms	390 ms	360 ms	360 ms	360 ms	360 ms	360 ms
VF[b]	VF[b]	VF[b]	300 ms	300 ms	320 ms	320 ms	320 ms	320 ms	270 ms	270 ms	300 ms	320 ms	320 ms
Initial	Initial	VT	24	24	16	16	12	12	24	24	16	16	16
		VF	30/40	30/40	30/40	30/40	24/32	24/32	30/40	30/40	30/40	30/40	30/4
Redetection	Redetection	VT	12	12	12	12	12	12	16	16	12	12	12
		VF	12/16	12/16	12/16	12/16	12/16/	12/16/	12/16	12/16	12/16	12/16	12/1

[a]VT diagnostic interval; [b]VF diagnostic interval. VT, ventricular tachycardia; VF, ventricular fibrillation.

Table 3 Arrhythmia types and shock characteristics of the implanted devices in each patient
Patient
Interval between infection and shock delivery
Electrical storm
Type of arrhythmia
Ventricular rate (beats/min)
Initial QT interval (ms)
Post-infection QT interval (ms)
ATP frequency
Shock frequency
Shock type
Hospital stays
Patient outcome
SVT, sustained ventricular tachycardia; VT, ventricular tachycardia; TDP, torsades de pointes; AF, atrial fibrillation; VF, v

Table 4 Auxiliary examination results of each patient post-admission	**Table 4** Auxiliary examination results of each pati
Patient	1
WBC count ($\times 10^9$)	7.49
Serum potassium (mmol/L)	3.7
Serum calcium (mmol/L)	1.95
CTnI (ng/mL)	0.002
NT-proBNP (pg/mL)	2,586
Serum creatinine (μmol/L)	159

WBC, white blood cell; CTnI, cardiac troponin I; NT-proBNP, N-terminal pro brain natriuretic peptide

Figure Legends

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`image1.emf` available at https://authorea.com/users/623240/articles/646065-clinical-characteristics-of-shocks-in-patients-with-implanted-cardioverter-defibrillator-following-covid-19-infection

Figure 1 A shock event from Case One. The figure shows a serial tracing of the same patient for one event.