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Implantation of Cardiac Electronic Devices in Active COVID-19 Patients. Results from an International Survey

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**Brief title: CIED procedures in active COVID-19 patients.**

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**Abstract**

**Aims.** A substantial decrease in cardiac implantable electronic device (CIED) implantations has been observed during the COVID-19 pandemic. However, the implantation rates, as well as the clinical and procedural characteristics and outcomes in patients with known active COVID-19 disease are unknown. We performed an international survey on CIED procedures during active COVID-19 disease, during which personal protective equipment was needed.

**Methods and Results.** Fifty-three centers, belonging to 13 countries from 4 continents provided information on 166 patients who underwent a CIED procedure during known active COVID-19 disease. CIED procedure rate in 133,655 hospitalized COVID-19 patients ranged from 0 to 16.2 per 1000 patients ( $p < 0.001$ ). Most devices were implanted due to high degree / complete AV block (107, 64.5%) or sick sinus syndrome (35, 21.1%). In the 166 survey patients, a 30-day complication rate of 13.9% and a 180-day mortality rate of 9.6% were found, including 1 patient with a lethal outcome as a direct result of the procedure. Differences in patient and procedural characteristics and outcomes were found between North America and Europe. An older population (76.6 vs. 66 years,  $p < 0.001$ ) with a non-significant higher complication rate (16.5% vs. 7.7%,  $p = 0.2$ ) were observed in Europe, while a higher rate of critically ill patients (33.3% vs. 3.3%,  $p < 0.001$ ) and mortality (26.9% vs. 5%,  $p = 0.002$ ) were observed in North America.

**Conclusion.** CIED procedure rates during known active COVID-19 disease ranged from 0 to 16.2 per 1000 hospitalized COVID-19 patients worldwide. High complication and mortality rates were found following these procedures. Operators should take into consideration these high rates when selecting active COVID-19 patients who should undergo implantation of CIED.

**Keywords:** CIED procedure, active COVID-19, personal protective equipment, complications, mortality

## **Introduction**

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since late December 2019 the world has faced a pandemic caused by COVID -19, with over 160 million people affected leading to over 3 million deaths<sup>1</sup>. The main clinical manifestation of COVID-19 is respiratory disease, but cardiac manifestation has been reported in a substantial number of hospitalized patients, including cardiac arrhythmias. In a recent worldwide case series 18.3% of admitted COVID-19 patients suffered a cardiac arrhythmia.<sup>2</sup> About 70% of patients who developed an arrhythmia, presented atrial tachyarrhythmias, with bradyarrhythmia seen in approximately 20% of patients. Atrioventricular block (AVB) was noted in 1.57% of COVID-19 admitted patients, and sinus pauses >3 sec. in only 0.22%.<sup>2</sup> Among COVID-19 patients with telemetric monitoring 3.5% had AVB.<sup>3</sup> Several studies have reported a substantial decrease in cardiac implantable electronic device (CIED) implantation rates during the pandemic, none of which reported the procedure rate in patients with active COVID-19 disease.<sup>4-9</sup> There are only a few case reports and small case series in the literature of patients with COVID-19 who were implanted with a CIED while having active disease, and none reported procedural complications.<sup>10-20</sup> The implanting physician and supporting staff need to wear personal protective equipment (PPE) during the procedure with possible impairment in their ability to perform the procedure as a result. Optimal indications, timing and periprocedural management are unclear. The Heart Rhythm Society, American College of Cardiology, and the American Heart Association released a joint statement with recommendations regarding the management of electrophysiologic procedures which are based mainly on expert opinion, acknowledging there are limited published data currently available on arrhythmia management in COVID-19 patients.<sup>21</sup> It is unknown whether early implantation

during active COVID-19 disease is beneficial or associated with a higher complication or mortality rate, and whether different device types may carry a different risk of complications. As many centers implanted only few devices and in order to gather clinically relevant information, we conducted an international survey. This survey included 44 centers in 13 countries from 4 continents. We sought to assess the rate of device implantation, the patient and procedural characteristics and the outcomes of all types of CIED implantations and replacements during active COVID-19 disease.

## **Methods**

The Shaare Zedek Medical Center Institutional Review Board committee approved the study. All centers complied by local IRB registry protocols. Share Zedek Medical Center served as the coordinating center.

### **Data source and center selection**

A Medline search using the terms “COVID-19 or SARS-CoV-2 and device implantation or atrioventricular block or bradyarrhythmias” was performed to select worldwide centers with experience in the diagnosis and management of active COVID-19 and device implantations. In addition, multiple world-known electrophysiologists were contacted and offered to participate in an international multicenter survey on device implantations in active COVID-19 patients.

### **Study inclusion and exclusion criteria**

Patients were eligible if they fulfilled both conditions: a) they were diagnosed with active COVID-19 illness (confirmed by nasopharyngeal PCR testing) during the procedure; b) the operator and supporting staff needed to use PPE, in compliance with hospital recommendations.



Patients were excluded from the study in the following instances: 1) they underwent implantation of a temporary transvenous pacing (TVP) or of an implantable loop recorder; 2) CIED were implanted after recovery from COVID-19 without use of PPE; 3) CIED were implanted in active but unrecognized COVID-19 patients without the use of PPE.

### **COVID-19 disease severity**

Disease severity was classified according to the following degrees: 1. Mild: no need for O2 support; 2. Moderate: need for O2 support via nasal cannula or mask; 3. Severe: need for non-invasive ventilation (high-flow, CPAP, etc); 4. Critical: mechanical ventilation or multi-organ failure or need for inotropic support.

### **Center recruitment**

Fifty-three (42%) of the 126 initially contacted centers, belonging to 13 countries from 4 continents agreed to participate in the survey.

### **Data acquisition**

Participating centers were requested to provide data on the number of device procedures in active COVID-19 patients and the number of hospitalized COVID-19 patients from the beginning of the pandemic until data collection date in March-April 2021. In addition, deidentified clinical data including demographics, comorbidities, COVID-19 disease severity, procedural indication and details including device type, implantation technique, PPE and subjective operator feeling of impairment in the ability to perform the procedure, procedural complication, mortality cause and timing, and 1 and 3 months follow up (FU), were collected in a uniform excel sheet by all centers.

### **Statistical analysis**

Characteristics were described by means  $\pm$  standard deviations or median with interquartile ranges for continuous variables and as numbers and percentages for categorical variables. Comparisons were performed by dividing study group to (1) Procedure complications (Yes/No); (2) Continent (North America/ Central America/ Europe) and (3) Mortality (Yes/No). Relations between categorical variables were evaluated by chi-square and Fisher's exact tests. The effect of categorical variables on continuous measurements was tested by student-T and Mann-Whitney tests or by One way ANOVA and Kruskal–Wallis tests. The choice of a parametric or nonparametric test depended on the distribution of a continuous variable. Multivariable logistic regression model with stepwise backwards elimination was applied in order to identify independent predictors for procedure complications. Criteria for entrance into the model was univariate  $P < 0.2$ . All tests were two-sided.  $P < 0.05$  was considered statistically significant. Analyses were carried out using SPSS Statistics for Windows, Version 25.0. (IBM Corp, Armonk, NY, USA).

## **Results**

Fifty-three centers from 44 cities, belonging to 13 countries in 4 continents participated in the study. The 53 participating centers composed of 33 centers which implanted CIEDs in active COVID-19 patients and 20 which replied no device implantation that met the inclusion criteria occurred in their center, of whom 14 provided the number of hospitalized COVID-19 patients since the beginning of the pandemic and until the data collection, and in 6 this data was unavailable (3 from Israel, 2 from Canada and 1 from Hong Kong).

### **CIED procedure rate**

Forty-four centers provided the number of hospitalized COVID-19 patients at their center since the beginning of the pandemic till data collection (In 3 centers which provided data on CIED

implantations, the total number of hospitalized COVID-19 patients was unavailable, XXX). CIED procedure rate in 133,655 hospitalized known COVID-19 patients ranged from 0 to 16.2 per 1000 patients. The rate of CIED procedures per 1000 hospitalized COVID-19 patients per country and continent is presented in figure 1. The procedural rate varied significantly between the different countries and continents and ranged between 0 and 16.2, with crude rate of 1.17 per 1000 hospitalized COVID-19 patients. The average implantation rate was higher in European compared to American centers [1.61 and 0.4 respectively,  $p < 0.0001$ ].

### **Clinical characteristics**

The study population included 166 patients (61.4% males), mean age  $74.6 \pm 12$  years, who underwent a CIED implantation ( $n=159$ ) or replacement ( $n=7$ ) during active COVID-19 illness, during which the operating physician and staff used PPE. The clinical and procedural characteristics, the complications and mortality of all patients are presented in Table 1. The number of CIED procedures, complications and mortality by month and continent is presented in Figure 2.

### **Indication for CIED**

The majority of devices were implanted due to high degree or complete AV block ( $n=107$ , 64.5%), followed by sick sinus syndrome ( $n=35$ , 21.1%). A smaller proportion ( $n=8$ , 4.8%) were implanted for secondary prevention of ventricular arrhythmias, cardiac resynchronization therapy (CRT) ( $n= 5$ , 3%) while device replacements were performed in 7 (4.2%) patients. Other indications were primary prevention ICD, 1 syncope with LBBB, and 1 pacemaker- dependent patient who underwent CRTD extraction due to infective endocarditis and was later reimplemented with a single chamber pacemaker. A single chamber PM or Micra VVI was implanted in 55 patients, of whom 35(63.6%) had no history of AF.

### **Personal protective equipment**

Three types of PPE were used during the procedures and varied between countries. A full bodysuit including N95, faceshield, full body protective suits, sterile gloves and sterile coat, was used in 103 (62%) cases. N95 and faceshield only in addition to sterile gloves and coat was used in 56 (33.7%) cases, and N95 only in addition to sterile gloves and coat was used in 7 (4.2%) cases. The use of full bodysuit was associated with operators feeling impairment in their ability to perform the procedure. In centers with 80-100% use of full body suit 12/19 (63.2%) of the operators reported feeling impairment in their ability due to protective equipment as compared to 4/14 (28.6%) in centers with <50% (0-40%) use of full body suit,  $p < 0.001$ ). Operators reported the subjective feeling of being hot, sweaty, stressed and having impaired eyesight due to fog accumulation on the faceshield and eyeglasses. Anti-fog technology was used in only 6 (3.6%) of cases and included antifog spray, and 1 case of ventilator connected to the bodysuit providing airflow inside the bodysuit for prevention of heat, sweat and fog formation.

### **Complications**

Complications occurred in 23 (14%) of the patients. Table 2 details all patients' complications and their clinical and procedural characteristics. One patient who underwent Micra AV implantation (vascular ultrasound was not used for vascular access and a Perclose was used for femoral vein closure), was transferred to another hospital to continue COVID-19 care, where she suffered a hemorrhagic shock due to vascular bleeding and retroperitoneal hematoma (possibly due to Perclose dislodgement) leading to death. Two patients experienced more than 1 complication. One patient suffered from early right ventricular lead dislodgement requiring repositioning, cardiac tamponade after repositioning requiring urgent percutaneous drainage, and at 1-month, atrial lead dislodgement requiring repositioning. Another patient suffered from a

significant pocket hematoma and mild pocket infection treated conservatively with antibiotic therapy.

Multivariable analysis model revealed that independent predictors for complications were procedure performed in Europe (OR=6.18 95% CI [1.23-31.10]; p=0.027), and with an anesthesiologist (OR=3.47 95% CI [1.12-10.69]; p=0.031).

One operator reported contracting COVID-19 as a result of performing a PM implantation procedure in an active COVID-19 patient. The PPE that was used during the procedure was N95 mask and a faceshield, without a full body protective suit, as per protocol in that center. He suffered a severe disease requiring ICU care, and later fully recovered.

### **Mortality**

Sixteen (9.6%) patients of the entire cohort expired after a median follow-up of XXX (Table 1).

Death within 30 days and between 31-180 days from the procedure occurred in 10 (6%) and 6 (3.6%) patients, respectively. One patient expired as a direct result of a procedural complication, while all other early deaths were attributed to COVID-19 complications unrelated to the procedure. Mortality increased gradually with COVID-19 severity and was 4.1%, 6.8%, 14.3% and 38.9% in mild, moderate, severe and critical disease severity, respectively (p<0.001).

Mortality increased with the use of anesthesia delivered by an anesthesiologist: it was 7.2%, 4.8%, 12.5% and 40% in patients receiving local anesthesia only, in those sedated without anesthesiologist, in those sedated by an anesthesiologist and those receiving general anesthesia, respectively (p=0.007). Mortality was lower during procedures without the presence of an anesthesiologist (6.8% vs. 20.6%, p=0.015). Increased mortality was observed in patients who were implanted with single chamber PM and Micra (either VVI or AV Micra), p<0.001. Patients who expired had significantly more diabetes mellitus (56.3% vs 30%; p=0.03).

## Follow up

At 1-month FU, abnormal lead parameters (high thresholds) were found in 4 (2.4%) patients, and a pocket infection and pocket hematoma in 1 patient each. Six (3.6%) patients were lost to FU and in 10 (6%) patients less than 30 days passed from the procedure to data collection. At 3-month FU, 3 (1.8%) patients remained with abnormal parameters, 22 (13.3%) were lost to FU, and in 44 (26.7%) less than 3 months passed from the procedure to data collection.

## Differences between continents

Multiple differences were found in baseline patients' and procedural characteristics between the different continents. The clinical and procedural characteristics of all the patients according to continent are presented in table 3.

### *Clinical differences*

Mean age was  $65.9 \pm 14$ ,  $73.8 \pm 11$  and  $76.6 \pm 11$  in North America, Central America and Europe respectively;  $p < 0.001$ . The procedural indication differed between continents, Central America implantations were only due to high degree or CAVB, while in North America and Europe other indication for device implantation were reported,  $p = 0.076$ . The use of anticoagulation was significantly more frequent in Europe 55(45.5%) vs. North America and Central America, 6(23%) and 0, respectively. Steroid therapy was more frequently used in Europe 25.2% than in North America (12.5%) or Central America (0%). COVID-19 severity distribution differed with a higher rate of critically ill patients in North (33.3%) and Central America (33.3%). vs Europe (3.3%),  $p < 0.001$ .

### *Procedural differences*

The type of CIED used markedly differed according to continent. In Central America, only conventional pacemakers were implanted, while in North America, 30.7% of the implantations

included leadless pacemakers and a high rate of defibrillators ( $P<0.001$ ). The type of anesthesia also differed significantly with presence of an anesthesiologist in 73.1%, 0 and 12.4% of patients from North America, Central America and Europe, respectively ( $p<0.001$ ). Finally, the type of PPE differed significantly: full bodysuit was used in 7.7%, 0 and 83.5% of patients in North America, Central America and Europe respectively;  $p<0.001$ .

#### *Outcome differences*

Complication rates were 7.7%, 5.6% and 16.5% in North America, Central America and Europe respectively ( $p=0.27$ ). Mortality rates were 26.9%, 16.7% and 5% in North America, Central America and Europe respectively ( $p=0.002$ ).

## **Discussion**

This study reports the global rates of CIED implantation or replacements in hospitalized patients with known active COVID-19 disease. We present the largest international cohort of patients who underwent a CIED implantation or replacement during active COVID-19 disease for which the operator and staff had to use PPE. In accordance with the published joint statement recommendations<sup>21</sup> the vast majority of implantations were due to urgent or emergent indications.

### **Previous studies**

Several large studies have been conducted throughout the world during the last 2 decades for assessing the complication rates following implantation of CIEDs. The MOST trial with a patient population of sinus node dysfunction who underwent dual-chamber pacemaker implantation, reported a complication rate after PM implantation of 4.8% at 30 days and 5.5% at 90 days.<sup>22</sup> The FOLLOWPACE study included patients who received a first PM for a conventional reason

for chronic pacing, reported a 12.4% complication rate within 60 days. The use of anticoagulant drugs was an independent predictor for complications within 2 months.<sup>23</sup>

In 2 recent multicenter Australian studies involving 81000 and 32000 patients undergoing a new implantation of a mixed device type, an in-hospital and 90-day complication rate of 3.3% and 8.2%; and 8% and 9.6% in private and public hospitals was found, respectively.<sup>24, 25</sup> In addition, in-hospital and 30-day mortality was low (0.46% and 0.7%, respectively). Finally, in patients who needed a reoperation, 30-day mortality increased to 2.76%.<sup>24</sup>

A large US cohort of 92000 patients undergoing CRT implantation found a 6.1% in-hospital complication rate and 0.76% mortality. Complications increased with older age, increase in comorbidities and non-elective procedures.<sup>26</sup> The Micra investigational device exemption (IDE) prospective study found device complications occurred in 3.4% of patient<sup>27</sup>, while real world data reported an even lower rate of 1.51%.<sup>28</sup>

### **Results of present study**

We found a high complication rate of 13.9% at 30 days, and a mortality rate of 9.6% at 6 months, 6% within 30 days and 3.6% more within 31-180 days of the procedure, much higher than any previous reported large study on CIED implantation or replacements out of the setting of COVID-19 disease.<sup>22-28</sup> The higher complication rate seen in our cohort may be related to the acute COVID-19 illness, the existence of high comorbidities rate and the fact that non-elective procedures could have been postponed. In addition, the use of PPE, reported by many operators to impair their ability to perform the procedure, could have contributed to the high complication rate, even though the difference between PPE types and complication rate did not reach statistical significance. Other unique factors that can explain the high complication rate observed in our cohort are psychological stress on the operator due to personal exposure and risk of



contracting COVID-19. “Rushing through” the procedure in attempt to shorten procedural time and minimize self-risk, as well as fog formation on eyeglasses and faceshield impairing operator’s vision might also have played a role. Finally, increased patients’ age in addition to higher rate of anticoagulation and steroid therapy use, and higher rate of full bodysuit use, may explain higher complication rate seen in Europe.

### **Differences according to continents**

Higher mortality was seen in North America compared with Europe. A higher rate of severely and critically ill patients were implanted in the US. This is in accordance with other US studies. Chinitz et al. reported the outcomes of a small series of 7 COVID-19 patients who were treated for severe bradyarrhythmias requiring pacing (3 TVP, 4 permanent leadless pacemakers), in whom death from complications of COVID-19 infection occurred in 57% (4/7) during the initial hospitalization, and in 71% (5/7) within three months of presentation.<sup>20</sup> Another study on leadless pacemaker implantations reported 1 of 3 COVID-19 positive patient experienced in-hospital mortality on the third postoperative day secondary to hypoxic respiratory failure triggered by COVID-19.<sup>15</sup> The use of leadless pacemakers was suggested to reduce operator and staff exposure, and to reduce complications and hospitalization.<sup>15</sup> This approach was indeed seen in the US centers in our study, with a higher rate of leadless pacemakers implanted in the US, and in patients who expired. In addition, a single chamber PM or Micra VVI were implanted in 55 (33.1%) patients, of whom 35(63.6%) without a history of AF, and a significantly higher rate in patients who expired (56.3% vs 30.7%). This may reflect the implanting physician’s attempt to minimize and shorten the procedure in sicker patients. These types of device implantations however were not associated with a lower complication rate. None of the differences in procedural technique was associated with a higher mortality. The significantly higher rate of

anesthesiologist used in procedures of patients who expired seems also to reflect the physicians' perception of a sicker patient.

### **Clinical implications**

Due to the high mortality rate observed in critically ill patients, implanting permanent CIED may be postponed when possible and medications or a TVP may be used until patient stabilization, in order to minimize costs and staff exposure. Likewise, in attempt to lower complication rate, whenever possible, the procedure should be postponed until patients' recovery, when PPE will be unnecessary, and the procedure will not pose a risk to the operator and supporting staff. Nevertheless, given the known complications associated with TVP<sup>29-31</sup> and the resulting difficulty in handling such patients, a definitive recommendation for preferring TVP and deferring permanent PM implantation should be made in an individual basis.

### **Limitations**

This is a retrospective cohort study. As in some countries and continents only a single center participated, the CIED procedure rate might not present an accurate estimation of the entire country and continent. Although data originated from 13 different countries, it might not reflect on procedural complication and mortality rate in other countries not participating in the study. In addition, the centers choosing to participate are relatively large academic centers and may not reflect on procedural complication and mortality in other smaller non-academic hospitals. Several centers could not provide the total number of hospitalized COVID-19 patients and therefore results regarding implantation rate may vary; however, this was not the main goal of the current study. A larger randomized prospective study is needed to further investigate the cause of the high complication rate observed in patients hospitalized with COVID-19 and undergoing CIED implantation.

## Conclusion

CIED procedure rates during known active COVID-19 disease ranged from 0 to 16.2 per 1000 hospitalized COVID-19 patients. A high complication and mortality rate of 13.9% and 9.6% respectively was found. Operators should take into consideration these high rates when selecting active COVID-19 patients who should undergo implantation of CIED.

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### Figure legends

Figure 1: The rate of CIED procedures per 1000 hospitalized COVID-19 patients per country.

The number of centers that contributed data from each country and the number of procedures performed used for rate calculation are presented beneath the graph. The procedural rate varied significantly between 0 and 16.2 per 1000 hospitalized patients,  $p < 0.001$ . Of note, 6 centers without CEID implantation (see text) and 3 centers who provided data on CEID implantations (2 from Israel and 1 from the US with 2, 1 and 5 implanted patients, respectively) could not provide data on the total number of hospitalized COVID-19 patients.

Figure 2: The number of CIED procedures, complications and mortality by month and continent.

The number of procedures is presented per continent at the background, complications and mortality in the purple and red columns.

