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Food and Chemical Toxicology 145 (2020) 111742

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Cardiac arrest and drug-related cardiac toxicity in the Covid-19 era. Epidemiology, pathophysiology and management

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ARTICLE INFO

Keywords:
Covid-19
Cardiac arrest
Drug toxicity
Cardiopulmonary resuscitation
Heart complications
Covid-19 transmission

ABSTRACT

SARS-CoV-2 (Covid-19) infection has recently become a worldwide challenge with dramatic global economic and health consequences. As the pandemic is still spreading, new data concerning Covid-19 complications and related mechanisms become increasingly available. Accumulating data suggest that the incidence of cardiac arrest and its outcome are adversely affected during the Covid-19 period. This may be further exacerbated by drug-related cardiac toxicity of Covid-19 treatment regimens. Elucidating the underlying mechanisms that lead to Covid-19 associated cardiac arrest is imperative, not only in order to improve its effective management but also to maximize preventive measures. Herein we discuss available epidemiological data on cardiac arrest during the Covid-19 pandemic as well as possible associated causes and pathophysiological mechanisms and highlight gaps in evidence warranting further investigation. The risk of transmission during cardiopulmonary resuscitation (CPR) is also discussed in this review. Finally, we summarize currently recommended guidelines on CPR for Covid-19 patients including CPR in patients with cardiac arrest due to suspected drug-related cardiac toxicity in an effort to underscore the most important common points and discuss discrepancies proposed by established international societies.

1. Introduction

Heart involvement is one of the complications induced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, Covid-19) infection, clinically presented as acute coronary syndrome, myocarditis and acute heart failure (Rizzo et al., 2020). Possibly as a consequence, increased cases of cardiac arrest (CA) have been reported during the pandemic (Baldi et al., 2020a). Recently this issue has been the subject of intensive investigation aiming to provide insight to mechanisms and the actual incidence of Covid-19-related CA. Moreover, the approach to patients with CA by rescuers and the application of appropriate treatments due to risk of transmission of the virus pose a great challenge.

2. Epidemiology

Recently, increased incidence by 58% of out-of-hospital CA (OHCA) in Lombardy was reported as compared to the same period in 2019 (Baldi et al., 2020a). Interestingly, most of the incremental percentage was attributed to suspected or confirmed Covid-19 cases, leading to worse prognosis (Baldi et al., 2020a, 2020b). Furthermore, in out-of-hospital cardiopulmonary (CPR) from trained rescuers, a higher death rate (Pranata et al., 2020) and a lower rate of return of spontaneous circulation was observed, as compared with previous years (Baldi et al., 2020a; Pranata et al., 2020; Lai et al., 2020; Shekhar et al., 2020). Similarly, in the area of Paris the proportion of patients admitted alive after OHCA was decreased during the pandemic (Marijon et al., 2020). Interestingly, Mountantonakis et al. also reported a 4.97-fold increased incidence in OHCA and almost doubling of deaths at home after OHCA (71% vs 38%) in New York Metropolitan Area, in comparison with the

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https://doi.org/10.1016/j.fct.2020.111742
Received 1 August 2020; Accepted 17 August 2020
Available online 8 September 2020

Abbreviations

ACS	acute coronary syndromes
AED	automated external defibrillator
AGP	aerosol generating procedures
CA	cardiac arrest COVID-19 Corona Virus Disease 2019
CPR	cardiopulmonary resuscitation
DIC	disseminated intravascular coagulation
ECG	electrocardiogram
ICU	Intensive Care Unit
IHCA	in-hospital cardiac arrest
LV	left ventricle
OHCA	out-of-hospital cardiac arrest
PEEP	positive end-expiratory pressure
PPE	personal protection equipment
RV	right ventricle SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
VT	ventricular tachycardia

corresponding period in 2019 (Mountantonakis et al., 2020). The lower incidence of shockable rhythm both in in-hospital CA (IHCA) (Sheth et al., 2020) and OHCA (Lai et al., 2020), longer times of arrival of emergency medical care, less frequent CPR offered by bystanders compared to the previous years may partially explain these findings (Baldi et al., 2020a, 2020b; Marijon et al., 2020; Waalewijn et al., 2002). These observations are indicative of the direct impact of an overloaded health care system on effective treatment of emergencies during the pandemic. Delays due to time needed by the rescuers to wear protective equipment as well as fear of lay rescuers contacting Covid-19 patients and of patients seeking medical help could also contribute to both the higher OHCA incidence and poor outcomes observed (Marijon et al., 2020; Cunningham et al., 2020). Notably, reduced hospital admissions were observed during the pandemic in comparison with the corresponding period at previous years (Wong et al., 2020; Tam et al., 2020). In a study conducted in Wuhan, China, Shao et al. demonstrated that among 136 patients with Covid-19 infection and IHCA, the primary cause of the event was mainly attributed to respiratory conditions (87%) (Shao et al., 2020a). Most of these patients (89.7%) had asystole as the main rhythm at CA with extremely poor survival rate, a non-shockable rhythm commonly associated with hypoxia (Shao et al., 2020a; Chen et al., 2018; Teodorescu et al., 2010). This is contrasted to published data before the pandemic in the general hospitalized population, with asystole ranging 23.9–49.4% (Chen et al., 2018; Shao et al., 2016; Benjamin et al., 2019). Importantly, in 93% of cases, CA occurred in patients under continuous electrocardiographic monitoring, which minimized the possibility of missing cases of initial ventricular rhythm (Teodorescu et al., 2010; Herlitz et al., 1994). These data suggest that in patients with Covid-19 infection, IHCA will likely occur in advanced stages of the disease with severe respiratory failure leading to asystole

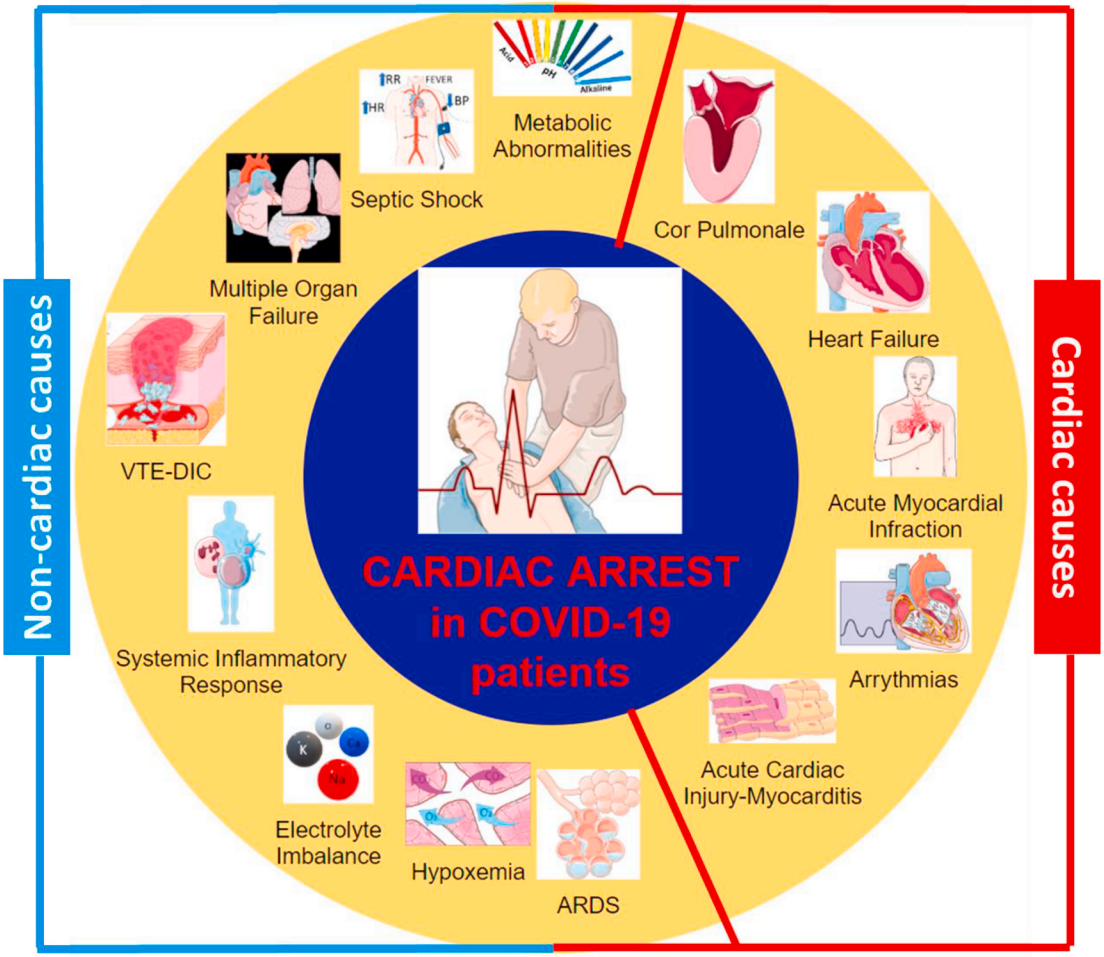

Fig. 1. Cardiac and non-cardiac causes of cardiac arrest in Covid-19 infection. ARDS, acute respiratory distress syndrome; VTE, venous thromboembolism; DIC, disseminated intravascular coagulation. Certain items on this figure have been adapted from Servier Medical Art by Servier (https://smart.servier.com – licensed under Creative Commons Attribution 3.0 Unported License).

with poor prognosis. Given that a large proportion of the OHCA patients in Lombardy province had confirmed or suspected Covid-19 infection, such a mechanism could also apply to OHCA. Overall, the available epidemiological data point towards a multifactorial increase in incidence of OHCA due to the combined direct effect of the viral infection and indirect effects from an overloaded medical system and fear of infection by both lay rescuers and patients.

3. Mechanisms linking cardiac arrest with Covid-19 disease

3.1. Cardiac causes of CA in Covid-19 infection

Conditions linked to Covid-19 related CA are depicted in Fig. 1. This review is focused on pathophysiology of Covid-19 related cardiac arrest and therefore in-depth discussion of cardiovascular complications of Covid-19 infection in general is out of the scope of this work. Covid-19 may both directly and indirectly affect the cardiovascular system manifested with complications known to trigger CA such as acute myocardial infarction, acute cardiac injury, myocarditis, arrhythmias and acute heart failure (Chen et al., 2018, 2020a; Stefanini et al., 2020; Akhmerov and Marbán, 2020). The presence of Covid-19 viral elements in endothelial cells with characteristics of endotheliitis has been demonstrated (Akhmerov and Marbán, 2020; Varga et al., 2020) in accordance with previous data from other SARS viruses (Oudit et al., 2009).

Despite a reduction of patients presenting with acute myocardial infarction during the pandemic (Mountantonakis et al., 2020; Stefanini et al., 2020; Garcia et al., 2020), severe Covid-19 infection may be associated with higher incidence of acute coronary syndromes (ACS) which is a major condition leading to CA. (Chen et al., 2018; Stefanini et al., 2020; Bilaloglu et al., 2020) Because ACS may be the first clinical presentation of Covid-19 infection (Stefanini et al., 2020), further research should clarify the prevalence of OHCA due to ACS as an early complication of Covid-19 infection. ACS in Covid-19 infection may be induced by increased risk of atherosclerotic plaque rupture due to high inflammatory burden (Ross, 1999; Driggin et al., 2020) or direct virus-induced endotheliitis (Varga et al., 2020; Nikitskaya et al., 2016), high thrombotic tendency (Akhmerov and Marbán, 2020; Kang et al., 2020; Terpos et al., 2020) and mismatch of myocardial supply-demand balance due to increased cardiac metabolic or hemodynamic instability (Driggin et al., 2020). Regarding thromboses, Covid-19 infection has been correlated with both arterial and venous thromboembolic disease (Driggin et al., 2020). As summarized by Terpos et al., in Covid-19 patients elevated D-Dimers and fibrin degradation products associated with disseminated intravascular coagulation (DIC) have been reported (Terpos et al., 2020). These conditions led to increased incidence of thrombotic complications in Covid-19 patients admitted to Intensive Care Unit (ICU), but were also correlated to a higher in-hospital mortality (Klok et al., 2020; Tang et al., 2020). Covid-19 infection may be complicated with decompensation of pre-existing left-ventricular heart failure or induction of heart failure due to stress-induced cardiomyopathy or myocardial injury (Driggin et al., 2020; Zhou et al., 2020). Left ventricle (LV) heart failure is known as a major risk factor for CA but a direct connection between heart failure due to Covid-19 infection and cardiac arrest has not been proven to-date (Chen et al., 2018; Driggin et al., 2020; Zhou et al., 2020). Right ventricular failure occurs in the context of pulmonary hypertension and acute cor pulmonale in severe parenchymal lung disease due to Covid-19 infection (Chen et al., 2018; Zochios et al., 2017). Creel-Bulos et al. reported pulmonary thromboembolism as a probable cause of acute cor pulmonale and subsequent CA in Covid-19 confirmed patients (Creel-Bulos et al., 2020). Indeed, a high prevalence of pulmonary embolism has been recognized in patients with Covid-19 infection and has been correlated with IHCA (Lodigiani et al., 2020; Poissy et al., 2020; Shao et al., 2020b).

3.2. Drug cardiac toxicity related to cardiac arrest in Covid-19 infection

Table 1 depicts the drugs currently being administered or tested for treatment in Covid-19 infection that may potentially lead directly or indirectly to CA. Arrhythmias consist the main cardiac drug toxicity related to Covid-19 treatment and are a common manifestation in patients with Covid-19 infection predisposing to CA. (Wang et al., 2020; Liu et al., 2020a; Guo et al., 2020) Arrythmias arise as a result of both Covid-19 complications and of treatment-related toxicity for the infection and are attributed to cardiac injury, heart failure, metabolic derangements and neurohormonal or inflammatory stress due to the viral infection and hypoxemia (Akhmerov and Marbán, 2020; Driggin et al., 2020). Indeed, an increased incidence of malignant arrhythmias (ventricular tachycardia or ventricular fibrillation) was reported in patients with elevated troponin T levels and Covid-19 infection (Guo et al., 2020). Regarding electrolytic imbalances, hypokalemia often mediated by gastrointestinal symptoms, has been detected in patients with Covid-19 infection (Chen et al., 2020a, 2020b; Li et al., 2020). Hypokalemia may prolong QT in Covid-19 patients and increase risk of polymorphic ventricular arrhythmias and CA. (Fisch, 1973) Irrespective of electrolytes, QT prolongation is often found in Covid-19 infection and has been linked to systemic inflammation. The latter leads to significant QTc prolongation, rapidly normalized after reduction of C-reactive protein and cytokine levels, through cytokine-mediated ventricular electrical remodeling, regardless of concomitant antimicrobial therapy (Lazzerini et al., 2020). In addition, increased interleukin-6 (IL-6) levels contribute to risk of QTc prolongation through suppression of I_{Kr} in heterologous cells and myocytes (Vabret et al., 2020; Wu et al., 2020; Aromolaranet al., 2018). IL-6 increases in response to myocardial ischemia (Ikonomidis et al., 2005) and constitutes a marker of severity and poor prognosis of the disease (Vabret et al., 2020). In support, QT prolongation has been found in patients with cardiovascular manifestations of Covid-19 infection such as myocardial ischemia and myocarditis (Tisdale et al., 2013; Gittleman et al., 1951).

Aside from the disease pathophysiology, concomitant medication for Covid-19 infection also predisposes to arrhythmias. Drug toxicity in Covid-19 patients related with cardiac arrest is summarized in Table 1. Although trials are still on-going to establish robust indications, some drugs currently administered for Covid-19 are arrhythmiogenic such as hydroxychloroquine and azithromycin. These drugs may cause or worsen QT prolongation and subsequently provoke torsade de pointes by blocking the human ether a go-go gene (hERG) potassium channel, which mediates the rapid part of the delayed rectifier potassium channel IKr. This results in a longer duration of both ventricular repolarizations and ventricular action potential (White, 2007; Sanguinetti et al., 1995; Saleh et al., 2020). Clinical observations have confirmed that hydroxychloroquine when administered to patients with Covid-19 infection may prolong QTc, a phenomenon that is further aggravated with concurrent azithromycin treatment (Mercuro et al., 2020; Ramireddy et al., 2020; Cavalcanti et al., 2020). Interestingly, Rosenberg et al. also reported an increased incidence of CA, arrhythmias and QTc prolongation in patients who received these drugs, with no beneficial effect on in-hospital mortality, providing evidence against their utility (Rosenberg et al., 2020). Similarly, Cavalcanti et al. did not find any improvement of clinical status in hospitalized patients with mild-to-moderate Covid-19 infection who received hydroxychloroquine and/or azithromycin. (Cavalcanti et al., 2020) It should be noted that hydroxychloroquine may less likely induce other adverse effects associated with CA including heart failure (Tönnesmann et al., 2012), conduction system abnormalities (Tönnesmann et al., 2012), cardiomyopathy (Page et al., 2016), hypokalemia (Chary et al., 2020a) and diarrhea (Rosenberg et al., 2020). Interestingly, a recent randomized clinical trial indicated no additive toxicity in regard to QTc to the group with co-administration of hydroxychloroquine and azithromycin in comparison to group of hydroxychloroquine alone. (Cavalcanti et al., 2020) Other pharmaceutical agents have also been administered in Covid-19 patients, which

Table 1
Drug toxicity in Covid-19 patients related with cardiac arrest.

Pharmaceutical agent	Mechanism related to cardiac arrest	Ongoing Clinical Trials	Interactions with drugs enhancing risk of cardiac arrest*	References
Chloroquine/ Hydroxychloroquine**	Causes QT prolongation by blocking the hERG potassium channel (common mechanism) and TdP	Phase 2/3/4	CYP3A4 substrate	Tönnesmann et al. (2012), Page et al. (2016), Saleh et al. (2020), Sanguinetti et al. (1995), Liu et al. (2020),
	Associated with HF, conduction system abnormalities, cardiomyopathy, hypokalemia, diarrhea		Severe with amiodarone, flecainide, mexiletine, sotalol, dofetilide	Rosenberg et al. (2020), Chary et al. (2020)
Azithromycin***	Causes QT prolongation by blocking the hERG potassium channel and TdP	Phase 2/3/4	Weak CYP3A4 inhibitor, Severe with amiodarone, flecainide, disopyramide, sotalol, dofetilide, propafenone	Sanguinetti et al. (1995), Howard PA et al. (2013), Trifiro G et al. (2017)
Lopinavir - ritonavir	Causes cardiac conduction abnormalities May cause QT prolongation May cause electrolytic imbalances due to vomiting and diarrhea	Phase 2/3/4	CYP3A4 inhibitor and substrate Severe with amiodarone, dronedarone, disopyramide, dofetilide, sotalol, flecainide	Cao et al. (2020)
Remdesivir	May cause multiple-organ-dysfunction syndrome, septic shock, diarrhea	Phase 3	Unknown interaction with other drugs	Grein et al. (2020)
Tocilizumab	May lead to QT interval shortening (uncertain clinical relevance)	Phase 2/3	Mild with amiodarone, quinidine	Lazzerini et al. (2015) Kobayashi et al. (2018) Toniati et al. (2020)
Interferon	May enhance lung injury and lead to respiratory failure	Phase 2/3/4		Ziegler CGK (2020)
	May cause cardiotoxicity, including arrhythmias, ischemia, infarction, and reversible cardiomyopathy immediately after infusion			Floyd et al. (2005)

Data concerning clinical trials' phase taken from U.S. National Library of medicine (https://clinicaltrials.gov).
Additional data from ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic.
(Last updated on June 10, 2020).
*Interaction with these drugs raises the risk of arrhythmia or/and QT prolongation.
**Hydroxychloroquine has lower toxicity, higher safety and higher dose capability than chloroquine.
*** Concomitant medication with hydroxychloroquine raises the risk of QT prolongation even higher.
Abbreviations: CYP3A4 = cytochrome P450 3A4; hERG= human ether a go-go related gene; HF = heart failure; TdP = Torsades de pointes.

may contribute to increased risk of CA. In a recent study, Deftereos et al. reported a clinical benefit for hospitalized patients with Covid-19 infection who received colchicine (Deftereos et al., 2020). Although colchicine had a favorable safety profile, it led to significantly more frequent diarrhea than the control group (45,5% vs 18%). Interestingly, the authors did not observe any significant difference regarding electrolytic imbalance between colchicine group and control group (Deftereos et al., 2020). However, until more evidence is available to confirm colchicine's safety profile in Covid-19 patients, the clinical applicability of these findings should be cautiously balanced with vigilance on prompt electrolyte correction and arrhythmia monitoring. Lopinavir/ritonavir, another treatment combination in Covid-19 patients, can cause QT prolongation with an unknown mechanism as well as to electrolytic imbalances due to vomiting and diarrhea (Cao et al., 2020). Moreover, lopinavir-ritonavir are CYP3A4 inhibitors, and therefore cannot be used with major CYP3A4 substrates such as chloroquine, as they may enhance its toxicological effects including QTc prolongation (Cao et al., 2020; Lim et al., 2004). Favipiravir, another nucleoside analogue used for Covid-19 infection, may also lead to electrolytic imbalances through diarrhea while a case has been reported of QTc prolongation (Hayden and Shindo, 2019; Chinello et al., 2017). Tocilizumab, a monoclonal antibody acting as an IL-6 inhibitor, currently tested in Covid-19 patients, has been reported to shorten QT interval (Lazzerini et al., 2015; Kobayashi et al., 2018; Toniati et al., 2020). Given that short QT syndrome may lead to malignant ventricular arrhythmias, further research is needed to investigate the clinical relevance of this effect on QT by tocilizumab (Giustetto et al., 2006). Also administration of interferons may lead to respiratory failure and cause cardiotoxicity (Table 1). (Ziegler et al., 2020; Floyd et al., 2005) Finally remdesivir, a novel antiviral drug, which is being tested in Covid-19 patients has been associated with diarrhea, septic shock and multiple-organ-dysfunction syndrome (Grein et al., 2020).

3.3. Non-cardiac causes of CA in Covid-19 infection

As expected, non-cardiac causes of CA are associated with worse prognosis, due to high prevalence of non-shockable rhythm (Wallmuller et al., 2012; Meaney et al., 2010; Girotra et al., 2012). This underlines the importance of prevention of Covid-19 severe disease, as CPR may be futile in such cases. Covid-19 infection is often associated with systemic non-cardiac complications which may lead to CA, including multiple organ failure, acute respiratory distress syndrome (ARDS) with severe hypoxemia, severe sepsis and septic shock (Chen et al., 2018; Zhou et al., 2020). In the latter, hypovolemia, vasodilation, hypoxemia, metabolic abnormalities, ventricular dysfunction and acidosis are probable pathophysiologic pathways contributing to CA. (Cawcutt and Peters, 2014; Russell et al., 2018; Makino et al., 2005) ARDS is one of the most common clinical manifestations in Covid-19 infection and is associated with high risk of CA (Chen et al., 2018; Zhou et al., 2020), through RV dysfunction (Walley, 2018). Moreover, hypercapnia enhances pulmonary vasoconstriction contributing to an increase in mean pulmonary arterial pressure in ARDS, resulting to impairment in RV function (Mekontso Dessap et al., 2016; Stengl et al., 2013). RV systolic dysfunction may also be induced by high positive end-expiratory pressure (PEEP) in patients under mechanical ventilation (Schmitt et al., 2001). These conditions linking impairment of RV function with ARDS predispose to CA. (Chen et al., 2018; Zochios et al., 2017)

4. Risk of transmission and summary of recommendations for cardiopulmonary resuscitation (CPR) during the pandemic

4.1. Risk of transmission of Covid-19 infection during cardiopulmonary resuscitation

Airborne transmission of SARS-CoV-2 during breathing or speaking

has recently been confirmed, even from asymptomatic patients (Prather et al., 2020). There are insufficient data on the risk of transmission of Covid-19 infection during CPR. Although there is limited evidence, some data suggest that chest compressions, intubation or assisted ventilation may cause aerosol dispersion of respiratory secretions, increasing the likelihood of exposure (Couper et al., 2020a; Working Group of the Resuscitation Council (UK), 2020). However, there are no corresponding data for defibrillation. It is particularly challenging to elucidate the contribution of each of these interventions as the cause of aerosol generation because they are administered simultaneously in an emergency setting. Even though the viral particles, generated by aerosol, can remain in the air with a half-life of approximately 1 h (Couper et al., 2020a; Edelson et al., 2020), a recent review article found no published evidence of airborne transmission to rescuers during CPR from previous outbreaks of SARS or MERS. Furthermore, a recent systematic review failed to find any association of transmission of SARS-CoV-2 with chest compressions or defibrillation (Couper et al., 2020a). Another reason that increases the risk of infection of Covid-19 during CPR is that a relatively large number of personnel works simultaneously at close distance (Edelson et al., 2020; Couper et al., 2020b; Nolan et al., 2020).

4.2. Recommendations for CPR procedures during the pandemic

Integrated main recommendations by major national and international societies are summarized in Table 2. In general, all hospitalized patients in areas with high incidence of Covid-19 infection should be considered as positive for Covid-19 if CA occurs (DeFilippis et al., 2020). Thus, a high level of vigilance should make readily applicable all recommended measures for CPR as soon as an area is characterized as high-risk for Covid-19.

There is general agreement that compromising the safety of healthcare providers during CPR is unacceptable because this would lead to further strain for healthcare systems (Working Group of the Resuscitation Council (UK), 2020; Edelson et al., 2020; Nolan et al., 2020). Intensive training for immediate availability and easy access to necessary equipment are essential to achieve better CPR outcome (DeFilippis et al., 2020). All resuscitation team members should wear the full personal protection equipment (PPE) for Aerosol Generating Procedures (AGP) before starting CPR (Working Group of the Resuscitation Council (UK), 2020; Edelson et al., 2020; Couper et al., 2020b; Nolan et al., 2020). According to the U.S. Centers for Disease Control and Prevention (CDC), PPE should consist of N95 respirators, eye protection, gloves and gowns in secluded rooms that limit the airborne dispersion of infectious aerosol (Centers for Disease Control and Prevention, 2019). In contrast, European Resuscitation Council (ERC) recommends FFP2 or N95 only in the absence of FFP3 or N99 masks (Nolan et al., 2020).

Although endotracheal intubation is a procedure with an increased risk of transmission of infectious aerosol, it should be performed early as the resulting closed circuit carries a lower risk of aerosolization than any other form of positive-pressure ventilation. American Heart Association (AHA) recommends preferable use of mechanical CPR devices to reduce the required rescuers while ERC suggests its use when need for chest compressions is prolonged (Edelson et al., 2020; Nolan et al., 2020). In the event of CA in prone position, which is a commonly recommended position in Covid-19 ICU patients, turning to the supine position is required in non-intubated patients, ineffective compressions, inability to rapidly restore spontaneous circulation and when risk of equipment disconnections and aerosolization is low. Chest compressions in prone patients are administered with hands over T7-10 vertebral bodies and defibrillator pads are placed in the anterior-posterior or bi-axillary position (Edelson et al., 2020; Nolan et al., 2020).

All the above-mentioned international societies are in agreement for the majority of their recommendations. However, there are some critical discrepancies. Specifically, both ERC and International Liaison Committee on Resuscitation (ILCOR) suggest defibrillation without PPE for AGP, as an accepted option (Couper et al., 2020b; Nolan et al., 2020).

Table 2
Summarized guidelines for cardiopulmonary resuscitation in suspected or confirmed Covid-19 adults with cardiac arrest.

Recommendations	Source
General principles	
Consider resuscitation appropriateness (DNR)	AHA, ERC
Minimize the number of rescuers	AHA, ERC, ILCOR, RC UK
Do not place face next to the victims' mouth/nose to assess breathing Inspect for signs of life/pulse and normal breathing	ERC, ILCOR, RC UK
Communicate Covid-19 status to any new providers	AHA
Lay Rescuers	
Do not open the airway	ERC, ILCOR
Use an automated external defibrillator without PPE for AGP	AHA, ERC, ILCOR, RC UK
Consider compression-only resuscitation	AHA, ERC, ILCOR, RC UK
Cover patients' mouth with a cloth or a face mask during compressions	AHA, ERC, RC UK
Healthcare Personnel	
Increase level of care and monitor closely suspected or confirmed Covid-19 patients	AHA, ERC, RC UK
Identify early high-risk patients for cardiac arrest and transfer them in negative pressure room	AHA, ERC, RC UK
Apply PPE for AGP before participating in CPR	AHA, ERC, ILCOR, RC UK
Close the door of the room where CPR is administered	AHA
Consider defibrillation without PPE for AGP	ERC, ILCOR
Deliver up to 3 continuous shocks (if shockable rhythm) until someone with PPE for AGP arrives	ERC
Place a simple oxygen mask on the patient's face during compressions	ERC, RC UK
Attach a HEPA or HME filter to any manual or mechanical ventilation	AHA, ERC, ILCOR
Prioritize intubation with a cuffed tube	AHA, ERC, ILCOR
Perform intubation by the most skilled provider	AHA, ERC, ILCOR, RC UK
Pause chest compressions for intubation	AHA, ILCOR
Consider video-laryngoscopy	AHA, ERC, ILCOR
Minimize disconnection of closed-circuit mechanical ventilation	AHA, ERC
Use a bag mask with tight seal before intubation	AHA, ERC, ILCOR
Use a 30:2 compression: ventilation rate in non-intubated patients	AHA, ERC, ILCOR
Use passive oxygenation before intubation	AHA
Pause chest compressions during non-mechanical ventilation	AHA, ERC, ILCOR
Use supraglottic airway if intubation is delayed to minimize aerosol generation	AHA, ERC, ILCOR
Consider mechanical compression device	AHA, ERC, ILCOR

AGP = Aerosol Generating Procedures; AHA = American Heart Association; CPR = cardiopulmonary resuscitation; DNR= do not resuscitate; ERC = European Resuscitation Council; HEPA = high efficiency particulate air; HME = heat and moisture exchanger.;ILCOR = International Liaison Committee on Resuscitation; PPE = Personal Protective Equipment; RC UK = Resuscitation Council of UK.

However, AHA refers that PPE for AGP is a prerequisite for starting CPR and comments that its use can be omitted in case of OHCA, where an automated external defibrillator (AED) may be available but there is no access to PPE for AGP (Edelson et al., 2020). Similarly, UK Resuscitation Council do not recommend defibrillation without PPE for AGP in case of IHCA (Working Group of the Resuscitation Council (UK), 2020; Hassager et al., 2020). Furthermore, ERC suggests delivering up to three shocks, in case of shockable rhythm until someone with PPE for AGP starts chest compressions while other societies do not refer that option (Nolan et al., 2020). Since available data do not indicate aerosol production during defibrillation, the option for not donning PPE for AGP seems reasonable to minimize delays. Also, the guidance for pausing chest compressions during intubation is not uniformly suggested by all societies (Edelson et al., 2020; Couper et al., 2020b). Tracheal

intubation is deemed a high-risk procedure for Covid-19 transmission and corresponding risk for chest compressions is ambiguous (Couper et al., 2020a; Cook et al., 2020). On the other hand, any pause during chest compressions, has a negative impact on survival (Edelson et al., 2020). AHA suggests passive oxygenation with a non-breathing face mask instead of bag mask ventilation since compression only CPR is not inferior to standard CPR and passive oxygenation carries lower transmission risk than bag mask ventilation (Edelson et al., 2020; Cook et al., 2020; Brouwer et al., 2015; Riva et al., 2019). As a result, passive oxygenation is a potential option but other factors such as time to intubation should be considered. It is important to underline that, the level of evidence of the existing guidelines, for cardiac arrest in Covid-19 pandemic, is weak as these are based on limited data, collected during a short period, and on expert opinion recommendations.

4.3. Recommendations for prevention and management of drug-related cardiac arrest during covid-19 pandemic

As mentioned above, some of the medications used for Covid-19 infection treatment may induce cardiac toxicity predisposing to cardiac arrest through direct or indirect mechanisms. Thus, appropriate management of drug-related cardiac toxicity is of great importance. According to major national and international societies there is no modification on basic life support (BLS) or advanced life support (ALS) algorithm for management of drug-related cardiac arrest in Covid-19 patients (Working Group of the Resuscitation Council (UK), 2020; Edelson et al., 2020; Couper et al., 2020b; Nolan et al., 2020). Herein we summarize relevant recommendations for prevention of cardiac arrest, published before or during Covid-19 pandemic.

In order to prevent torsade de pointes ventricular tachycardia (VT) induced by QTc Covid-19 medication such as azithromycin and hydroxychloroquine, patients should be assessed for possible contraindications before therapy initiation. Evaluation of QTc with a baseline electrocardiogram (ecg), monitoring ecg after treatment initiation, pausing class III antiarrhythmic drugs, targeting higher normal potassium levels and supplementation with magnesium are recommended for torsade de pointes risk reduction (Lakkireddy et al., 2020). Furthermore, history of VT, congenital long QTc, renal insufficiency, structural and functional heart abnormalities should be assessed before treatment initiation in order to balance the benefit for infection outcome and proarrhythmic risk (Hendren et al., 2020). Management of torsade de pointes VT should include withdrawing of these drugs and bradycardic medication, correcting potassium abnormalities, administrating intravenous magnesium and using isoproterenol or temporary transvenous pacing if arrhythmia persists. (Dolenska, 2009).

In case of sustained monomorphic VT in Covid-19 patients treated with azithromycin or hydroxychloroquine, amiodarone administration should be avoided. Instead, electrical cardioversion, especially in intubated patients, and intravenous administration of lidocaine or procainamide or esmolol are recommended as first option. The combination of amiodarone may augment the pro-arrhythmic effects of azithromycin or hydroxychloroquine via incremental QTc prolongation (European Society of Cardiology, 2020).

Both hyperkalemia and hypokalemia are possible causes of cardiac arrest. Hydroxychloroquine or chloroquine mediated hypokalemia does not deplete total body potassium levels and as a result nonaggressive correction of blood potassium is proposed. This approach is important in order to avoid rebound hyperkalemia (Chary et al., 2020b).

5. Conclusion

Taken together, the Covid-19 pandemic poses a great challenge to the effectiveness of healthcare system, especially in treatment of emergencies with increased incidence such as CA. The disease itself, inability to intervene on time and the measures to decrease risk of airborne transmission during CPR, have detrimental effects on chances of survival for these patients. The fact that numerous medications, currently administered or tested for Covid-19, predispose to CA poses an additional risk in those patients. The mechanisms and causes associated with increased incidence of CA have been elucidated to an adequate extent. However further investigation is warranted regarding the effectiveness of preventive strategies and optimal planning to reduce CA incidence and to maximize effective treatment in Covid-19 patients. For example, quick correction of electrolyte imbalances, thorough ECG pre-treatment assessment, intensification of research on development of new therapies to prevent or minimize cytokine storm or targeting IL-6 should be applied for this purpose (Poissy et al., 2020; Lazzerini et al., 2020; Russell et al., 2018). While these issues are being resolved, it is of utmost importance to adhere to most recent recommendations from scientific medical organizations and follow and adapt quickly changing evidence on the field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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