REVIEW ARTICLE

Sudden Death in the Out-of-hospital Setting in Times of COVID-19

Muerte súbita en el ámbito prehospitalario en época de COVID-19

MARIO D. FITZ MAURICE, FERNANDO DI TOMMASO, NADIA D. FORMICA MAZRAANI, PABLO AGÜERO, PAULA C. SASTRE, ALFREDO HIRSCHSON PRADO

ABSTRACT

One in five adult deaths in developed countries is due to cardiovascular causes. Half of these deaths occur suddenly and a large percentage in the out-of-hospital setting. Numerous studies have demonstrated that the access of the general population to learning simple and pragmatic cardiopulmonary resuscitation maneuvers and the presence of automated external defibrillators translate into a large increase in survival without sequelae in victims of sudden out-of-hospital cardiac death. Today the special situation represented by the COVID-19 pandemic questions all we have learned so far and faces us with two extremely complex situations. On the one hand, the cardiovascular involvement and the consequent increase in malignant ventricular arrhythmias generated by this infection, both in healthy patients and in those with pre-existent diseases, have led to an increase in the incidence of sudden out-of-hospital death. On the other hand, it forces us to rethink all the actions set in motion at the moment a patient presents with an episode of sudden out-of-hospital cardiac death, as the possibility of transmission of this highly contagious disease is now added during the resuscitation maneuvers. Finding a risk-benefit balance that allows increasing the patient's survival with the least possible risk for the person who is performing the resuscitation is the real challenge we are encountering today.

Keywords: Death, Sudden, Cardiac - Cardiopulmonary Resuscitation – Defibrillators –Ventricular Fibrillation - Tachycardia, Ventricular - Coronavirus Infections - COVID-19

RESUMEN

Una de cada cinco muertes de adultos en países desarrollados se debe a causas cardiovasculares; la mitad de esas muertes se produce de forma súbita y un gran porcentaje en el ámbito extrahospitalario. Múltiples estudios demostraron que el acceso de la población general al aprendizaje de maniobras de reanimación cardiopulmonar sencillas y pragmáticas y la presencia de desfibrilador externo automático se traducen en un gran aumento de sobrevida sin secuelas en casos de muerte súbita cardíaca extrahospitalaria. Hoy en día existe una situación especial representada por la pandemia por COVID-19, que deja bajo un interrogante todo lo aprendido hasta la fecha y nos enfrenta a dos situaciones sumamente complejas. Por un lado, la afectación cardiovascular y el aumento consecuente de arritmias ventriculares malignas que genera esta infección, tanto en pacientes sanos como en sujetos con patologías preexistentes, han puesto de manifiesto un aumento en la incidencia de episodios de muerte súbita extrahospitalaria. Por otro lado, se vuelve necesario reevaluar todo el accionar puesto en marcha cuando un paciente presenta un episodio de muerte súbita cardíaca extrahospitalaria, ya que ahora se agrega la posibilidad de transmisión de esta enfermedad de alta contagiosidad durante las maniobras de reanimación. Volver a encontrar un equilibrio riesgo-beneficio que permita aumentar la sobrevida del paciente con el mínimo riesgo posible para la persona que realiza la reanimación es el verdadero desafío hoy en día.

Palabras clave: Muerte Súbita Cardíaca - Reanimación Cardiopulmonar - Desfibriladores - Fibrilación Ventricular - Taquicardia Ventricular - Infecciones por Coronavirus - COVID-19

Abbreviations

SD	Sudden death	**AED**	Automated external defibrillator
CPA	Cardiopulmonary arrest	**VF**	Ventricular fibrillation
CPR	Cardiopulmonary resuscitation	**VT**	Ventricular tachycardia
COVID-19	Coronavirus disease 2019		

INTRODUCTION

Sudden death (SD) is probably the most important challenge for modern cardiology, (1) and represents an outstanding global public health issue. This is understandable, considering that in the Western world 450,000 to 500,000 deaths occur every year, equivalent to one event per minute. (1) Today we have the impact produced by the pandemic generated by the SARS-CoV-2 virus, causing the disease known as COVID-19 (coronavirus disease 2019). On January 30, 2020, the

Rev Argent Cardiol 2020;88:241-246. http://dx.doi.org/10.7775/rac.v88.i3.18015

Address for reprints: Hospital Bernardino Rivadavia. Área de Electrofisiología - Av. Gral. Las Heras 2670 - C1425ASQ - Buenos Aires, Argentina
Email: mdfitzmaurice@gmail.com

World Health Organization (WHO) declared a global emergency due to this virus, which already accumulates 5.4 million infected persons and over 300,00 deaths worldwide.

Increasing evidence shows that SARS-CoV-2 is not always limited to the respiratory system, but has also important implications for the cardiovascular system. Patients with cardiovascular risk factors, as well as patients with established cardiovascular and cerebrovascular disease have been identified as particularly vulnerable populations, with higher morbidity and mortality when suffering from COVID-19. (2, 3)

Although mortality associated with COVID-19 is generally due to respiratory distress syndrome and multiorgan failure, there are also many occasions in which the second cause of death is myocardial injury and the onset of ventricular arrhythmias. (4-7)

Moreover, an alarming fact is the increased number of out-of-hospital cardiac arrest episodes in certain areas greatly impacted by COVID-19, as demonstrated by a registry in the Italian region of Lombardy, (8). This study showed 60% increase in the rate of out-of-hospital cardiac arrest during the peak of the COVID-19 pandemic (compared with the same period in 2019), in addition to a 3-minute delay in the arrival of the medical emergency service in 2020 with respect to 2019 and 15.6% decrease in cardiopulmonary resuscitation (CPR) attempts by witnesses of the event.

This opens a debate as to how we must adapt to this new situation, since, on the one hand, we find a larger number of patients who suffer out-of-hospital events, and on the other, we see that the actions implanted are not enough. Probably this is due to two causes: 1) as the healthcare system is collapsed in some areas, it presents a slower response; 2) because of the risk of acquiring the infection, witnesses of cardiac arrest would rather not get involved, or when they do it, it is too late.

Undoubtedly, this pandemic has changed the risk-benefit balance of CPR maneuvers due to the possibility of generating significant damage to the person who assists the affected person. We should, therefore, promote practices that guarantee the best results and minimize the damage to patients with COVID-19, non-infected patients and persons who participate in reanimation maneuvers.

DEFINITIONS AND EPIDEMIOLOGY

Sudden death is defined as death occurring unexpectedly within the first hour of onset of symptoms or in the absence of witnesses, when the deceased has been observed to be in good conditions less than 24 hours prior to death. (9)

In 80% of cases, sudden cardiac death (SCD) occurs in the context of known or unknown coronary heart disease. In most cases, ischemia initiates processes of ventricular tachyarrhythmia deteriorating into ventricular fibrillation, which is finally responsible for SD. Congenital or acquired structural cardiomyopathy accounts for 15-20% of cases, (10) with ventricular arrhythmia as the main cause. In a significantly lower percentage of cases, primary electrical phenomena, as long QT syndrome or the Brugada syndrome are the causes of SCD.

Despite preventive or therapeutic measures to reduce the burden of ischemic heart disease and heart failure have decreased cardiovascular mortality in developed countries in the last 20 years, this cause of mortality is still high. It is estimated that in the United States alone, more than 366,000 persons will suffer from out-of-hospital SCD this year. (11)

Although the incidence of SD in the population may be small compared with populations at specific risk, it is the great common denominator of persons at risk, resulting in a larger number of SD cases in general, mainly in the male population over 35-40 years of age (Figure 1). (10, 12)

PATHOPHYSIOLOGY OF MYOCARDIAL INJURY IN COVID-19

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (13) It is an RNA virus, member of the coronavirus family (Coronaviridae), similar to SARS-CoV. (14) Same as SARS-CoV, SARS-CoV-2 infects humans when it binds through its spike protein to the angiotensin converting enzyme 2 (ACE2) receptor, present in the cell surface. (14) Infected patients exhibit a series of manifestations that may affect different organs and systems. This occurs because ACE2 is expressed not only in the respiratory system, but also in the human cardiovascular system, including the heart.

In addition to direct tissue invasion, SARS-CoV-2 can also produce an exaggerated immune response in the host that, frequently, leads to a cytokine storm, a phenomenon that may significantly contribute to multiorgan dysfunction. (13) Effectively, elevated cytokine levels have been reported in this disease; particularly, Il-6 is commonly increased in patients with COVID-19, which is also associated with higher in-hospital mortality. (13)

Accrued data indicate greater morbidity and mortality due to cardiovascular disease in these patients. (13) Growing evidence suggests that subjects with COVID-19 are at much higher risk of arrhythmic events, with important implications for survival. (13) Palpitations have been reported as one of the most common early symptoms of the disease (7.3%). (13) It is currently believed that myocardial injury could represent the main promoter of increased risk for arrhythmia in these patients, added to the proarrhythmic character of some drugs used in its treatment. (13) Myocardial injury, reflected by increased troponin levels, has been demonstrated in many individuals, especially in those with severe disease who presented with higher incidence of ventricular tachycardia/ventricular fibrillation (VT/VF). (13)

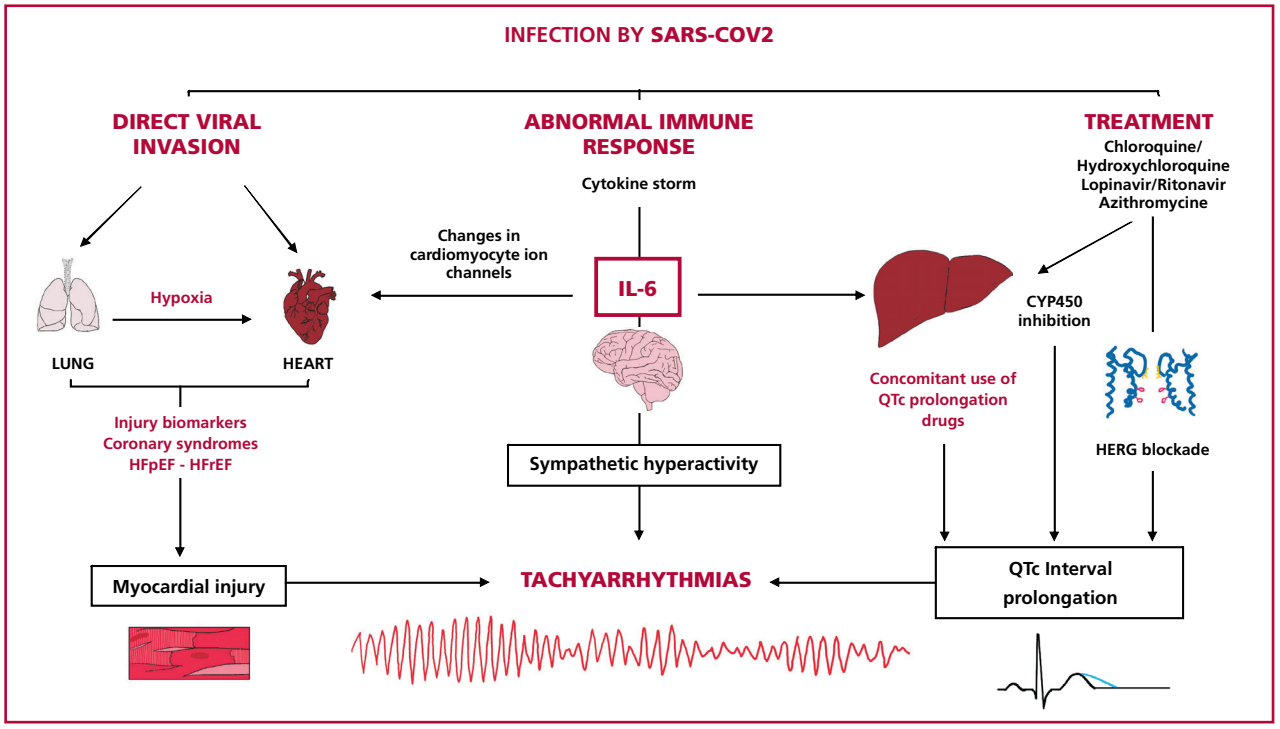

Fig. 2. Underlying mechanisms involved in the risk for arrhythmias in patients with COVID-19.

Strong evidence based on clinical studies point out inflammation as a relevant risk factor for long QT syndrome (LQTS) and torsades de pointes (TdP), mainly due to direct electrophysiological effects of cytokines on the myocardium. (10) Il-6, TNF-α and Il-1 have been shown to prolong the ventricular action potential by modulating the expression or function (or both) of several cardiomyocyte ion channels, specifically, K+ and Ca2+ channels (inflammatory cardiac channelopathies). (15) This risk becomes particularly important in patients presenting underlying LQTS and, even more, in those in which the QT interval is within normal limits at rest (Figure 2). (13) History of Brugada syndrome is also relevant, as potentially deadly arrhythmic events may occur in the context of febrile episodes.

DEFIBRILLATION AND CARDIOPULMONARY RESUSCITATION IN THE CONTEXT OF THE COVID-19 PANDEMIC

Treatment of SCD secondary to VF or VT is ventricular defibrillation, and the sooner it is performed the greater the possibility of reverting to sinus rhythm (SR). Therefore, the main determinant of survival is early intervention with CPR and early defibrillation. The success of maneuvers is time-dependent, and the myocardial ATP level as well as potentially recoverable activity decrease significantly per minute since the onset of cardiopulmonary arrest (CPA). For the first minute the success of defibrillation is above 90% and decreases 7-10% per minute without CPR. (Figure 3). (16)

To achieve this goal, the survival chain concept has been developed, consisting of four steps: acknowledgement and activation of the emergency medical service (EMS), early onset of CPR, early defibrillation and advanced vital support. Early, high-quality CPR associated with adequate use of automated external defibrillators (AED) is the best predictor of greater survival at 30 days and a good neurological status at the time of hospital discharge.

In the last 30 years, the survival rate of patients with SD has improved, and is associated with two important aspects: first, the public health programs and second, the development and use of AED. (17, 18)

Our group performed a retrospective, descriptive, observational study including 137 rugby clubs belonging to URBA/UI. (17) The implementation of CPR coaching programs and access to AED proved to be useful for the early approach of events of SD. Both training as well as access and device signaling allowed the fast treatment of these cases. From a total of 8 events of SD, all received primary care and had access to AED, and 75% were admitted alive to hospital.

Although these data encourage the implementation of measures at a large scale, overall survival is still low, as well as the percentage of patients with good neurological status at discharge (between 11.4% and 16.5%). Currently these results are especially relevant, as in the context of COVID-19 infection fear of probable contagion and its consequences may lead to delay the care of these patients, mainly in the out-of-hospital setting.

We are facing a new challenge in which the survival

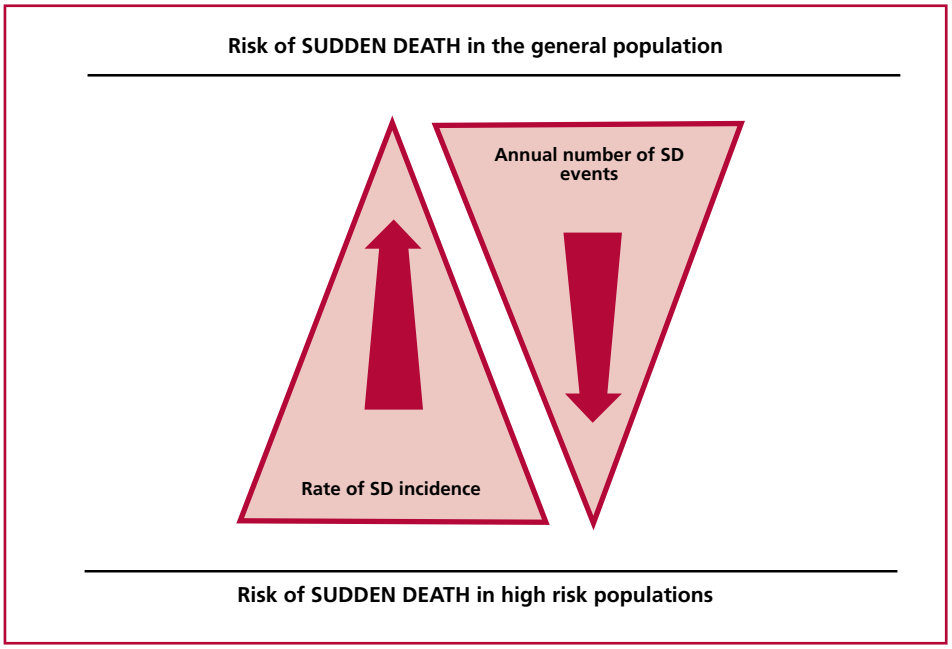

Fig. 1. Evaluation of the risk for sudden death (SD) in different scenarios. While the rate of SD incidence is higher in specific high-risk populations, the total annual number of SD events is higher in the general population.

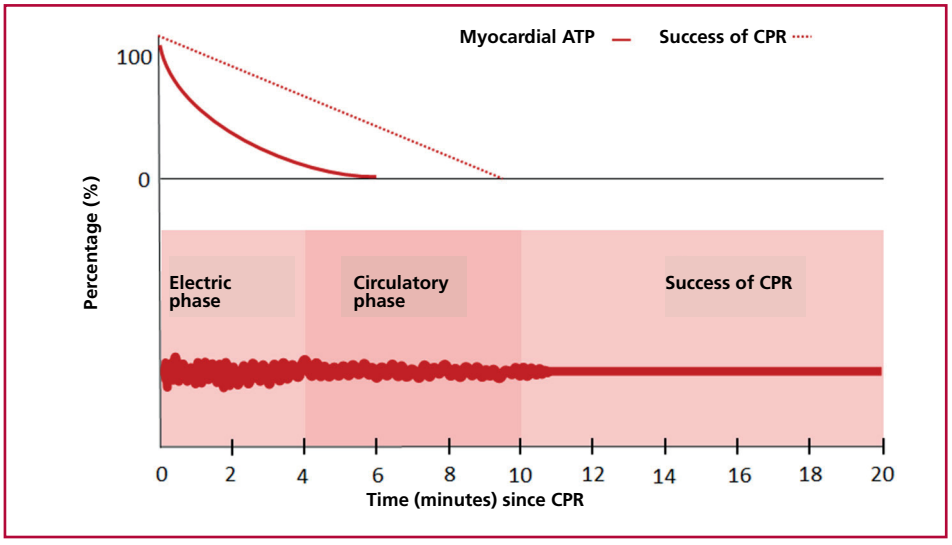

Fig. 3. Three-phase resuscitation model. Relationship between time elapsed, myocardial ATP level, myocardial activity level and success of cardiopulmonary resuscitation.

chain is being adapted (Figure 4), since it is necessary to adopt new measures to decrease the possibility of infection without reducing the probability of survival.

When the emergency service is activated, the dispatcher will be in charge of guiding the spectators who are performing the resuscitation maneuvers to make them effective as well as achieving the least possible risk of infection. Concomitantly, he is in charge of sending the vehicle with the complete personal protection equipment (PPE), adequate for the procedures that may provoke aerosolization.

One of the key points that should be stressed is that persons willing to initiate these CPR maneuvers must wear a homemade or commercial mask and the victim must have the mouth and nose covered. It is also important to point out that the number of persons present in the place should be maximally limited.

The classical strategy of "look, listen and feel" aimed at recognizing a cardiac arrest must be abandoned, as well as attempts at opening the patient's mouth. The patient's unconsciousness and absence of respiratory movements must lead to the diagnosis of CPA and enable the onset of resuscitation maneuvers. In case of doubt about the patient's status, it is nevertheless recommended to start the thoracic compressions until the emergency service arrives.

A maneuver that is absolutely discouraged is mouth-to-mouth ventilation. In studies prior to the COVID-19 pandemic, the hands-only CPR technique, (16) considered in the latest guidelines as the preferred technique, has led to an increase in "CPR attempts" and entails less risk of contagion for the spectator in the context of this pandemic.

A point to emphasize especially at this moment,

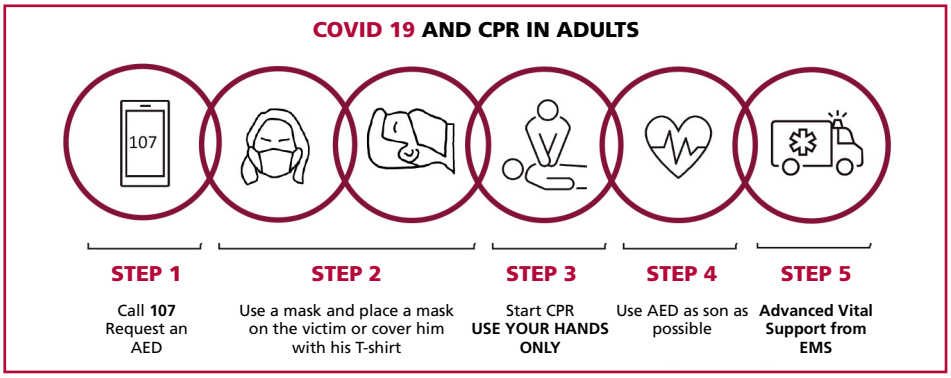

Fig. 4. Cardiopulmonary resuscitation in adults and COVID-19.

and here the concept of public defibrillation achieves key relevance, is that if an AED is available within 30 seconds of assessing the victim for a defibrillatable rhythm, an electrical discharge can be administered. This is very important, sine if we can achieve the return of the patient to spontaneous circulation, we could avoid the onset of thoracic compression maneuvers, reducing the risk of contagion.

Regarding the use of AED, although its association to aerosol generation has not been demonstrated, we should nevertheless encourage the installation and use of models presenting longer cables, thus allowing the reanimator to keep greater distance from the victim.

In the light of the COVID-19 pandemic, several international health organizations have developed new CPR regulations to help spectators treat victims of cardiac arrest, in order to provide the best survival opportunities without compromising the rescuers' safety. Again, education is a highly relevant aspect, as well as the development of public health programs aimed at training the general population in CPR maneuvers and use of AED. The optimization of emergency services is also a key link, as its agents are in charge of guiding those who are performing the resuscitation maneuvers so that they are effective with the least possible risk of infection.

CONCLUSIONS

The myocardium is vulnerable to several factors, such as ischemia, left ventricular dysfunction and genetic predisposition, and this is increased in the patient with COVID-19 infection. In addition, the possibility of infection in the context of CPR maneuvers has changed certain concepts referred to its implementation, to ensure resuscitation maneuvers of quality that do not attempt against the possibilities of patient survival and reduce to a minimum the chance of infection. If we associate this with AED availability, we are not only affording the patient greater opportunity of survival, but can also decrease to a minimum the risk of transmitting COVID-19 infection.

Beyond these important concepts, the truth is we are in a process of learning, and therefore, these recommendations may have to be changed in the near future, due to their continuous update.

Conflicts of interest

Drs. Fits Maurice and Di Tommaso are directors of Instituto Nacional de Arritmias (INADEA), an institution dedicated to cardioprotection. The remaining authors have no conflicts of interest.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ehical approval

Not applicable

REFERENCES

1. Arimany-Manso J, Escobar-Robledo L, Massó Van-Roessel A, Bayés de Luna A. Actualización de la muerte súbita cardíaca: epidemiología y estratificación del riesgo. Rev Esp Med Legal 2018;44: 5-12. https://doi.org/10.1016/j.reml.2017.10.002

2. Clerkin K J, Fried J A, Raikhelkar J, Sayer G, Griffin J M, Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation 2020;141:1648–55. https:// doi.org/10.1161/circulationaha.120.046941

3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. March 11, 2020. https://doi.org/10.1016/S0140-6736(20)30566-3

4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9. https://doi.org/10.1001/jama.2020.1585

5. Zheng Y-Y, Ma Y-T, Zhang J-Y and Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020 March 5. https://doi.org/10.1038/s41569-020-0360-5

6. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020 March 12. https://doi: 10.1016/j.ijid.2020.03.017.

7. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi 2020;49:E009. https:// doi.org/10.3760/cma.j.cn112151-20200312-00193

8. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy [published online ahead of print, 2020 Apr 29]. N Engl J Med 2020;NEJMc2010418. https:// doi.org/10.1056/NEJMc2010418

9. Zipes DP, Camm AJ, Borggrefe M,Buxton AE, Chaitman B, Fromer M,Gregoratos G, Klein G, Moss JA et al.ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Eur Heart J 2006;27:2099-40. https://doi.org/10.1016/S0140-6736(20)305-3

10. Tavora F, Crowder C, Kutys R, Burke A. Discrepancies in initial death certificate diagnoses in sudden unexpected out of hospital deaths: the role of cardiovascular autopsy. Cardiovasc Pathol 2008; 17: 178-182https://doi.org/10.1016/j.carpath.2007.07.010

11. Mozaffarian D, Anker SD, Anand I, Linker TD, Sullivan MD, Cleland JGF, et al. Prediction of Mode of Death in Heart Failure: The Seattle Heart Failure Model. Circulation 2007;116: 392-398.https://doi.org/10.1161/CIRCULATIONAHA.106.687103
12. Ochoa LA. Exclusión social y muerte súbita cardíaca. Rev Cubana Salud Pública. 2015; 36. https://doi.org/10.1016/S0140-6736305-6
13. Driggin E, Madhavan MV, Bikdeli B,Chuich T, Laracy J, Biondi-Zoccai G. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. J Am Coll Cardiol 2020 Mar 18. pii: S0735-1097(20)34637-4. https://doi.org/10.1016/j.jacc.2020.03.031.
14. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi L. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol 2019; 19:63-64.https://doi.org/10.1038/s41577-018-0098-z
15. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death Structure, function and time-dependence of risk. Circulation 1992; 85:I2-I10.https://doi.org/10.1161/circulationaha.120.056941
16. Neumar R, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122: S729-S767. https://doi.org/10.1161/CIRCULATIONAHA.110.970988
17. Fitz Maurice M, Di Tommaso F, Barros Pertuz MC, Alvarez Mendoza W, Spagnuolo D, Lucas V. Muerte Súbita en clubes deportivos de rugby. Rev Argent Cardiol 2018;86:41-5. https:// doi.org/10.7775/rac.86.1.12263
18. Riva G, Hollenberg J, Svensson L, Herlitz J, Rosenqvist M, Svensson L. Increase in BYSTANDER-CPR in Sweden is associated with increased rates of compression-only CPR. BMJ Open 2017; 7(Suppl 3): A1-A18. http:// doi.org/10.1136/bmjopen-2017-EMSabstracts.11