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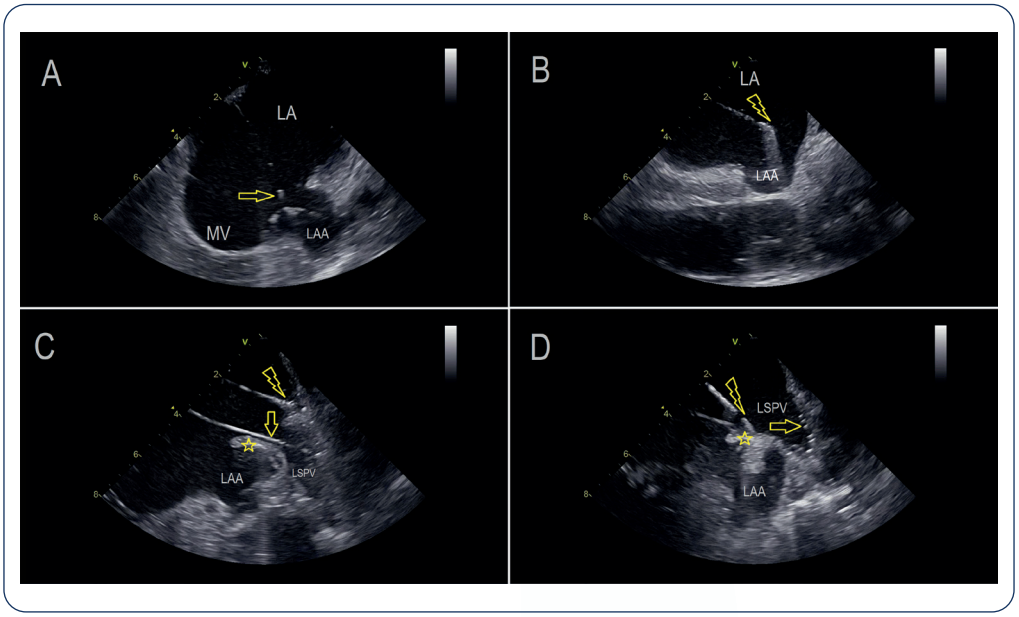

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Editorial

Covid-19 in Brazil: Learning How to Walk in the Dark Without Leaving Anything Behind

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"If you have ups and downs, celebrate it because it means you're alive!"

The SARS-CoV-2 pandemic had its first case in Brazil on February 4, 2020 in the state of São Paulo. Like a real meteor, it practically paralyzed the planet without a more effective therapeutic approach to fight the virus, in addition to practices adopted worldwide only decades or even hundreds of years ago, with a very low level of robust modern evidence.[1] Brazil had the advantage of previewing the pandemic as it was a few weeks behind its Asian and European peers, so it was able to identify the hits and failures of these countries in their preparation to face the problem.

We have then found out by chance that we have the world's third biggest number of ICU beds, second only to the USA and Germany,[2] but we are also faced with an enormous heterogeneity between states, limitations and bureaucracy for the purchase of personal protective equipment and testing kits. This has prevented some pandemic approaches taken by other countries from being adopted here, either due to the impossibility of a lockdown in a continental country, or due to the speed and costs to identify the cases of transmission. Besides, limitations on the number of tests to be done has left us without a precise guide as to the spread of the pandemic, making it difficult to plan the timely, orderly and efficient allocation of scarce resources.

The solution to that was to adopt our own strategies, which would allow us to walk in the dark while at least having a better idea of how far along the path we were. This information is essential for important decisions impacting not only the economic scenario of Brazil, but also the entire healthcare chain of a population that has been deprived of access to outpatient services and elective treatments due to the pandemic. Theoretical epidemiological mathematical models proved to be little capable of predicting our real figures, either because they overestimate the lethality of the disease that seems to stand closer to 0.2–0.5%,[3] or because they are based on data from past pandemics with other transmission dynamics. Interestingly, the models that were most suitable for modeling at what point in the pandemic we are resulted from curve adjustment strategies or Baysean models using data from other countries or based on the preliminary data that we already had on our curves.[4,5] These models appeared relatively spontaneously and outside traditional research groups, but proved to be more assertive in determining different moments of the pandemic.[6]

In a simpler way, but also using data on how the pandemic has previously progressed in other countries, we analyzed the charts of new cases per day from 30 countries with the highest number of covid-19 cases according to the following criteria: countries had reached a peak and presented at least 5 days of decline or stabilization of new daily cases.[7] China was excluded as it concentrated thousands of previous cases on a later day; Brazil was excluded because it was subject to the application of the result. Five countries that did not have mandatory isolation were included. Of the 30 countries, 18 were considered to have completed the full pandemic cycle, with a number of new daily cases <70% of the peak of new cases per day. Using the date of the 1st, 100th and 200th case or 10th death, the times between these dates and the peak of new cases/day were determined. From these results, it was found that 95% of the countries studied had their peaks 55±8 days from the 1st case, 31±5 days from the 100th case, 27±5 days from the 200th case and 19±4 days from the 10th death. With this data, it would have been possible to establish the peaks of new cases, deaths and use of the hospital system in different states and cities in Brazil, even without being sure of the exact number of cases due to underreporting, based on the behavior of the pandemic in countries with different healthcare systems and mitigation measures. Death peak dates were established after 14 days of peak of cases and use of the hospital system after 26 days of peak of cases, considering incubation times, manifestation of symptoms, hospitalization and potential clinical worsening.[8] With these criteria, we estimated the different peaks in each of the Brazilian states with the highest number of cases, as shown in Table 1 (limited only to the forecast from the 100th case to exemplify the model). What cannot be predicted with any of these models is the descending portion of the curve, faster in some places and much slower, showing a plateau in others, requiring hospital beds for longer times, a potential virulence effect that is different from the virus after many mutations.[9]

Keywords

Coronavirus; COVID-19; Pandemics; Catastrófica Illness/mortality; Hospitalization/economics; Equity in Access to Health Services; Diagnostic Tests/methds; Personal Protective Equipment; Masks; Ventilators Mechanical.

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Table 1 – Prediction of state peaks of new cases/day, deaths and hospital use based on modeling from 30 countries (shown only with an estimate from the 100th case). Estimated data for research purposes, pending modification and verification

State	1st Case	100th Case	200th Case	10th Death	Peak 100th Case	Lower 95%CI	Upper 95%CI	Death Peaks (100)	Hospital Peak (100)
SP (Metrop. Area)	Feb 4th	Mar 2nd	Mar 6th	Mar 6th	Apr 2nd	Mar 28th	Apr 6th	Apr 16th	Apr 28th
CE	Feb 14th	Mar 7th	Mar 10th	Mar 15th	Apr 7th	Apr 2nd	Apr 11th	Apr 21st	May 3rd
GO	Mar 2nd	Mar 8th	Mar 11th	Mar 26th	Apr 8th	Apr 3rd	Apr 12th	Apr 22nd	May 4th
SC	Feb 28th	Mar 14th	Mar 17th	Apr 4th	Apr 14th	Apr 9th	Apr 18th	Apr 28th	May 10th
RJ	Feb 27th	Mar 15th	Mar 18th	Mar 18th	Apr 15th	Apr 10th	Apr 19th	Apr 29th	May 11th
DF	Feb 26th	Mar 15th	Mar 18th	Apr 4th	Apr 15th	Apr 10th	Apr 19th	Apr 29th	May 11th
BA	Feb 26th	Mar 16th	Mar 19th		Apr 16th	Apr 11th	Apr 20th	Apr 30th	May 12th
RN	Mar 8th	Mar 18th	Mar 21st	Apr 7th	Apr 18th	Apr 13th	Apr 22nd	May 2nd	May 14th
RS	Mar 9th	Mar 21st	Mar 25th	Apr 8th	Apr 21st	Apr 16th	Apr 25th	May 5th	May 17th
MG	Mar 17th	Mar 23rd	Mar 27th	Apr 2nd	Apr 23rd	Apr 18th	Apr 27th	May 7th	May 19th
MT	Mar 19th	Mar 24th	Mar 27th	Apr 26th	Apr 24th	Apr 19th	Apr 28th	May 8th	May 20th
PR	Mar 12th	Mar 26th	Apr 1st	Apr 6th	Apr 26th	Apr 21st	Apr 30th	May 10th	May 22nd
AM	Mar 18th	Mar 28th	Apr 1st		Apr 28th	Apr 23rd	May 2nd	May 12th	May 24th
PE	Mar 12th	Apr 2nd	Apr 5th	Apr 1st	May 3rd	Apr 28th	May 7th	May 17th	May 29th
MA	Mar 20th	Apr 5th	Apr 7th	Apr 6th	May 6th	May 1st	May 10th	May 20th	Jun 1st
PA	Mar 18th	Apr 6th	Apr 10th	Apr 11th	May 7th	May 2nd	May 11th	May 21st	Jun 2nd
PB	Mar 19th	Apr 11th	Apr 17th	Apr 9th	May 12th	May 7th	May 16th	May 26th	Jun 7th
AL	Mar 10th	Apr 17th	Apr 21st	Apr 18th	May 18th	May 13th	May 22nd	Jun 1st	Jun 13th
PI	Mar 19th	Apr 17th	Apr 21st	Apr 18th	May 18th	May 13th	May 22nd	Jun 1st	Jun 13th

CI: confidence interval.

But if we are used to being guided by more precise figures in cardiology, how do we know if the estimates are correct and if we have been drifting away from the actual figures? We have then looked for official sources that could allow us to infer and check these calculations. Unfortunately, at least until this date of the pandemic, there has been tremendous confusion regarding data reporting, which has caused the interpretation of the pandemic phase in Brazil to be greatly impaired. Due to delayed determination of SARS-CoV-2 infections, many cases have been reported days and even weeks late, causing the official authorities to report numbers of confirmed cases as numbers of actual daily cases, confusing press bulletins and often causing unnecessary fuss, especially when accumulated numbers of weekends and holidays were late announced on Tuesdays.[10] In order to try to understand the numbers, it is necessary to check different sources with adjusted numbers and, above all, to look for more realistic statistics on the information on deaths occurring in the country, as this metric is much more robust from the point of view of reporting despite reflecting what happened 14 days prior. In this regard, it is worth mentioning the important contribution of the data reported on the Transparency Portal organized by the National Association of Registrars of Vital Statistics, which allows a more accurate monitoring of the number of deaths from Covid-19 or suspected deaths on the actual date of the occurrence, rather than on the reporting date.[11] Along with this data, information on monitoring hospitalizations for Serious Acute Respiratory Syndromes through the InfoGripe system also helped to continuously monitor trends and confirm or not the forecasts made.[12]

Despite all these tools at hand, the social isolation measures were taken in a very controversial way, often not considering the stage of the pandemic cycle we were at, with a late adoption, and sometimes following a course of action without presenting consistent data that would justify the measures taken. Given the great difference between the structure of resources found in the country and the phases of the pandemic in each state, the degrees of isolation should certainly be quite different since each measure individually or together has different effects on reducing viral transmission. In this sense, we must also remember the Pareto principle, where 20% of what we do reaches 80% of the result: the correct application of well-done social distancing, with 25% reduction from the original distancing, allows an effective transmission response to be maintained once R0 is initially reduced.[13] Therefore, relatively simple measures of advising the population to wash their hands, keeping away from others, wearing masks, etc., as long as they are well applied, can often be better than attempts at taking drastic yet disorderly actions not well understood by

the population concerned and without proper preparation.

The decision of what to do and at what point in the pandemic is crucial so that we do not turn the goal of saving lives into a merely appealing pitch with consolidated results that result in more deaths than lives saved. The second and third order effects that occur in any therapy can often be more harmful than the treatment itself, especially when it is carried out without proper planning. Very common in situations where centralization tries to simplify extremely complex processes that involve multiple chains (as we have in a famous example of pencil making),[14] the final effect can be exactly the opposite of what we are pursuing. And here we have several situations where an unnecessary extension of confinement measures can lead to a greater number of deaths than from the disease itself. As of writing this, the number of deaths from Covid-19 in Brazil is about 10,000 patients and we have almost 45 days of isolation. Due to an expected 30% reduction in primary angioplasty surgeries, increased transfer times and rehospitalizations due to untreated acute coronary syndromes,[15–17] an excess of cardiovascular deaths of over 3,000 is estimated in this period. Missing outpatient visits of various specialties increases the risk of death by up to 1.5 times, adding to this excess another 9,000 unnecessary deaths.[18] The 1% increase in unemployment or the drop in Gross Domestic Product alone is associated with an increase in deaths of up to 1.63 times in the economically active population, adding another 3,500 excess deaths to this amount.[19] Mortality calculations due to failure of therapies for neoplasms and misdiagnoses in Brazil do not yet exist, but in the USA and England, excess deaths were estimated at 34,000 and 6,000 respectively.[20] All of these deaths are associated with several causes, mainly due to the lack of timely access to overburdened healthcare systems solely focused on one cause of mortality. These will be the invisible deaths of the pandemic and isolation because they were not predicted as the side effects to single-point measures.

What will come in the next weeks and months is beyond the views expressed here and will depend, to a great extent, on how we will choose to defuse this health crisis, sooner or later. Expensive spending on chronic diseases is likely to increase dramatically in the coming months,[21] overburdening a government already in debt. Unemployment and declining income will lead many Brazilians to migrate to a Public Healthcare System already burdened from the demand repressed over these months. At the same time, other solutions to increase the efficiency of the systems will be improved as they have been in this short period of time, such as digital prescriptions and telemedicine.[22] This increase in medical productivity can partly alleviate these increases in demand and costs, making our healthcare system to demonstrate the resilience and effectiveness that has made us to witness a mortality per million up to 10 times less than other European countries at the same stage of the disease, despite all our difficulties. What we do know is that we will be ready for new challenges, as optimists have always surprised us as to how human inventiveness is capable of overcoming obstacles.

References

1. Nussbaumer-Streit B, Mayr V, Dobrescu AI, Chapman A, Persad E, Klerings I, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. Cochrane Database Syst Rev. 2020;4(4):CD013574.
2. Wikipedia. List of countries by hospital beds. [Cited in 2020 Apr 20] Available from: https://en.wikipedia.org/wiki/List_of_countries_by_hospital_beds.
3. Eich B B. https://docs.google.com/spreadsheets/d/1zC3kW1sMu0sjnT_vP1sh4zL0tF6fIHbA6fcG5RQdqSc/htmlview#gid=0. 2020.
4. Breban R, Vardavas R, Blower S. Theory versus data: how to calculate R0? PLoS One. 2007;2(3):e282.
5. Murray CJ. Forecasting COVID-19 impact on hospital bed-days, ICU-days, ventilator-days and deaths by US state in the next 4 months. medRxiv. 2020 Mar. 30.
6. Dana S, Simas AB, Filardi BA, Rodriguez RN, Valiengo LLC, Gallucci-Neto J. Brazilian modeling of COVID-19 (BRAM-COD): a Bayesian Monte Carlo approach for COVID-19 spread in a limited data set context. medRxiv. 2020 May 17.
7. Worldometer. Coronavirus Cases; 2020. [citado 20 abr. 2020]. Disponível em: https://www.worldometers.info/coronavirus/coronavirus-cases/.
8. 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. 2020;395(10229):1054-62.
9. Yao H, Lu X, Chen Q, Xu K, Chen Y, Cheng L, et al. . Patient-derived mutations impact pathogenicity of SARS-CoV-2. medRxiv. 2020 Apr. 23.
10. Ministério da Saude. Painel Coronavírus. Rio de Janeiro, DF: Ministério da Saúde; 2020. [citado 20 abr. 2020]. Disponível em: https://covid.saude.gov.br/.
11. Brasil. Portal da Transparência [Internet].Especial COVID-19. Painel Registral; 2020. [citado 20 abr. 2020]. Disponível em: https://transparencia.registrocivil.org.br/especial-covid.
12. Fiocruz. Info Gripe [Internet]. Rio de Janeiro: Fiocruz; 2020. [citado 20 abr. 2020]. Disponível em: http://info.gripe.fiocruz.br/.
13. Lai S, Ruktanonchai NW, Zhou L, Prosper O, Luo W, Floyd JR, et al. Effect of non-pharmaceutical interventions to contain COVID-19 in China. Nature. 2020.[Epub ahead of print].
14. Lopes B. Milton Friedman, a história de um lápis: A perspectiva e a lição que talvez passou despercebido; 2018. [citado 20 abr. 2020]. Disponível em: https://medium.com/@brunolopes_61254/milton-friedman-a-hist%C3%B3ria-de-um-l%C3%A1pis-a-perspectiva-e-a-li%C3%A7%C3%A3o-que-talvez-passou-despercebido-500de4c7a84a.
15. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J. 2020;41(19):1852-3.
16. Balk M, Gomes HB, Quadros AS, Saffi MAL, Leiria TLL. Comparative analysis between transferred and self-referred STEMI patients undergoing primary angioplasty. Arq Bras Cardiol. 2019;112(4):402-7.
17. Oliveira LMSM, Costa IMNBC, Silva DGD, Silva JRSS, Barreto-Filho JAS, Almeida-Santos MA, et al. Readmission of patients with acute coronary syndrome and determinants. Arq Bras Cardiol. 2019;113(1):42-9.
18. McQueenie R, Ellis DA, McConnachie A, Wilson P, Williamson AE. Morbidity, mortality and missed appointments in healthcare: a national retrospective data linkage study. BMC Med. 2019;17(1):2.

19. Roelfs DJ, Shor E, Davidson KW, Schwartz JE. Losing life and livelihood: a systematic review and meta-analysis of unemployment and all-cause mortality. Soc Sci Med. 2011;72(6):840-54.

20. Lai AG, Pasea L, Banerjee A, Denaxas S, Katsoulis M, Chang WH, et al. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. Preprint. 2020 Abr 20. Disponível em: https://www.researchgate.net/publication/340984562_Estimating_excess_mortality_in_people_with_cancer_and_multimorbidity_in_the_COVID-19_emergency?channel=doi&linkId=5ea8b957a6fdcc7050976a3e&showFulltext=true. 2020.

21. Stevens B, Pezzullo L, Verdian L, Tomlinson J, George A, Bacal F. The economic burden of heart conditions in Brazil. Arq Bras Cardiol. 2018;111(1):29-36.

22. Lopes MACQ, Oliveira GMM, Ribeiro ALP, Pinto FJ, Rey HCV, Zimerman LI, et al. Guideline of the Brazilian Society of Cardiology on Telemedicine in Cardiology - 2019. Arq Bras Cardiol. 2019;113(5):1006-56.

Why We Build Models – From Clinical Cardiology Practice to Infectious Disease Epidemics

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Francisco, 64 years old, comes to your office for a preventive health evaluation. He has a history of well-controlled hypertension and is otherwise well. His past medical history is unremarkable. No family history of cardiovascular disease or smoking and LDL-cholesterol (LDL-C) of 90 mg/dL. After discussing with the patient, you are unsure if this patient's risk benefit profile would favor the use of statins. Instead of trusting your personal feelings, you decide to use the Framingham risk score (FRS) to decide if statins would be recommended.[1] The calculated Framingham score is 8.1% and you decide not to initiate statins at this point.

One month later, Francisco returns to your office with typical angina on major exertion but has no signs of unstable disease. Once again, to avoid overconfidence on your initial impression, you decide to use the Diamond and Forrester (DF) chest pain prediction rule, which estimates the pretest probability of obstructive coronary artery disease (CAD).[2] For a male at his age, the rule suggests a pretest probability of 94% (high probability), so you decide to request an invasive angiography in the outpatient setting.

A couple of days before the test, Francisco calls you complaining of worsening chest pain similar to the previous presentation, but now at rest. You tell the patient to go to the emergency room, where troponins are normal and resting ECG has 1 mm ST-segment depression in the inferior leads. Calculated TIMI risk score is 1, indicating low risk.[3] The patient is admitted for 48 hours, undergoes a negative treadmill test limited by poor physical performance and is discharged home with appropriate medication. One week later, he returns to the hospital with ST-segment elevation myocardial infarction. He is rushed to the Cath lab and a severe lesion in the mid right coronary artery is documented. He undergoes a percutaneous coronary intervention. After three days in the hospital, he is discharged home.

Keywords

Cardiovascular Diseases; Biomarkers; Risk Factors; Risk Assessment; Risk Reduction Behavior; Prevention and Control; Coronavirus; COVID-19; Pandemics.

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Were the FRS, the DF or the TIMI risk scores correct or incorrect? Were the scores able to predict what happened to the patient? The FRS stratified the patient as low risk, meaning less than 10% risk of a major cardiovascular event in 10 years. The DF suggested an almost certain presence of obstructive CAD, whereas the TIMI risk score suggested low (5%) risk of death, recurrent myocardial infarction (MI) or severe ischemia requiring urgent revascularization in two weeks. Yet, the patient presented MI less than one week later.

Cardiologists are used to risk scores derived from risk prediction models. Models are simplifications of real life, and such simplifications make models generalizable to a broader population and externally valid to other individuals beyond the initial cohort of patients where they were developed. The models select a limited number of variables considered of higher importance to predict the desired outcome, but several assumptions are made based on each of those variables and the population they apply to. If such assumptions change, the model may no longer be valid or it might need to be recalculated or recalibrated to fit the new environment. For example, the FRS considers smoking as present or absent. Thus, past smokers are considered of similar risk to non-smokers. Also, individuals smoking two cigarettes a day are considered just like those smoking three packs a day. While those aspects may lead to imprecision when estimating the risk of an individual, they can have much broader implications when such changes in the value of each parameter occur at the population level. For example, when the FRS was derived, an average smoker would smoke one to two packs a day. Currently, most smokers smoke less than a quarter than that. Thus, applying the old version of the FRS in the current reality might result in an incorrect risk estimation.

This issues with models are known to cardiologists, and most scores are, at some point, updated to recalibrate and improve precision using new or recalibrated variables. Using the example case above, one might suggest the use of the atherosclerotic cardiovascular disease (ASCVD) score instead of the FRS. Using the ASCVD score, the 10-year risk of major cardiovascular events would be 10.6% and, according to newer guidelines, statins would be recommended to reduce this patient's cardiovascular risk.[4] This updated risk stratification score is expected to be more accurate.

In other situations, we may even consider the model as no longer useful and the entire approach should be different. For example, one could say 1 mm ST-segment depression at rest would characterize high risk irrespective

of other clinical characteristics. In such case, the patient would have been sent to the Cath lab upon the initial presentation and would not have had MI.

Finally, if the patient made into the Cath lab before clinical worsening, he could have been adequately managed medically with aspirin, statins, betablockers and other therapies. In such scenario, this patient could have lived another 10 years without any other clinical manifestation of ASCVD. Would his initial FRS be then interpreted as right or wrong?

Models should not be judged right or wrong long after they are developed. The appropriate question is whether the model had been adequately designed to the situation where it is being used, whether the outcome it aims to predict is of interest and whether the information is incremental to what is currently known. When such premises are met, models can lead to more well-informed decisions that may have a meaningful impact. In the case above, the adequate use of the ASCVD score in the initial presentation or a different interpretation of the ST-segment depression could have led to changes in management and completely modify the history of the disease for this patient.

While even the most experienced clinical cardiologists are unsurprised by such peculiarities of risk prediction models, they are not always well understood by lay people. A similar problem is now seen with the raising relevance assigned to epidemiological models for the prediction of the COVID-19 outbreak. An initial model published by the Imperial College London suggested that the outbreak could have a major impact across the world,[5] leading to millions of deaths related to COVID-10 in the United States and the United Kingdom. The model also estimated the impact of potential interventions leading to a colossal reduction in deaths. Other models followed, with much lower numbers, sometimes orders of magnitude lower than prior worst-case scenarios leading to several voices in the scientific community, the lay press and the general public to raise strong criticism against those initial models, most of which using current or newer projections to illustrate how "wrong" the initial model was.

The development of epidemiological models for COVID-19 have little resemblance to the simpler models used for risk prediction in cardiology. Yet, both use current and prior data to project a future scenario trying to estimate the value of interventions to reduce the risk of negative outcomes. However, due to the limited time since COVID-19 was discovered, several parameters related to the behavior of the virus are estimated based on restricted preliminary data. Sometimes, when no data is available, parameters are only best guesses based on related conditions or prior comparable situations. Additionally, such models are dependent on the viral transmission, a complex process that may involve hard-to-estimate parameters, such as the average number of social interactions each individual has or demographic density in each area. Some of those inputs might not be available and, once again, the best-informed guess is used by modelers. An example is the use of some data from Peru in an ICL model for the Brazilian case for pieces of data that were unavailable for Brazil. With such limited data inputs, it should come as no surprise that such models include immense variability.

Yet, this is only part of the issue when interpreting post-outbreak models. Although specific changes in the interventions can be considered in the model, it is impossible to predict how the government or the population will behave in the future, just like one cannot predict if the patient will start smoking when the cardiovascular risk is initially calculated. Even if social distancing is considered in the model, its true impact depends on how much the population follows such measures. For example, while strict measures to increase social distancing had been proposed for the city of São Paulo, the government recognizes they did not achieve more than half of the expected effect. Thus, its impact is also expected to be lower.

Yet, even if models are successful, they might be interpreted as being wrong in the future. For example, the aforementioned model from the ICL presented such a catastrophic scenario that it led to substantial policy changes across the world. If those changes led to a substantially lower death rate due to its early and effective implementations, such reduction in deaths could lead to claims that the model was "wrong" because it overestimated deaths.

Another important aspect of models in an epidemic such as COVID-19 is that the earlier they are developed, the less information is available, leading to a less precise model. However, the earlier the model is developed, the larger the impact of interventions derived from it. In a world of perfect information, COVID-19 could have been extinct if the information we currently have were available when the first case was diagnosed and the first case and its contacts were isolated. On the other extreme, perfect details of transmission and viral spread would be of little social impact after the outbreak ended. Hence, we are left to live with the uncertainty and imprecisions derived from models, particularly if we expect that such models will appear in time to guide effective policy interventions.

Thus, to have successful models, we need to accept, understand and acknowledge such limitations. Additionally, we need to be humble enough to adjust the sails to the ever-changing wind conditions update and improve our models along the way. Each model should only be judged bearing in mind the time when it was developed, including the limited knowledge available back then. In the end, it would be just like Francisco's case: we could have improved the initial risk prediction and the course of his life with a better initial model to estimate his cardiovascular risk. Yet, after his myocardial infarction, even perfect information on his cardiovascular risk would be of little value. Just like in clinical medicine, when those epidemiological models are evaluated, we should refrain from being next day's doctors who are always right after the diagnosis is known. Instead of aggressively pointing fingers at models that are known to be uncertain, let us be humble and practical when evaluating them. Was the model able to better inform interventions at its time and was it able to reduce, even by a little, the imprecisions we had? If yes, then the models were useful, even if wrong.

References

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories.Circulation. 1998;97(18):1837-47.
2. Diamond GA, Forrester JS. Análise da probabilidade como auxílio no diagnóstico clínico da doença coronariana-arterial. N Engl J Med. 1979;300(24):1350-8.
3. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. O escore de risco TIMI para angina instável/iA de elevação não-ST: Um método para prognóstico e tomada de decisão terapêutica. JAMA. 2000;284(7):835-42.
4. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, eet al.D iretriz da ACC/AHA de 2013 sobre a avaliação do risco cardiovascular: um relatório do American College of Cardiology/(25):2935-59.

One year follow-up Assessment of Patients Included in the Brazilian Registry of Acute Coronary Syndromes (ACCEPT)

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Abstract

Background: **There is lack of prospective data on evolution within one year of acute coronary syndromes (ACS) in a representative population of Brazilian patients.**

Objectives: **To assess the prescription of evidence-based therapies, the incidence of severe outcomes and the predictors for these outcomes in a multicenter Brazilian registry of ACS patients.**

Methods: **The ACCEPT is a prospective observational study, which included patients hospitalized with a diagnostic of ACS in 47 Brazilian hospitals. The patients were followed for a 1 year and data were collected on the medical prescription and the occurrence of major cardiovascular events (cardiovascular mortality, reinfarction and cerebrovascular accident - CVA). Values of $p < 0.05$ were considered statistically significant.**

Results: **A total of 5,047 patients were included in this registry from August 2010 to April 2014. The diagnosis of ACS was confirmed in 4,782 patients (94.7%) and, among those, the most frequent diagnosis was ACS with ST segment elevation (35.8%). The rate of major cardiovascular events was 13.6 % within 1 year. Adherence to prescription of evidence-based therapy at admission was of 62.1%. Age, public service, acute myocardial infarction, CVA, renal failure, diabetes and quality of therapy were associated independently with the occurrence of major cardiovascular events.**

Conclusions: **During the one-year follow-up of the ACCEPT registry, more than 10% of the patients had major cardiovascular events and this rate ranged according with the quality of therapy. Strategies must be elaborated to improve the use of evidence-based therapies to minimize the cardiovascular events among the Brazilian population. (Arq Bras Cardiol. 2020; 114(6):995-1003)**

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Introduction

The group of cardiovascular diseases, particularly acute coronary syndrome (ACS), represents the leading cause of mortality and disability in Brazil and worldwide.[1-3] In addition to its current high frequency, there is a perspective of increase in this group of diseases in developing countries, such as Brazil.[1-5] Despite the high morbidity and mortality of ACS currently, several strategies of proven efficacy to reduce the risk of complications in these patients have been developed.[6,7] However, there are flaws in evidence-based therapies when applied to ACS patients, as has been identified in previous clinical practice registries.[8-10] Those multicenter registries assessed mainly the intra-hospital period or a 30-day period from the acute event. However, they lacked long-term data on the follow-up of these patients.[8-10] Among the previous 30-day follow-up database is the partial data release (without complete sample data) of the ACCEPT study.[10] As previously reported in the 30-day follow-up partial release,[10] the ACCEPT study group intended to continue the investigation, with the enrollment of a greater number of patients and the inclusion of 12-month follow-up data. Thus, the present analysis performed, once more, the assessment of the baseline characteristics and initial adherence of medical prescriptions to evidence-based therapies in a larger population (about twice as many patients compared to the initial publication with the intermediate data) and included data on the incidence rate of severe clinical outcomes during the follow-up.

Objectives

In addition to the final results after 30 days with the overall study population, this one year follow-up assessment has the following objectives:

- To assess the rate of major cardiovascular events within 12 months in a sample of Brazilian post-ACS patients;

- To evaluate the conformity of medical prescriptions to evidence-based therapies within 12 months in a sample of Brazilian post-ACS patients;

- To identify predictors of major cardiovascular events within 12 months in a sample of Brazilian post-ACS patients.

Methods

Study Design

The ACCEPT (Acute Coronary Care Evaluation of Practice Registry) registry is a project conceived by the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia - SBC), whose methods have been previously published.[10,11] In sum, it is a prospective, voluntary, multicenter study, which gathered 53 centers from the five Brazilian federal regions, with the following distribution: Southeast (50.9%), Northeast (13.2%), South (24.5%), Midwest (5.7%) and North (5.7%). Patient inclusion occurred from August 2010 to April 2014, in public hospital care centers (Unified Health System - SUS), health maintenance organizations, or private health care, according with the following distribution: SUS 2669/4782 (55.8%), health maintenance organizations 1968/4782 (41.2%) and private hospitals 145/4782 (3%).

Study participants

Patients diagnosed with the different types of ACS were included: unstable angina (UA), acute myocardial infarction (MI) without ST-segment elevation (NSTEMI) and with ST-segment elevation (STEMI). The main inclusion criteria were: ischemic symptoms of suspected ACS associated with ischemia-like ECG changes and/or myocardial injury biomarkers above the upper limit of normality. Patients transferred from other institutions with more than 12 hours after symptoms onset were excluded.

Study procedures and variables analyzed

The study procedures and variables analyzed in the ACCEPT study have been previously published.[10,11] In sum, data collection occurred at admission (index visit) and a second data collection was performed after 7 days or at discharge (whichever occurred first). After these two first visits, the study included visits at 30 days, 6 months and 12 months, which could take place in person, at routine medical care, or by phone.

Due to the pragmatic features of the study, the identification of patients' comorbidities (e.g.: arterial hypertension, dyslipidemia) could be performed as follows: patients' self-assessment, use of medication (antihypertensive and lipid-lowering) or investigators' evaluation (in the latter case, the centers were oriented to follow the recommendations on diagnosis criteria adopted by the current guidelines of the Brazilian Society of Cardiology). Physical examination data could be obtained by direct measurement (obesity was defined by BMI > 30 Kg/m^2). Other criteria were based on the registry of medical records of a variable collected by interview (e.g.: stress, ex-smoker if cessation date was > 6 months).

The evidence-based treatment plan that was considered in the ACCEPT was not modified throughout the study and was based on current guidelines.[6,7] This treatment plan can be divided as follows:

- Index event admission: Double antiaggregation, parenteral anticoagulant, statin and betablocker in addition to reperfusion therapy in case of STEMI.

- Outpatient therapy post discharge: Double antiaggregation, statin, beta-blocker and ACE inhibitors/ARBs.

The cardiovascular events of interest analyzed in the population included were: cardiovascular mortality, non-fatal cardiac arrest, reinfarction and cerebrovascular accident (CVA).[10,11] These outcomes were reported by the investigator according to recommended criteria,[10,11] without an independent adjudication committee to confirm the events.

Statistical analysis

The analysis of normally distributed continuous variables was performed using histograms. Normally distributed continuous variables were described as mean ± standard deviation. The means were compared between the three diagnosis groups

using the variance analysis ANOVA. Categorical variables were described by absolute and relative frequencies. The proportions were compared using the Chi-square test or Fisher's exact test. Generalized Estimating Equations (GEE) models were used to assess drug therapy over time. To compare the major cardiovascular events according with the final diagnosis, Cox proportional hazards model and Kaplan-Meier curves were used. The identification of independent predictors for the composite endpoint (cerebrovascular accident (CVA), reinfarction and death) was performed using Cox proportional hazards model with the final diagnosis and the baseline factor analyzed. This analysis of predictors was initially performed in a univariate fashion and variables with a p <0.15 were included in the multivariate analysis. P-values were presented as two-sided and p < 0.05 was considered statistically significant in the final analyses. Additionally, in the multivariate analysis, an interaction test was performed between the selected variables. All analyses were performed using R Statistical software, version 3.6.1.

Results

Between August 2010 and April 2014, 5,047 patients were recruited from this nationwide registry, 265 of whom (5.25%) had undiagnosed chest pain and were excluded from the clinical follow-up because they did not fulfill the research inclusion criteria. Thus, 4,782 ACS patients were actually included in the analysis and followed in this prospective registry, in 53 hospitals from the 5 Brazilian federal regions. In a total of 410 patients (8.6%), it was not possible to obtain the final 12-month data.

Baseline Characteristics

The patients' clinical profile revealed the inclusion of approximately 70% of patients diagnosed with AMI at admission, almost one-third had diabetes, and around 90% presented at least one risk factor, with the most frequent being systemic arterial hypertension (Table 1).

Medical prescription adherence to evidence-based therapies

The prescription adopted soon after admission shows that full adherence to medications currently recommended in the guidelines was of 62.1 % (Table 2). This adherence includes dual antiplatelet therapy (aspirin/P2Y12 inhibitor) combined with parenteral anticoagulants, statins and betablockers.

Out of the 1,714 patients presented with AMI (STEMI), 1,412 (82.4%) individuals were treated with some modality of reperfusion of the myocardium (either fibrinolysis or primary percutaneous coronary intervention). When analyzing the prescription of reperfusion therapies for AMI, there are distinct and decreasing percentages, according to the Brazilian federal region: 87.3%, 84.5%, 72.8%, 66.7% and 65.7%, (p < 0.001), for the South, Southeast, Northeastern, Midwest, and Northern Brazilian states, respectively. As the severity of the clinical presentation of these three components of the ACS increased, there was a progressive increase in the prescription of invasive strategies, either coronary angiography (68.0%, 83.1% and 90.4%; p < 0.001), or myocardial revascularization procedures (38.2%, 54.4% and 76.4%; p < 0.001), in case of unstable angina, NSTEMI and STEMI, respectively. The preferred revascularization procedure in these patients was percutaneous coronary intervention with rates > 95% of coronary stent use in patients treated percutaneously. The percentage of percutaneous revascularization among all ACS patients ranged according with the diagnosis: unstable angina, NSTEMI and STEMI (33.6%, 47.4% and 75.1%, respectively; p <0.001).

We observed that the prescription of a P2Y12 inhibitor at hospital discharge varied according with the type of ACS (66.4% for unstable angina, 77.7% for NSTEMI and 90.9% for STEMI; p<0.001), and type of coronary disease treatment the patient received (PCI (94.2%), surgical (25%) or clinical (66.2%); p <0.001).

The evolution of the main therapies, from admission to discharge, at the end of 30 days and in 6 and 12 months shows a progressive reduction in the use of the therapies recommended, especially in relation to therapy with the use of P2Y12 receptor inhibitors (Figure 1).

Clinical Outcomes

Clinical outcomes were measured cumulatively at the end of the first 12 months of evolution (Figure 2). Among patients with UA, there was no association between the occurrence of the composite events (mortality, reinfarction or cerebrovascular accident (CVA)) at the end of the first 12 months and the performance of myocardial revascularization procedure (Table 3). In the presence of NSTEMI, a significant reduction was observed in the incidence of major cardiovascular events, including cardiovascular mortality, among those submitted or not to myocardial revascularization (mortality = 6.29 per 100 people/year *versus* 12.06 per 100 people/year; p < 0.001 and major cardiovascular outcomes = 13.18 per 100 people/year *versus* 17.96 per 100 patients/year; p = 0.038), respectively. STEMI patients had a significant reduction in mortality rates and incidence rates of major cardiovascular events when submitted to myocardial revascularization (mortality = 8.02 per 100 people/year *versus* 18.54 per 100 people/year; p < 0.001 and cardiovascular events = 13.11 per 100 people/year 21.69 per 100 people/year; p < 0.001). In the multivariate analysis (Table 4), the following factors were associated with the occurrence of major cardiovascular events: age, public health care, AMI, CVA, renal failure, diabetes and quality of therapy (complete or not). There was no significant interaction between the covariables.

The rate of events among SUS patients was 16.6 per 100 patients/year, whereas in the private associated network it was 9.10 per 100 patients/year (p<0.01). In the analysis per federal region, the 1-year death rate was significantly higher in the Northern region (19.8%; CI95% 12.6-27.0), followed by the Southeast (8.0%; CI95% 7.0-9.1), South (6.8%; CI95% 4.8-8.7) and Northeast regions (5.6%; CI95% 3.7-7.5). The Midwest region had the lowest number of patients with intermediate mortality rate between the Northern region and the rest of Brazil (14.2%; CI95% 2.8-25.5). When comparing the predictors of events between the North region and the 3 regions with the lowest rates of events (South, Southeast and Northeast), we observed a greater incidence of STEMI (51.0% x 35.3%; p <0.01), SUS health care (100% x 51.8%; p < 0.01) and incomplete treatment among the patients from the North region of Brazil (47.9% x 37.2%; p < 0.01).

Table 1 – Baseline characteristics of the patients included according to the type of acute coronary syndrome

	Patients' final diagnosis				
	Unstable Angina (n=1453)	AMI without ST elevation (n=1615)	AMI with ST elevation (n=1714)	Total (n=4782)	p-value
Age; mean ± SD	63.9 ± 11.9 (n=1449)	64.7 ± 12.4 (n=1603)	60.8 ± 12.4 (n=1702)	63.1 ± 12.4 (n=4754)	<0.001(1)
Sex (Female)	588/1453 (40.5%)	489/1615 (30.3%)	460/1714 (26.8%)	1537/4782 (32.1%)	<0.001
Transferred from another service (Yes)	179/1451 (12.3%)	393/1614 (24.3%)	803/1713 (46.9%)	1375/4778 (28.8%)	<0.001
Healthcare (Supplemental Insurance/Private)	757/1453 (52.1%)	775/1615 (48%)	581/1714 (33.9%)	2113/4782 (44.2%)	<0.001
Systolic Arterial Pressure; mean ± SD	138.1 ± 24.1 (n=1452)	137.9 ± 28 (n=1615)	131.5 ± 26 (n=1713)	135.7 ± 26.4 (n=4780)	<0.001(1)
Diastolic Arterial Pressure; mean ± SD	81.4 ± 13.9 (n=1452)	81.3 ± 16.4 (n=1615)	80.4 ± 16.4 (n=1713)	81 ± 15.7 (n=4780)	0.142(1)
Heart rate; mean ± SD	74.6 ± 15.3 (n=1452)	77.6 ± 18 (n=1615)	79.4 ± 17.2 (n=1713)	77.4 ± 17 (n=4780)	<0.001(1)
Dyslipidemia	971/1453 (66.8%)	915/1615 (56.7%)	734/1713 (42.8%)	2620/4781 (54.8%)	<0.001
Previous AMI	507/1451 (34.9%)	535/1614 (33.1%)	267/1713 (15.6%)	1309/4778 (27.4%)	<0.001
Angina history	774/1452 (53.3%)	554/1614 (34.3%)	406/1713 (23.7%)	1734/4779 (36.3%)	<0.001
Hypertension	1197/1453 (82.4%)	1252/1615 (77.5%)	1116/1713 (65.1%)	3565/4781 (74.6%)	<0.001
Family History of Coronary Disease	643/1453 (44.3%)	658/1615 (40.7%)	699/1713 (40.8%)	2000/4781 (41.8%)	0.081
CVA	137/1453 (9.4%)	125/1615 (7.7%)	98/1713 (5.7%)	360/4781 (7.5%)	<0.001
Stress and/or Depression	506/1451 (34.9%)	419/1614 (26%)	466/1713 (27.2%)	1391/4778 (29.1%)	<0.001
Renal Failure	88/1452 (6.1%)	99/1615 (6.1%)	72/1713 (4.2%)	259/4780 (5.4%)	0.021
Diabetes Mellitus	477/1453 (32.8%)	582/1615 (36%)	453/1713 (26.4%)	1512/4781 (31.6%)	<0.001
Diabetes treated with insulin	134/474 (28.3%)	150/582 (25.8%)	84/453 (18.5%)	368/1509 (24.4%)	-
Heart Failure	180/1452 (12.4%)	156/1615 (9.7%)	87/1713 (5.1%)	423/4780 (8.8%)	<0.001
Percutaneous Coronary Intervention	489/1450 (33.7%)	406/1614 (25.2%)	209/1713 (12.2%)	1104/4777 (23.1%)	<0.001
CABG	223/1452 (15.4%)	213/1615 (13.2%)	68/1713 (4%)	504/4780 (10.5%)	<0.001
Previous use of ASA	861/1453 (59.3%)	703/1615 (43.5%)	383/1713 (22.4%)	1947/4781 (40.7%)	<0.001
Abdominal Obesity	531/1452 (36.6%)	552/1615 (34.2%)	521/1713 (30.4%)	1604/4780 (33.6%)	0.001
Sedentary lifestyle	949/1453 (65.3%)	968/1615 (59.9%)	962/1713 (56.2%)	2879/4781 (60.2%)	<0.001
Peripheral arterial disease	130/1453 (8.9%)	135/1615 (8.4%)	126/1713 (7.4%)	391/4781 (8.2%)	0.252
Smoking					
Never	761/1453 (52.4%)	756/1615 (46.8%)	664/1713 (38.8%)	2181/4781 (45.6%)	<0.001
Ex-smoker	487/1453 (33.5%)	503/1615 (31.1%)	387/1713 (22.6%)	1377/4781 (28.8%)	
Current smoker	205/1453 (14.1%)	356/1615 (22%)	662/1713 (38.6%)	1223/4781 (25.6%)	

P-value: Chi-square test. (1) ANOVA test

Discussion

This database is considered the largest prospective Brazilian registry of ACS patients, and showed that more than two thirds of the events are classified as acute myocardial infarction at admission. The patients' profile indicates a predominance of the male sex (70%), almost one-third of patients with diabetes, and systemic arterial hypertension as the most frequent risk factor (74.6%). Almost 40% of the patients did not receive at least one of the evidence-based therapies at admission and the conformity to recommendations varied according to the federal region, to the type of ACS and to the revascularization strategy adopted. The risk of major cardiovascular events within a year was 13.6 per 100 people/year and, out of the seven factors associated with these events, two are related with the health care characteristics: financing (public vs. private) and quality of therapy (complete or incomplete).

The ACCEPT partial results, released in 2013,[10] included 2,584 patients and analyzed 2,485, after the exclusion of non-confirmed cases of ACS. In the present analysis, 2,463 patients were added, totaling 5,047 enrolled patients by the end of the study (4,782 cases of confirmed ACS). In addition

Table 2 – Use of medication by patients with Acute Coronary Syndrome at the admission stage

Medication	Unstable Angina	AMI without ST elevation	AMI with ST elevation	Total	p
ASA	1399/1449 (96.5%)	1580/1615 (97.8%)	1688/1713 (98.5%)	4667/4777 (97.7%)	0.001
Betablocker	1144/1449 (79%)	1323/1615 (81.9%)	1352/1713 (78.9%)	3819/4777 (79.9%)	0.052
P2Y12 inhibitor	1239/1449 (85.5%)	1483/1615 (91.8%)	1671/1713 (97.5%)	4393/4777 (92%)	<0.001
Clopidogrel	1213/1449 (83.7%)	1401/1615 (86.7%)	1531/1713 (89.4%)	4145/4777 (86.8%)	<0.001
Prasugrel	11/1449 (0.8%)	17/1615 (1.1%)	15/1713 (0.9%)	43/4777 (0.9%)	0.685
Ticagrelor	23/1449 (1.6%)	80/1615 (5%)	149/1713 (8.7%)	252/4777 (5.3%)	<0.001
Parenteral Anticoagulant	1151/1449 (79.4%)	1468/1615 (90.9%)	1500/1713 (87.6%)	4119/4777 (86.2%)	<0.001
Enoxaparina	837/1449 (57.8%)	1039/1615 (64.3%)	1086/1713 (63.4%)	2962/4777 (62%)	<0.001
Fondaparinux	113/1449 (7.8%)	206/1615 (12.8%)	174/1713 (10.2%)	493/4777 (10.3%)	<0.001
Unfractionated heparin	214/1449 (14.8%)	240/1615 (14.9%)	282/1713 (16.5%)	736/4777 (15.4%)	0.319
GP IIb/IIIa Inhibitors	23/1449 (1.6%)	91/1615 (5.6%)	292/1713 (17%)	406/4777 (8.5%)	<0.001
Abciximab	3/1449 (0.2%)	10/1615 (0.6%)	119/1713 (6.9%)	132/4777 (2.8%)	<0.001
Tirofiban	20/1449 (1.4%)	82/1615 (5.1%)	173/1713 (10.1%)	275/4777 (5.8%)	<0.001
ACE inhibitor	890/1449 (61.4%)	1059/1615 (65.6%)	1263/1713 (73.7%)	3212/4777 (67.2%)	<0.001
Statin	1302/1449 (89.9%)	1467/1615 (90.8%)	1576/1713 (92%)	4345/4777 (91%)	0.108
Lovastatin	0/1293 (0%)	0/1461 (0%)	1/1568 (0.1%)	1/4322 (0%)	
Pravastatin	40/1293 (3.1%)	44/1461 (3%)	56/1568 (3.6%)	140/4322 (3.2%)	
Sinvastatin	581/1293 (44.9%)	619/1461 (42.4%)	914/1568 (58.3%)	2114/4322 (48.9%)	
Rosuvastatin	102/1293 (7.9%)	103/1461 (7%)	60/1568 (3.8%)	265/4322 (6.1%)	
Atorvastatin	570/1293 (44.1%)	695/1461 (47.6%)	537/1568 (34.2%)	1802/4322 (41.7%)	
Dual antiplatelet therapy	1211/1449 (83.6%)	1463/1615 (90.6%)	1649/1713 (96.3%)	4323/4777 (90.5%)	<0.001
Complete therapy	787/1449 (54.3%)	1062/1615 (65.8%)	1116/1713 (65.1%)	2965/4777 (62.1%)	<0.001

P-value: Chi-square test. Dual antiplatelet therapy: Aspirin and P2Y12 inhibitor. Complete therapy: Dual antiplatelet therapy, Parenteral Anticoagulant, Statin and Betablocker.

to sample size, another marked difference is the follow-up length, because, similarly to the publication of the ACCEPT intermediate data,[10] most publications of nationwide registries on ACS only reported data on intra-hospital outcomes or at 30 day of follow-up.[12,13] The ERICO study, released in 2015, reported a one year follow-up of patients admitted due to ACS in a public hospital in the state of São Paulo.[14] Thus, the present analysis included, in an unprecedented manner, 12-month follow-up data of a large contemporary population of ACS patients from several Brazilian federal regions, including the conformity assessment of medical prescriptions to the guidelines evidence-based therapies within 12 months. The initial adherence of medical prescriptions identified in the ACCEPT study was similar to the one seen in other developing countries,[15] although it was below that of centers participating in quality programs in those same countries.[9] During the one year follow-up, there was a decrease in prescription of all therapies, especially of P2Y12 inhibitors, whose administration was far below what was observed in the international registries of developed countries.[16,17]

At the 12-month follow-up, a residual risk of 13.6 per patient/year was also identified for major cardiovascular events (reinfarction, death and CVA). The connection of these events with the performance of revascularization seemed more evident in cases of AMI, because, in unstable angina, the combined analysis of cardiovascular outcomes did not reveal a lower rate among the patients submitted to revascularization. Since this is an observational non-randomized study, such evidence does not allow for the establishment of a cause-effect relation, but it reinforces the external validity of the concept generated by clinical trials on the benefits of revascularization for ACS patients, especially for those at a higher risk.[18,19]

One strategy to minimize the bias of observational studies is to include the several collected data in a model which allows to identify the individual relation in an independent manner. Among the factors identified in a multivariate analysis, two were related to health care: public *versus* private and quality of therapy (complete or not). The quality of therapy was based on the evidence-based recommendations for this population.[6,7] The relation between outcome and quality of therapy has been demonstrated in several previous publications,[8,15] and showed additional importance

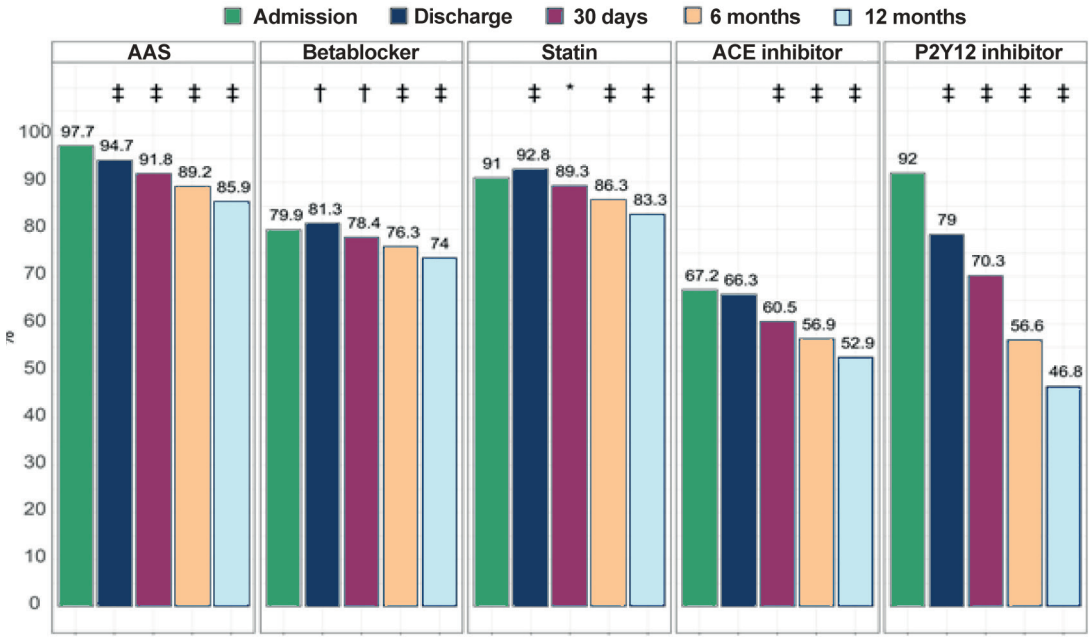

Figure 1 - *Adherence to evidence-based therapies in the first year of follow-up. To compare the continuity of medical prescription in follow-up with admission, a model of Generalized Estimating Equations (EEG) was adjusted for binary data, to take into consideration the dependence between observations. ‡ P-value < 0.001; Comparison between follow-up and admission; † P-value < 0.01; Comparison between follow-up and admission; * P value < 0.05; Comparison between follow-up and admission*

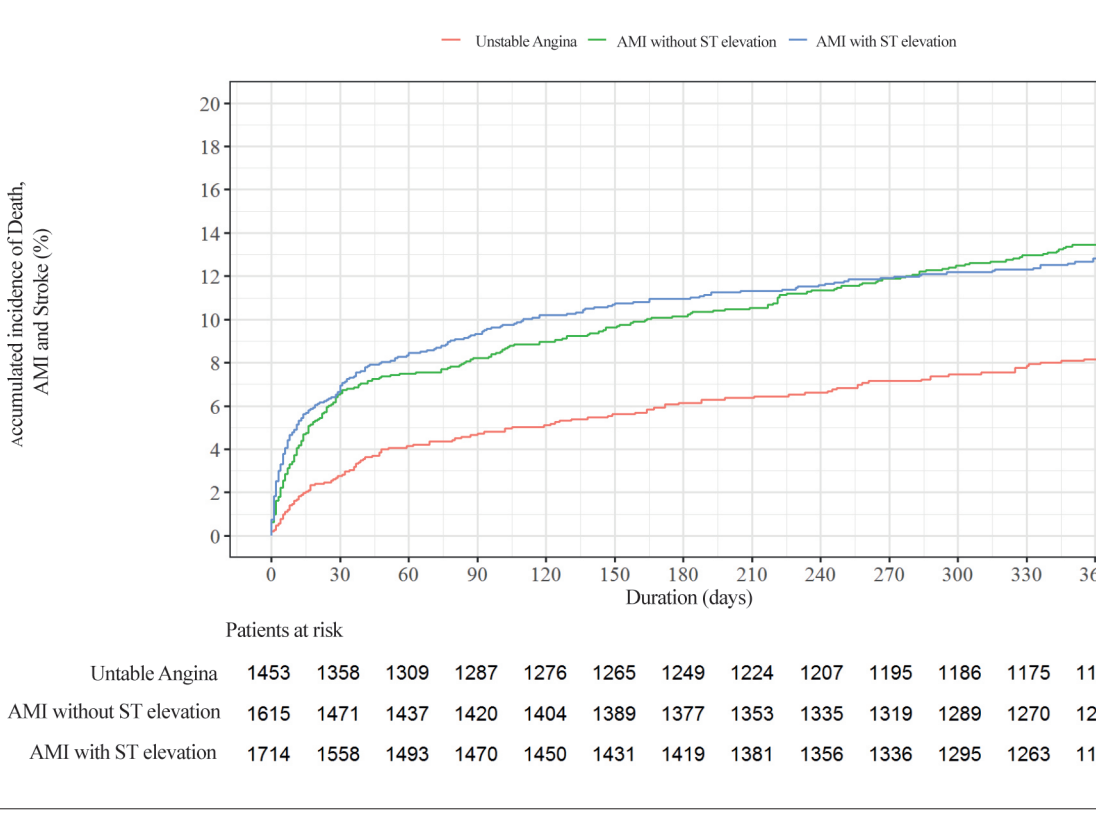

Figure 2 – *One-year clinical outcomes according with the diagnosis.*

Table 3 – Relationship between the revascularization procedure and clinical outcomes in the 3 types of acute coronary syndrome

Events in revascularized patients compared to non-revascularized patients	Unstable Angina HR [95% CI]	AMI without ST elevation HR [95% CI]	AMI with ST elevation HR [95% CI]
Severe Bleeding	2.03 [0.75 ; 5.44]	1.15 [0.55 ; 2.41]	1.28 [0.37 ; 4.50]
Cardiorespiratory Arrest	0.27 [0.09 ; 0.79]	0.54 [0.34 ; 0.87]	0.54 [0.36 ; 0.83]
Myocardial Reinfarction	1.69 [1.03 ; 2.76]	1.28 [0.85 ; 1.90]	0.87 [0.53 ; 1.43]
Cerebrovascular Accident (CVA)	1.18 [0.26 ; 5.28]	0.80 [0.30 ; 2.13]	1.02 [0.34 ; 3.11]
Death	0.33 [0.17 ; 0.65]	0.53 [0.37 ; 0.76]	0.45 [0.33 ; 0.63]
Cardiovascular death	0.45 [0.20 ; 1.06]	0.43 [0.28 ; 0.66]	0.43 [0.31 ; 0.62]
Composite endpoint	0.97 [0.66 ; 1.42]	0.75 [0.57 ; 0.98]	0.64 [0.48 ; 0.85]

Composite endpoint: Death, Myocardial reinfarction and CVA. HR: Hazard Ratio.

Table 4 – Multivariate analysis of factors associated with the occurrence of composite events (CVA, reinfarction or death).

	Multivariate	
Variables	**HR [95% CI]**	**p-value**
Age		
Age (5-year increase)	1.16 [1.11;1.20]	<0.001
Sex		
Female	1.10 [0.91;1.33]	0.328
Healthcare (Supplemental Insurance/Private)		
Supplemental Insurance/Private	0.57 [0.47;0.69]	<0.001
Dyslipidemia		
Yes	0.98 [0.81;1.19]	0.826
AMI		
Yes	1.29 [1.03;1.63]	0.030
Angina		
Yes	0.95 [0.78;1.16]	0.613
Hypertension		
Yes	1.08 [0.85;1.36]	0.534
CVA		
Yes	1.38 [1.06;1.80]	0.017
Renal Failure		
Yes	2.08 [1.59;2.71]	<0.001
Diabetes		
Yes	1.48 [1.23;1.78]	<0.001
CHF		
Yes	1.10 [0.83;1.45]	0.502
Percutaneous coronary intervention		
Yes	1.00 [0.80;1.27]	0.961
CABG		
YES	0.94 [0.72;1.25]	0.684
ASA use		
Yes	1.18 [0.96;1.47]	0.120
Smoking		
Never	ref	ref
Ex-smoker	1.22 [0.99;1.50]	0.055
Current smoker	1.27 [1.00;1.62]	0.047
Complete therapy		
Yes	0.72 [0.61;0.86]	<0.001
Final Diagnosis		
Unstable Angina	ref	ref
AMI with ST elevation	1.76 [1.39;2.23]	<0.001
AMI with ST elevation	2.04 [1.59;2.62]	<0.001

**Variables with p values < 0.15 in the univariate analysis were included in the multivariable model. ** The variables with p values > 0.15 in the univariate analysis were: Transfer from another service, Family History of Coronary Disease, Abdominal Obesity, Sedentary Lifestyle and Peripheral Arterial Disease.*

for the external validity of the effects identified in controlled clinical trials. The explanation for the difference in the outcomes identified between the patients from public or private-sector, could be owed to the difference in healthcare quality. However, since the multivariate model identified that private healthcare is associated with better outcomes independently of the quality of therapy, a possible explanation would be the patients' social/educational level itself. These data were not collected for direct inclusion in the multivariate model of this analysis. However, in previous studies, they were identified as factors associated with clinical outcomes in this population.[15,20]

Study limitations

One limitation of this study regards the patients' profile, since this is a voluntary registry, whose participant services showed clinical research capacity. Therefore, the results may not be applicable to populations that do not fit these characteristics (for instance, hospitals with more limited structure). In any case, even in centers with potential for high-quality care, relevant gaps were identified when applying scientific evidence. Another limitation is related to assessment of adherence to evidence-based therapies, because this analysis was based on medical adherence in terms of the prescription of evidence-based therapies. We did not collect data on the eligibility, the actual administration of the therapies prescribed and the reasons for prescription discontinuity. Thus, considering that the adherence on the part of the patients was not assessed in this registry, the gap on the use of evidence-based therapies could be even bigger than that found in the ACCEPT registry, which evaluated the medical prescription. Finally, the clinical outcome assessment presents limitations regarding the absence of events adjudication and missing data of the 12-month follow-up of 410 patients. Nevertheless, the assessment of clinical outcomes in pragmatic observational studies is usually performed by notification of the investigator physician, without the use of a specific committee for adjudication, which would represent a scenario closer to the identification of events in real clinical practice. As for the follow-up, taking into account that the follow-up losses occurred at different moments, the analyses were performed using the Cox model. Consequently, the patients were censored in the last registered contact, in order to minimize the differences in follow-up length.

Conclusion

In the largest prospective study ever published on patients with ACS in Brazil, we identified a mean rate of major

cardiovascular events, within 1 year, above 13 per 100 patients/year, but which reached values above 16.6 per 100 patients/year in the public service context (SUS). Since there are flaws in the prescription of evidence-based therapies from admission, which are intensified during the follow-up, the creation of strategies to increase adherence of evidence-based prescription could minimize the risk of such events among the Brazilian population.

Author contributions

Conception and design of the research: Barros e Silva PGM, Berwanger O, Guimarães JI, Andrade J, Paola AAV, Malachias MVB, Piva e Mattos LA, Precoma DB, Bacal F, Dutra OP; Acquisition of data: Barros e Silva PGM, Santos ES, Sousa AC, Cavalcante MA, Andrade PB, Carvalho F, Vargas Filho H; Analysis and interpretation of the data and Writing of the manuscript: Barros e Silva PGM; Obtaining financing: Berwanger O, Guimarães JI, Andrade J, Paola AAV, Malachias MVB, Piva e Mattos LA, Precoma DB, Bacal F, Dutra OP; Critical revision of the manuscript for intellectual content: Berwanger O, Santos ES, Sousa AC, Cavalcante MA, Andrade PB, Carvalho F, Vargas Filho H, Guimarães JI, Andrade J, Paola AAV, Malachias MVB, Piva e Mattos LA, Precoma DB, Bacal F, Dutra OP.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the HCor under the protocol number 117/2010. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Potential Conflict of Interest

Pedro Gabriel Melo de Barros e Silva reported fees and research grants from Pfizer, Roche Diagnostics and Bayer. Otavio Berwanger reported grants and personal fees from Astra Zeneca, Bayer, and Boehringer Ingelheim; grants from Amgen and Roche Diagnosis; and personal fees from Novo Nordisk and Novartis.

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Study Association

This study is not associated with any thesis or dissertation work.

References

1. World Health Organization (WHO).Cardiovascular Diseases. [Internet]. [Cited in 2019 Dec 12]Available from: http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
2. Brasil. Ministério da Saúde. [Cited in 2020 Jan 23]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2011/c08.def
3. Kochanek KD, Xu JQ, Murphy SL, Minino AM, Kung HC. Deaths: preliminary data for 2009. Natl Vital Stat Rep.2011;59(4):1-51.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498-504.
5. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009;119(3):480-6..
6. Piegas LS, Feitosa G, Mattos LA, Nicolau JC, Rossi Neto JM, Timerman A, et al. Sociedade Brasileira de Cardiologia. Diretriz da Sociedade Brasileira de Cardiologia sobre Tratamento do Infarto agudo do Miocárdio com Supradesnível do Segmento ST. Arq Bras Cardiol.2009;93(6 supl.2):e179-e264.
7. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJDG, Franci A, Sociedade Brasileira de Cardiologia. Diretrizes da Sociedade Brasileira de Cardiologia sobre Angina Instável e Infarto Agudo do Miocárdio sem Supradesnível do Segmento ST. Arq Bras Cardiol. 2014; 102(3Supl.1):1-61
8. Peterson ED, Roe MT, Mulgund J, deLong ER, Lytle BL, Brindis RG, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. JAMA. 2006;295(16):1912-20.
9. de Barros E Silva PGM, Ribeiro HB,Macedo TA, Lopes RD, do Amaral Baruzzi AC, et al. Improvement in quality indicators using NCDR® registries: First international experience. Int J Cardiol. 2018 Sep 15;267:13-5.
10. Piva e Mattos LA, Berwanger O, Santos ES, Reis HJ, Romano ER, Petriz JI, et al. Clinical outcomes at 30 days in the Brazilian Registry of Acute Coronary Syndromes (ACCEPT). Arq Bras Cardiol. 2013;100(1):6-13.
11. Mattos LA. Rationality and methods of ACCEPT registry - Brazilian registry of clinical practice in acute coronary syndromes of the Brazilian Society of Cardiology. Arq Bras Cardiol. 2011;97(2):94-9.
12. Soeiro AM, Silva PGMBE, Roque EAC, Bossa AS, Biselli B, Leal CAT, et al. Prognostic Differences between Men and Women with Acute Coronary Syndrome. Data from a Brazilian Registry. Arq Bras Cardiol. 2018;111(5):648-53.
13. Nicolau JC, Franken M, Lotufo PA, Carvalho AC, Marin Neto JA, Lima FG, et al. Use of demonstrably effective therapies in the treatment of acute coronary syndromes: comparison between different Brazilian regions. Analysis of the Brazilian Registry on Acute Coronary Syndromes (BRACE). Arq Bras Cardiol. 2012;98(4):282-9.
14. Santos IS, Goulart AC, Brandão RM, Santos RC, Bittencourt MS, Sitnik D, Pereira AC, Pastore CA, Samesima N, Lotufo PA, Bensenor IM. One-year Mortality after an Acute Coronary Event and its Clinical Predictors: The ERICO Study. Arq Bras Cardiol. 2015;105(1):53-64.
15. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D,Reddy KS, et al.Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet. 2008;371(9622):1435-42.
16. Ferrières J, Sartral M, Tcherny-Lessenot S,Belger M, APTOR trial investigators. A prospective observational study of treatment practice patterns in acute coronary syndrome patients undergoing percutaneous coronary intervention in Europe. Arch Cardiovasc Dis. 2011;104(2):104-14.
17. Bueno H, Pocock S, Danchin N, Annemans L, Grewgson J, Medina J, et al. International patterns of dual antiplatelet therapy duration after acute coronary syndromes. Heart. 2017;103(2):132-8.

18. Li Yi, Liu N, Lu J. Outcomes in patients with non-ST-elevation acute coronary syndrome randomly assigned to invasive versus conservative treatment strategies: A meta-analysis. Clinics (Sao Paulo) 2014; 69(6):398-404.

19. Bavry A, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol. 2006;48(7):1319-25.

20. Al-Zakwani I, M Mabry R, Zubaid M, Alsheikh-Alii AA, Almahmeed W, Shehab A, et al. Association between education and major adverse cardiac events among patients with acute coronary syndrome in the Arabian Gulf. BMJ Glob Health. 2019;4(1):e001278.

Chemotherapy-Related Anatomical Coronary-Artery Disease in Lung Cancer Patients Evaluated by Coronary-Angiography SYNTAX Score

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Abstract

Background: **Chemotherapy-related coronary artery disease (CAD) is becoming an emerging issue in clinic. However, the underlying mechanism of chemotherapy-related CAD remains unclear.**

Objective: **The study investigated the association between chemotherapy and atherosclerotic anatomical abnormalities of coronary arteries among lung cancer patients.**

Methods: **Patients undergoing coronary angiography (CAG) between 2010 and 2017, who previously had lung cancer, were examined. Risk factors associated with CAD and information about lung cancer were evaluated. We assessed coronary-artery abnormalities by SYNTAX score (SXscore) based on CAG. In logistic-regression analysis, we defined high SXscore (SXhigh) grade as positive if ≥22. Data were analyzed through descriptive statistics and regression analysis.**

Results: **A total of 94 patients were included in the study. The SXscore was higher in the chemotherapy group than in the non-chemotherapy group (25.25, IQR [4.50–30.00] vs. 16.50, IQR [5.00–22.00], p = 0.0195). The SXhigh rate was greater in the chemotherapy group than in the non-chemotherapy group (58.33% vs. 25.86; p = 0.0016). Both univariate (OR:4.013; 95% CI:1.655–9.731) and multivariate (OR:5.868; 95% CI:1.778–19.367) logistic-regression analysis revealed that chemotherapy increased the risk of greater SXhigh rates. Multivariate stepwise logistic-regression analysis showed the risk of more severe anatomical CAD is increased by chemotherapy as a whole by 5.323 times (95% CI: 2.002–14.152), and by platinum-based regimens by 5.850 times (95% CI: 2.027–16.879).**

Conclusions: **Chemotherapy is associated with anatomical complexity and severity of CAD, which might partly account for the higher risk of chemotherapy-related CAD among lung cancer patients. (Arq Bras Cardiol. 2020; 114(6):1004-1012)**

Keywords: **Coronary Artery Disease/physiopathology; Lung Neoplasms/drug therapy; Lung Neoplasms/complications; Propensity Score; Score Syntax; Angioplasty/methods; Risk Factors.**

Introduction

Modern treatment strategies have led to an improvement in the chances of surviving a diagnosis of cancer. However, these gains can come at a cost.[1] Cardiovascular toxicity is a potential short- or long-term complication of various anticancer therapies and is becoming one of the most concerning side effects of anti-cancer therapy.[2] Heart conditions that may be induced by anticancer chemotherapeutic agents include cardiac dysfunction, cardiac ischemia, arrhythmia, stroke and pulmonary-artery hypertension.[1,3,4] Chemotherapy-related coronary artery disease (CAD) is becoming an emerging clinical problem difficult to manage due to various clinical manifestation and complicated pathophysiological mechanisms.[5-7] Chemotherapy-induced coronary-artery events that occurred shortly after administration of chemotherapeutic agents, possibly due to acute thrombosis or vasospasm, have been reported.[3,8] However, the pathogenesis of chronic chemotherapy-related CAD remains unclear.

Lung cancer is the most common incident cancer and the leading cause of cancer death.[9] Chemotherapy is an important treatment for this disease.[10,11] Chemotherapeutic agents for lung cancer, including taxanes, cisplatin, carboplatin, bevacizumab, sorafenib and erlotinib[3,10,12] are known to cause acute myocardial infarction (AMI). It is important to investigate the long term effect of chemotherapy on anatomical changes of coronary artery among lung cancer patients.

Complexity and lesion characteristics of the coronary artery are well-recognized predictors of periprocedural complications and long-term mortality.[13-15] The SYNTAX score (SXscore) was developed to prospectively characterize the

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coronary vasculature by number of lesions and their functional impacts, locations and complexity.[16-18] It is an important tool for grading complexity of coronary artery disease (CAD) and for risk-stratifying patients who are being considered for revascularization. In addition, it has demonstrated good value as a predictor of major adverse cardiac events, including cardiac death. Higher SXscores, indicative of more-complex diseases, are hypothesized to represent a greater therapeutic challenge and to pose potentially worse cardiac prognoses.[16,17,19-21]

Recent studies used SXscore to quantify the severity of CAD among cancer patients, which looked mostly at the effect of radiotherapy on CAD.[20,21] In the present study, we used SXscore to evaluate the complexity and severity of CAD among lung cancer patients to investigate the relationship between chemotherapy and CAD. We also observed the effect of radiotherapy and other risk factors on anatomical severity of coronary arteries among those patients.

Methods

Study design and patients

We used a hospital-based cross-sectional study design. The study patients were admitted to Chinese PLA General Hospital to undergo coronary angiography (CAG) due to suspected angina pectoris or stenosed coronary artery, showed by computer tomography angiography, between 2010 and 2017. Furthermore, the patients should have previously received definite diagnoses of lung cancer. Patients who had previously undergone percutaneous coronary intervention were excluded.

We thoroughly examined the patients' electronic medical records for history of lung cancer, including diagnosis, age at time of diagnosis, location and treatment history (chemotherapy and radiotherapy). We reviewed sex, age at time of CAG, body mass index (BMI), family history of cardiovascular diseases (CVDs), tobacco use, hypertension, diabetes, hyperlipidemia and lipid profile. These data were extracted using a clinical-research data platform created by Xiliu Data. Some data were checked by telephone with the patients themselves or their families.

Coronary angiography and SXscore

From the baseline diagnostic angiogram, we separately scored each coronary lesion with stenosis ≥50% in a vessel ≥1.5 mm diameter. Next, we added the scores to provide the overall SXscore, which we had calculated prospectively using the SXscore algorithm (described in full elsewhere in the literature).[16,17,22] All angiographic variables pertinent to SXscore calculation were computed by two blinded experienced interventional cardiologists. When the SXscore of each patient differed between the two cardiologists, they would discuss the angiogram and come up with a common SXscore for each patient. Final SXscores were calculated per patient and saved in a dedicated database. Two representative examples with SXscores based on CAG are shown in Figure 1.

In the study, a Sxscore of 22 was the upper tertile. We defined SXscore grades as SXlow (<22) or SXhigh (≥22). Through logistic-regression analysis, high SXscore grade was determined as positive if SXscore ≥22.

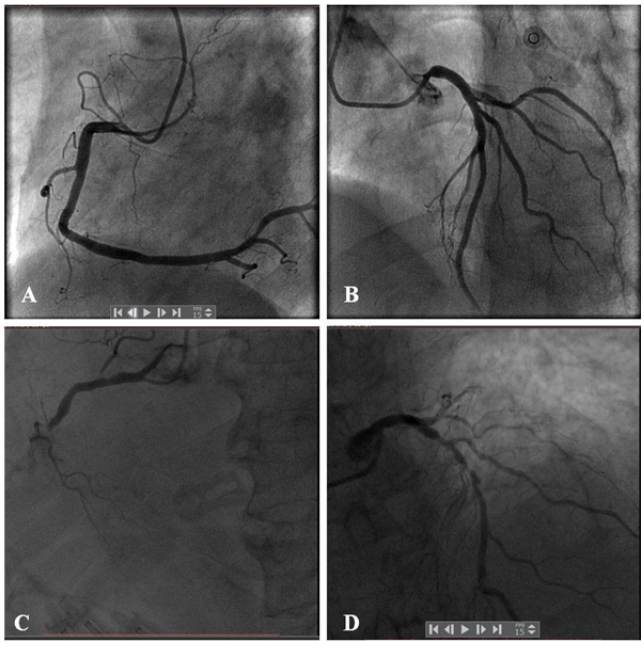

Figure 1 – *SXscore of coronary artery based on CAG. Representative CAGs of a patient with SXlow (SXscore = 2; A–B) and a patient with SXhigh (SXscore = 38; C–D).*

Statistical analysis

Baseline descriptive statistics are presented as frequencies and percentages for categorical variables and mean ± standard deviation (SD) and median (interquartile range [IQR]) for continuous variables. The normality of data was assessed using the Skewness and Kurtosis normality test. Differences between the study groups were assessed by chi-square test or Fisher's exact test for categorical data, and by student's t test for continuous data. We used student's t test to compare the groups' means when variables were normally distributed, and a non-parametric test when they were not normally distributed. Chi-square or Fisher's exact test were used to examine differences for categorical measures. We assessed the relationships between chemotherapy and CAD complexity by logistic-regression analysis, adjusting related covariates that included age, gender, BMI, smoking, family history of CVDs, hypertension, diabetes and hyperlipidemia. Odds ratios (ORs) and 95% confidence intervals [CIs] were calculated. P values were 2-tailed, and we set the level of significance at 0.05. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Patient characteristics

A total of 94 patients who had previously had lung cancer and who underwent CAG at Chinese PLA General Hospital, between 2010 and 2017, were included in the study. Out of these, 73 were males and 21 females (M:F = 3.48). Eighty-five patients were diagnosed with non-small cell lung cancer, and the other 9 patients with small cell lung cancer. Thirty-six patients had histories of chemotherapy. Among the patients with chemotherapy, 28 patients received platinum-based regimens. Platinum-based regimens combining gemcitabine or docetaxel, and other agents, were used in non-small cell lung cancer patients, and double-platinum chemotherapy combined with etoposide was used in small cell lung cancer patients. One patient received anthracycline (pharmorubicin), which is known to have cardiac toxicity. Five patients received tyrosine kinase inhibitors (gefitinib). Three patients lacked detailed information about chemotherapy regimens. Fifty-eight patients did not receive any chemotherapy.

There were no significant differences regarding conventional CAD risk factors (hypertension, hyperlipidemia, diabetes or smoking history) between the chemotherapy and non-chemotherapy groups. In the chemotherapy group, more patients took radiotherapy than in the non-chemotherapy group ($p < 0.0001$). The time interval range from cancer diagnosis to CAG was discrepant between the two groups. Patient characteristics are listed in Table 1.

Analysis of association between chemotherapy and high SXscore

Patients who underwent chemotherapy developed more-severe anatomical CAD than those who did not undergo chemotherapy. The SXscore was significantly higher in the chemotherapy group than in the non-chemotherapy group (25.25,IQR [4.50–30.00] vs. 16.50, IQR[5.00–22.00]; $p = 0.0195$). According to the SXscore grade definition, the percentage of SXhigh was significantly higher in the chemotherapy group than in the non-chemotherapy group (58.33% vs. 25.86%; $p = 0.0016$). Details are shown in Table 2.

Radiotherapy is another important treatment for lung cancer. In our study, the SXscore was higher in the radiotherapy group than in the non-radiotherapy group (22.00, IQR[5.00–30.00] vs. 19.00, IQR[5.00–25.00]; $p = 0.3045$). The percentage of SXhigh was higher in the radiotherapy group than in the non-radiotherapy group (52.38% vs. 34.25%; $p = 0.1319$). However, there was no significant difference for either SXscore or SXhigh rates between the radiotherapy and non-radiotherapy groups. Compared with radiotherapy, chemotherapy showed worse effects on anatomical abnormalities of coronary arteries among lung cancer patients. Results are presented in Table 2.

Univariate logistic-regression analysis showed that chemotherapy significantly increased the SXhigh rate by 4.013 times (95% CI:1.655–9.731). The OR of radiotherapy for SXhigh was 2.112 (95% CI: 0.790–5.646), which showed no obvious statistical significance. Smoking as a conventional cardiovascular risk factor was shown to significantly increase the SXhigh rate by 3.182 times (95% CI:1.327–7.628). The ORs of other cardiovascular risk factors for SXhigh were >1, but showed no obvious statistical significance. In multivariate logistic-regression analysis, chemotherapy was shown to increase the risk of CAD with more-severe anatomical abnormalities by 5.868 times (95% CI: 1.778-19.367). The ORs of radiotherapy and smoking for SXhigh were 1.124 (95% CI: 0.286–4.416) and 3.035 (95% CI: 1.036–8.893), respectively. Results are shown in Table 3.

In multivariate stepwise logistic regression adjusted for related CAD risk factors (age, gender, BMI, smoking, family history of CVDs, hypertension, diabetes and hyperlipidemia) and lung cancer–related risk factors (history of radiotherapy and chemotherapy), chemotherapy as a whole and smoking were shown to significantly increase the SXhigh rate by 5.323 times (95% CI: 2.002–14.152) and by 3.646 times (95% CI: 1.374–9.678), respectively. Moreover, we detected that the effects of platinum-based regimen on anatomical CAD were similar: the OR of platinum-based regimen was 5.850 (95% CI: 2.027–16.879), and the OR of smoking was 3.670 (95% CI: 1.303–10339). Results are shown in Table 4.

Discussion

To the best of our knowledge, this study is the first to quantitatively demonstrate that chemotherapy is related to anatomical complexity and severity of CAD among lung cancer patients, using SXscore based on coronary angiograms.

Antineoplastic therapy is frequently hindered by the development of cardiovascular complications such as heart failure, myocardial infarction, hypertension, thromboembolism, QT prolongation and bradycardia.[23] Until now, the most often reported chemotherapy-induced heart conditions have been cardiac dysfunction and heart failure, as evaluated by echocardiography.[1,24,25] Chemotherapy-related coronary-artery events are becoming important clinical problems among the cancer population who received

Table 1 – Patient characteristics stratified by history of chemotherapy

Characteristic	Chemotherapy group (n = 36)	Non-chemotherapy group (n = 58)	p value
Gender			0.6257
Male	27 (75.00%)	46 (79.31%)	
Female	9 (25.00%)	12 (20.69%)	
Age at CAG (years)			0,077
<60	3 (8,33%)	13 (22,41%)	
≥60	33 (91.67%)	45 (77,59%)	
Interval time from cancer diagnosis to CAG (years)			0.000
≤2	17 (47.22%)	48 (82.76%)	
>2	19 (52.78%)	10 (17.24%)	
Types of lung cancer			0.081
Non-small cell lung cancer	30 (83.33%)	55 (94.83%)	
Small cell lung cancer	6 (16.67%)	3 (5.17%)	
Regimens of chemotherapy			NA
Platinum +	28 (77.78%)	--	
Tyrosine kinase inhibitors only	5 (13.89%)	--	
Not-verified regimens	3(8.33%)	--	
Radiotherapy			<0.0001
No	19 (52.78%)	54 (93.10%)	
Yes	17 (47.22%)	4 (6.90%)	
BMI	24.81 ± 2.89	25.32 ± 2.79	0.3944
Hypertension			
No	12 (34.29%)	27 (46.55%)	
Yes	23 (65.71%)	31 (53.45%)	
Diabetes			0.9343
No	28 (80.00%)	46 (80.70%)	
Yes	7 (20.00%)	11 (19.30%)	
Hyperlipidemia			0.5157
No	29 (82.86%)	50 (87.72%)	
Yes	6 (17.14%)	7 (12.28%)	
Smoking			0.8938
No	18 (51.43%)	29 (50.00%)	
Yes	17 (48.57%)	29 (50.00%)	
Alcohol consumption			0.1640
No	45 (73.77%)	56 (62.92%)	
Yes	16 (26.23%)	33 (37.08%)	
Cholesterol	4.15 ± 1.08	4.25 ± 1.10	0.6896
Triglyceride	1.38 ± 0.71	1.49 ± 0.99	0.7905
Low-density lipoprotein cholesterol	2.58 ± 0.96	2.48 ± 0.88	0.6999
High-density lipoprotein cholesterol	1.17 ± 0.34	1.33 ± 0.87	0.8345

BMI: body mass index; CAG: coronary angiography.

Table 2 – SXscore and SXscore grades in lung cancer patients stratified by chemotherapy or radiotherapy

Variables	Statistical variable	Chemotherapy stratification			Radiotherapy stratification		
		Chemotherapy group	Non-chemotherapy group (n = 58)	p value	Radiotherapy group (n = 21)	Non-radiotherapy group (n = 73)	p value
SXscore							0.3045
	Mean ± SD	20.00 ± 12.70	14.96 ± 10.47	0.0195	18.67 ± 12.58	16.38 ± 11.31	
	Median	25.25	16.50		22.00	19.00	
	Q1–Q3	4.50–30.00	5.00–22.00		5.00–30.00	5.00–25.00	
	Min–max	0.00–38.00	0.00–38.00		1.00–35.50	0.00–38.00	
SXscore grade				0.0016			0.1319
SXlow (<22)	N (%)	15 (41.67%)	43 (74.14%)		10 (47.62%)	48 (65.75%)	
SXhigh (≥22)	N (%)	21 (58.33%)	15 (25.86%)		11 (52.38%)	25 (34.25%)	

chemotherapy.[5-7] Acute coronary-artery events that occurred shortly after administration of chemotherapeutic agents were reported.[3,8] Haugnes et al.[26] showed a 5.7-fold higher risk of CAD and a 3.1-fold higher risk of myocardial infarction with cisplatin-based regimens compared with surgery alone, in a median observation time of 19 years.[26] The present study investigated the association between chemotherapy and anatomical abnormalities of coronary arteries among lung cancer patients.

Lung cancer is the most common incident cancer and the leading cause of cancer death.[9] The study assessed anatomical abnormalities of coronary arteries by the SXscore and investigated the relationship between chemotherapy and anatomical complexity of CAD among lung cancer patients. Results showed that both SXscore and SXhigh rates were significantly greater in patients who underwent chemotherapy compared with patients who did not. Multivariate stepwise logistic-regression analysis showed that the risk of more severe anatomical CAD is increased by chemotherapy as a whole by 5.323 times, and by platinum-based regimens by 5.850 times. The results indicate that chemotherapy is associated with the anatomical complexity and severity of CAD, which may at least partly explain the long-term higher morbidity of chemotherapy-related CAD, including myocardial infarction.[26] To our knowledge, no similar large study has quantitatively detected the association between chemotherapy and anatomical complexity and severity of CAD among lung cancer patients.

Although chemotherapy-related CAD is becoming an emerging issue, the underlying mechanism of chemotherapy-related CAD remains unclea. Acute coronary-artery events that occurred shortly after administration of chemotherapeutic agents were possibly due to acute thrombosis or vasospasm.[3,8] Our study indicated that long-term chemotherapy-related coronary events may be due to more severe anatomical abnormalities induced by chemotherapeutic agents. In the present study, about 90% of the study patients are non-small cell lung cancer patients, and the others are small cell lung cancer patients. Most of chemotherapy regimens for the study patients involved more than one chemotherapeutic agent, most of which contained platinum. In fact, platinum was the base of chemotherapy for most of the patients. In the study, five patients received gefitinib and one patient received anthracycline, which is known to have cardiac toxicity. It is reasonable to determine that endothelial cells play an important role during the pathogenesis of chronic anatomical CAD. Besides, chemotherapeutic agents-induced endothelial injuries might be the core cause of chemotherapy-related CAD. Each study patient took various chemotherapeutic agents. Thus, it was difficult to infer which played the most important role in the progress of chemotherapy-related CAD. Since platinum is the most used agent, it may be one of the most important agents to be further studied for illustrating the underlying mechanisms of chemotherapy-related CAD.

Radiotherapy plays a major role in the management of lung cancer.[27] Previous studies have shown the effect of radiation on heart diseases.[20,28-30] In the present study, both the SXscore and the SXhigh percentage were greater in the radiotherapy group in relation to the non-radiotherapy group. Nevertheless, no significant differences were observed between the two groups. In logistic-regression analysis, the OR of radiotherapy for the SXhigh was 2.112 (95% CI: 0.790–5.646), which means that radiotherapy is likely to increase the anatomical complexity of coronary arteries. However, the results could not show significant differences. The ambiguous results may be due to the smaller sample of patients receiving radiotherapy in the study population. Based on the results mentioned, we could say that chemotherapy may play a more important role than is currently thought in terms of CAD. However, it was not possible to determine that chemotherapy is worse than radiotherapy in terms of CAD, particularly due to the small sample and the lack of enough individual data for each chemotherapeutic agent. Still, we believe the results are interesting and deserve further study.

Heart disease manifesting after cancer may be due to several mechanisms: shared cardiovascular risks between cancer and cardiovascular disease, inflammatory states associated with malignancies and/or cardiotoxic effects of cancer therapy. Age, gender, tobacco use, family history of CAD, hypertension, type II diabetes and hyperlipidemia are the well-known risk factors for CAD.[31-35] Smoking is a well-known common risk factor for both CAD and lung cancer. In

Table 3 – Logistic-regression analysis for anatomical severity of the coronary artery in lung cancer patients

Variable	Univariate model		Multivariate model	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)		0.9427		0.642
<60	Ref		Ref	
≥60	1.042 (0.343–3.161)		0.723 (0.184–2.840)	
Gender		0.1278		0.362
Female	Ref		Ref	
Male	2.326 (0.781–7.140)		1.856 (0.490–7.021)	
BMI		0.4538		0.428
<25	Ref		Ref	
≥25	1.376 (0.597–3.168)		1.528 (0.536–4.355)	
Smoking		0.0095		0.043
No	Ref		Ref	
Yes	3.182 (1.327–7.628)		3.035 (1.036–8.893)	
Family history of CAD		0.2467		0.659
No	Ref		Ref	
Yes	2.011 (0.617–6.563)		1.379 (0.331–5.754)	
Hypertension		0.9667		0.748
No	Ref		Ref	
Yes	1.018 (0.437–2.372)		1.180 (0.431–3.234)	
Type II diabetes		0.5338		0.501
No	Ref		Ref	
Yes	1.393 (0.491–3.953)		1.561 (0.426–5.721)	
Hyperlipidemia		0.9732		0.616
No	Ref		Ref	
Yes	1.021 (0.306–3.410)		0.677 (0.147–3.118)	
Interval time from cancer diagnosis to CAG (years)		0.2914		0.899
≤2	Ref		Ref	
>2	1.484 (0.609–3.617)		1.075 (0.350–3.301)	
Radiotherapy		0.136		0.867
No	Ref		Ref	
Yes	2.112 (0.790–5.646)		1.124 (0.286–4.416)	
Chemotherapy		0.0021		0.004
No	Ref		Ref	
Yes	4.013 (1.655–9.731)		5.868 (1.778–19.367)	

BMI: body mass index; CAD: coronary artery disease; CAG: coronary angiography.

Table 4 – Multivariate stepwise logistic-regression model for anatomical severity of the coronary artery among lung cancer patients

Variables	OR	95% CI	p value
Total patients (n=94)			
Smoking	3.646	1.374-9.678	0.009
Chemotherapy	5.323	2.002-14.152	0.001
Patients except with TKI or NVR (n=86)			
Smoking	3.670	1.303-10.339	0.14
Chemotherapy	5.850	2.027-16.879	0.007

TKI: Tyrosine kinase inhibitors; NVR: Not verified regimens

our study, half of lung cancer patients were smokers, which is consistent with national data, showing that about 57% of lung cancer diagnosed patients were either current or former smokers.[36] In the study, other cardiovascular risk factors have shown to be likely to increase the severity of CAD. However, those risk factors did not show obvious statistical significance for increasing the SXscore. On the other hand, smoking showed a more significant effect, by increasing the risk for SXhigh by 3.646 times.

Moreover, the length of time of lung cancer may play a role in the progression of CAD. In the study, we collected the data on the time interval between cancer diagnosis and CAG. Although the time interval between cancer diagnosis and CAG was discrepant between the two groups (possibly because this is a small retrospective study), the multivariate logistic analysis, adjusted for the time interval variable, showed a significant difference regarding CAD severity between patients with chemotherapy and those without chemotherapy.

Our study has several limitations. First, it was a small sample single-center study, performed among a specific population of patients, who had had lung cancers and who required CAG due to suspected severe CAD. A lower number of patients received radiotherapy: among the 94 study patients, 21 used to receive radiotherapy. In particular, only 4 patients (6.9%) had a history of radiotherapy in the non-chemotherapy group. Therefore, the results from this specific small sample may be deviant. Second, it was a retrospective study, thus some valuable information on the study patients might be lacking. For instance, it would be helpful to know the stage of lung cancer at initial presentation, since those who received chemotherapy could have had more advanced disease and, consequently, more inflammation for a longer period of time, which may promote atherosclerosis and contribute to the results observed. However, we were not able to obtain such comprehensive information on the patients. Third, we did not investigate whether the SXscore was associated with long-term cardiovascular events in the study patients. Additional prospective, large-scale clinical studies may be required to verify the effect of chemotherapy on the anatomical abnormality of CAD and the underlying mechanisms of chemotherapy-related CAD.

Conclusions

In brief, the present study demonstrates that chemotherapy is associated with long-term anatomical complexity and CAD severity. The results could partly explain why cancer patients with a history of chemotherapy are at higher risk of suffering coronary events compared to those with no history of chemotherapy. However, due to the limitations mentioned, a large-scale prospective study, as well as further pathophysiological and molecular researches, are needed to further illustrate the association between chemotherapy and CAD, and the underlying mechanisms of chemotherapy-related CAD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conception and design of the research: Chen Y, Hu S; Acquisition of data: Yang Q, Gao H, Zhang M, Jing J, Zhu P; Analysis and interpretation of the data: Yang Q, Gao H, Zhang J, Zhou H, Hu S; Statistical analysis: Zhang J, Zhou H, Hu S; Obtaining financing: Hu S; Writing of the manuscript: Zhang J, Hu S; Critical revision of the manuscript for intellectual content: Yang Q, Chen Y, Hu S.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Chinese PLA General Hospital under the protocol number 52019-223-02. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin. 2016;66(4):309-25.
2. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23 Suppl 7:vii155-66.
3. Zerna C, Guenther M, Folprecht G, Puetz V. Acute ischaemic stroke and myocardial infarction after chemotherapy with vinorelbine for non-small cell lung cancer: a case report. J Chemother. 2017;29(1):49-53.
4. Suh KJ, Lee JY, Shin DY, Koh Y, Bang SM, Yoon SS, et al. Analysis of adverse events associated with dasatinib and nilotinib treatments in chronic-phase chronic myeloid leukemia patients outside clinical trials. Int J Hematol. 2017;106(2):229-39.
5. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 1. J Am Coll Cardiol .2017;70(20):2536-51.
6. Bertolini A, Flumanò M, Fusco O, Muffatti A, Scarinci A, Pontiggia G, et al. Acute cardiotoxicity during capecitabine treatment: a case report. Tumori. 2001;87(3):200-6.
7. Shoemaker L, Arora U, Rocha Lima C. 5-fluorouracil-induced coronary vasospasm. Cancer Control .2004;11(1):46-9.
8. Rao AS, Kumar R, Narayanan GS. A rare case of cisplatin-induced acute myocardial infarction in a patient receiving chemoradiation for lung cancer. J Cancer Res Ther. 2015;11(4):983-5.
9. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-32.
10. Pilkington G, Boland A, Brown T, Oyee J, Bagust A, Dickson R. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. Thorax. 2015;70(4):359-67.
11. Du L, Morgensztern D. Chemotherapy for Advanced-Stage Non-Small Cell Lung Cancer. Cancer J .2015;21(5):366-70.
12. Roy A, Khanna N, Senguttuvan NB. Rituximab-vincristine chemotherapy-induced acute anterior wall myocardial infarction with cardiogenic shock. Tex Heart Inst J. 2014;41(1):80-2.
13. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, et al. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. Int J Cardiol. 2009;135(1):60-5.
14. Ellis SG, Roubin GS, King SB, 3rd, Douglas JS, Jr., Weintraub WS, Thomas RG, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation .1988;77(2):372-9.
15. Ekici B, Kutuk U, Alhan A, Tore HF. The relationship between serum uric acid levels and angiographic severity of coronary heart disease. Kardiol Pol .2015;73(7):533-8.
16. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219-27.
17. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol. 2010;56(4):272-7.
18. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med. 2016;375(23):2223-35.
19. Girasis C, Garg S, Raber L, Sarno G, Morel MA, Garcia-Garcia HM, et al. SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. Eur Heart J. 2011;32(24):3115-27.
20. Hu S, Gao H, Zhang J, Han X, Yang Q, Zhang J, et al. Association between Radiotherapy and Anatomic Severity of Coronary Artery Disease: A Propensity Score Matching Comparison Among Adult-Onset Thoracic Cancer Survivors. Cardiology. 2018;140(4):239-46.
21. Reed GW, Rossi JE, Masri A, Griffin BP, Ellis SG, Kapadia SR, et al. Angiographic predictors of adverse outcomes after percutaneous coronary intervention in patients with radiation associated coronary artery disease. Catheter Cardiovasc Interv. 2019;94(3):E104-E110.
22. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med .2009;360(10):961-72.
23. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004;109(25):3122-31.
24. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013;31(33):4222-8.
25. Giza DE, Iliescu G, Hassan S, Marmagkiolis K, Iliescu C. Cancer as a Risk Factor for Cardiovascular Disease. Curr Oncol Rep. 2017;19(6):39.
26. Haugnes HS, Wethal T, Aass N, Dahl O, Klepp O, Langberg CW, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol. 2010;28(30):4649-57.
27. Rossi A, Tay R, Chiramel J, Prelaj A, Califano R. Current and future therapeutic approaches for the treatment of small cell lung cancer. Expert Rev Anticancer Ther. 2018;18(5):473-86.
28. Hu S, Chen Y, Li L, Chen J, Wu B, Zhou X, et al. Effects of adenovirus-mediated delivery of the human hepatocyte growth factor gene in experimental radiation-induced heart disease. Int J Radiat Oncol Biol Phys. 2009;75(5):1537-44.
29. Kupeli S, Hazirolan T, Varan A, Akata D, Alehan D, Hayran M, et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. J Clin Oncol. 2010;28(6):1025-30.
.30. van Rosendael AR, Daniels LA, Dimitriu-Leen AC, Smit JM, van Rosendael PJ, Schalij MJ, et al. Different manifestation of irradiation induced coronary artery disease detected with coronary computed tomography compared with matched non-irradiated controls. Radiother Oncol. 2017;125(1):55-61.
31. Brezinka V, Padmos I. Coronary heart disease risk factors in women. Eur Heart J. 1994;15(11):1571-84.
32. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152(1):56-64.
33. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355(8):763-78.
34. Barthelemy O, Jacqueminet S, Rouzet F, Isnard R, Bouzamondo A, Le Guludec D, et al. Intensive cardiovascular risk factors therapy and prevalence of silent myocardial ischaemia in patients with type 2 diabetes. Arch Cardiovasc Dis. 2008;101(9):539-46.
35. Jaumdally JR, Lip GY, Varma C. Traditional risk factors for coronary atherosclerosis in Indo Asians: the need for a reappraisal. Curr Pharm Des 2006;12(13):1611-21.
36. Li Y, Shi J, Yu S, Wang L, Liu J, Ren J, et al. Effect of socioeconomic status on stage at diagnosis of lung cancer in a hospital-based multicenter retrospective clinical epidemiological study in China, 2005-2014. Cancer Med 2017;6(10):2440-2452.

Original Article

Evaluating the Severity of Coronary Artery Disease in Patients Treated with Chemotherapy: The Further Need for Cardio-Oncology

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Short Editorial related to the article: Chemotherapy-Related Anatomical Coronary-Artery Disease in Lung Cancer Patients Evaluated by Coronary- Angiography SYNTAX Score

Cardiovascular toxicity related to cancer therapies has been recognized for years.[1] The number and types of toxicities have increased rapidly due to several factors including new and improved therapies and treatment regimens which have resulted in patients living longer. This is the basis for the burgeoning field of cardio-oncology to help identify cardiotoxicities and aim to minimize adverse outcomes.

Cardiomyopathies related to anthracyclines, which are typically irreversible, and trastuzumab, typically reversible, as well as more recently recognized cardiotoxicities including myocarditis related to immune checkpoint inhibitors have made the evaluation of concomitant cardiac disease critical in the care of patients being treated for cancer.[1,2] Coronary artery disease (CAD) is also a consequence of cancer therapies and adverse coronary events such as myocardial infarction and thrombosis can complicate treatment and result in poor outcomes. Thus, further understanding of the adverse effects of specific therapies is crucial to assessing patients' clinical statuses and making decisions on treatment strategies in order to maximize overall outcomes, both oncologic and cardiac. CAD and has been associated with radiation therapy.[3,4] The risk and anatomic severity of CAD related to radiotherapy treatment has been described.[5,6] In a study of 152 thoracic cancer survivors who underwent radiotherapy, the investigators observed that the study patients had higher SYNTAX scores and were at a higher risk of developing anatomically severe CAD, independent of chemotherapy.[6] While although CAD is known to be present in patients being treated with chemotherapy, independent of radiotherapy, the association between anatomic severity of CAD and chemotherapy is less well known.

Acute coronary syndromes, including coronary thrombosis, myocardial infarction, angina as well as vasospasm are known to be complications of several chemotherapy agents, which affects both short and long-term outcomes.[7] Traditional cardiovascular risk factors including hypertension, diabetes mellitus and tobacco abuse are present in patients with cancer and it has been suggested that pre-existing CAD increases the risk of developing treatment-related CAD.[8] Despite the effectiveness of chemotherapeutic agents against cancer, potential mechanisms leading to unintended cardiovascular events include endothelial dysfunction, platelet aggregation, reduced nitrous oxide levels, increased levels of reactive oxygen species and vasospasm.[9] However, the effect that different chemotherapy agents have in regards to the anatomic severity and complexity of CAD may further help to risk stratify patients undergoing chemotherapy in order to determine who may be at risk of adverse cardiac events and or who should have alterations in their treatment considered.

In this issue of *Arquivos Brasileiros de Cardiologia*, Yang et al.[10] investigated the association between chemotherapy and atherosclerotic anatomic abnormalities of coronary arteries, based on coronary angiography, in patients treated for lung cancer.[10] Their retrospective cross-sectional study group included 94 patients, 36 of whom received chemotherapy and the remaining did not. It should be noted that nearly half of those who received chemotherapy also had radiation therapy, whereas only 7% of those who did not have chemotherapy had radiation. The authors found that the severity of CAD, as assessed by the SYNTAX score, was higher in the chemotherapy group compared to the non-chemotherapy group. After univariate and multivariate analyses, they determined that chemotherapy increased the risk of a high SYNTAX score and chemotherapy increased the risk of more severe anatomical CAD by 5.323 times.

Patients in the cohort exhibited traditional CAD risk factors including older age, hypertension and tobacco abuse, however, only half smoked and approximately 20% had diabetes mellitus. There were no significant demographic differences between the chemotherapy and non-chemotherapy groups. Importantly, the authors reported the types of chemotherapy regimens the patients received. Platinum-based chemotherapies have been associated with up to a 1.5- to 7-fold higher long-term risk of CAD and myocardial infarction, however, the complexity of CAD is not well described.[7] In the population studied by Yang et al.[10] approximately 78% of patients were treated with platinum-based regimens. They observed an even greater risk of more severe anatomical CAD in this group. The authors conclude that chemotherapy is associated with anatomical complexity and severity of CAD and postulate that it might partly account for the higher risk of CAD among lung cancer patients. It is important to note that while although medical management should be the first treatment strategy employed for the treatment of CAD, invasive therapies are not prohibitive despite the presence of several comorbidities.

Keywords

Coronary Artery Disease/radiotherapy; Neoplasms; Cardiotoxicity; Survival Rate; Myocardial Infarction/complications; Thromboses/complications.

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Despite the presence of coagulopathies and thrombocytopenia which may be present in patients who receive chemotherapy, these should not be considered contraindications for invasive coronary therapies. It has been demonstrated that percutaneous coronary intervention (PCI) can be performed safely in patients with platelet counts greater than 30,000/mL after micropuncture access and achievement of careful hemostasis.[11] Thus, in patients with obstructive CAD, who fail medical therapy, a treatment strategy of PCI with drug-eluting stent placement with the least length of required dual antiplatelet therapy should still be considered.[12]

The limitations of the study are fairly described by the investigators. The sample was small, and this was a single-center retrospective study, performed among a specific population of patients, who had had lung cancer and underwent coronary angiography for suspicion of CAD. A lower number of patients received radiotherapy in the non-chemotherapy group. Half of the patients in the chemotherapy group also received radiation therapy, thus potentially amplifying the effect on the coronary arteries. As noted, it would be helpful to know the stage of lung cancer at initial presentation, since those who received chemotherapy could have had more advanced disease and, consequently, more inflammation for a longer period of time, which may promote atherosclerosis and contribute to the results observed. Additionally, the correlation between anatomical severity of CAD and long-term clinical cardiovascular events was not assessed. The future assessment of outcomes is important to determine if the presence of more complex CAD portends worse prognosis in this group of patients. Thus, understanding not only the association, but also the effect of chemotherapy on anatomical severity of CAD is important when both planning and monitoring a patient's treatment strategy.

Yang et al.[10] took the next step in understanding the significance of CAD in patients treated with chemotherapy by evaluating the severity and complexity of CAD. This highlights the growing need for the field of cardio-oncology to investigate the cardiovascular effects and outcomes in patients who have and are treated for cancer. In order to hopefully minimize unanticipated cardiac events, further investigations of this topic evaluating the many classes of chemotherapeutic agents and different types of cancer are important to our understanding of how best to treat patients and prevent adverse cardiovascular events. Monitoring of clinical outcomes and CAD assessment during future prospective clinical studies are necessary to validate the effect of chemotherapy on the anatomical severity and underlying mechanisms of CAD in patients treated for cancer.

References

1. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med. 2016;375(15):1457-67.
2. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018;19(9):e447-e58.
3. Filopei J, Frishman W. Radiation-induced heart disease. Cardiol Rev. 2012;20(4):184-8.
4. Halle M, Gabrielsen A, Paulsson-Berne G, Gahm C, Agardh HE, Farnebo F, et al. Sustained inflammation due to nuclear factor-kappa B activation in irradiated human arteries. J Am Coll Cardiol. 2010;55(12):1227-36.
5. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013;61(23):2319-28.
6. Hu S, Gao H, Zhang J, Han X, Yang Q, Zhang J, et al. Association between radiotherapy and anatomic severity of coronary artery disease: a propensity score matching comparison among adult-onset thoracic cancer survivors. Cardiology. 2018;140(4):239-46.
7. Iliescu CA, Grines CL, Herrmann J, Yang EH, Cilingiroglu M, Charitakis K, et al. SCAI Expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the cardiological society of india, and sociedad Latino Americana de Cardiologia intervencionista). Catheter Cardiovasc Interv. 2016;87(5):E202-23.
8. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-801.
9. Hassan SA, Palaskas N, Kim P, Iliescu C, Lopez-Mattei J, Mouhayar E, et al. Chemotherapeutic agents and the risk of ischemia and arterial thrombosis. Curr Atheroscler Rep. 2018;20(2):10.
10. Yang Q, Chen Y, Gao H, Zhang J, Zhang J, Zhang M, et al. Chemotherapy-related anatomical coronary-artery disease in lung cancer patients evaluated by coronary-angiography SYNTAX score. Arq Bras Cardiol. 2020; 114(6):1004-1012.
11. Iliescu C, Durand JB, Kroll M. Cardiovascular interventions in thrombocytopenic cancer patients. Tex Heart Inst J. 2011;38(3):259-60.
12. Giza DE, Marmagkiolis K, Mouhayar E, Durand JB, Iliescu C. management of CAD in patients with active cancer: the interventional cardiologists' perspective. Curr Cardiol Rep. 2017;19(6):56.

Catheter Ablation for Treatment of Atrial Fibrillation and Supraventricular Arrhythmias Without Fluoroscopy Use: Acute Efficacy and Safety

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Abstract

Background: **The use of ionizing radiation in medical procedures is associated with significant health risks for patients and the health care team.**

Objectives: **Evaluate the safety and acute efficacy of ablation for atrial fibrillation (AF) and supraventricular arrhythmias (SVTs) using an exclusively non-fluoroscopic approach guided by intracardiac echo (ICE) and 3D-mapping.**

Methods: **95 pts (mean age 60 ± 18 years, 61% male) scheduled for AF Ablation (69 pts, 45 paroxysmal AF and 24 persistent AF) or non-AF SVT (26 pts – 14 AV node reentry, 6 WPW, 5 right atrial (RA) flutters, 1 atrial tachycardia) underwent zero fluoro procedures. Nine patients (9.5%) had permanent pacemakers or defibrillator resynchronization (CRT-D) devices. Both CARTO (65%) and NAVx (35%) mapping systems were used, as well as Acunav and ViewFlex ICE catheters.**

Results: **Pulmonary vein isolation (PVI), as well as all other targets that needed ablation in both atria were reached and adequately visualized. No pericardial effusions, thrombotic complications or other difficulties were seen in these series. Difficult transseptal puncture (19 patients - 20%) was managed without fluoroscopy in all cases. No backup fluoroscopy was used, and no lead apparel was needed. Pacemaker interrogations after the procedure did not show any lead damage, dislocation, or threshold changes.**

Conclusions: **A radiation-free (fluoroless) catheter ablation strategy for AF and other atrial arrhythmias is acutely safe and effective when guided by adequate ICE and 3D-mapping utilization. Multiple different bi-atrial sites were reached and adequately ablated without the need for backup fluoroscopy. No complications were seen. (Arq Bras Cardiol. 2020; 114(6):1015-1026)**

Keywords: **Arrhythmias, Cardiac; Atrial, Fibrillation; Catheter Ablation; Fluoroscopy; radiation; Efficacy; Safety.**

Introduction

Catheter ablation is currently the most effective treatment for atrial fibrillation AF,[1,2] Atrial flutter, and supraventricular tachycardias (SVTs). It is widely performed in various centers around the world, giving the increasing prevalence of AF in the population and the modest response to anti-arrhythmic medications.

As with most percutaneous cardiac procedures, fluoroscopy has been a primary imaging modality to manipulate catheters in the vascular space and cardiac chambers. However, ionizing radiation has multiple potential deleterious effects for both patients and the healthcare team.[3-6] These effects are cumulative, and all of us are continuously exposed nowadays due to high usage in diagnostic and therapeutic imaging modalities.[7]

In that regard, the **ALARA** (**A**s **L**ow **A**s **R**easonably **A**chievable) principle has been proposed to minimize radiation use to the minimum needed to meet the objective.[3] In recent years, several efforts have succeeded in reducing radiation exposure during catheter ablation procedures, including a reduction in fluoroscopy times and doses,[8,9] better shielding, and especially regarding other non-fluoroscopic imaging modalities – namely 3D electroanatomical systems (EA) and intracardiac echocardiography (ICE).

Those fluoroscopy reduction tools have been increasingly used in the electrophysiology (EP) lab over the years, so that it became possible to guide the entire ablation procedure and thus avoid the use of X-ray[10] entirely. First reported about 10 years ago,[11-13] those Zero-Fluoro techniques are gaining popularity in the EP community, as they are as safe and as effective as the ones guided by fluoroscopy.[14-16]

Objectives

The purpose of this study was to demonstrate the feasibility and safety of catheter ablation of atrial fibrillation, atrial flutter, and supraventricular tachycardias without the use of fluoroscopy, using exclusively electroanatomic mapping and intracardiac echocardiography in a series of 95 consecutive patients in a single center.

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Methods

Description of the technique

All procedures were performed under general anesthesia, and venous access was obtained using ultrasound guidance, according to the specific need of the procedure, but generally consisted of two or three right femoral vein punctures, one left femoral vein puncture (for the ICE catheter), and one internal jugular vein puncture (in atrial fibrillation cases, for coronary sinus duodecapolar catheter placing). Monitoring during the procedure included 12-lead electrocardiogram and EA mapping cutaneous patches (Ensite NavX - St. Jude Medical, St. Paul, MN, USA or CARTO 3 – Biosense Webster Inc., Diamond Bar, CA, USA).

Navigation through the intravascular space

From the left femoral vein, an ICE catheter (ViewFlex Xtra – Abbott or Acunav – Biosense Webster) was advanced to the right atrium (RA), guided by visualization of echo-free spaces in the vascular system.

The ICE catheter was advanced through the left iliac vein while keeping an "echo-free space" close to the near-field of the ultrasound image (representing an absence of tissue contact at the tip of the ICE catheter). This technique allows the operator to discriminate between a free-advancement of the ICE catheter tip through the vascular lumen when echo-free space is visible and a palpable resistance to advancement when this image pattern is not obtained.

Whenever the path to the inferior vena cava was not so clear, a retained guidewire technique, using long wires from the left femoral vein allowed advancing the ICE catheter following a clear wire image in the lumen. That is of particular value in patients with thin iliac veins, where echo-free space is not very clear.

Upon reaching the inferior vena cava, it is possible to identify the cavoatrial junction where, at the level of the liver, and a parenchymatous image with clearly visible intrahepatic veins is appreciated. At this moment, it is essential to identify and avoid the inadvertent progression of the ICE catheter through the hepatic veins and correctly direct it to the right atrium (RA), which can be done with gentle anterior deflection. Once in the RA, all standard views can be obtained using the conventional technique of clockwise or counterclockwise torque from the home view. The catheter is then prolapsed to the right ventricle using anterior deflection, while keeping the tricuspid valve visible, and sectional views of the pericardial space were obtained to rule out any baseline pericardial effusion. Back to the RA, a posterior deflection with a gentle clockwise torque allows a longitudinal view of the superior vena cava (SVC). This view allows adequate visualization of catheters coming from superior veins and is the standard view to start advancing transseptal guidewires and sheaths (figure 1).

A long guidewire was then inserted through the right femoral vein, and smooth progression to the SVC was confirmed by ICE imaging. It is possible to visualize the right atrial appendage near the SVC ostium, and the inadvertent misplacement of the guidewire in this structure can then be avoided. A long transeptal sheath was advanced over the wire and placed in the SVC (using ICE, one can see the sheath itself "covering" the guidewire, while the distal, unsheathed part of the guidewire remains bright).

When multipolar catheters are inserted through the femoral veins using short sheaths, it is possible to see catheter advancement using EA mapping and ICE image, until electrical potentials appear in the distal poles, confirming "arrival" at the RA.

Catheter positioning

When the CARTO system was used, an irrigated ablation catheter with contact force sensor was then advanced under EA and ICE visualization and a limited right atrial map was constructed, mostly to create a matrix (allowing other catheters to be visualized in EA maps) and to delineate the septum and coronary sinus (CS) anatomy (video 1). This step is not needed when the NAVx system is used, where any catheter can be visualized without the need for matrix creation. The CS was then cannulated with the multipolar catheter, under EA and ICE visualization (ICE can clearly visualize the proximal CS and the ostium, as well as the catheter going in). The progression of these multipolar catheters was monitored and confirmed using EA mapping (if the catheter is coming from the femoral vein, the inferior vena cava geometry is created) or ICE imaging (if the catheter is coming from the internal jugular vein, it can be clearly seen coming from the SVC). If a duodecapolar catheter was used, the distal 10 poles were placed in the CS and the proximal poles in the RA. A quadripolar catheter was placed in the RV using the same technique.

AF Cases

In AF cases, once a limited RA geometry was created (CARTO system only), two guidewires were inserted from the right femoral vein and advanced to the SVC, with adequate positioning being visualized on ICE. Two long transseptal sheaths (fixed curve and deflectable) were advanced over the wire to the SVC. Importantly, heparin was given as soon peripheral access was obtained, before any catheter insertion, aiming at an activated clotting time (ACT) > 350s. Those levels were maintained until left atrial instrumentation ended by continuous infusion and rebolus as needed.

Two transseptal punctures were separately performed under ICE visualization, coming down to the septum from the SVC (figure 1 and video 2). After each septal perforation, a guidewire was advanced to the left superior pulmonary vein (PV), thus allowing for safe passage over the wire sheath positioning in the left atrial (LA) cavity. The ablation catheter and a multipolar mapping catheter were then positioned in the PVs. All these steps were clearly visualized on ICE, which could also be placed in the LA cavity through one of the transseptal accesses for a very high definition visualization (done in the last 15 cases of these series). A multipolar esophageal catheter was placed, and its position guided by ICE visualization.

The LA and PV anatomies were reconstructed with a high-density map using the multipolar catheter (video 3). In particular, the ridge between the left superior PV and left atrial

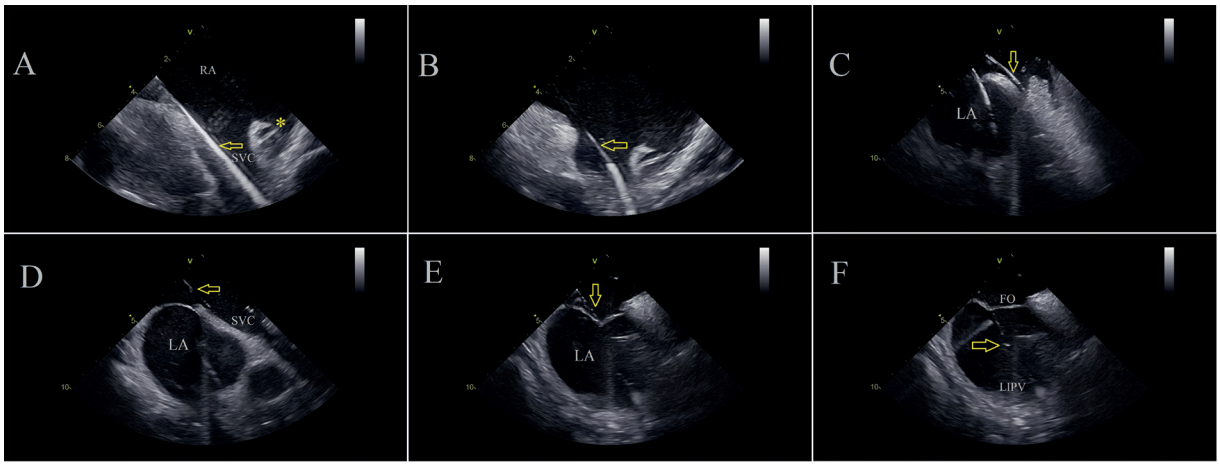
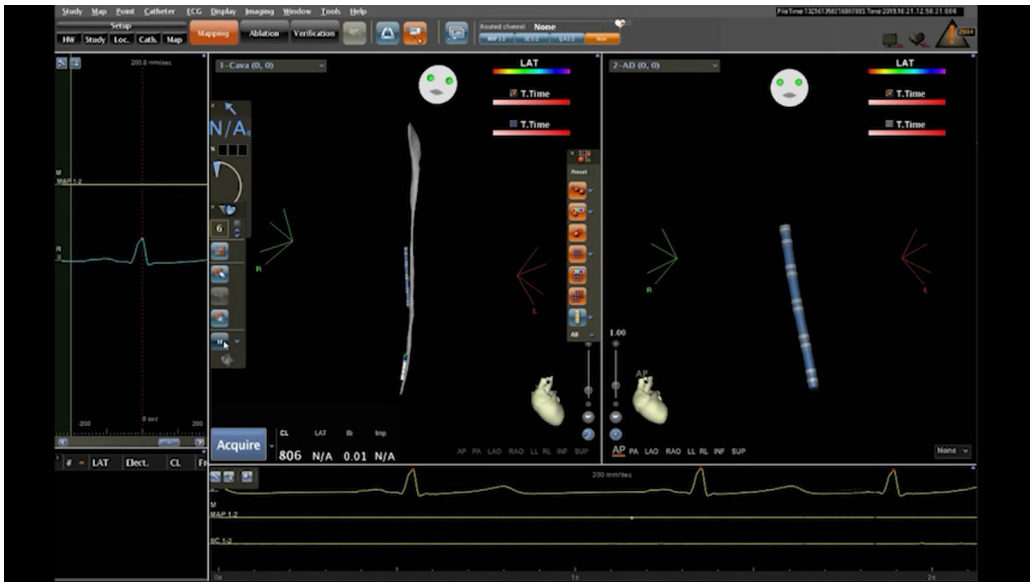


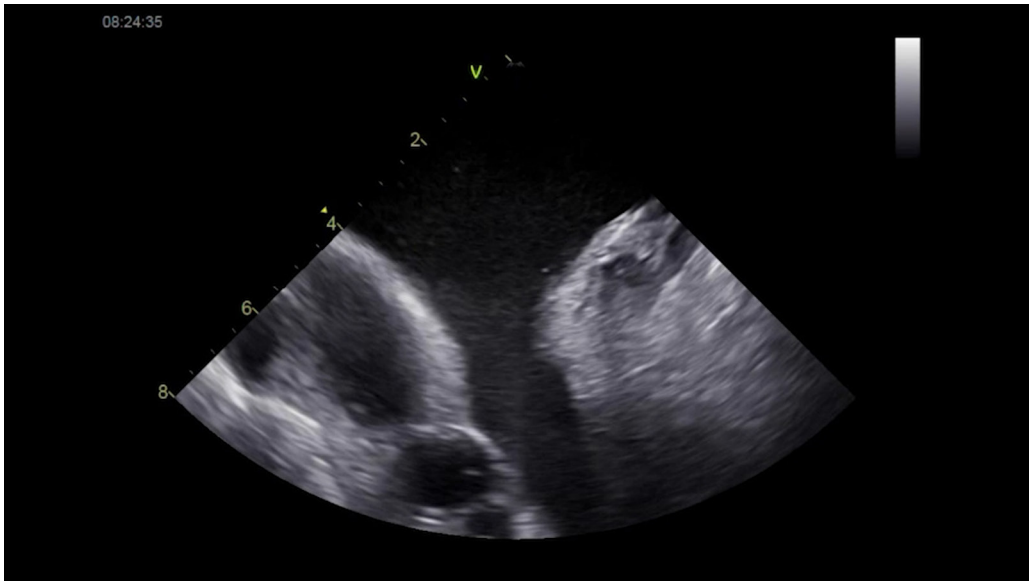
Figure 1 – *ICE imaging sequence showing the steps for the zero-fluoro double transseptal puncture. A) A guidewire (arrow) is advanced to the superior vena cava (SVC); in the picture, the right atrium (RA) is also visualized, as well as the right atrial appendage (*), confirming correct wire positioning. B) A long transseptal sheath (arrow) is advanced over the wire to the SVC, erasing the brightness of the wire as it is advanced. C) The transseptal sheath + needle assembly (arrow) in the SVC, to be pulled down to the fossa ovalis. The left atrium (LA) is visualized, as well as a transseptal access that has been previously performed. D) Sheath + needle (arrow) pulldown along the septum on its way to the fossa ovalis. E) Sheath + needle tenting the fossa ovalis (arrow), confirming adequate positioning to provide access to the LA. F) Puncture of the fossa ovalis (FO) and needle enhancement visualized in the LA cavity (arrow). The transseptal puncture is performed in a posterior location, confirmed by visualization of the left inferior PV (LIPV) in the ultrasound plane.*



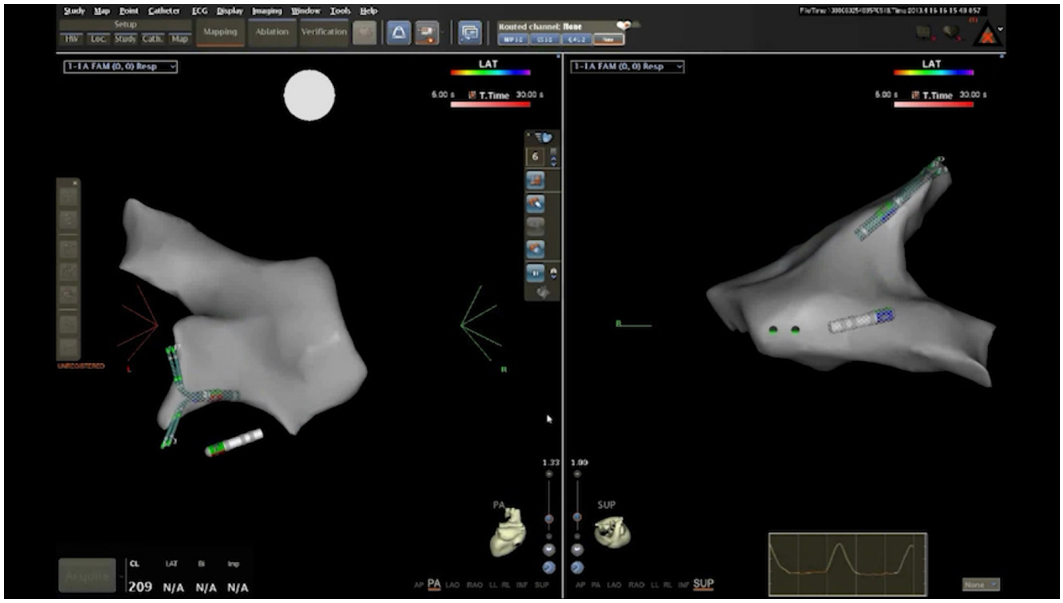
Video 1 – *Catheter insertion from the femoral access to the RA guided by the electroanatomic mapping system. After the catheters arrive in the RA (decapolar catheter followed by the ablation catheter [RF]), marked by the appearance of electrograms, the RA anatomy is created, followed by cannulation of the coronary sinus (CS) – first by the RF catheter and followed by the decapolar one.*
Access the video here: https://bit.ly/2XWhIbE.

appendage was visualized on ICE (with the catheter placed in the right ventricle or in the LA cavity itself – figure 2) and its position manually annotated in the EA map. After calibrating the contact sensor, point-by-point circumferential PV isolation was performed for both pairs of veins (figure 3 and video 4), using 40W of maximal power and contact force between 10-20g. Whenever esophageal temperature rose in the posterior segments, shorter (5-10 seconds) RF applications and/or lower power (25-30W) were used. Adenosine challenge (18 mg) was used to confirmed PV isolation without dormant conduction.

High-dose Isoproterenol infusion at a rate of 20 mcg/10 min was performed in search of inducible extra-pulmonary foci,



Video 2 – *Zero-fluoro transseptal puncture. After the ICE catheter is positioned in the RA, the LA and SVC are visualized. The guidewire arrives in the SVC, followed by sheath advancement. Sheath position in the SVC is confirmed by saline injection, showing craniocaudal flow. Septal tenting and perforation are shown, followed by wire advancement to the left PV. The sheath is then confirmed in the LA cavity by saline bubble visualization. The second transseptal sheath is then pulled down from the SVC to the septum, followed by a second septal perforation. Access the video here: https://bit.ly/2XWhIbE.*



Video 3 – *High definition anatomic reconstruction of LA and PVs. With the multipolar mapping catheter, the anatomic acquisition is obtained by sequentially moving the mapping catheter, while the ablation catheter is parked in the mitral annulus. Two different views are shown (posterior and superior). Access the video here: https://bit.ly/2XWhIbE.*

which were ablated when present. In patients with documented typical atrial flutter, the ablation catheter was then pulled to the RA, and a linear, ICE guided lesion was performed in the cavotricuspid isthmus (CTI). Detailed ICE visualization was essential to avoid tangling the catheter with pacemaker leads, when present. In challenging anatomies (e.g., prominent Eustachian ridge or the presence of pouches), ICE is critical to ensure adequate tissue contact throughout the CTI.

Regaining access to the LA, whenever needed, was easily accomplished using previously tagged transeptal access sites in the EA map. During the procedure, to ensure safety, the ICE catheter was frequently prolapsed to the right ventricle

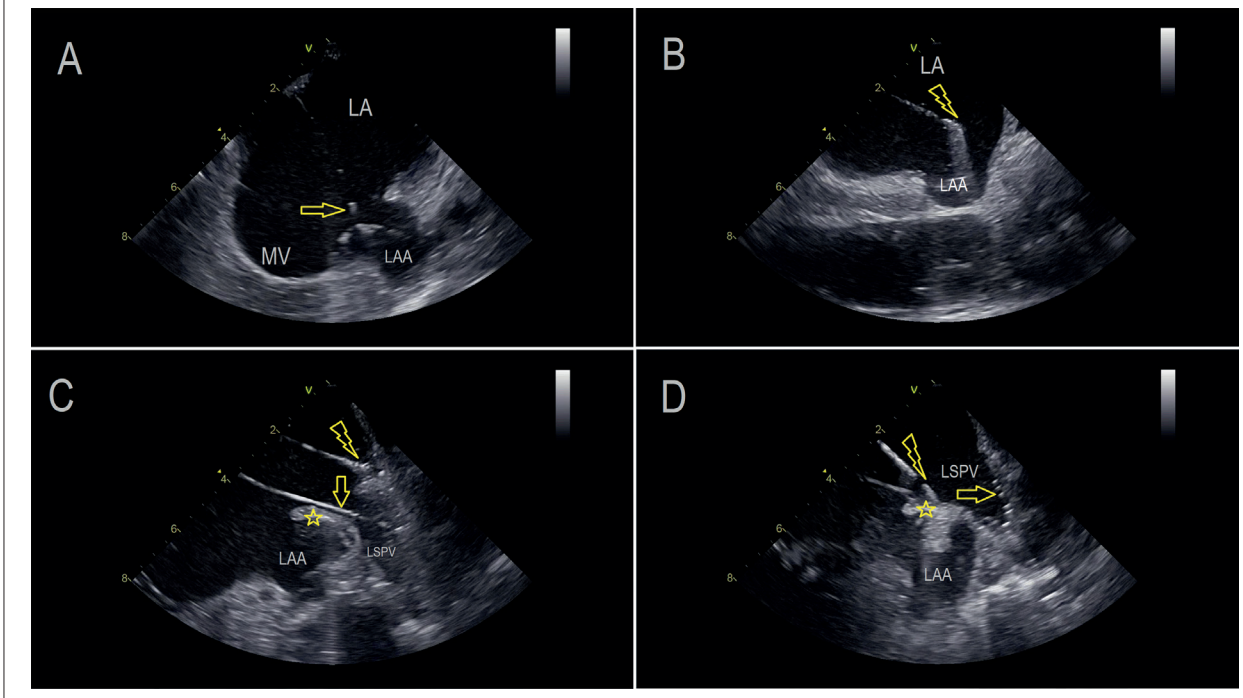


Figure 2 – *ICE imaging sequence examples of LA mapping and ablation. These were recorded after the ICE catheter was placed in the LA cavity across the septum. A) A multipolar high-density mapping catheter (Pentarray – Biosense Webster, marked by arrow) is collecting anatomic and electric data around the left atrial appendage (LAA). MV – mitral valve. B) The tip of the contact force-sensor ablation catheter is floating in the LA cavity. As it is not touching any structure, this is a good spot to calibrate the sensor as zero force. This step is needed before initiating RF delivery. C) The ablation catheter is highlighted at the roof of the LA around the LSPV. The mapping catheter (arrow) is inside the LSPV monitoring its electrical connection to the LA. It is clear that the ablation catheter is in the PV antrum and not delivering energy inside the vein. D) Ablation in the ridge (*) between the LSPV and the LAA. The mapping catheter is inside the LSPV (arrow).*

to check for pericardial effusion, at the following times: (1) at baseline, (2) after transeptal punctures, (3) after left PV isolation, (4) after right PV isolation, (5) and at the end of procedure. ICE also allows for immediate detection of clot formation, which cannot be seen with other non-ultrasound imaging modalities.

In pacemaker patients, device interrogation was performed before and after the procedure to guarantee lead integrity.

Femoral vein access care was performed with figure-of-eight sutures with Prolene "0" to achieve full hemostasis. Protamine at a maximal dose of 50 mg IV was given to allow for partial reversal of anticoagulation. Deambulation was allowed after 6h, and oral anticoagulation was resumed on the same day.

SVT Cases

For SVT cases, a routine somewhat similar to AF cases was used. To facilitate multipolar catheter advancement in the absence of transseptal sheaths, long sheaths that deliver the catheters in the inferior vena cava (IVC) were preferred, thus avoiding the anatomical tortuosity of the femoral and iliac vessels.

Starting from that site, progression to the RA was marked by the appearance of atrial electrograms and ICE visualization, as described. Anatomical landmarks such as His bundle and CS, SVC, IVC, and right atrial appendage ostia were tagged in the EA maps under ICE guidance (figure 4).

Population studied

We report a series of consecutive, unselected cases of catheter ablation procedures for the treatment of atrial tachyarrhythmias (AF, atrial flutter, and SVTs) performed without fluoroscopy, exclusively guided by ICE and EA mapping. Excel software (2019 version) was used for data tabulation. The main goals are to describe the feasibility of this innovative approach and to show the safety profile of this technique.

From May/2019 to December/2019, 95 consecutive patients (mean age 60 ± 18 years, 61% males) referred for ablation underwent the zero fluoro approach, with the following procedure distribution: AF Ablation (69 pts [73%], 45 paroxysmal AF [47%] and 24 persistent AF [25%]) or non-AF SVT (26 pts [27%] – 14 AV node reentry [15%], 6 WPW syndrome [6% - 4 in the mitral and 2 in the tricuspid annulus], 5 right atrial (RA) typical flutters [5%], 1 atrial tachycardia [1%]). In AF pts, the mean LA volume was 36 ± 4 ml/m^2 and 36% (25 pts) had structural heart disease, including rheumatic (3 pts - 3%) and other types of valvular disease (8 pts - 8%), coronary artery disease (17 pts - 17%), post-open heart surgery pts (12 pts - 12%, which usually have LA, RA and septal scars and sutures). Patients and procedural characteristics are summarized in table 1 and figure 5.

The protocol included an overnight hospital stay in a telemetry bed. No routine imaging was required before

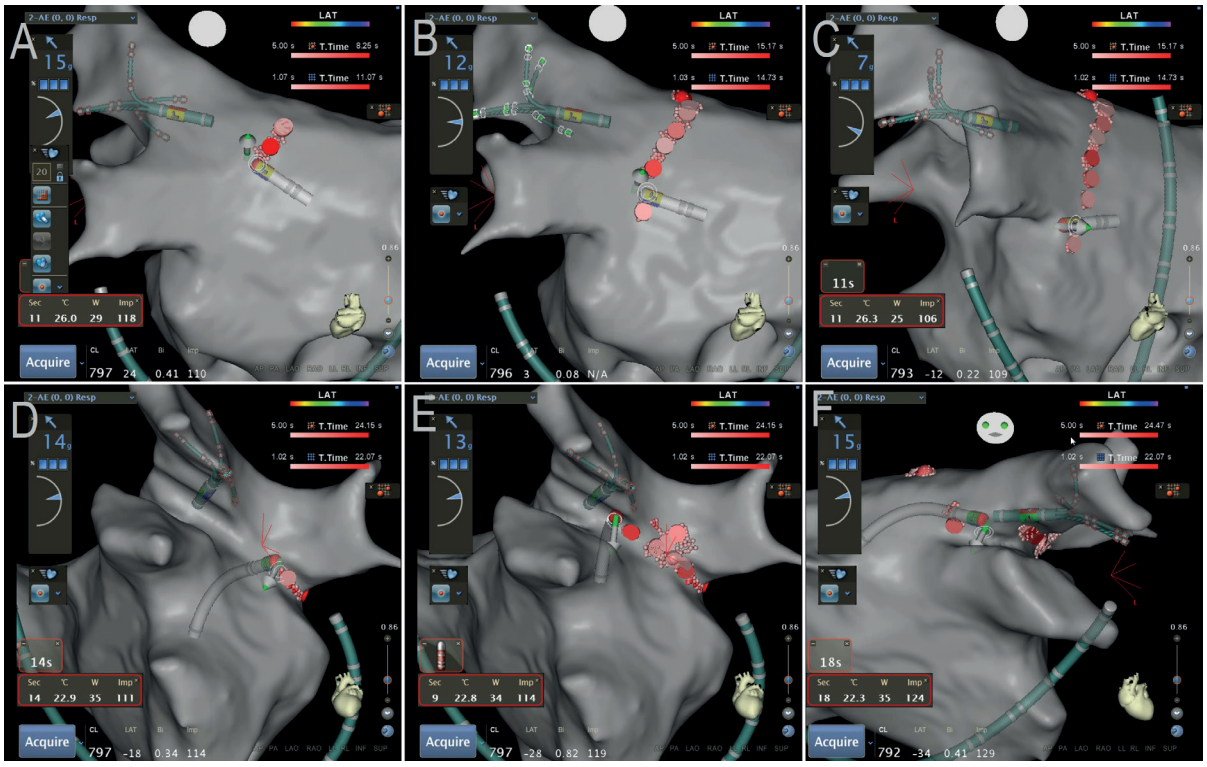
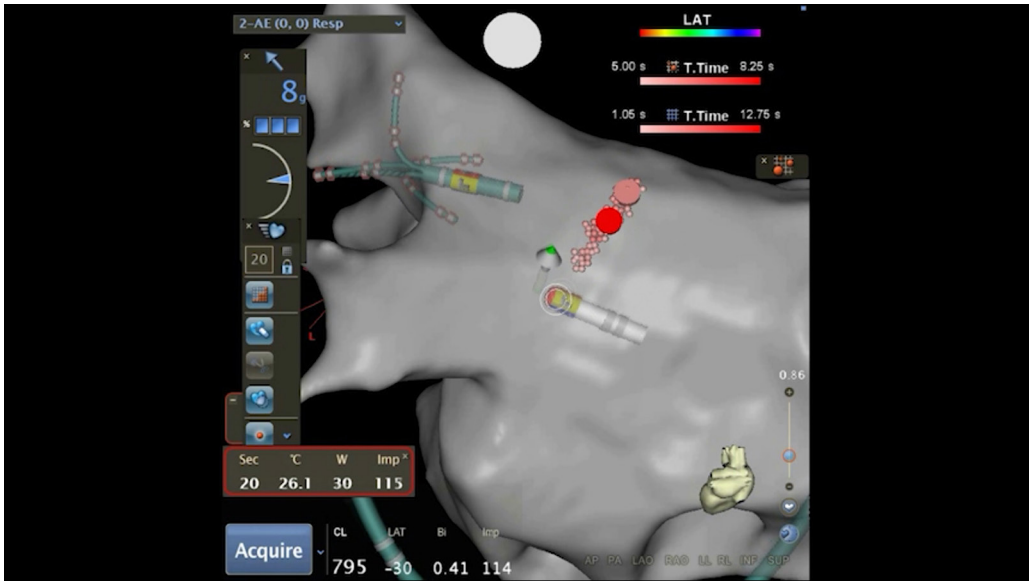


Figure 3 – *Sequence of imagens during circumferential ablation around the left PVs for isolation. Shown are the CARTO-guided 3D images of ablation lesions (pink and red dots) placed around the left PVs. Note that the ablation catheter provides contact-force information, the arrow depicting the force vector and on top-left, the number of grams quantifying the tissue contact (between 7 and 15g in this example), darker dots meaning more tissue contact and energy delivery. Also shown is a multipolar mapping catheter in the LSPV (Pentarray – Biosense Webster) to monitor its electrical activity and confirm isolation.*



Video 4 – *CARTO-guided 3D images of RF delivery (pink and red dots) placed around the left PVs. The ablation catheter provides contact-force information, the arrow showing the force vector, and on top-left, the number of grams quantifying the tissue contact. Ablation lesions covering the full circumference around the left PVs are shown. Access the video here: https://bit.ly/2XWhIbE.*

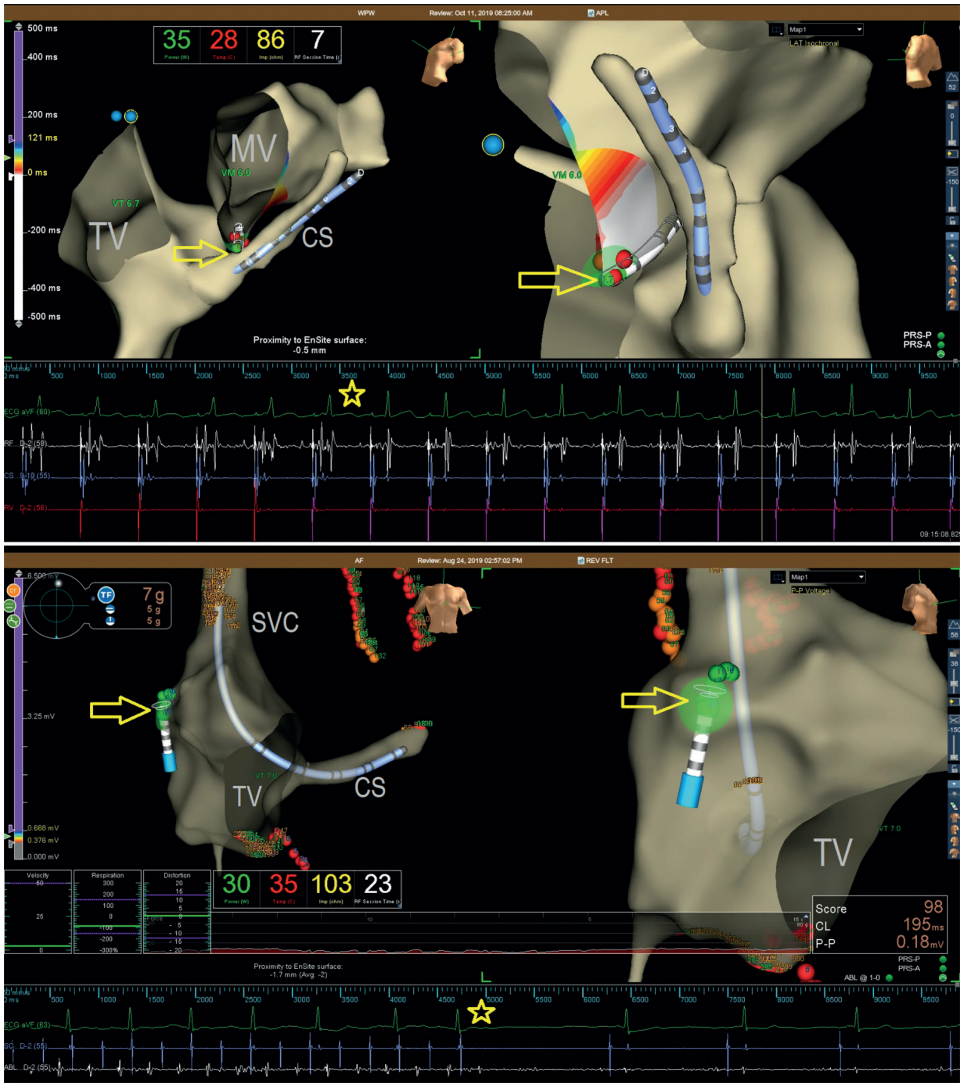


Figure 4 – *Mapping and ablation for supraventricular tachycardia. Ablation of an accessory pathway (WPW) in the mitral annulus is shown in the upper panel, where the ablation catheter (arrow) is positioned in the septal part of the annulus. RF application leads to the immediate elimination of conduction and normalization of the QRS (*). In the lower panel, an atrial tachycardia was mapped and ablated in the RA (arrow), with interruption of the arrhythmia (*) and return to normal sinus rhythm. MV – mitral valve. TV – tricuspid valve. SVC – superior vena cava. CS – coronary sinus.*

Table 1 – Patients' characteristics

Characteristics	N = 95
Age (years)	60 ± 18
Male gender	58 (61%)
Carto system	62 (65%)
Navx system	33 (35%)
Body Mass Index (BMI)	22.5 ± 2.8
Arterial Hypertension	71 (75%)
Diabetes Mellitus	48 (51%)
Ischemic Heart Disease	31 (33%)

hospital discharge. CT scans were performed neither at baseline nor in the follow-up, while other radiation-free imaging methods were used at the discretion of the follow-up physician.

Results

No pericardial effusions, thrombotic complications, or other difficulties were seen in these series. All targets in both atria that needed ablation were reached and adequately visualized. All intended ablations were performed, meaning that the lack of fluoroscopic imaging did not hamper RF delivery. Those sites included the PV antra, LA posterior wall, anterior wall, septum, LA appendage, RA appendage, CS,

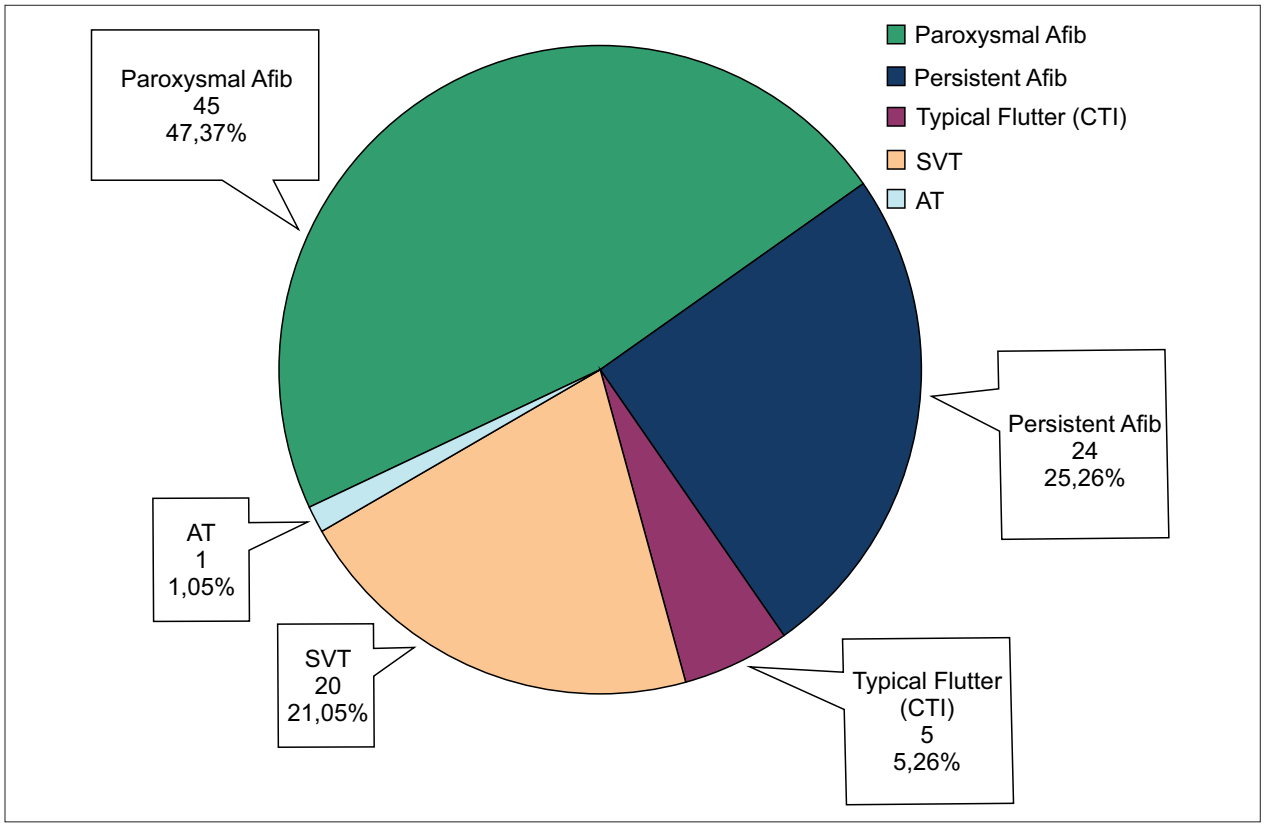


Figure 5 – *Distribution of patients according to the type of arrhythmia. AT – atrial tachycardia; CTI – cavotricuspid isthmus. SVT – supraventricular tachycardia (AV node reentry or WPW).*

CTI, mitral and tricuspid annulus, slow pathway, and crista terminalis. No backup fluoro was used, and no lead apparel was needed in any patient.

Interestingly, difficult transseptal puncture (due to small fossa, floppy septum, or fibrous septum), which occurred in 19 patients (20%), was managed without fluoroscopy use in all cases. This is a significant finding, since there is a common belief that transseptal fluoroscopic visualization of the entire sheath-needle assembly is essential both for septal perforation, penetration, and sheath over the wire exchange. All these steps were clearly visualized using ICE to its best advantage. The same applied to the negotiation of tortuous venous branches to advance the ICE catheter – all cases were successfully managed without fluoroscopy by careful visualization of the echo-free space and guidewire insertion.

Permanent pacemaker leads were present in 9 patients (9,5%), 7 dual chamber (DDD) pacemakers, and 2 CRT-D devices with 3 leads (RA, RV, and CS leads). Five patients (56%) were pacemaker-dependent due to complete AV block without any escape rhythm. In 3 of these cases, RA mapping and ablation (CTI and atriotomy scar-related flutters) were performed on top of LA instrumentation and PV isolation. All these cases were also adequately completed without fluoroscopy. Importantly, device interrogations after the procedure did not show any lead damage, dislocation, or threshold changes. Of note, care must be taken to differentiate the guidewire from lead imaging on ICE.

Discussion

This series of cases highlights the feasibility, safety, and efficacy of a zero fluoro approach when treating both AF and different types of atrial arrhythmias, even in the presence of pacemaker leads (and even in pacer-dependent patients). For that matter, it is of utmost importance that ICE, and EA mapping be used to their best advantage.[17-21]

Our series represents a pioneer experience in Brazil and Latin America using a radiation-free approach. It resulted from a long-lasting concern about radiation reduction and steady implementation of non-X-ray steps to our ablation protocol. We already had significant expertise from using ICE and EA in every AF case for the last 16 years, which surely made our learning curve easier. In that regard, no increase in costs was seen in our series, as precisely the same catheters were used as in the procedures using fluoroscopy.

The ability to use EAM and ICE to provide adequate visualization of every step of the procedure has already been reported. Razminia et al.[22] retrospectively compared safety and efficacy between two groups (60 non-fluoroscopic and 60 fluoroscopic ablation procedures). No significant increase in complications or procedure time was observed, with comparable efficacy. The fluoroscopic group had an average X-ray exposure of 33 minutes in AF ablation cases. Bulava et al.[14] reported on 80 patients randomized to either fluoroscopically-guided PVI or PVI without fluoroscopy using

ICE and the CARTO 3 system with contact force ablation catheters. No difference in arrhythmia-free 12-month survival was found. No severe complications were recorded in either group. In this series, the fluoroscopy group had an average exposure of 3 min for AF ablations, showing that the operators were already experts in the use of non-fluoroscopic imaging. Taken together, these data suggest that the adoption of radiation reduction measures can dramatically affect x-ray exposure even in fluoroscopically-guided procedures, with no safety concerns.

EA mapping is a fundamental part of the procedure since it provides a reliable geometry to guide the roving catheter and RF applications but could potentially provide misleading information if not stringently used. The initial description by Reddy et al.[12] reported a series of 20 consecutive AF ablation procedures without the use of fluoroscopy, relying only on ICE images and the NavX EA system to create geometry. In this series, EA image integration with a previously acquired left atrium CT scan was used in the majority of patients, requiring femoral artery access and aortic root mapping to create a reliable fusion between aortic anatomy from EA mapping and CT image. New technologies, such as multielectrode mapping catheters and software can provide a less traumatic, fast, and reliable geometry, with a high-density map and better anatomy delineation, comparable to a CT scan reconstruction, without the need to expose the patient to radiation and avoiding arterial access during the procedure. In our series, no patient was submitted to pre-ablation CT scans. Also, the EA systems provide ablation catheter tip color-coding orientation that allows easily reproducible movements and an excellent correlation between torque, deflection, and contact force.

In our country, only two companies currently provide EA mapping systems - Carto 3 system (Biosense Webster, Diamond Bar, CA, USA) and Ensite-NavX system (St. Jude Medical, St. Paul, MN, USA). When these two systems were compared for mapping and CTI catheter ablation, Macias et al. showed[4] that the results (acute success, complications, and recurrence rates) from both EA mapping systems were similar. In our study, Carto 3 was used in 67.8% of patients, and the NavX system in 32.2% of all procedures (Table 1), with similar results.

ICE visualization is critical in every step of a non-fluoroscopic complex ablation. With thorough ICE scanning, all the steps can be adequately monitored, even when catheters come out of the sheath tip (making sure it does not force the atrial wall). There is no blind step using this approach, even when advancing catheters or wires in the venous system to the heart. CS visualization and cannulation are better than with fluoroscopy, not to mention the transseptal punctures, which are undoubtedly best visualized on ICE. Baykaner et al.[23] recently reported on 747 zero-fluoroscopy transeptal punctures, performed in 646 patients in 5 different centers across the US, using different approaches to reach the fossa ovalis. The transseptal access was associated with a low total complication rate (0.7%). In our study, a total of 142 transseptal punctures were performed with no complications. Indeed, a somewhat short learning curve is needed to become comfortable with and proficient in ICE manipulation. But it definitively gives better and more detailed information than fluoroscopy.

Razminia et al.[15] reported a 5-year follow-up of fluoroless ablations in a series of 500 patients. These procedures were safely and effectively performed, with similar rates of recurrence and complications when compared with the standard technique. In our series, we also did not observe any significant complications. As this technique becomes the standard practice for even more complex procedures, such as ventricular tachycardias, a rise in complications rate could be expected. As such, reports on the safety and effectiveness for the patient are extremely important and will, together with more widespread training in ICE and EA mapping, be vital to large-scale adoption of these procedures in clinical practice.

All the tools needed for a successful radiation-free ablation are already available in most EP labs and familiar to most EP physicians.[24] Engagement in this field only needs a motivated team with a change in mindset. Once one does it, there is no way back. It is highly beneficial to patients – who can frequently undergo more than one ablation, usually have other diagnostic or therapeutic modalities that use radiation (e.g., CT scans, coronary interventions) over their lifespan, which are usually unaccounted for or neglected. The risk is cumulative over time. We have to keep that in mind, especially when cancer statistics show a worrying steep rise and when the impact can occur years after exposure.

Radiation-free interventions also allow safe ablation treatment of pregnant patients. The most recently published ESC Guidelines for the treatment of supraventricular arrhythmias[25] gives an **IIa** indication in experienced centers. Even for standard SVT cases, where simple procedures under conscious sedation and using two catheters are frequently performed, it is worthwhile using ICE and general anesthesia. They allow for safe and comfortable procedures for both pts and physicians and add the possibility of using transient apnea to enhance catheter stability when dealing with arrhythmias near the AV node / His bundle.

Zero fluoroscopy is also highly beneficial to the health care team. First, reducing the radiation exposure is obviously desired for people who have been exposed daily for years. It is a matter of concern to read reports of an increase of up to 1% in one's lifetime risk of cancer;[3,7] it is uncomfortable to read reports that 85% of brain cancers in interventional physicians occur on the left hemisphere,[26-28] suggesting a causal relation to occupational exposure to radiation effects (since the left side is known to be more exposed than the right). Not to mention the considerable benefit of avoiding using heavy lead aprons, which, over time, makes orthopedic issues an almost unanimous occurrence.[29-31] The authors cannot stress enough the massive relief that standing hours without having to wear heavy lead aprons represents.

It is also highly beneficial to patients and all the healthcare team. Multiple exposures to radiation are common in the modern era, with the readily available imaging modalities. We usually do not realize the cumulative nature of multiple exposures and their potential detrimental effects over the long term. Patients undergoing ablation not uncommonly have had or will have repeated exposure to CT, fluoroscopy, coronary and peripheral angiography, as well as nuclear scans. A radiation-free procedure with at least similar costs, safety, and effectiveness as the standard fluoro-based alternative, even when additional hardware is implanted in the heart, is thus highly valuable. A

motivated team with a mindset change is critical in that regard. It is our perception that, after a learning curve, in most instances, the visualization and manipulation are indeed more precise than that with fluoroscopy, without any blind parts.

Limitations

We report on a relatively small number of patients and lack a control group. Zero fluoroscopy procedures were performed by operators with a large experience in ICE and 3D mapping, and the reproducibility of our results by less experienced operators may vary due to the need for a steeper learning curve. However, we believe that these results are meaningful and represent the basis for further evaluations about the safety and efficacy of these techniques.

Conclusions

A radiation-free (fluoroless) catheter ablation strategy for AF and other atrial arrhythmias is acutely safe and effective when guided by adequate ICE and 3D mapping utilization. Multiple different bi-atrial sites could be reached and adequately ablated without the need for backup fluoroscopy. No complications were seen.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Saad EB, Slater C, Inácio Jr. LAO, Santos GV, Dias LC, Camanho LEM; Writing of the manuscript: Saad EB, Slater C.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017;14(10):e275-e444.
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140(2):e125-e51.
3. Heidbuchel H, Wittkampf FH, Vano E, Ernst S, Schilling R, Picano E, et al. Practical ways to reduce radiation dose for patients and staff during device implantations and electrophysiological procedures. Europace. 2014;16(7):946-64.
4. Perisinakis K, Damilakis J, Theocharopoulos N, Manios E, Vardas P, Gourtsoyiannis N. Accurate assessment of patient effective radiation dose and associated detriment risk from radiofrequency catheter ablation procedures. Circulation. 2001;104(1):58-62.
5. Lickfett L, Mahesh M, Vasamreddy C, Bradley D, Jayam V, Eldadah Z, et al. Radiation exposure during catheter ablation of atrial fibrillation. Circulation. 2004;110(19):3003-10.
6. Ector J, Dragusin O, Adriaenssens B, Huybrechts W, Willems R, Ector H, et al. Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. J Am Coll Cardiol. 2007;50(3):234-42.
7. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med. 2009;361(9):849-57.
8. Bourier F, Reents T, Ammar-Busch S, Buiatti A, Kottmaier M, Semmler V, et al. Evaluation of a new very low dose imaging protocol: feasibility and impact on X-ray dose levels in electrophysiology procedures. Europace. 2016;18(9):1406-10.
9. Duran A, Hian SK, Miller DL, Le Heron J, Padovani R, Vano E. Recommendations for occupational radiation protection in interventional cardiology. Catheter Cardiovasc Interv. 2013;82(1):29-42.
10. Lerman BB, Markowitz SM, Liu CF, Thomas G, Ip JE, Cheung JW. Fluoroless catheter ablation of atrial fibrillation. Heart Rhythm. 2017;14(6):928-34.
11. Ferguson JD, Helms A, Mangrum JM, Mahapatra S, Mason P, Bilchick K, et al. Catheter ablation of atrial fibrillation without fluoroscopy using intracardiac echocardiography and electroanatomic mapping. Circ Arrhythm Electrophysiol. 2009;2(6):611-9.
12. Reddy VY, Morales G, Ahmed H, Neuzil P, Dukkipati S, Kim S, et al. Catheter ablation of atrial fibrillation without the use of fluoroscopy. Heart Rhythm. 2010;7(11):1644-53.
13. Macias R, Uribe I, Tercedor L, Jimenez-Jaimez J, Barrio T, Alvarez M. A zero-fluoroscopy approach to cavotricuspid isthmus catheter ablation: comparative analysis of two electroanatomical mapping systems. Pacing Clin Electrophysiol. 2014;37(8):1029-37.
14. Bulava A, Hanis J, Eisenberger M. Catheter ablation of atrial fibrillation using zero-fluoroscopy technique: a randomized trial. Pacing Clin Electrophysiol. 2015;38(7):797-806.
15. Razminia M, Willoughby MC, Demo H, Keshmiri H, Wang T, D'Silva OJ, et al. Fluoroless catheter ablation of cardiac arrhythmias: a 5-year experience. Pacing Clin Electrophysiol. 2017;40(4):425-33.
16. Yang L, Sun G, Chen X, Chen G, Yang S, Guo P, et al. Meta-analysis of zero or near-zero fluoroscopy use during ablation of cardiac arrhythmias. Am J Cardiol. 2016;118(10):1511-8.
17. Enriquez A, Saenz LC, Rosso R, Silvestry FE, Callans D, Marchlinski FE, et al. Use of intracardiac echocardiography in interventional cardiology: working with the anatomy rather than fighting it. Circulation. 2018;137(21):2278-94.
18. Saad EB, Costa IP, Camanho LE. Use of intracardiac echocardiography in the electrophysiology laboratory. Arq Bras Cardiol. 2011;96(1):e11-7.

19. Rolf S, Hindricks G, Sommer P, Richter S, Arya A, Bollmann A, et al. Electroanatomical mapping of atrial fibrillation: review of the current techniques and advances. J Atr Fibrillation. 2014;7(4):1140.

20. Nedios S, Sommer P, Bollmann A, Hindricks G. Advanced mapping systems to guide atrial fibrillation ablation: electrical information that matters. J Atr Fibrillation. 2016;8(6):1337.

21. Demo H, Willoughby C, Jazayeri MA, Razminia M. Fluoroless catheter ablation of cardiac arrhythmias. Card Electrophysiol Clin. 2019;11(4):719-29.

22. Razminia M, Manankil MF, Eryazici PL, Arrieta-Garcia C, Wang T, D'Silva OJ, et al. Nonfluoroscopic catheter ablation of cardiac arrhythmias in adults: feasibility, safety, and efficacy. J Cardiovasc Electrophysiol. 2012;23(10):1078-86.

23. Baykaner T, Quadros KK, Thosani A, Yasmeh B, Mitra R, Liu E, et al. Safety and efficacy of zero fluoroscopy transseptal puncture with different approaches. Pacing Clin Electrophysiol. 2020;43(1):12-8.

24. Razminia M, D'Silva O. Fluoroless catheter ablation of cardiac arrhythmia: is it ready for prime time? Pacing Clin Electrophysiol. 2020;43(1):19-20.

25. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(5):655-720.

26. Blettner M, Schlehofer B, Samkange-Zeeb F, Berg G, Schlaefer K, Schuz J. Medical exposure to ionising radiation and the risk of brain tumors: Interphone study group, Germany. Eur J Cancer. 2007;43(13):1990-8.

27. Carozza SE, Wrensch M, Miike R, Newman B, Olshan AF, Savitz DA, et al. Occupation and adult gliomas. Am J Epidemiol. 2000;152(9):838-46.

28. Roguin A, Goldstein J, Bar O, Goldstein JA. Brain and neck tumors among physicians performing interventional procedures. Am J Cardiol. 2013;111(9):1368-72.

29. Klein LW, Miller DL, Balter S, Laskey W, Haines D, Norbash A, et al. Occupational health hazards in the interventional laboratory: time for a safer environment. Radiology. 2009;250(2):538-44.

30. Goldstein JA, Balter S, Cowley M, Hodgson J, Klein LW, Interventional Committee of the Society of Cardiovascular Interventions. Occupational hazards of interventional cardiologists: prevalence of orthopedic health problems in contemporary practice. Catheter Cardiovasc Interv. 2004;63(4):407-11.

31. Ross AM, Segal J, Borenstein D, Jenkins E, Cho S. Prevalence of spinal disc disease among interventional cardiologists. Am J Cardiol. 1997;79(1):68-70.

Catheter Ablation Without Use of X-rays to Treat Atrial Fibrillation and Atrial Arrhythmia

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Short Editorial related to the article: Catheter Ablation for Treatment of Atrial Fibrillation and Supraventricular Arrhythmias Without Fluoroscopy Use: Acute Efficacy and Safety

Radiofrequency ablation is a well-established method and is increasingly used in the treatment of tachyarrhythmia. Traditionally, it is done by placing fluoroscopy-guided intracavitary catheters. Over the years, however, a number of problems related to exposure to radiation have become more evident, such as cataracts, genetic mutations, cancer.[1] It is not by chance that the number of tumors in the left cerebral hemisphere, which receives the greatest amount of radiation, is greater than in the right hemisphere, in interventionists. It is important to remember that the risk of cancer is linear with exposure, without a defined threshold, and that there is a cumulative effect. In longer procedures, even severe skin lesions can develop in patients. To reduce these risks to patients and the medical staff, several actions were taken: fluoroscopic devices and methods with less radiation, personal protective equipment, such as an apron, thyroid protection, goggles, cap and even leaded gloves.[2] Protection increased, but at the expense of orthopedic problems due to the weight that was carried, in so many procedures, for so long.[3] New solutions were created, such as suspended lead aprons. But along with this increase in personal protection, the idea of effectively performing the procedure with the least amount of radiation possible gained momentum. For this, the development of three-dimensional mapping systems was the driving force required. This, associated with the use of ablation catheters by contact, made it possible to perform procedures, including complex ones, manipulating catheters and applying energy efficiently and safely, without requiring fluoroscopic imaging. In less complex procedures, especially on the right side of the heart, ablations without fluoroscopy were described.[4,5] In pregnant women, it has become a feasible solution. Even for the more complex procedures, "near-zero" fluoroscopy was recommended. "Near-zero" because it was still necessary to use fluoroscopy at times, such as transseptal puncture, for example.

At the same time, ultrasound has been increasingly used in invasive cardiac procedures and, more specifically, in electrophysiology. Vascular ultrasound is used to support vascular punctures and to reduce AV fistulas and pseudoaneurysms. Transesophageal echo is useful to rule out atrial appendage thrombus and to assist transseptal puncture. Even more useful is intracardiac echo, which assists transseptal puncture, shows pulmonary vein ostia, rules out pericardial effusion, shows recesses during cavotricuspid isthmus ablation and confirms adequate catheter contact.

The idea that ultrasound could be used to replace what was still done with fluoroscopy was described more than 10 years ago, and it is slowly gaining space in the literature.[6] In Brazil, Dr. Eduardo Saad was the first to use intracardiac echocardiography in complex ablation procedures, and now his group publishes the first series of cases performed in Brazil and Latin America with zero use of fluoroscopy, which does not even require the lead apron.[7] Ninety-five patients underwent the procedure using only intracardiac echocardiography and three-dimensional mapping, 69 of whom underwent atrial fibrillation ablation, including 9 patients with permanent pacemaker. The procedures were carried out successfully and without major complications. Even the most difficult transseptal punctures were performed without fluoroscopy. "Backup fluoroscopy was not used, and no lead clothing was needed," the authors say.

Similar results with high success and few complications have been described by other groups.[8,9] Moreover, comparative studies have shown that the energy application time does not increase and medium-term success (1 year) is maintained.[10] Most of the data refer to supraventricular tachyarrhythmias, but they also have good results for ablation of extrasystole and ventricular tachycardia.[11]

While the concept that it is possible and desirable to do the procedures without fluoroscopy is accepted and becomes the norm, other techniques are sought, in addition to the association of three-dimensional mapping with intracardiac echocardiography. Recent studies describe the performance of transseptal puncture and atrial fibrillation ablation without intracardiac echocardiography, but using transseptal puncture needles such as a "bipolar catheter",[12] or identifying the oval fossa with 3-D mapping only.[13]

There seems to be no doubt that the future points to ablation without fluoroscopy. Even because ethical and legal issues should push in this direction. But what are the obstacles to the regular use of this technique today? Firstly, it is necessary to have in mind the situations in which the technique has not yet been tested and where it seems to be more difficult to apply, such as in epicardial ablation or in arrhythmias related to complex congenital heart diseases. Secondly, the cost. Not every insurance covers the use of intracardiac echocardiography, and most patients are unable to afford this

Keywords

Radiofrequency Ablation/methods; Radio Waves/adverse effects; Personal Protective Equipment; Fluoroscopy; Arteriovenous Fistula; Efficacy; Safety.

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cost. Thirdly, inertia. Most electrophysiologists are used to traditional techniques, get good results, and are not willing to go through a new learning curve. For procedures such as atrial fibrillation ablation, these obstacles do not appear to outweigh the benefits of the technique. I believe that the doubt remains regarding low-complexity procedures, such as ablation of supraventricular tachycardia, which has been successfully performed, with very rare complications and very low doses of radiation. If the gain obtained with three-dimensional mapping and use of intracardiac echocardiography outweighs the cost and the need to place a more calibrated sheath for the echocardiogram probe, it is yet to be better defined.

Ablation without fluoroscopy is a major progress and is now ready to be implemented on a large scale. But, as with every major progress in science, it is already waiting for the next step in evolution. The procedures in general are being performed progressively in less invasive ways. Open surgeries are replaced by catheter and laparoscopic procedures. As for cardiac arrhythmias, ablations have been performed without the need for catheter placement, but using mapping by external electrode systems, and stereotaxis ablation, with external beam radiation (such as radiotherapy). Initially developed and described in the treatment of ventricular tachycardias,[14] the technique is now also potentially to be used in ablation of atrial fibrillation.[15]

Ablation is an indispensable therapy and will remain as such as the usual treatment for tachyarrhythmia. Fluoroscopy is harmful and will be eliminated by electrophysiological procedures. This is a pressing issue and concerns the whole world. It is time to dispense with the lead apron. Here, as opposed to what is popularly said, the less the better. And if it's zero, that's even better.

References

1. Rehani MM, Ortiz-Lopez P. Radiation effects in fluoroscopically guided cardiac interventions: Keeping them under control. Int J Cardiol. 2006; 109(2):147-51.
2. Heidbuchel H, Wittkampf F, Vano E,Ernst S, Schilling RJ, Picano E, et al. Practical ways to reduce radiation dose for patients and staff during device implantations and electrophysiological procedures. Europace. 2014; 16(7):946-64.
3. Ross AM, Segal J, Borenstein D, Jenkins E, Cho S. Prevalence of spinal disc disease among interventional cardiologists. Am J Cardiol. 1997; 79(1):68-70.
4. Alvarez M, Bertomeu-Gonzalez V, Arcocha M. Nonfluoroscopic Catheter Ablation. Results From a Prospective Multicenter Registry. Rev Esp Cardiol. 2017; 70(9):699-705.
5. Chen G, Wang Y, Proietti R, Wang X, Ouyang F, Ma CS, et al. Zero-fluoroscopy approach for ablation of supraventricular tachycardia using the Ensite NavX system: a multicenter experience. BMC Cardiovasc Disord. 2020; 20(1):48.
6. Ferguson JD, Helms A, Mangrum J, ahapatra S, Mason P, Bilchick K, et al. Catheter ablation of atrial fibrillation without fluoroscopy using intracardiac echocardiography and electroanatomic mapping. Circ Arrhythm Electrophysiol. 2009 Dec; 2(6):611-9.
7. Saad EB, Slater C, Oliveira Jr LAI, Santos GV, Dias LC, Camanho LE. Ablação por cateter sem uso de raios x para tratamento de fibrilação atrial e arritmias atriais. Arq Bras Cardiol. 2020; 114(6):1015-1026.
8. Sadek MM, Ramirez FD, Nery PB , Golian M, Redpath CJ, Nair GM, et al. Completely non-fluoroscopic catheter ablation of left atrial arrhythmias and ventricular tachycardia. J Cardiovasc Electrophysiol. 2019; 30(1):78-88.
9. Reddy VY, Morales G, Ahmed H, Neuzil P, Dukkipati S, Kim S, et al. Catheter ablation of atrial fibrillation without the use of fluoroscopy. Heart Rhythm. 2010; 7(11):1644-53.
10. Bulava A, Hanis J, Eisenberger M. Catheter ablation of atrial fibrillation using zero-fluoroscopy technique: a randomized trial. Pacing Clin Electrophysiol. 2015; 38(7):797-806.
11. Johnson A, Mejia-Lopez E, Bilchick K. Catheter ablation of ventricular arrhythmias without fluoroscopy using intracardiac echocardiography and electroanatomic mapping. [abstract] In: 40th Annual Heart Rhythm Scientific Sessions, May 08 November 2019. San Francisco,California.
12. Guarguagli S, Cazzoli I, Kempny A, Gatzoulius MA, Ernst S. A New Technique for Zero Fluoroscopy Atrial Fibrillation Ablation Without the Use of Intracardiac Echocardiography. JACC Clin Electrophysiol. 2018; 4(12):1647-8.
13. Weber R, Minners J, Allgeier HJ, Jadidi A, Muller-Edenborn B, Neumann FJ, et al. 3D mapping for the identification of the fossa ovalis in left atrial ablation procedures: a pilot study of a first step towards an electroanatomic-guided transseptal puncture EP Europace. 2020; 22(5):732-8.
14. Cuculich PS, Schill MR, Kashaniand R, Mutic S, Lang A, Cooper D, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. N Engl J Med. 2017; 377(24):2325-36.
15. Qjan P, Azpiri J, Assad J, Gonzales EM, Cordona Ibarra CE, de la Pena C, et al. Noninvasive stereotactic radioablation for the treatment of atrial fibrillation: First-in-man experience. J Arrhythmia.2020;36(1):67-74.

Evaluation of the Cardiac Effects of a Water-Soluble Lectin (Wsmol) from *Moringa Oleifera* Seeds

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Abstract

Background: **Moringa oleifera seeds, which are used for water clarification, contain a lectin named WSMoL which has shown in vitro antibacterial and immunomodulatory activity. Due to their nutritional value and therapeutic potential, the leaves and seeds of this tree are eaten in some communities. Some plant lectins are non-toxic to mammals, but others have been reported to be harmful when ingested or administered by other means.**

Objective: **As one of the steps needed to define the safety of WSMoL, we evaluated possible cardiotoxic effects of this purified protein.**

Methods: **WSMoL was administered for 21 consecutive days to mice by gavage. Electrophysiological, mechanical, and metabolic cardiac functions were investigated by in vivo and ex vivo electrocardiographic recordings, nuclear magnetic resonance, and high-resolution respirometry.**

Results: **The treatment with WSMoL did not induce changes in blood glucose levels or body weight in comparison with control group. Moreover, the heart weight/body weight and heart weight/tibia length ratios were similar in both groups. Lectin ingestion also did not modify glucose tolerance or insulin resistance. No alterations were observed in electrocardiographic parameters or cardiac action potential duration. The heart of mice from the control and WSMoL groups showed preserved left ventricular function. Furthermore, WSMoL did not induce changes in mitochondrial function (in all cases, $p > 0.05$).**

Conclusions: **The administration of WSMoL demonstrated a cardiac safety profile. These results contribute to the safety evaluation of using M. oleifera seeds to treat water, since this lectin is present in the preparation employed by some populations to this end. (Arq Bras Cardiol. 2020; 114(6):1029-1037)**

Keywords: ***Moringa Oleífera*** **(WSMoL), Lectins, Glycosides; Carbohydrates; Heart; Water Security; Mice.**

Introduction

Moringa oleifera Lamarck (Moringaceae) is a tree that is native to the south Himalaya region, widely cultivated on Asia and throughout the tropics mainly due to its use for water clarification. It has been employed in traditional medicine, as well as in food, cosmetic, and pharmaceutical industries,[1,2] and it is also used to treat different diseases, such as cancer and chronic and infectious diseases.[3,4]

A water-soluble lectin isolated from the seeds of *M. oleifera* (WSMoL) has shown insecticidal activity,[5-7] and *in vitro* studies demonstrated its antibacterial activity against corrosive and pathogenic bacteria.[8-10] WSMoL demonstrated *in vitro* anti-inflammatory activity on lipopolysaccharide-stimulated murine macrophages,[11] and it was able to activate human lymphocytes from peripheral blood mononuclear cell cultures, showing an immunomodulatory effect.[12] It has also been proven that WSMoL is one of the coagulant proteins found in *M. oleifera* seeds[8,13] and it is able to reduce the turbidity and ecotoxicity of water samples collected from a polluted stream.[14]

It is well demonstrated that many antibiotics and some classes of anti-inflammatory drugs are usually associated with cardiotoxic effects.[15,16] The injurious events of these drugs in the cardiovascular system include the occurrence of heart failure with systolic ventricular dysfunction, arrhythmias, and myocardial ischemia.[17] Classically, as a consequence of cardiotoxicity, changes on the electrocardiogram (ECG) can be observed, such as QT interval prolongation, which has been observed in patients who have used several classes of antimicrobials, including macrolides and fluoroquinolones.[18-20] Among macrolides, intravenous administration of erythromycin presents the greatest risk. It increases the QT interval, and fatal arrhythmias have been reported when it was used alone or in combination with other QT-prolonging drugs.[16] Thus, protection of cardiac function is currently a constant challenge for the pharmaceutical industry, regulatory authorities, and physicians facing adverse clinical reactions to various therapeutic agents in clinical practice.

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WSMoL has emerged as a potential antibacterial drug and as an immunomodulatory agent. Some plant lectins are non-toxic to mammals,[21,22] but others have been reported to be harmful when ingested or administered by other means, such as intraperitoneal injection.[23] Thus, as one of the steps needed to define the safety of WSMoL, this study evaluated this protein's possible cardiotoxic effects.

Methods

Plant material and lectin isolation

Moringa oleifera seeds were collected in Recife (Pernambuco, Brazil) with the authorization (no. 38690) of the Chico Mendes Institute for Biodiversity Conservation (ICMBio, acronym in Portuguese) and stored at −20 ºC. A sample of the collected material was stored as a voucher specimen (number 73345) at the Dárdano de Andrade Lima herbarium of the Agronomy Institute of Pernambuco. The access was recorded (A6CAB4C) in the National System For The Management Of Genetic Heritage And Associated Traditional Knowledge (SisGen, acronym in Portuguese).

WSMoL was isolated from seed powder according to the protocol previously described by Coelho et al.[5] Briefly, proteins were extracted in distilled water, and, after filtration and centrifugation, the extract was treated with ammonium sulfate at 60% saturation[24] for 4 h at 28 °C. After another centrifugation, the precipitate was resuspended in water and dialyzed for 8 h against distilled water (4 h) and 0.15 M NaCl (4 h). The dialyzed fraction (100 mg of proteins) was loaded onto a chitin column equilibrated with 0.15 M NaCl (20 mL/h flow rate) and WSMoL was eluted with 1.0 M acetic acid. The isolated lectin was dialyzed against distilled water with three liquid changes for eluent elimination. Carbohydrate-binding activity of the lectin was monitored during the purification process by the hemagglutinating activity assay according to the method described by Paiva and Coelho.[25]

Animals

Adult male C57BL/6 mice were used and maintained at the Carlos Chagas Filho Biophysics Institute (IBCCF, acronym in Portuguese) of the Federal University of Rio de Janeiro (UFRJ, acronym in Portuguese) under controlled conditions of constant temperature (23 °C), in a standard light/dark cycle of 12h/12h with free access to food and water. All experiments were performed in accordance with the Ethical Principles in Animal Research adopted by the Brazilian College of Animal Experimentation, and the the applied protocols received approval from the Committee on Ethics in Animal Research of UFRJ, under protocol number DFBCICB041. The mice were used for experiments for 21 days.

Experimental conditions

The animals were separated into two experimental groups: CNTRL (control group) and WSMoL (animals treated with WSMoL). Several studies by our group have extensively performed experiments with WSMoL using concentrations ranging from 10 μg/ml to 0.2 mg/ml[5-12] in order to test several biological effects of WSMoL. In the present study, in order to test its cardiotoxicity of this purified protein, a 10 times higher concentration of WSMoL was used. Thus, the animals of the WSMoL group were treated with the lectin (purified protein) via gavage, at a concentration of 5 mg/kg body weight (equivalent to 2 mg/ml) for 21 days. The animals in the CNTRL group were treated with milli-Q water via gavage for 21 days.

Cardiac hypertrophy

In order to evaluate the existence of possible cardiac hypertrophy, the mice's hearts were weighed, and data were normalized by calculating the heart weight/body weight (HW/BW) and heart weight/tibia length (HW/TL) ratios.[26,27] After weighing, the animals were euthanized by cervical dislocation. Subsequently, the hearts were extracted, washed with phosphate buffered saline (PBS), dried to remove liquid excess, and weighed. The length of the tibia was measured with a caliper.

Fasting glucose, intraperitoneal glucose tolerance test, and intraperitoneal insulin tolerance test

Fasting blood glucose (FBG) concentrations were determined from tail vein blood using an automated glucometer (Contour™ TS Bayer). For intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin tolerance test (IPITT), mice were fasted for 6 h and 4 h, respectively. After the fasting period, animals received intraperitoneally 2 g/kg of glucose for IPGTT or 0.5 IU/kg of insulin for IPITT,[28] and FBG levels were monitored 0, 15, 30, 60, 120 min after injection from a tail snip. The area under the curve (AUC) was calculated using all the time points, discounting baseline glucose values from each animal.

Electrocardiography and echocardiography

In order to assess the cardiac electrical activity *in vivo*, an electrocardiogram (ECG) recording was carried out in conscious animals using a noninvasive method,[29] namely, two subcutaneous electrodes were implanted under isoflurane anesthesia in the right and left forepaws, corresponding to ECG lead I. At the time of registration, the electrodes were connected by flexible cables to a homemade DC-coupled differential amplifier (kindly provided by Dr. Ariel Escobar, University of California, Merced, USA) using a 500 Hz low-pass filter and an acquisition frequency of 1 kHz. The signal was digitized using Digidata 1440A (Axon Instruments, San José, CA, USA) and recorded using a Labview-based acquisition program (National Instruments, Austin, TX, USA). The durations of the following intervals were analyzed: PR, RR, QRS, and QJ.

Cardiac function was evaluated by *in vivo* echocardiography (ECHO) using the Vevo 770 High-Resolution Imaging System (VisualSonics, Toronto, Canada) coupled to a 30 MHz transductor, under isoflurane anesthesia. Images were acquired in bidimensional mode and analyzed by a blinded investigator. Left ventricular end-diastolic volume, end-systolic volume, ejection fraction, and fractional area change were calculated using Simpson's method. In brief, these parameters of cardiac function were evaluated in a long parasternal axis view and four high-temporal resolution B-mode short-axis images, taken at different ventricular levels, as described previously.[30]

Action potential

In order to perform intact cardiac action potential (AP) records, a Langendorff retrograde perfusion system was used to maintain the hearts functional *ex vivo* for hours, as previously described.[31,32] To avoid tissue damage by the formation of blood clots, animals were injected intraperitoneally with Na^+-heparin 15 min before euthanization by cervical dislocation. Hearts were rapidly removed, cannulated by the aorta, and perfused continuously with an oxygenated Tyrode solution containing the following, (in mM): NaCl 140, KCl 5.3, $CaCl_2$ 2, $MgCl_2$ 1, NaPO4H2 0.33, HEPES 10, and glucose 10. The pH was calibrated to 7.4 with NaOH at 32 ºC. To decrease mechanical contraction, the hearts were perfused with Tyrode containing 4 mM of Blebbistatin (Selleckchem, Houston, TX, USA).

To record electrical signals, borosilicate glass (10-40 MΩ) microelectrodes were used. These microelectrodes were filled with 3 M KCl solution and inserted into a holder (MEH1SF12, World Precision Instrument [WPI], Sarasota, FL, USA) embedded in a micromanipulator (MM33 links, WPI) connected to the input of a pre-amplifier (Electro 705, WPI). The microelectrodes were placed on the surface of the left ventricle and the reading of the microelectrode was set to zero. Amplified signals were digitalized (NI USB 6281, National Instrument) and analyzed with a homemade program in LabView (kindly developed and provided by Dr. Ariel Escobar, University of California, Merced, CA, USA).

The parameters analyzed were action potential duration (APD) at 30% and 90% repolarization (APD_{30} and APD_{90}, respectively).

Isolation of mice heart mitochondria

Isolation of mitochondria from the hearts was adapted from the protocol described by Affourtit et al.[33] with minor modifications. The hearts were rapidly dissected and rinsed in ice-cold Chappell-Perry (CP) buffer containing the following (in mM): KCl 100, Tris-HCl 50, EGTA 2 at pH 7.2). The hearts were weighed, minced with razor blades and washed 4 to 5 times with CP buffer. The tissue was subsequently incubated for 5 min with CP buffer supplemented with 0.5% albumin, 5 mM MgCl2, 1 mM ATP, and 125 U/100 mL protease type VIII, at a proportion of 1 mL/100 mg of tissue. The hearts were then homogenized (Ultra-turrax homogenizer [IKA®, Campinas, SP, Brazil], low setting, 3 s, 3 times) and the resultant homogenate was centrifuged. The supernatant was centrifuged and the pellet was washed and resuspended into ice-cold CP buffer and finally centrifuged. The final mitochondrial pellet was resuspended into a small volume of CP buffer. The protein dosage of the obtained preparation was performed by the method described by Lowry et al.[34]. The isolated mitochondrial preparations were subjected to high resolution respirometry to measure the fluxes of oxygen consumption.

High resolution respirometry

For the analyses of the oxygen consumption, isolated mitochondria were used. The experiments were performed on a high-resolution O2k-respirometer (Oroboros Instruments, Innsbruck, Austria, EU) at 37°C with mitochondrial respiration media (MIR05) containing the following (in mM): EGTA 0.5, $MgCl_2$ 3, K-MES 60, taurine 20, KH_2PO_4 20, HEPES 20, sucrose 110 and 1 g/L fat free BSA at pH 7.1. The protocol used to evaluate mitochondrial function was adapted from Pesta and Gnaiger,[35] consisting of sequential addition of multiple substrates and inhibitors, namely, the following: 5 mM pyruvate, 2.5 mM malate, 10 mM glutamate, 100 μM adenosine 5'-diphosphate (ADP), 1 mM ADP, 10 mM succinate, 0.2 μg/mL oligomycin, and 2 μM antimycin A. Respiratory control ratio (RCR) was calculated by the oxygen flux after addition of succinate in the presence of ADP, divided by the flux after oligomycin. The maximal phosphorylative capacity of electron transport system (OXPHOS) was calculated by the oxygen consumption following addition of succinate minus residual oxygen consumption (ROX), which was estimated after the addition of antimycin A. The non-specific leak of protons was determined by oxygen flux insensitive to oligomycin minus ROX. Another distinct protocol was performed by changing the sequence of the substrates in order to calculate the electron leakage, the ratio of hydrogen peroxide (H_2O_2) production by O_2 flux. The order of titration of this protocol was the following: 5 mM pyruvate, 2.5 mM malate, 10 mM glutamate, 10 mM succinate, 1 mM ADP, and 0.2 μg/mL oligomycin. Data were analyzed in DatLab 5 software (Oroboros Instruments) and expressed in pmol O_2/mg/s.

Mitochondrial H_2O_2 production

Mitochondrial H_2O_2 was measured by monitoring the resorufin appearance rate at 563/587 nm (excitation/emission) in a fluorescence spectrophotometer (Varian Cary Eclipse, Agilent Technologies, Santa Clara, CA, USA). The same concentration of isolated mitochondria used in the oxygen consumption experiments was added in 2 mL of MIR05 supplemented with 5.5 μM Amplex red, 2 U/mL peroxidase, and 40 U/mL superoxide dismutase. The assays of H_2O_2 production were performed at 37 ºC, and the substrates, inhibitors, and uncouplers were added every 2 min in the following order: 5 mM pyruvate, 2.5 mM malate, 10 mM glutamate, 10 mM succinate, 1 mM ADP, 0.2 μg/mL oligomycin, 2 titres of 0.5 μM carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone (FCCP), and 2 μM antimycin A. The data generated in arbitrary units of fluorescence were analyzed in Origin Pro-8 software (Origin Lab Corporation, Northampton, MA, USA) and normalized to pmol of H_2O_2/mg/min from standard calibration curves of H_2O_2 performed in the presence of the same number of isolated mitochondria for each experiment.

Statistical analysis

Values are expressed as mean ± SD or median (with interquartile range). In order to compare the results between CNTRL and WSMoL, unpaired Student's t test was used, when appropriate. On the other hand, data showing non-Gaussian distribution (Kolmogorov-Smirnov test) were compared by the Mann-Whitney test. Differences between variables were considered significant when p value was < 0.05. All analyses were performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). We did not use statistical methods to predetermine sample size. Samples sizes were estimated on the basis of sample availability and previous experimental studies of the cardiovascular system.[29,30]

Results

The 21-day treatment with WSMoL did not induce changes ($p > 0.05$) in blood glucose levels (Figure 1A) or body weight (Figure 1B) in comparison with CNTRL group. In addition, the HW/BW (Figure 1C) and HW/TL (Figure 1D) ratios were similar ($p > 0.05$) in both groups, indicating that no cardiac hypertrophy was developed. The treatment also did not modify glucose tolerance (Figure 1E) or insulin resistance (Figure 1F) in comparison with untreated mice ($p > 0.05$), revealing absence of alterations in carbohydrate metabolism.

Figure 2 shows the ECG parameters at day 21 of treatment. The PR, RR, QRS, and QJ intervals (Figure 2C–F) were not significantly different ($p > 0.05$) between the WSMoL and CNTRL groups. The APD_{30} and APD_{90} were similar ($p > 0.05$) between untreated and treated mice (Figure 2G–J). Thus, the data obtained here consistently demonstrated that WSMoL treatment was safe for the electrical behavior of mouse heart.

Since some antibiotics have been shown to be able to impair left ventricular function and structure, we studied the left ventricular function in detail by ECHO (Figure 3). The mice from both CNTRL and WSMoL groups showed preserved left ventricular structure and function, as indicated by the absence of significant differences ($p > 0.05$) in the following parameters: ejection fraction (Figure 3A), fractional area change (Figure 3B), stroke volume (Figure 3C), end-diastolic volume (Figure 3D), end-systolic volume (Figure 3E), and left ventricular mass (Figure 3F). Taken together, these data show that WSMoL treatment did not impair left ventricular function.

Finally, in order to verify whether WSMoL interferes in the physiology of heart mitochondrial function, we performed experimental approaches to analyze two important mitochondrial functions: oxidative phosphorylation and reactive oxygen species production. The 21-day treatment with WSMoL did not induce alterations in the mitochondrial oxygen consumption, as can be observed in Figure 4A–E. In addition, the treatment did not interfere in the rate of H_2O_2 production in the presence of different substrates, inhibitors, and uncouplers (Figure 4F), nor did it alter electron leakage (Figure 4G) when compared to the CNTRL group.

Discussion

The high toxicity of some drugs currently used for treatment of several diseases is a major concern in health systems. For example, several classes of antibiotics are cardiotoxic.[18-20] In this scenario, natural compounds have been increasingly studied due to their potential for drug discovery and development.[36] However, it is also important to evaluate the safety of natural compounds used for food and medical purposes. Previous studies by our group demonstrated the antibacterial and immunomodulatory activities of WSMoL,[8-10] which is also a coagulant protein from *M. oleifera* seeds. In this study, we evaluated possible cardiotoxic effects of orally administrated WSMoL on mice. Safety studies are imperative, even when lectins are administered orally, since it has been reported that some proteins of this class can cross the intestinal barrier and be found systemically.[37]

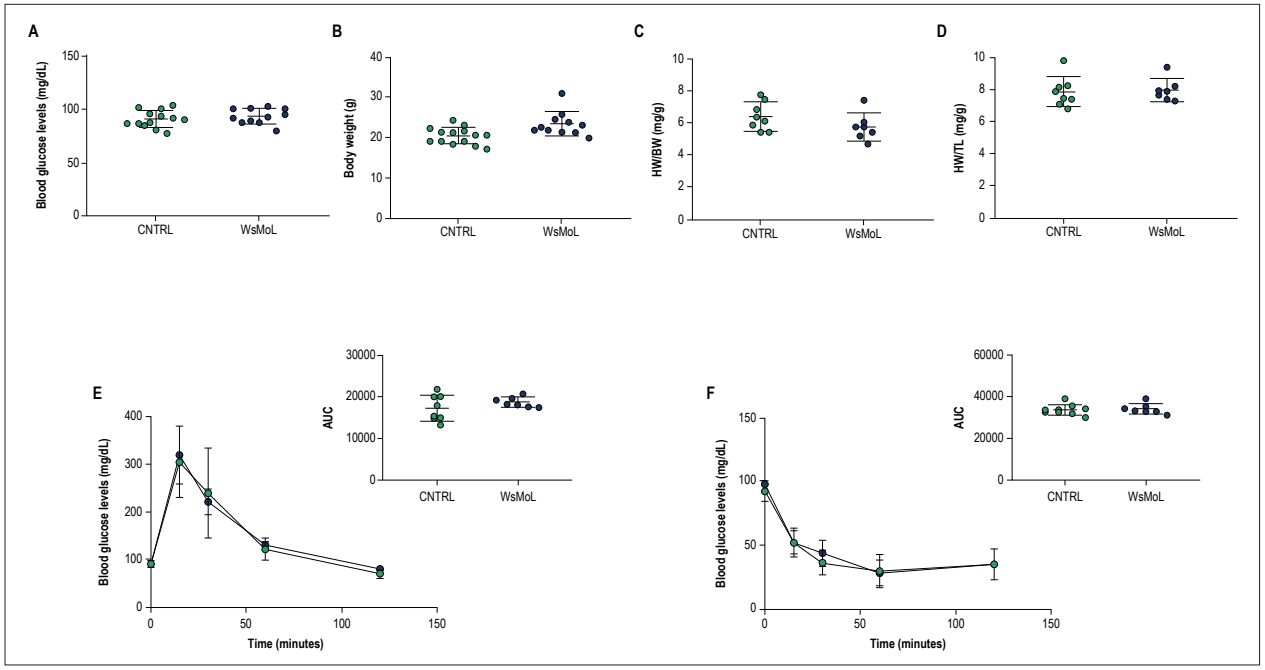

Figure 1 – *WSMoL treatment for 21 days did not induce metabolic alterations. (A) Blood glucose levels after 21 days of treatment with saline (CNTRL) or WSMoL (WSMoL) solution (CNTRL n = 14 mice and WSMoL n = 11 mice), (B) body weight of CNTRL and WSMoL groups (CNTRL n = 14 mice and WSMoL n = 11 mice), (C) heart weight/ body weight ratio (CNTRL n = 8 mice and WSMoL n = 7 mice) and (D) heart weight/tibia length ratio, showing that the treatment with 5mg/kg body weight of WSMoL preserves cardiac structure (CNTRL n = 8 mice and WSMoL n = 7 mice), (D) intraperitoneal glucose tolerance test and (E) intraperitoneal insulin tolerance test with their correspondent AUC graphs on inset (CNTRL n = 9 mice and WSMoL n = 7 mice). Each dot represents individual values and lines represent mean values. ○: CNTRL mice; ●: WSMoL mice. Comparisons between groups were performed using unpaired Student's t test. The results are shown as mean ± SD.*

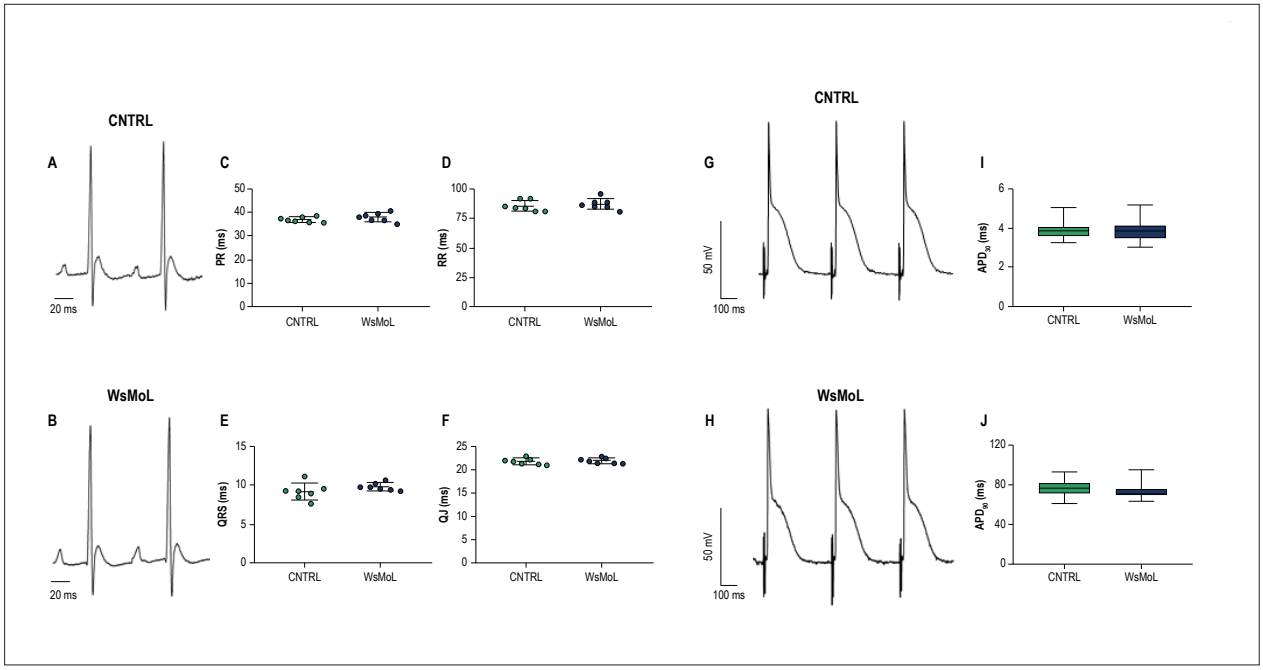

Figure 2 – *WSMoL did not impair in vivo or in vitro cardiac electrical activity. Representative in vivo ECG recordings of (A) CNTRL and (B) WSMoL groups. (C) PR, (D) RR, (E) QRS and (F) QJ intervals summarized the data obtained after 21 days of WSMoL treatment (CNTRL n = 7 mice; 2,034 measurements and WSMoL n = 7 mice; 2,038 measurements). Each dot represents individual values and lines represent mean values. Representative in vitro recordings of ventricular action potential of (G) CNTRL and (H) WSMoL groups are showed. The effect of WSMoL treatment on action potential duration at (I) 30% and (J) 90% repolarization are summarized (CNTRL n = 5 hearts; 483 measurements, and WSMoL n = 4 hearts; 545 measurements). Each dot represents individual measurements and lines represent mean values. Comparisons between groups were performed using unpaired Student's t test, and data that did not show Gaussian distribution (Kolmogorov-Smirnov test) were compared by the Mann Whitney test. ○: CNTRL mice; ●: WSMoL mice. The results are shown as mean ± SD for data with Gaussian distribution and as median and interquartile range for data with non-Gaussian distribution.*

There is a belief that the natural origin of a product guarantees its safety to humans. However, some natural compounds may exert toxic effects, including on the cardiac level. For example, the alkaloid aconitine, an ingredient of Fuzi (a traditional Chinese medicine), was pointed out as the cause of bidirectional ventricular tachycardia.[38]

It is also well known that several antibiotics are able to block hERG potassium channels, prolonging the QT interval and the APD.[39-41] Guo et al.[42] observed a prolongation of APD using erythromycin in neonatal mouse ventricular myocytes. Zhang M. et al.[43] also showed that azithromycin, when administered in guinea pigs, caused significant prolongations of APD_{50} and APD_{90}.

Accordingly, we evaluated the effects of WSMoL treatment on the cardiac electric activity both *in vivo* and *ex vivo*, in mice, observing that it was cardiologically safe.

Another effect observed in some antibiotics is the impairment of left ventricular function and structure, as observed by Zhang M. et al.[43]. Furthermore, some studies have shown that antibiotics and other natural compounds can impair mitochondrial function.[44,45] However, after 21 days of WSMoL treatment, we observed that left ventricular function and mitochondrial function were preserved.

Conclusion

The data presented here indicate that the administration of WSMoL by gavage did not have cardiotoxic effects on mice treated for 21 days. These results contribute to the safety evaluation of the use of *M. oleifera* seeds to treat water, since this lectin is present in the preparation employed by some populations to this end.

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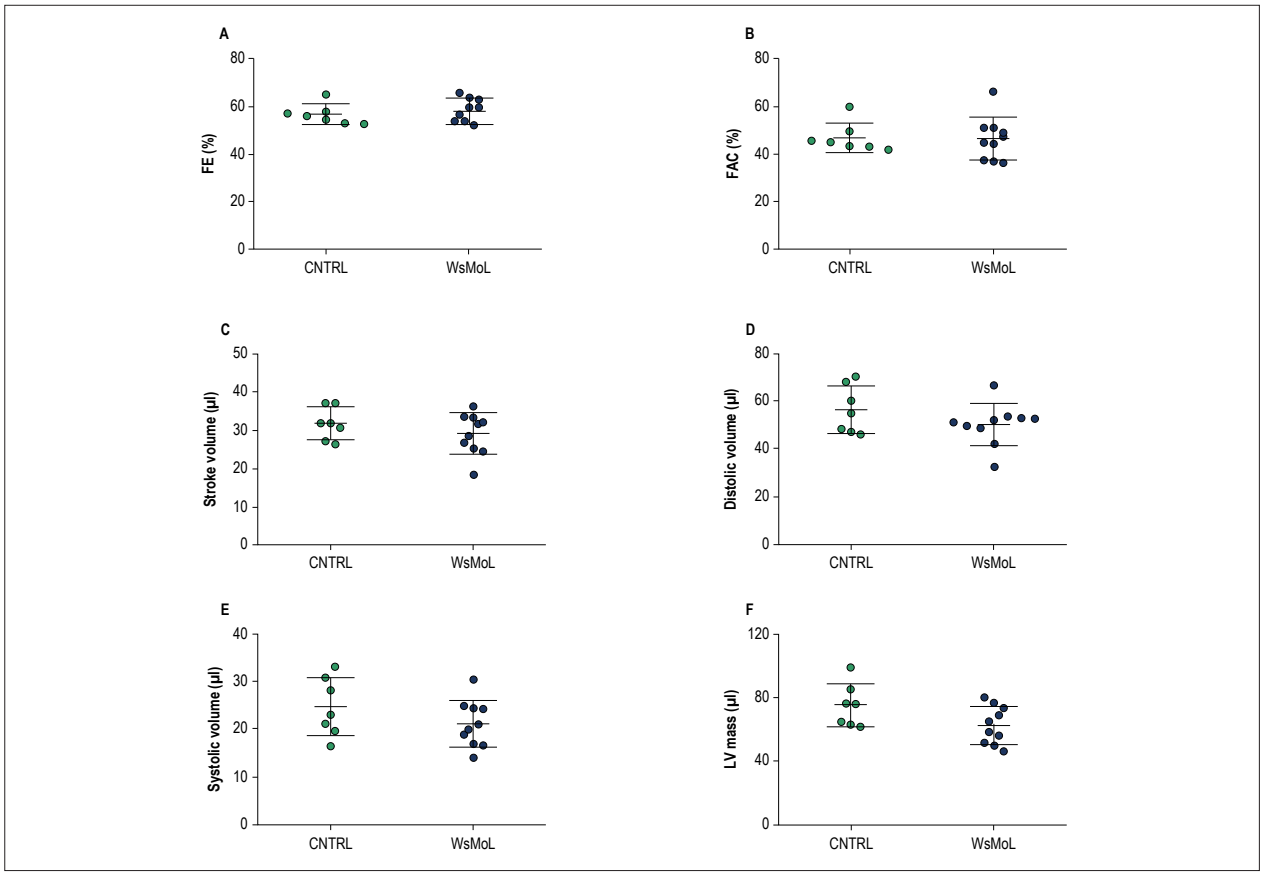

Figure 3 – *Left ventricular function and structure were preserved after WSMoL treatment. The results obtained by ECHO from both groups are summarized in the following: (A) ventricular ejection fraction, (B) fractional area change, (C) stroke volume, (D) final diastolic and (E) final systolic volume, and (F) left ventricular mass (CNTRL n = 7 mice and WSMoL n = 10 mice). Comparisons between groups were performed using unpaired Student's t test. Each dot represents individual values and lines represent mean values. ○: CNTRL mice; ●: WSMoL mice. The results are shown as mean ± SD.*

action potential recordings in intact hearts. Finally, the authors thank Professor Antonio Galina from Federal University of Rio de Janeiro for his support in the mitochondrial experiments.

Author contributions

Conception and design of the research and obtaining financing: Paiva PMG, Medei E; Acquisition of data: Rodriguez de Yurre A, da Silva JDF, Torres MK, Martins EL, Ramos IP, Silva WSFL, Sarpa JS, Guedes CCS; Analysis and interpretation of the data and statistical analysis: Rodriguez de Yurre A, d a Silva JDF, Martins EL, Ramos IP; Writing of the manuscript and critical revision of the manuscript for intellectual content: Rodriguez de Yurre A, da Silva JDF, Napoleão TH, Paiva PMG, Coelho LCBB, Medei E. Rodriguez de Yurre A and da Silva JDF contriuted equaly to this work.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is associated with postgraduate program in Biological sciences and physiology of UFRJ and postgraduate program in Biochemistry and physiology of UFPE.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal do Rio de Janeiro under the protocol number DFBCICB041. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

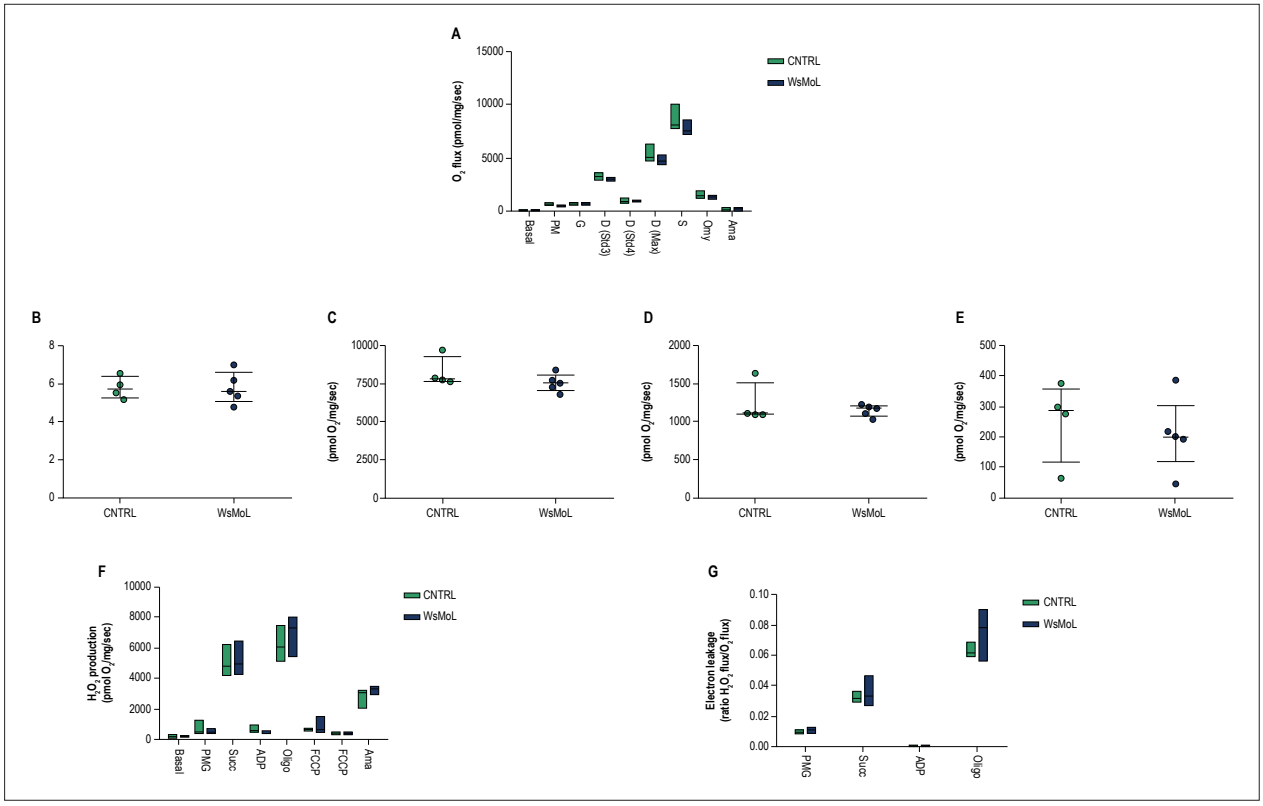

Figure 4 – *WSMoL did not alter mitochondrial function after 21 days of treatment. (A) O2 consumption fluxes in high-resolution respirometry of CNTRL and WSMoL groups, (B) respiratory control ratio (RCR), (C) maximal phosphorylative capacity of electron transport system (OXPHOS), (D) non-specific leak of protons (LEAK), (E) residual oxygen consumption (ROX), (F) rates of mitochondrial H2O2 production, and (G) electron leakage of CNTRL and WSMoL groups. (CNTRL n = 4 hearts and WSMoL n = 5 hearts). Each dot represents individual values and lines represent mean values. ○: CNTRL mice; ●: WSMoL mice. Comparisons between groups were performed using unpaired Student's t test, and data that did not show Gaussian distribution (Kolmogorov-Smirnov test) were compared by the Mann Whitney test. The results are shown as mean ± SD for data with Gaussian distribution and as median and interquartile range for data with non-Gaussian distribution.*

References

1. Hassan FAG, Ibrahim MA. Moringa oleifera: nature is most nutritious and multi purpose tree. Int J Sci Res Publ. 2013;3(4):1-5.
2. Santos A, Luz LA, Pontual EV, Napoleão TH, Paiva PMG, Coelho LCBB. Moringa oleifera: resource management and multiuse life tree. Adv Res. 2015;4(6):388-402.
3. Sreelatha S, Jeyachitra A, Padma PR. Antiproliferation and induction of apoptosis by Moringa oleifera leaf extract on human cancer cells. Food Chem Toxicol. 2011;49(6):1270-5.
4. Vergara-Jimenez M, Almatrafi M, Fernandez M. Bioactive components in Moringa oleifera leaves protect against chronic disease. Antioxidants. 2017;6(4):pii:E91.
5. Coelho JS, Santos ND, Napoleão TH, Gomes FS, Ferreira RS, Zingali RB, et al. Effect of Moringa oleifera lectin on development and mortality of Aedes aegypti larvae. Chemosphere. 2009;77(7):934-8.
6. de Oliveira CFR, de Moura MC, Napoleão TH, Paiva PMG, Coelho LCBB, Macedo MLR. A chitin-binding lectin from Moringa oleifera seeds (WSMoL) impairs the digestive physiology of the Mediterranean flour larvae, Anagasta kuehniella. Pestic Biochem Physiol. 2017 Oct;142:67-76.
7. Santos ND, de Moura KS, Napoleão TH, Santos GK, Coelho LC, Navarro DM, et al. Oviposition-stimulant and ovicidal activities of Moringa oleifera lectin on Aedes aegypti. PloS One. 2012;7(9):e44840.
8. Ferreira RS, Napoleão TH, Santos AF, Sá RA, Carneiro-da-Cunha MG, Morais MM, et al. Coagulant and antibacterial activities of the water-soluble seed lectin from Moringa oleifera. Lett Appl Microbiol. 2011;53(2):186-92.
9. Moura MC, Trentin DS, Napoleão TH, Primon-Barros M, Xavier AS, Carneiro NP, et al. Multi-effect of the water-soluble Moringa oleifera lectin against Serratia marcescens and Bacillus sp.: antibacterial, antibiofilm and anti-adhesive properties. J Appl Microbiol. 2017;123(4):861-74.
10. Moura MC, Napoleão TH, Coriolano MC, Paiva PM, Figueiredo RC, Coelho LC. Water-soluble Moringa oleifera lectin interferes with growth, survival and cell permeability of corrosive and pathogenic bacteria. J Appl Microbiol. 2015;119(3):666-76.
11. Araújo LC, Aguiar JS, Napoleão TH, Mota FV, Barros AL, Moura MC, et al. Evaluation of cytotoxic and anti-inflammatory activities of extracts and lectins from Moringa oleifera seeds. PLoS One. 2013;8(12):e81973.

12. Coriolano MC, de Santana Brito J, de Siqueira Patriota LL, de Araujo Soares AK, de Lorena VMB, Paiva PMG, et al. Immunomodulatory effects of the water-soluble lectin from Moringa oleifera seeds (WSMoL) on human peripheral blood mononuclear cells (PBMC). Protein Pept Lett. 2018;25(3):295-301.

13. de Moura KS, da Silva HR, Dornelles LP, Coelho LC, Napoleão TH, de Oliveira MD, et al. Coagulant activity of water-soluble moringa oleifera lectin is linked to lowering of electrical resistance and inhibited by monosaccharides and magnesium ions. Appl Biochem Biotechnol. 2016;180(7):1361-71.

14. Freitas JHES, de Santana KV, do Nascimento ACC, de Paiva SC, de Moura MC, Coelho LCBB, et al. Evaluation of using aluminum sulfate and water-soluble Moringa oleifera seed lectin to reduce turbidity and toxicity of polluted stream water. Chemosphere. 2016 Nov;163:133-41.

15. Costache II, Petriş A. Cardiotoxicity of anthracyclines. Rev Med Chir Soc Med Nat Iasi. 2011;115(4):1200–7.

16. Iannini PB. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. Expert Opin Drug Saf. 2002;1(2):121-8.

17. De Vecchis R, Ariano C, Di Biase G, Noutsias M. Malignant ventricular arrhythmias resulting from drug-induced QTc prolongation: a retrospective study. J Clin Med Res. 2018;10(7):593-600.

18. Li X, Wang M, Liu G, Zhou L, Wang Z, Li C. Macrolides use and the risk of sudden cardiac death. Expert Rev Anti Infect Ther. 2016;14(6):535-7.

19. Liu X, Ma J, Huang L, Zhu W, Yuan P, Wan R, et al. Fluoroquinolones increase the risk of serious arrhythmias: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96(44):e8273.

20. Quinn KL, Macdonald EM, Gomes T, Mamdani MM, Huang A, Juurlink DN, et al. Macrolides, digoxin toxicity and the risk of sudden death: a population-based study. Drug Saf. 2017;40(9):835-40.

21. da Silva PM, de Moura MC, Gomes FS, da Silva Trentin D, Silva de Oliveira AP, de Mello GSV, et al. PgTeL, the lectin found in Punica granatum juice, is an antifungal agent against Candida albicans and Candida krusei. Int J Biol Macromol. 2018 Mar;108:391-400.

22. Procópio TF, de Siqueira Patriota LL, de Moura MC, da Silva PM, de Oliveira APS, do Nascimento Carvalho LV, et al. CasuL: a new lectin isolated from Calliandra surinamensis leaf pinnulae with cytotoxicity to cancer cells, antimicrobial activity and antibiofilm effect. Int J Biol Macromol. 2017 May;98:419-29.

23. Dang L, Van Damme EJM. Toxic proteins in plants. Phytochemistry. 2015 Sep;117:51-64.

24. Green AA, Hughes WL. Protein fractionation on the basis of solubility in aqueous solutions of salts and organic solvents. In: Methods in Enzymology. Amsterdam: Elsevier BV; 1955.

25. Paiva PMG, Coelho LCBB. Purification and partial characterization of two lectin isoforms from Cratylia mollis mart. (camaratu bean). Appl Biochem Biotechnol. 1992;36(2):113-8.

26. Schaible TF, Scheuer J. Effects of physical training by running or swimming on ventricular performance of rat hearts. J Appl Physiol. 1979;46(4):854-60.

27. Yin FC, Spurgeon HA, Rakusan K, Weisfeldt ML, Lakatta EG. Use of tibial length to quantify cardiac hypertrophy: application in the aging rat. Am J Physiol. 1982;243(6):H941-7.

28. Arguin G, Bourzac J-F, Placet M, Molle CM, Paquette M, Beaudoin J-F, et al. The loss of P2X7 receptor expression leads to increase intestinal glucose transit and hepatic steatosis. Sci Rep. 2017;7(1):12917.

29. Monnerat G, Alarcón ML, Vasconcellos LR, Hochman-Mendez C, Brasil G, Bassani RA, et al. Macrophage-dependent IL-1β production induces cardiac arrhythmias in diabetic mice. Nat Commun. 2016 Nov;7:13344.

30. Benavides-Vallve C, Corbacho D, Iglesias-Garcia O, Pelacho B, Albiasu E, Castaño S, et al. New strategies for echocardiographic evaluation of left ventricular function in a mouse model of long-term myocardial infarction. PLoS One. 2012;7(7):e41691.

31. Ferreiro M, Petrosky AD, Escobar AL. Intracellular Ca^{2+} release underlies the development of phase 2 in mouse ventricular action potentials. Am J Physiol Heart Circ Physiol. 2012;302(5):H1160-72.

32. Mejía-Alvarez R, Manno C, Villalba-Galea CA, del Valle Fernández L, Costa R, Fill M, et al. Pulsed local-field fluorescence microscopy: a new approach for measuring cellular signals in the beating heart. Pflüg Arch. 2003;445(6):747-58.

33. Affourtit C, Quinlan CL, Brand MD. Measurement of proton leak and electron leak in isolated mitochondria. Methods Mol Biol. 2012;810:165-82.

34. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem. 1951;193(1):265-75.

35. Pesta D, Gnaiger E. High-resolution respirometry: OXPHOS protocols for human cells and permeabilized fibers from small biopsies of human muscle. Methods Mol Biol. 2012;810:25-58.

36. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. J Nat Prod. 2016;79(3):629-61.

37. Lehr CM. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Crit Rev Ther Drug Carrier Syst. 1994;11(2-3):119-60.

38. Zhao YT, Wang L, Yi Z. An unusual etiology for bidirectional ventricular tachycardia. Can J Cardiol. 2016;32(3):395.e5-6.

39. Han SN, Yang SH, Zhang Y, Duan YY, Sun XY, Chen Q, et al. Blockage of hERG current and the disruption of trafficking as induced by roxithromycin. Can J Physiol Pharmacol. 2013;91(12):1112-8.

40. Kauthale RR, Dadarkar SS, Husain R, Karande VV, Gatne MM. Assessment of temperature-induced hERG channel blockade variation by drugs. J Appl Toxicol. 2015;35(7):799-805.

41. Nogawa H, Kawai T, Yajima M, Miura M, Ogawa T, Murakami K. Effects of probucol, a typical hERG expression inhibitor, on in vivo QT interval prolongation in conscious dogs. Eur J Pharmacol. 2013;720(1-3):29-37.

42. Guo J, Zhan S, Lees-Miller JP, Teng G, Duff HJ. Exaggerated block of hERG (KCNH2) and prolongation of action potential duration by erythromycin at temperatures between 37 degrees C and 42 degrees C. Heart Rhythm. 2005;2(8):860-6.

43. Zhang M, Xie M, Li S, Gao Y, Xue S, Huang H, et al. Electrophysiologic studies on the risks and potential mechanism underlying the proarrhythmic nature of azithromycin. Cardiovasc Toxicol. 2017;17(4):434-40.

44. Singh R, Sripada L, Singh R. Side effects of antibiotics during bacterial infection: mitochondria, the main target in host cell. Mitochondrion. 2014 May;16:50-4.

45. Warmbrunn, MV, Schilling JM, Dhanani M, Glukhov E, Gerwick LG, Gerwick WH, et al. Novel marine compounds modulate mitochondrial function in H9c2 cells: potential new pharmaceutical targets to control cardiac metabolism. FASEB J. 2018;32(1 suppl):702.1.

Use of Moringa Oleifera Seeds in Water Treatment

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Short Editorial related to the article: Evaluation of the Cardiac Effects of a Water-Soluble Lectin (Wsmol) from Moringa Oleifera Seeds

Moringa oleifera Lamarck (MO) is a plant of the *Moringaceae* family, native to the Himalayas and adapted on several continents, is widely cultivated in Asia, Africa and the Americas.[1] Rapidly growing, the whole plant has a wide variety of applications in diet and folk medicine.

However, scientific evidence of its properties began to emerge only in the beginning of 2000. In experimental studies *in vitro* or *ex-vivo*, leaves and seeds showed several biological effects, such as anti-inflammatory and wound healing,[2] antitumor,[3] antidiabetic,[4] antioxidant[4,5] and sexual function.[6,7]

Due to their flotation properties and antimicrobial action, seeds have been used to purify water.[8] It is a low-cost method, which uses natural resources and easy handling that can offer quality in the water of poor communities. The seeds can absorb pollutants such as herbicides,[9] heavy metals,[10] medications[11,12] and act as larvicides and natural antimicrobials.[13]

Among the components present in *Moringa oleifera* seed, water-soluble lectin (WSMoL) has the property of *Aedes aegypti* larvicide and ovicide[14] and anti nematodes.[15]

As all scientific knowledge about *Moringa oleifera* is still based on experimental studies, there is a need to respect the stages of clinical research for use in humans. Thus, in 2019 in Brazil, the National Health Surveillance Agency (ANVISA) prohibited the manufacture, import, marketing, advertising and distribution of all foods containing *Moringa oleifera* (RESOLUTION-RE No. 1,478, OF 3 JUNE 2019)

Likewise, in relation to the use of seeds for water purification, a study to ensure safety is also necessary. In this context, in this edition of the *Arquivos Brasileiros de Cardiologia*, Yurre et al.[16] conducted a careful investigation of the cardiotoxic effects of WSMoL from *Moringa oleifera* seeds. The authors evaluated the possible cellular, structural, electrical and functional effects on the heart, effects on carbohydrate metabolism and body weight. It was a study that sought to test its null hypothesis and was successful in demonstrating, experimentally, the safety of using WSMoL for 21 days and it encourages new projects to evaluate the safety of using *Moringa oleifera* seeds for the purification of water for human use.

Keywords

Moringa Oleifera; Glycosides; Anti-Inflammatory Agents; Plant Lectins; Water Security.

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Referências

1. Matic I, Guidi A, Kenzo M, Mattei M, Galgani A. Investigation of medicinal plants traditionally used as dietary supplements: A review on *Moringa oleifera*.J Public Health Afr. 2018 Dec 21;9(3):841.
2. Udupa SL, Udupa AL, Kulkarni DR. Studies on anti-inflammatory and wound healing properties of Moringa oleifera and Aegle marmelos. Fitoterapia. 1994;65:119-23.
3. Sadek KM, Abouzed TK, Abouelkhair R, Nasr S. The chemo-prophylactic efficacy of an ethanol Moringa oleifera leaf extract against hepatocellular carcinoma in rats. Pharmaceutical Biology. 2017;55(1):1458-66.
4. Gupta R, Mathur M, Bajaj VK, Katariya P, Yadav S, Kamal R,et al. Evaluation of antidiabetic and antioxidant activity of Moringa oleifera in experimental diabetes. J Diabetes. 2012;4(2):164-71.
5. Shaat AR, Sadek KM, El-Far AH, Nasr SM, El-Sayed Y. Evaluation of antioxidant and hepatoprotective activities of moringa (moringa oleifera) leaves in diabetic rabbits. Eur J Pharmac Med Res. 2017;4(7):154-62.
6. Sadek KM. Chemotherapeutic efficacy of an ethanolic Moringa oleifera leaf extract against chromium-induced testicular toxicity in rats. Andrologia. 2014;46:1047-54.
7. Prabsattroo T, Wattanathorn J, Iamsaard S, Sompsat P, Sritragool O, Thukhummee W,et al. Moringa oleifera extract enhances sexual performance in stressed rats. J Zhejiang Univ Sci. 2015;16(3):179-90.
8. Nouhi S, Kwaambwa HM, Gutfreund P, Rennie AR. Comparative study of flocculation and adsorption behaviour of water treatment proteins from Moringa peregrina and Moringa oleifera seeds. Sci Rep. 2019;9(1):17945.
9. Cusioli LF, Bezerra CO, Quesada HB, Alves Baptista AT, Nishi L, Vieira MF, et al. Modified *Moringa oleifera* Lam. Seed husks as low-cost biosorbent for atrazine removal. Environ Technol. 2019 Aug 14:1-12.
10. Freitas JH, de Santana KV, da Silva PM, de Moura MC, Coelho LC, do Nascimento AE, et al. Evaluation of Moringa oleifera Seed Lectin as a Metal Remover in Aqueous Solutions. Protein Pept Lett. 2016;23(7):645-9.
11. Bagheri A, Abu-Danso E, Iqbal J, Bhatnagar A. Modified biochar from Moringa seed powder for the removal of diclofenac from aqueous solution.Environ Sci Pollut Res Int. 2020;27(7):7318-27.
12. Santos AF, Matos M, Sousa Â, Costa C, Nogueira R, Teixeira JA, et al. Removal of tetracycline from contaminated water by Moringa oleifera seed preparations. Environ Technol. 2016;37(6):744-51.
13. Moura MC, Trentin DS, Napoleão TH, Primon-Barros M, Xavier AS, Carneiro NP, et al. Multi-effect of the water-soluble Moringa oleifera lectin against Serratia marcescens and Bacillus sp.: antibacterial, antibiofilm and anti-adhesive properties.J Appl Microbiol. 2017;123(4):861-74.
14. Silva LLS, Fernandes KM, Miranda FR, Silva SCC, Coelho LCBB, Navarro DMD, et al. Exposure of mosquito (Aedes aegypti) larvae to the water extract and lectin-rich fraction of Moringa oleifera seeds impairs their development and future fecundity. Ecotoxicol Environ Saf. 2019 Nov 15;183:109583.
15. de Medeiros MLS, de Moura MC, Napoleão TH, Paiva PMG, Coelho LCBB, Bezerra ACDS, et al. Nematicidal activity of a water soluble lectin from seeds of Moringa oleifera. Int J Biol Macromol. 2018;108:782-9.
16. Yurre AR, Silva JD, Torres MK, Martins EL, Ramos IP, Lima da Silva WS, et al. Avaliação dos Efeitos Cardíacos de Lectina Solúvel em Água (WSMoL) de Sementes de Moringa Oleifera . Arq Bras Cardiol. 2020; 114(6):1029-1037.

Prevalence of Orthostatic Hypotension and the Distribution of Pressure Variation in the Longitudinal Study of Adult Health

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Abstract

Background: **Orthostatic hypotension (OH) has been neglected in clinical practice, and there are no studies on its prevalence in the Brazilian population.**

Objective: **To determine the prevalence of OH and blood pressure (BP) changes after the postural change maneuver in participants of the Longitudinal Study of Adult Health.**

Methods: **In this descriptive study of baseline data (N = 14,833 adults, ages 35 – 74 years), participants remained lying down for 20 minutes and subsequently stood up actively. BP measurements were taken while the participants were supine and at 2, 3, and 5 minutes after standing. OH was defined as a reduction of ≥ 20 mmHg in systolic BP and/or a reduction of ≥ 10 mmHg in diastolic BP at 3 minutes, and its prevalence was determined with a 95% confidence interval (CI). The distribution of BP variation after the postural change maneuver was determined in a subsample (N = 8,011) obtained by removing patients with cardiovascular morbidity and/or diabetes.**

Results: **The prevalence of OH was 2.0% (95% CI: 1.8 – 2.3), increasing with age. If the criterion applied were a BP reduction during any measurement, the prevalence would increase to 4.3% (95% CI: 4.0 – 4.7). Symptoms (dizziness, scotoma, nausea, etc.) were reported by 19.7% of participants (95% CI: 15.6 – 24.6) with OH and 1.4% (95% CI: 1.2 – 1.6) of participants without OH. The −2 Z-scores of BP variation before and after the postural change maneuver in the subsample were −14.1 mmHg for systolic BP and −5.4 mmHg for diastolic BP.**

Conclusion: **Prevalence of OH varies depending on when BP is measured. Current cutoff points may underestimate the actual occurrence of OH in the population. (Arq Bras Cardiol. 2020; 114(6):1040-1048)**

Keywords: **Hypotension, Orthostatic/epidemiology; Prevalence; Coronary Artery Disease; Blood Pressure; Standing Position.**

Introduction

Longitudinal studies have shown that orthostatic hypotension (OH) is a predictor of increased risk of overall mortality and other health issues, such as coronary artery disease, cerebrovascular disease, atrial fibrillation, heart failure, and new cases of hypertension.[1-5]

Current guidelines define OH as a sustained reduction of 20 mmHg in systolic blood pressure (SBP) and/or 10 mmHg in diastolic blood pressure (DBP) within 3 minutes after standing.[6] The same consensus statement also suggests a reduction of 30 mmHg in SBP in individuals with hypertension as a more adequate criterion.

Since the first definition of OH,[7] the number of studies investigating the prevalence of this finding in the general population has been low, and there has been great divergence in the methodology for measuring blood pressure (BP) and even in the criteria for definition. Most of the studies have been carried out in specific populations, such as elderly patients; patients with diabetes, hypertension, or Alzheimer's disease; or hospitalized or institutionalized individuals.[8]

Even though it is a simple and inexpensive assessment, BP measurement with the postural change maneuver is not commonly used in clinical practice, and few epidemiological studies have evaluated the measurement, its associated factors, and its implications for general health status. The prevalence of OH found in populations that most approximate the general population differs greatly according to age, varying, mostly, from around 5% (45 to 64 years of age) to 30% in studies including only elderly individuals (> 65 years).[4,9] Practically all of the studies carried out have been in populations from North America,[5,10] Europe,[1,2] and Asia,[11] and none of them have applied the criteria of a reduction of 30 mmHg in SBP for patients with hypertension.

This study's objectives were to determine the prevalence of OH in a Brazilian population, to verify its association with symptoms, and to describe the distribution of BP changes following the postural change maneuver.

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Methods

Study design and population

This is a descriptive study carried out with data collected at the baseline (2008 – 2010) of the Longitudinal Study of Adult Health (ELSA-Brazil), with a cohort of 15,105 civil servants of both sexes, between 35 and 74 years of age, whose main objective was to determine the incidence of chronic diseases and their determinants in the Brazilian population. The study is being carried out in six centers of investigation located in public higher education and research institutes, the participants being active or retired civil servants from these institutes. Details on sampling, recruiting, and data collected at the baseline have been previously published.[12,13] This study included all the participants of the ELSA-Brazil, with the exception of those who did not have complete data on the postural change maneuver. The final sample was composed of 14,833 individuals (Figure 1).

Postural change maneuver and orthostatic hypotension

To perform the postural change maneuver, participants remained lying down for approximately 20 minutes while they were submitted to the protocol for measuring ankle-brachial index (ABI). Three BP measurements were obtained in the right arm in the supine position, with two-minute intervals between them. The average of the last two measurements was used as the supine BP value. Subsequently, the assessor instructed the participant the stand up (with help, if necessary) and to maintain an upright posture, standing only on his or her feet. BP was measured again at 2, 3, and 5 minutes after standing, without supporting the participant's arm.[14] Assessors were instructed to take note of spontaneously reported symptoms (dizziness, visual alterations, nausea, etc.) on a specific form. Depending on the intensity of symptoms, it was possible to alter the protocol and measure BP in the seated position.

Assessors received routine training, certification, and periodic recertification. Supervisors who were trained and certified on the central level trained local teams.[14]

All BP measurements were obtained using a validated oscillometric device (Omron HEM 705CPINT, Japan),[15] and cuff size was chosen according to arm circumference. It was necessary to use a mercury sphygmomanometer (Unitec, Brazil) for 27 participants, owing to failure to read the oscillometric device. Another 14 participants were unable to maintain orthostasis for all BP measurements, and their BP increased when they returned to the supine position. For these individuals, a correction is made based on the average BP variations or the individuals who remained standing with the same values of reduced pressure.

OH was defined as the presence of a reduction in SBP of ≥ 20 mmHg and/or DBP of ≥ 10 mmHg in the measurement at 3 minutes after standing.[6,7] Subsequently, prevalence was evaluated considering a BP reduction in any measurement or applying a reduction of ≥ 30 mmHg in SBP for patients with hypertension.

Statistical analysis

The prevalence of OH was determined by sex, age range, race/color, and level of schooling. Data on prevalence were shown as frequency and 95% confidence intervals (CI). With the aim of avoiding the influence of the cardiovascular diseases or diabetes, the prevalence of OH was recalculated for a subsample generated by the removal of patients with hypertension (whether or not they were using anti-hypertensive medication), diabetes, self-reported heart failure, prior coronary disease (infarction or stent placement), and stroke. The average and standard deviation (SD) for age were also described for each subsample. Furthermore, the prevalence of symptoms related to postural change in individuals with or without OH was verified.

Average and SD were also described for variations in BP (pressure variation: orthostatic BP minus supine BP) by age range and overall, for variations in both SBP and DBP. Finally, the prevalence of OH was calculated considering pressure reductions at 2, 3, and 5 minutes and applying the criterion of a reduction of ≥ 30 mmHg in SBP at 3 minutes for patients with hypertension. A Venn diagram was also developed for the three different measurements. Analyses were carried out using Microsoft Office Excel and IBM SPSS Statistics 21.

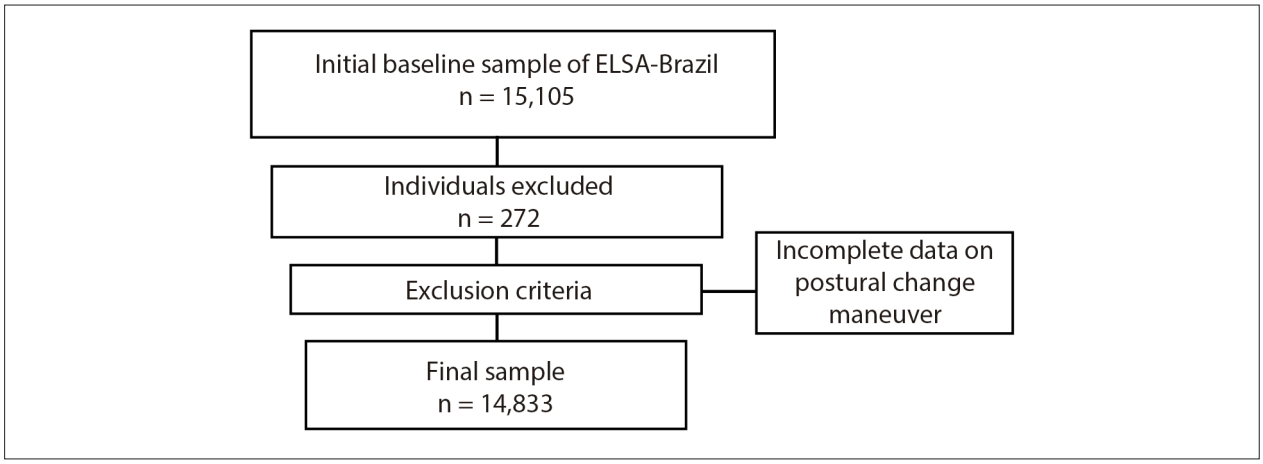

Figura 1 - *Fluxograma do estudo.*

Ethics

The ELSA-Brazil received approval from the Research Ethics Committees of the institutions involved, and all participants signed a consent form.[16]

Results

The prevalence of OH by sex, age range, race/color, and level of schooling in the study population and the subsample is shown in Table 1. The average age of the total study population was higher than that of the subsample (52.1 ± 9 years *versus* 49.1 ± 8.2 years, respectively; $p < 0.01$). The prevalence of OH in these two groups was 2.0% (95% CI: 1.8 –2.3) and 1.5% (95% CI: 1.3 – 1.8), respectively. In the entire population, considering individuals under the age of 60 and those 60 or over separately, the prevalence of OH was 1.6% (95% CI: 1.4 – 1.9) and 3.2% (95% CI: 2.8 – 4.1), respectively. In the subsample, these values were 1.4% (95% CI: 1.1 – 1.7; average age of 47.2 years) and 2.6% (95% CI: 1.8 – 3.8; average age of 64.3 years), respectively. The effect of age is ever clearer when grouping individuals by decades. It was observed that the prevalence below the age of 55 was practically identical in the total population and the subsample. After this age, the subsample presented a lower prevalence. Another factor that impacted prevalence was level of schooling; there was a progressive increase in prevalence among participants with lower levels, in both the total population and the subsample.

Protocol changes were reported in 775 (5.2%) individuals. Of these cases, 33.7% (260 individuals, 1.8% of the total population) reported the occurrence of signs and symptoms suggestive of OH (dizziness, difficulty standing without support, nausea, and rarely vomiting). Protocol changes in other cases generally resulted from physical limitations that complicated performance of the maneuver, use of the arm or the left leg (ABI), and use of the mercury sphygmomanometer.

Report of symptoms associated with OH occurred in only 1.4% (95% CI: 1.2 – 1.6) of individuals without OH; this value increased to 19.7% (95% CI: 15.6 –24.6) in individuals with OH and to 43% (95% CI: 33.0 – 53.6) when defining OH as a reduction in both pressures.

Average values and SD of SBP and DBP with the postural change maneuver for the entire cohort and the subsample are described by sex and age range in Table 2. It was observed that, on average, pressure variations were positive, with no differences between sexes and age groups.

Figure 2A shows pressure variations by range of difference. It was observed that the variation was generally situated from −10 to +10 mmHg for SBP, with increases of up to 10 mmHg in DBP. SBP increased in 66.4% of the population, and DBP increased in 88.0%. Figure 2B contains the histogram of the variations in the subsample. Average values minus two SD and the current reference value are indicated. The variations follow normal and similar distribution, and the current cutoff points are located between two and three SD below the average.

The prevalence at 3 minutes, when applying the criterion of a reduction of 30 mmHg for individuals with hypertension was 1.5% (95% CI: 0.3 – 1.7), with a total of 222 participants. Furthermore, with respect to measurement at 3 minutes,

Table 1 - Prevalence of orthostatic hypotension by sociodemographic data, ELSA-Brazil (2008 – 2010)

Variables		Orthostatic hypotension		
		Present	Total	Prevalence (95% CI*)
Study population (n = 14,833)				
Sex	Male	135	6,796	2.0 (1.7 - 2.4)
	Female	165	8,037	2.0 (1.8 - 2.4)
Age range	35 to 44 years	39	3,298	1.2 (0.9 - 1.6)
	45 to 54 years	93	5,825	1.6 (1.3 – 2.0)
	55 to 64 years	116	4,157	2.8 (2.3 - 3.3)
	65 to 74 years	52	1,553	3.3 (2.6 - 4.3)
Color/race	Black	59	2,342	2.5 (2.0 - 3.2)
	Mixed	81	4,110	1.9 (1.6 - 2.4)
	White	139	7,679	1.8 (1.5 - 2.1)
	Yellow/Indigenous	13	525	2.5 (1.5 - 4.2)
Highest level of schooling completed	Primary	57	1,883	3.0 (2.3 - 3.9)
	Secondary	110	5,133	2.1 (1.8 - 2.6)
	Tertiary	133	7,817	1.7 (1.4 - 2.0)
Total		300	14,833	2.0 (1.8 – 2.2)
Subsample of the study population† (n = 8,011)				
Sex	Male	56	3,289	1.7 (1.3 - 2.2)
	Female	66	4,722	1.4 (1.1 - 1.8)
Age range	35 to 44 years	33	2,570	1.3 (0.9 - 1.8)
	45 to 54 years	50	3,388	1.5 (1.1 - 1.9)
	55 to 64 years	30	1,688	1.8 (1.2 - 2.5)
	65 to 74 years	9	365	2.5 (1.3 - 4.6)
Color/race	Black	16	1,223	1.3 (0.8 - 2.1)
	Mixed	39	2,219	1.8 (1.3 - 2.4)
	White	63	4,181	1.5 (1.2 - 1.9)
	Yellow/Indigenous	3	284	1.1 (0.4 - 3.1)
Highest level of schooling completed	Primary	15	645	2.3(1.4 - 3.8)
	Secondary	39	2,643	1.5 (1.1 - 2.0)
	Tertiary	68	4,723	1.4 (1.1 - 1.9)
Total		122	8,011	1.5 (1.3 - 1.8)

**95% CI: 95% confidence interval; †: Study population following the exclusion of patients with hypertension, diabetes, history of heart failure, severe coronary disease, infarction, and stroke, as well as those using anti-hypertensive medication.*

Table 2 - Variation in systolic and diastolic pressure (mmHg) at 3, in the total study population and the subsample, by sex and age range, ELSA-Brazil (2008 – 2010)

Age range by sex		Δ SBP (mmHg)				Δ DBP (mmHg)			
		Average (μ)	Standard deviation (σ)	μ-2σ	μ-3σ	Average (μ)	Standard deviation (σ)	μ-2σ	μ-3σ
Study population (n = 14,833)									
	Total	3.62	9.72	−15.81	−25.53	7.05	6.56	−6.07	−12.64
Total	Male	3.80	9.51	−15.21	−24.72	7.33	6.63	−5.93	−12.56
	Female	3.47	9.89	−16.31	−26.20	6.81	6.50	−6.18	−12.67
	Total	4.05	8.34	−12.63	−20.97	8.67	6.34	−4.00	−10.34
35 to 44 years	Male	3.99	8.44	−12.89	−21.33	9.22	6.13	−3.05	−9.18
	Female	4.10	8.25	−12.40	−20.65	8.19	6.48	−4.76	−11.24
	Total	3.59	9.06	−14.53	−23.59	7.29	6.51	−5.74	−12.26
45 to 54 years	Male	4.04	8.74	−13.44	−22.18	7.81	6.69	−5.57	−12.26
	Female	3.21	9.30	−15.39	−24.69	6.85	6.33	−5.82	−12.15
	Total	3.23	10.70	−18.16	−28.86	6.15	6.44	−6.74	−13.18
55 to 64 years	Male	3.27	10.56	−17.85	−28.40	6.22	6.38	−6.55	−12.94
	Female	3.20	10.81	−18.41	−29.22	6.09	6.49	−6.89	−13.38
	Total	3.91	11.81	−19.70	−31.51	5.13	6.64	−8.15	−14.79
65 to 74 years	Male	3.86	11.21	−18.57	−29.78	4.55	6.57	−8.58	−15.15
	Female	3.96	12.38	−20.79	−33.17	5.70	6.67	−7.63	−14.30
Subsample of the study population* (n = 8,011)									
	Total	3.77	8.93	−14.09	−23.03	7.48	6.43	−5.39	−14.96
Total	Male	3.76	8.83	−13.90	−22.73	7.89	6.40	−4.90	−15.79
	Female	3.78	9.01	−14.23	−23.24	7.19	6.44	−5.70	−14.38
	Total	4.17	8.35	−12.53	−20.88	8.70	6.30	−3.91	−17.39
35 to 44 years	Male	3.99	8.53	−13.08	−21.61	9.25	6.16	−3.07	−18.49
	Female	4.32	8.21	−12.10	−20.31	8.27	6.38	−4.49	−16.54
	Total	3.59	8.67	−13.76	−22.43	7.31	6.35	−5.39	−14.62
45 to 54 years	Male	3.92	8.33	−12.74	−21.07	7.83	6.28	−4.74	−15.66
	Female	3.36	8.89	−14.43	−23.32	6.95	6.37	−5.79	−13.90
	Total	3.50	9.80	−16.11	−25.91	6.37	6.38	−6.38	−12.74
55 to 64 years	Male	3.00	9.75	−16.49	−26.23	6.41	6.41	−6.40	−12.82
	Female	3.79	9.83	−15.87	−25.70	6.34	6.36	−6.38	−12.69
	Total	3.89	10.80	−17.71	−28.52	5.64	6.88	−8.13	−11.27
65 to 74 years	Male	3.65	10.92	−18.19	−29.11	4.80	6.62	−8.43	−9.61
	Female	4.08	10.73	−17.39	−28.12	6.29	7.04	−7.79	−12.57

*Δ: difference in pressure before and after standing; μ: average; σ: standard deviation; *: Study population following the exclusion of patients with hypertension, diabetes, history of heart failure, severe coronary disease, infarction, and stroke, as well as those using anti-hypertensive medication.*

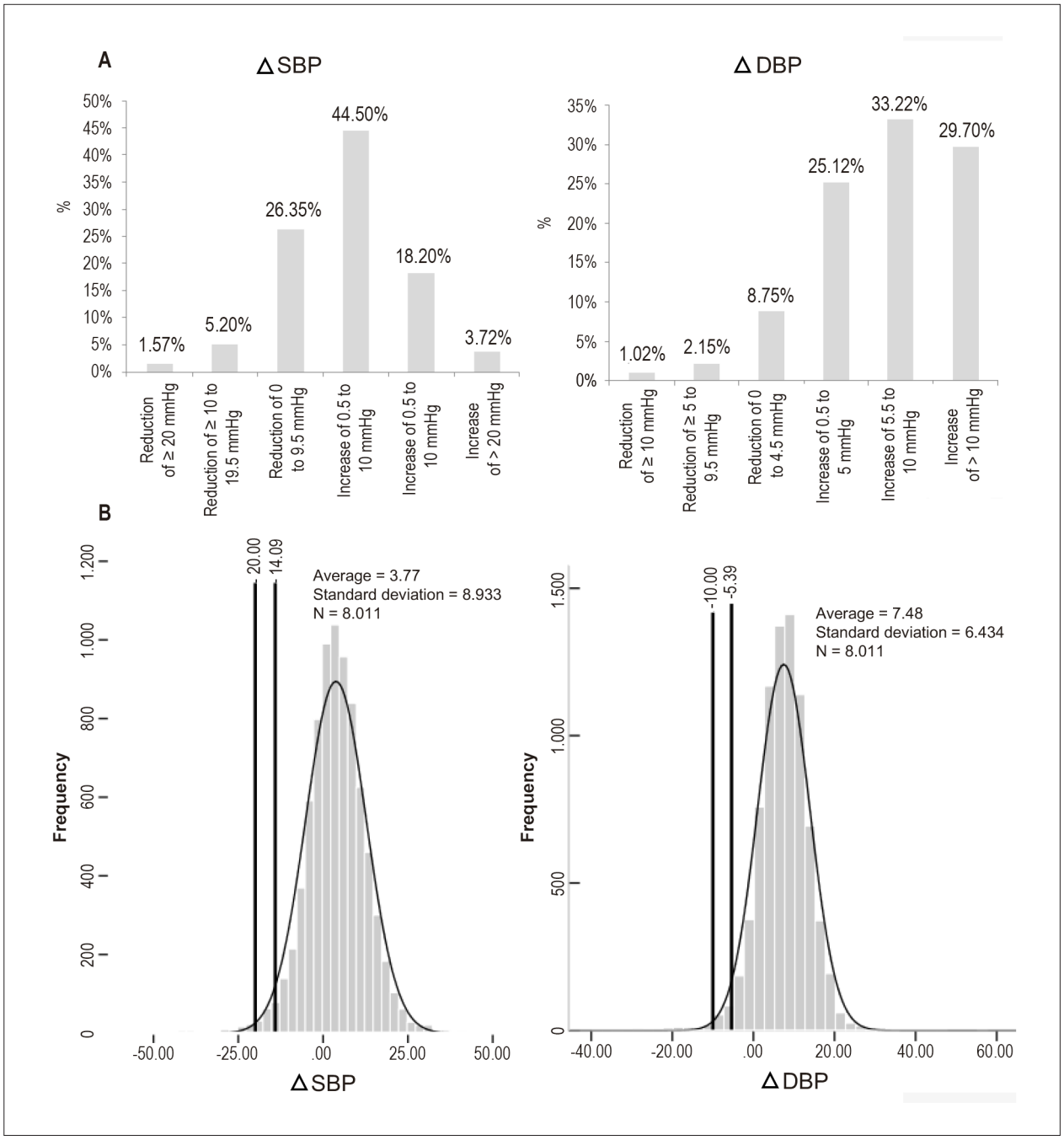

Figure 2 – *A) Alteration in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3 minutes after standing, by age group, in the entire study population, ELSA-Brazil (2008 – 2010). B) Histogram of SBP and DBP variation at 3 minutes after standing, in the subsample of the study population, ELSA-Brazil (2008 – 2010).*

considering a reduction in both pressures, prevalence was 0.6% (95% CI: 0.5 – 0.7); considering a reduction in SBP alone, prevalence was 1.6% (95% CI: 1.4 – 1.8), and, considering a reduction in DBP alone, it was 1.0% (95% CI: 0.9 – 1.2).

Figure 3 shows the Venn diagram for OH at 2, 3, and 5 minutes. It may be observed that 265 individuals presented OH at 2 minutes, a prevalence of 1.8% (95% CI: 1.6 – 2.0), whereas 385 individuals presented OH at 5 minutes, a prevalence of 2.6% (95% CI: 2.4 – 2.9). In the total sample, 94 individuals presented OH at all measurements. Once again, no significant differences were observed for sex or race/color, but there was an important progression with age and with lower levels of schooling. The presence of symptoms related to OH was reported in 10.2% (95% CI: 7.1 – 14.4) of individuals who presented OH at 2 minutes and 17.4% (95% CI: 13.9 – 21.5) of those who presented OH at 5 minutes.

The prevalence of OH, considering the existence of a reduction in pressure at 2 or 3 minutes, increases to 2.9%

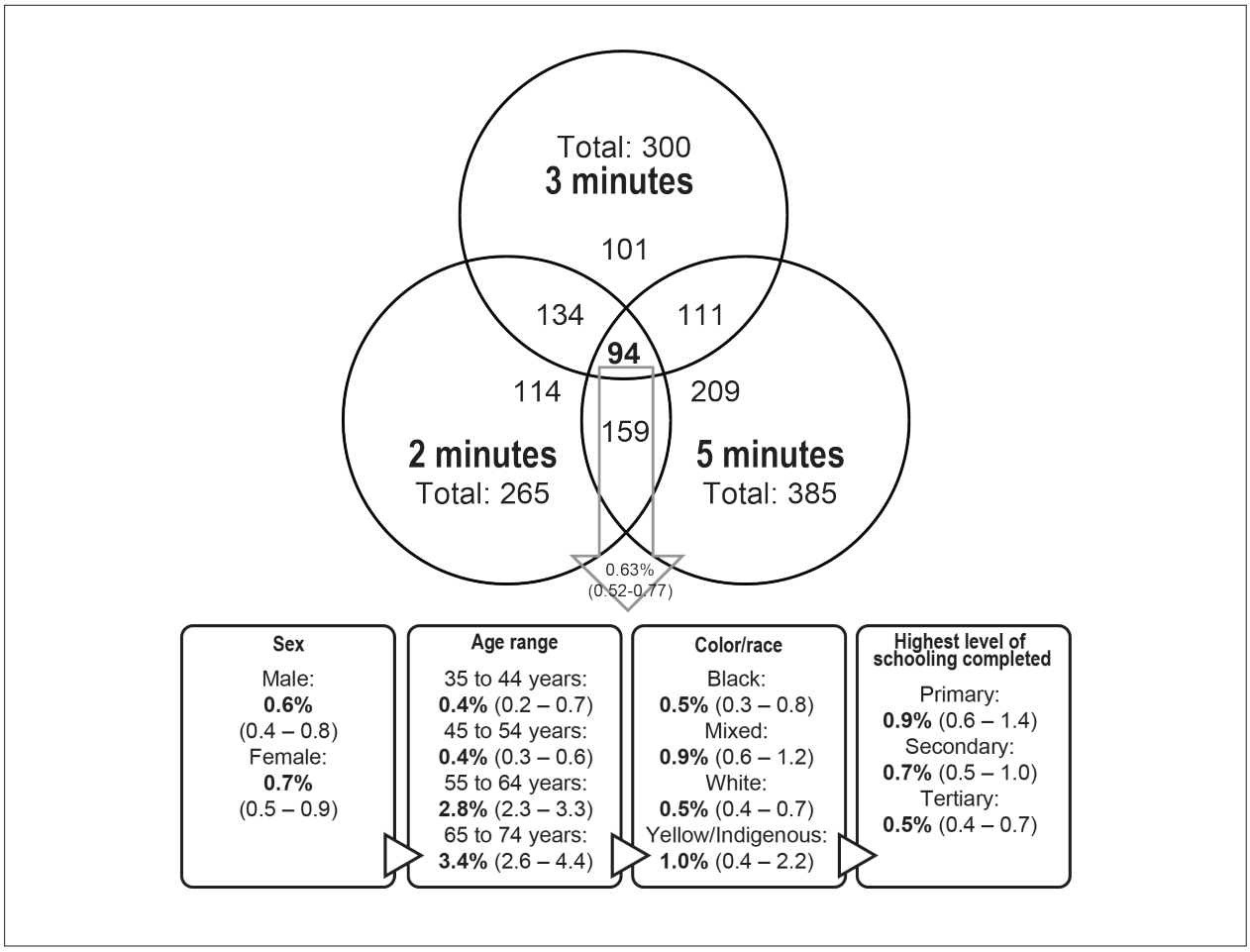

Figure 3 - *Venn diagram for orthostatic hypotension at 2, 3, and 5 minutes, including description of total prevalence and prevalence by sociodemographic data of individuals with orthostatic hypotension during all three measurements, ELSA-Brazil (2008 – 2010).*

(95% CI: 2.7 – 3.2), and it reaches 4.3% (95% CI: 4.0 – 4.7) when considering a reduction in pressure in at least one of the three measurements. In the population over the age of 60, these values would be 5.1% (95% CI: 4.4 – 5.9) and 7.3% (95% CI: 6.5 – 8.2), respectively.

Discussion

To the best of our knowledge, this is the first study on the prevalence of OH in a large sample of the Brazilian population. It is noteworthy that the finding of 2.0% was similar in men and women, and it showed clear growth with age, especially after the age of 55. In the subsample generated with fewer confounding factors, prevalence decreased to 1.5%. This decreased results mainly from differences in age ranges over 55.

The comparability of the data between studies on OH is complicated, given the diversity of the characteristics of the populations, especially with respect to age range, and to the heterogeneity of methods used to perform the postural change maneuver. In non-specific populations similar to the general population, prevalence is found to vary from 2.73%[5] to 58.6%.[17] The lowest (2.73%) was described in the participants of the Atherosclerosis Risk in Communities (ARIC) Study, whose average age was 53 years, making it similar to the baseline of the ELSA-Brazil. In the ARIC, BP was measured in the supine position and then while standing, every 30 seconds for 2 minutes, using the average of these measurements (excluding the first one) to define OH. It is worth noting that the participants were normotensive. In contrast, in Cooke et al. (58.6%),[17] average age was 73 years, and BP was measured continuously (beat-to-beat), for 3 minutes on a tilt table at 70°. OH was defined as any drop in pressure at any moment during monitoring, regardless of duration. Thus, the differences in prevalence result from the diversity of the populations and the methods, the only common feature being the cutoff points for reduction in pressure. In our sample, considering a reduction in pressure at 2 or 3 minutes, or a reduction in any measurement, the prevalence increased to 2.9% and 4.3%, respectively; the latter is more than double the prevalence at the third minute alone (2.0%), which has been the most reported moment in studies described in the literature.

There is a great deal of variation with respect to timing of measurement. There are studies measuring BP after standing

for 3 minutes;[18] after 1 and 3 minutes, considering a reduction in one of the measurements in relation to the measurement in the supine position;[19] with seated participants;[20] after 1 minute;[3] after 1, 2, and 3 minutes;[21] after 1, 2, and 5 minutes;[22] considering a reduction in any measurement; measuring continuously, considering a reduction between 60 and 110 seconds;[23] and others.[11,24]

The current guidelines recommend defining OH as a reduction in pressure within 3 minutes[6] after standing. There is, however, no consensus regarding the best moment within this period. In order to determine the most appropriate moment, one study[25] evaluated 407 elderly patients (average age of 78.7 ± 7.8 for patients with OH and 74.1 ± 8.6 for patients without OH at 3 minutes) 1, 3, and 5 minutes after standing. The prevalences were 21.86%, 21.37%, and 19.90%, respectively, and the parameters associated with OH were the same during the three moments. It stands out that 29 elderly patients presented OH only during the first minute, 18 only during the third, and 12 only during the fifth. The authors suggest adopting 1 minute for use in clinical practice, because it requires less time (which is especially important in elderly patients) and identifies the majority of cases. It is worth noting that, were the definition of OH based on a reduction in pressure at any moment, the prevalence would be higher.

Other studies[26,27] suggest longer evaluations, of up to 10 minutes, given that many participants develop OH in a delayed manner. In our study, with a lower average age (52.1 ± 9.1 years), some participants also developed more delayed reductions in pressure, given that prevalence was higher at 3 minutes than that at 2, and it was highest at 5.

It is necessary to use caution in interpreting data from continuous BP monitoring after standing. In these cases, a physiological decline in pressure may be expected after standing, especially in elderly patients, who are more susceptible to a sudden decrease in venous return and systolic output, until compensation mechanisms stabilize BP. Finucane et al.[10] observed stabilization within 30 seconds in individuals between 50 and 59 years of age and within over 30 seconds in older individuals. Keeping this initial reduction in mind, it may be inappropriate to consider a reduction at any moment as OH. Studies conducted in this manner have found very high prevalences, such as that of 58.6% found by Cooke et al.[17] These values must contain a large quantity of false positives. Cooke et al.[17] mention that, were they to consider sustained reductions in BP with a minimum duration of 60 seconds, the prevalence would drop to 23.3%, and it would be only 9% if they considered reductions sustained for 180 seconds.

With these considerations regarding the heterogeneity of populations and methods, the comparison between studies should proceed cautiously. Studies in populations with age ranges similar to the ELSA-Brazil showed prevalences between 2.73%[5] and 7.4%[28] with the articles referring to to cohorts of the ARIC[4,5,28] and the Malmo Preventive Project (MPP) standing out.[1,2] The variations results from exclusions in the samples depending on the outcomes of each article. Most articles of the ARIC present a prevalence of approximately 5%. In all of them, the average age was around 53 years. The articles of the MPP present a prevalence of approximately 6% and very similar samples, with an average age of 48 years.

It is noteworthy that studies on prevalence in individuals under the age of 45 are scarce. We found only one[20] with individuals from 18 to 100 years of age (average age of 49). However, the prevalence by age range was not mentioned.

The increase in the prevalence of OH with aging is linked to a series of causes. The following may be cited: changes in baroreflex function, inadequate vasoconstrictor responses, reduced cardiac and vascular compliance, decreased blood volume, and lower efficiency of skeletal muscles to act as a pump facilitating venous return.[29] Moreover, as age advances, the prevalence of arterial hypertension is greater, and this condition is associated with OH. This, however, does not appear to have occurred in our study, seeing that the pressure increase in the total population for in the ELSA-Brazil was similar to that observed in the subsample, in relation to both SBP and DBP (Table 2).

In our population, in addition to age range, lower level of schooling also indicated a tendency to increase OH; this feature was observed both in the general sample and the subsample, with an attenuation in the latter group. It stands out that these differences in age are factors adjacent to these findings, given that groups with lower levels of schooling presented a higher average age (56.5 years in the category with lower schooling and 51.9 in the total population; in the subsample, these averages were 53.4 and 49.3 years, respectively).

In relation to the presence of symptoms, we observed that the prevalence of OH was significantly higher when a symptom characteristic of a reduction in cerebral blood flow was reported, especially when the reduction occurred in both pressures. In the Cardiovascular Health Study,[18] 20% of individuals with OH presented symptoms, and, in the Rotterdam Study,[30] this indicator was 13.9%. These values are close to those detected in the ELSA-Brazil, confirming that OH is asymptomatic in most individuals. The presence of symptoms is relevant to indicate new diagnostic evaluations and make therapeutic decisions. In the meanwhile, there are no guidelines regarding clinical decision making in patients with OH who have no symptoms.[31]

The distribution of pressures variation resulted in Z scores from −2 to −14.09 mmHg for SBP and −5.39 mmHg for DBP in the subsample of patients without hypertension (with or without medication), diabetes, history of heart failure, severe coronary disease, infarction, or stroke. Rose et al.,[5] with a sample of 6,951 participants, following the exclusion of patients with hypertension, found a value similar in the fifth percentile of the reduction in SBP (−15.25 mmHg), even using a different method. It is noteworthy that documents that defined OH[6,7] reported a cutoff point of −20 mmHg for SBP and −10 mmHg for DBP. Considering that the pressure variation presents a Gaussian distribution, the cutoff points currently recommended for defining the presence of OH would go beyond those predicted by a standard statistical criterion, namely, considering excessive variation as individuals located in the 5% below the distribution of the curve. The definition of a cutoff point beyond this limit increases the probability of false negatives, or be it, individuals with OH who would not receive adequate diagnosis and advice depending on the establishment of cutoff points based on empirical and not experimental findings.

In relation to the prevalence of OH, considering the criterion of a reduction of ≥30 mmHg in patients with hypertension, a

small decrease in prevalence was observed (from 2% to 1.5%), obviously owing to the fact that the cutoff point was shifted to the left. The suggestion of 30 mmHg is justified in the guidelines[6] due to the higher initial BP in patients with hypertension. However, in patients with hypertension in the ELSA, fewer than half presented uncontrolled BP, posing a doubt as to how to proceed in this situation, given that the definition does not address it. We found no allusion to the prevalence of OH in patients with hypertension applying this criterion in other studies.

Regarding the prevalence in other measurements, it stands out that there was an increase as time progressed, and many individuals presented OH in only one of the three pressure measurements. The simultaneous present during the three moments was only 0.6%, also showing a relation to aging, and it was 4.3% in any measurement. An associative analysis with the main factors related to OH found in the literature may indicate which moment(s) would be most appropriate for evaluating OH in this population.

Regarding the presence of symptoms and the prevalence of OH during the three moments, the individuals who presented OH at 3 minutes were the ones who most reported symptoms. It is worth remembering that there is no information regarding the exact moment when the symptoms were reported, and the symptom may have been related or occurred immediately after standing or closer to the pressure measurement at 5 minutes. The presence of symptoms, especially dizziness and syncope, may have a great impact on the individuals' health, given that it may affect their mobility and safety.

It is necessary to use caution when extending the findings in our sample to the general population, as it is a professional cohort. However, the sample was large enough to allow for subgroup analysis, and a great part of the spectrum of diversity in age, race/color, and level of schooling that exists in Brazil is represented in both sexes of the sample. Therefore, in the absence of population data, the data from the ELSA-Brazil currently constitute the best reference for the presence of OH in the Brazilian population.

Conclusion

The prevalence of OH in a sample of Brazilian civil servants was around 2%, considering the pressure measurements obtained at 3 minutes after standing. This prevalence was equal in both sexes, and age was the factor that most influenced prevalence. The pressure measurement at 3 minutes after standing is the one that best correlates with the presence of symptoms. Current cutoff points (−20 mmHg in SBP and −10 mmHg in DBP) may underestimate the real occurrence of OH in the population.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Velten APC, Bensenor I, Lotufo P, Mill JG; Acquisition of data and obtaining financing: Bensenor I, Lotufo P, Mill JG; Analysis and interpretation of the data: Velten APC, Bensenor I, Mill JG; Statistical analysis: Velten APC; Writing of the manuscript: Velten APC, Mill JG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the National Research Ethics Commission (CONEP) under the protocol number CAAE 0016.1.198.000-06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals. Eur Heart J. 2010;31(1):85-91.
2. Fedorowski A, Engström G, Hedblad B, Melander O. Orthostatic hypotension predicts incidence of heart failure: the Malmö Preventive Project. Am J Hypertens. 2010;23(11):1209–15.
3. Fedorowski A, Hedblad B, Engström G, Gustav Smith J, Melander O. Orthostatic hypotension and long-term incidence of atrial fibrillation: the Malmö Preventive Project: J Intern Med. 2010;268(4):383–9.
4. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke : the Atherosclerosis Risk in Communities (ARIC) study, 1987-1996. Stroke. 2000;31(10):2307–13.
5. Rose KM, Holme I, Light KC, Sharrett AR, Tyroler HA, Heiss G. Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC study. J Hum Hypertens. 2002;16(11):771–7.
6. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69–72.
7. Kaufmann H. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Clin Auton Res. 1996;6(2):125–6.
8. Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. J Intern Med. 2013;273(4):322–35.
9. Veronese N, Bolzetta F, De Rui M, Zambon S, Corti MC, Musacchio E, et al. Serum 25-hydroxyvitamin D and orthostatic hypotension in old people: The Pro.V.A. study. Hypertension. 2014;64(3):481–6.

10. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). Circulation. 2014;130(20):1780–9.

11. Shin C, Abbott RD, Lee H, Kim J, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study. J Hum Hypertens. 2004;18(10):717–23.

12. Aquino EM, Araujo MJ, Almeida MC, Conceição P, Andrade CR, Cade NV, et al. Participants recruitment in ELSA Brasil (Brazilian Longitudinal Study For Adult Health). Rev Saude Publica. 2013;47(Suppl 2):10–8.

13. Aquino EM, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, et al. Brazilian Longitudinal Study of Adult health (ELSA-Brasil): objectives and design. Am J Epidemiol. 2012;175(4):315–24.

14. Mill JG, Pinto K, Griep RH, Goulart A, Foppa M, Lotufo P, et al. Medical assessments and measurements in ELSA-Brasil. Rev Saude Publica. 2013;47(Suppl 2):54–62.

15. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP 5332, and Nissei DS-175. Blood Press Monit. 1996;1(1):55–61.

16. Aquino EM, Vasconcellos-Silva PR, Coeli CM, Araújo MJ, Santos SM, Figueiredo RC, et al. Ethical issues in longitudinal studies: the case of ELSA-Brasil. Rev Saude Publica. 2013;47(Suppl 2):19–26.

17. Cooke J, Carew S, Quinn C, O'Connor M, Curtin J, O'Connor C, et al. The prevalence and pathological correlates of orthostatic hypotension and its subtypes when measured using beat-to-beat technology in a sample of older adults living in the community. Age Ageing. 2013;42(6):709–14.

18. Alagiakrishnan K, Patel K, Desai R V, Ahmed MB, Fonarow GC, Forman DE, et al. Orthostatic hypotension and incident heart failure in community-dwelling older adults. J Gerontol A Biol Sci Med Sci. 2014;69A(2):223–30.

19. Curreri C, Giantin V, Veronese N, Trevisan C, Sartori L, Musacchio E, et al. Orthostatic changes in blood pressure and cognitive status in the elderly: the Progetto Veneto Anziani Study. Hypertension. 2016;68(2):427–35.

20. Vara-González L, Muñoz-Cacho P, Sanz de Castro S. Postural changes in blood pressure in the general population of Cantabria (northern Spain). Blood Press Monit. 2008;13(5):263–7.

21. Verwoert GC, Mattace-Raso FUS, Hofman A, Heeringa J, Stricker BH, Breteler MM, et al. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. J Am Geriatr Soc. 2008;56(10):1816–20.

22. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, van den Meiracker AH, Schalekamp MAA, et al. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. J Hypertens. 2006;24(2):339–44.

23. Finucane C, O'Connell MD, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. J Am Geriatr Soc. 2017;65(3):474–82.

24. O'Connell MD, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: the Irish Longitudinal Study on Aging-TILDA. Arch Gerontol Geriatr. 2015;60(3):507–13.

25. Soysal P, Aydin AE, Koc Okudur S, Isik AT. When should orthostatic blood pressure changes be evaluated in elderly: 1st, 3rd or 5th minute? Arch Gerontol Geriatr. 2016 Jul-Aug;65:199–203.

26. Campos AC, De Almeida NA, Ramos AL, Vasconcelos DF, Freitas MP, Toledo MA. Orthostatic hypotension at different times after standing erect in elderly adults. J Am Geriatr Soc. 2015;63(3):589–90.

27. Pavy-Le Traon A, Piedvache A, Perez-Lloret S, Calandra-Buonaura G, Cochen-De Cock V, Colosimo C, et al. New insights into orthostatic hypotension in multiple system atrophy: a european multicentre cohort study. J Neurol Neurosurg Psychiatry. 2016;87(5):554-61.

28. Bell EJ, Agarwal SK, Cushman M, Heckbert SR, Lutsey PL, Folsom AR. Orthostatic hypotension and risk of venous thromboembolism in 2 Cohort Studies. Am J Hypertens. 2016;29(5):634–40.

29. Kanjwal K, George A, Figueredo VM, Grubb BP. Orthostatic hypotension. J Cardiovasc Med. 2015;16(2):75–81.

30. Wolters FJ, Mattace-Raso FUS, Koudstaal PJ, Hofman A, Ikram MA, Heart Brain Connection Collaborative Research Group. Orthostatic hypotension and the long-term risk of dementia: a Population-Based Study. PLoS Med. 2016;13(10):e1002143.

31. Miller ER 3rd, Appel LJ. High prevalence but uncertain clinical significance of orthostatic hypotension without symptoms. Circulation. 2014;130(20):1772–4.

The Uncommon Orthostatic Hypotension in Brazil: Are We Underestimating the Problem?

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Short Editorial related to the article: Prevalence of Orthostatic Hypotension and the Distribution of Pressure Variation in the Longitudinal Study of Adult Health

Blood pressure (BP) homeostasis depends on complex physiological mechanisms that involve continuous interactions of the cardiovascular, renal, neural, and endocrine systems. These mechanisms must also guarantee the maintenance of adequate cardiac output, even in situations of rapid circulatory variations. One of these situations is related to the dynamic posture changes, from lying to standing, when the rapid reduction in venous return can affect preload, stroke volume, and mean BP. Orthostatic hypotension (OH) is a manifestation of autonomic dysfunction and occurs when cardiovascular adaptive mechanisms fail to compensate for those changes when assuming the standing position.[1]

Diagnosing OH requires the demonstration of significant persistent BP decrease during orthostasis, either by the bedside active-standing test or a tilting test. National and international guidelines have endorsed the definition of OH as a ≥20 mmHg drop in systolic blood pressure (SBP) or a ≥10 mmHg drop in diastolic blood pressure (DBP) within 3 minutes after standing, regardless of the presence of symptoms.[2-4] This definition was first established by a consensus in 1996 and was based on several small physiology studies as well as on pragmatic considerations.[5] Upon this definition, growing evidence has been shown that OH predicts all-cause mortality[6,7] and incidence of cardiovascular disease,[7,8] being even more relevant than the ambulatory BP monitoring-derived nighttime reverse dipping for predicting cardiovascular events[9]. A recent meta-analysis involving 121,913 individuals and a median follow-up of 6 years reported that OH was associated with a 50, 41, and 64% greater risks of all-cause death, coronary heart disease, and stroke, respectively.[8]

In order to determine the prevalence of OH in a Brazilian population, Velten and colleagues present in this issue of the Archives a detailed analysis of the blood pressure behavior following postural maneuvers in 14,833 individuals from the ELSA-Brasil study.[10] The ELSA-Brasil cohort included 15,105 civil servants aged 35 to 74 years old from 5 universities and 1 research institute located in different regions of Brazil. The study was carried out from 2008 through 2010 and was designed to address the incidence of cardiovascular diseases and major associated risk factors among active or retired employees from those institutions.[11] The reported prevalence of OH in this population was 2.0%, and increasing with age, reaching up to 3.3% in individuals between 65 and 74 years old. Among those with positive screening for OH, the presence of symptoms was noted in 19.7 vs. only 1.4% among those without OH. Symptoms were reported in up to 43% of individuals who had a concomitant fall in SBP and DBP.

For beyond an epidemiological study, in a country where much of these data are scarce or absent, this study raises some issues that deserve to be addressed. First, the prevalence of OH in this cohort was low. Unfortunately, there are no other studies in the literature that have investigated the prevalence of OH in Brazil, and this is also another merit of the authors. International epidemiologic surveys have found that the prevalence of OH varies from 5 to 20 percent but can reach up to 30% in individuals over 70 years of age.[1,12] The prevalence was still much lower in this work by Velten et al.[10] than in previous reports, even in individuals aged over 64 years. The reasons for this discrepancy were not clear. A significant portion of the elderly beyond the age of 74 were excluded and could raise this number, but the baseline characteristics of the ELSA-Brasil study still pointed to a population with a high frequency of risk factors: 63.1% were overweight, 61.5% had high cholesterol, 35.8% presented with high blood pressure, and 20.3% had impaired glucose tolerance.[11] If the low prevalence could only reflect a specific population, this topic will be resumed later in this paper.

Second, as part of the protocol assessment, the postural change maneuver included BP measurements at 2, 3, and 5 minutes after standing. The authors point out that the prevalence of OH could more than double to up to 4.3% when considering the reduction in BP in at least one of the three measurements. However, when comparing only the 3- and 5-minute measurements, the prevalence of OH rises from 2.0 to 2.6%. Even though these individuals tend to be more symptomatic at 5 minutes, the increase in sensitivity for screening is small, and certainly does not justify extending the measurements beyond 3 minutes during an office evaluation.

But perhaps one of the most interesting aspects of this work was the calculation of Z-scores for BP variations, observing values lower than those established by guidelines for a specific subset of the population. The distribution of BP variation resulted in -2 Z-scores of -14.09 mmHg for SBP and -5.39 mmHg for DBP in the subsample of patients without hypertension, diabetes, history of heart failure, coronary heart disease, previous myocardial infarction, or stroke. This

Keywords

Hypotension, Orthostatic/complications; Epidemiology; Cardiovascular Diseases; Stroke; Myocardial Infarction; Hypertension; Adult, Health

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means that, in this cohort of Brazilian adults, the current national and international thresholds may underestimate the presence of OH. This difference could even explain its lower prevalence in this Brazilian cohort. Since there are autonomic reflexes involved in the physiologic blood pressure response upon standing,[1] it is reasonable to admit that we could have different variations for different populations. In other words, one number could not fit for all. The study by Velten et al.[10] provides data for a broader discussion regarding this issue. Obviously, more data will be needed in diverse populations, since the ELSA-Brasil study evaluated only a specific sample of employees from six Brazilian institutions.

Regardless of whether to engage into discussions about the thresholds for OH in the country — if a drop of 20 or 14 mmHg in SBP —, this does not change the fact that the problem could continue to be neglected in clinical practice. There is a formal recommendation to measure BP 1 minute and 3 minutes after standing from a seated position in all patients at the first office evaluation to address OH.[2-4] Lying and standing BP measurements should also be considered in subsequent visits in elderly, diabetic patients, and people with other conditions in which orthostatic hypotension may frequently occur. However, even knowing the possible implications for the incidence of cardiovascular events, OH is often misdiagnosed and may be an overlooked issue in clinical practice.

Approximately two-thirds of patients with OH could not be detected if sequential BP measurements at upright position are not performed in common practice.[13] Even in a clinical study designed to evaluate the effectiveness of ambulatory BP monitor in detecting OH, only 76% of the 505 patients were screened during regular office visits.[14] Lack of time during consultations could be one of the main factors. In addition, it can now be argued that the OH prevalence in middle-aged individuals is indeed low, questioning whether we should perform systematic screening as recommended. Nevertheless, there are no doubts about the prognostic implications of OH, especially in the very elderly. Perhaps this discussion about postural hypotension deserves due attention in order to improve our sensitivity by identifying who really needs to be evaluated and what would be the expected BP variations for each group of individuals.

References

1. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis, and Treatment. J Am Coll Cardiol. 2015;66(7):848-60.
2. Malachias MVB, Souza WKSB, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT, et al., Sociedade Brasileira de Cardiologia. 7ª Diretriz Brasileira de Hipertensão Arterial. Arq Bras Cardiol. 2016;107(Supl.3):1-83.
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
4. Williams B, Mancia G, Spiering W,Agabiti Rosel E, Azizi H, Burnier H, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104.
5. Kaufmann H. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Clin Auton Res. 1996; 6(2):125–6.
6. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM, et al. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. J Am Geriatr Soc. 2008;56(10):1816-20.
7. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the Atherosclerosis Risk in Communities (ARIC) study, 1987-1996. Stroke. 2000;31(10):2307-13
8. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015;36(25):1609–17.
9. Fagard RH, De Cort P. Orthostatic hypotension is a more robust predictor of cardiovascular events than nighttime reverse dipping in elderly. Hypertension. 2010;56(1):56-61.
10. Velten APC, Bensenor I, Lotufo P, Mill JG. Prevalence of Orthostatic Hypotension and the Distribution of Pressure Variation in the Longitudinal Study of Adult Health. Arq Bras Cardiol. 2020; 114(6):1040-1048
11. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto M, et al. Cohort profile: longitudinal study of adult health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75.
12. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res. 2008;18(Suppl 1):8-13.
13. Carlson JE. Assessment of orthostatic blood pressure: measurement technique and clinical applications. South Med J. 1999;92(2):167–73.
14. Cremer A, Rousseau AL, Boulestreau R, Kuntz S, Tzourio C, Gosse P, et al. Screening for orthostatic hypotension using home blood pressure measurements. J Hypertens. 2019 May;37(5):923-27.

Coronavirus Disease 2019 and the Myocardium

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Abstract

Infection with the coronavirus known as COVID-19 has promoted growing interest on the part of cardiologists, emergency care specialists, intensive care specialists, and researchers, due to the study of myocardial involvement based on different clinical forms resulting from immunoinflammatory and neurohumoral demodulation.

Myocardial involvement may be minimal and identifiable only by electrocardiographic changes, mainly increased cardiac troponins, or, on the other side of the spectrum, by forms of fulminant myocarditis and takotsubo syndrome.

The description of probable acute myocarditis has been widely supported by the observation of increased troponin in association with dysfunction. Classical definition of myocarditis, supported by endomyocardial biopsy of inflammatory infiltrate, is rare; it has been observed in only one case report to date, and the virus has not been identified inside cardiomyocytes.

Thus, the phenomenon that has been documented is acute myocardial injury, making it necessary to rule our obstructive coronary disease based on increased markers of myocardial necrosis, whether or not they are associated with ventricular dysfunction, likely associated with cytokine storms and other factors that may synergistically promote myocardial injury, such as sympathetic hyperactivation, hypoxemia, arterial hypotension, and microvascular thrombotic phenomena.

Systemic inflammatory and myocardial phenomena following viral infection have been well documented, and they may progress to cardiac remodeling and myocardial dysfunction. Cardiac monitoring of these patients is, therefore, important in order to monitor the development of the phenotype of dilated myocardiopathy.

Keywords

Myocardium/injuries; Troponin; Inflammatory Diseases; Myocarditis; Takotsubo Syndrome; Biomarkers; Coronavirus; COVID-19; Pandemics; Cardiomyopathy, Dilated; Thrombotic Microangiopathies

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This review presents the main etiological and physiopathological findings, a description of the taxonomy of these types of cardiac involvement, and their correlation with the main clinical forms of the myocardial component present in patients in the acute phase of COVID-19.

Introduction

Myocardial injury, as shown by increased cardiac biomarkers, was identified among the first cases of COVID-19 in China. The National Health Council of China reported that almost 12% of patients without known cardiovascular disease (CVD) showed elevated levels of troponin or cardiac arrest during hospitalization.[1]

These findings have stimulated research and interest on the part of cardiologists, intensive care specialists, and clinical researchers, due to early recognition of these abnormalities, as well as the search for physiopathological mechanisms and their real impacts on prognosis.

In addition to this, individuals with previous CVD have been shown to be at a higher risk of developing severe forms and higher mortality.

Accordingly, it is of fundamental importance to understand the spectrum of myocardial involvement, whether primary or secondary, in addition to the etiological and physiopathological mechanisms involved, in order to promote the development of therapeutic strategies that can prevent and diminish myocardial aggression during the acute phase.

SARS-CoV-2 and the mechanism of direct cellular aggression

SARS-CoV-2 infection is caused by binding of the spike protein on the surface of the virus to the human angiotensin converting enzyme 2 (ACE-2) receptor after activation of the spike protein by transmembrane protease, serine 2 (TMPRSS2).

ACE-2 is expressed in the lungs, mainly in the type-II alveolar cells, and it seems to be the predominant means of entry.[2-4] SARS-CoV-2, in binding to ACE-2, causes downregulation of this enzyme, determining an increase in levels of angiotensin II, which may lead to deleterious effects in the activation of the renin-angiotensin-aldosterone system, such as vessel constriction, changes in vascular permeability, myocardial remodeling, and acute pulmonary injury, which may partially justify the frequent pulmonary symptoms in this syndrome[5] (Figure 1).[6]

ACE-2 is also highly expressed in the heart, neutralizing the effects of angiotensin II in states with excessive activation

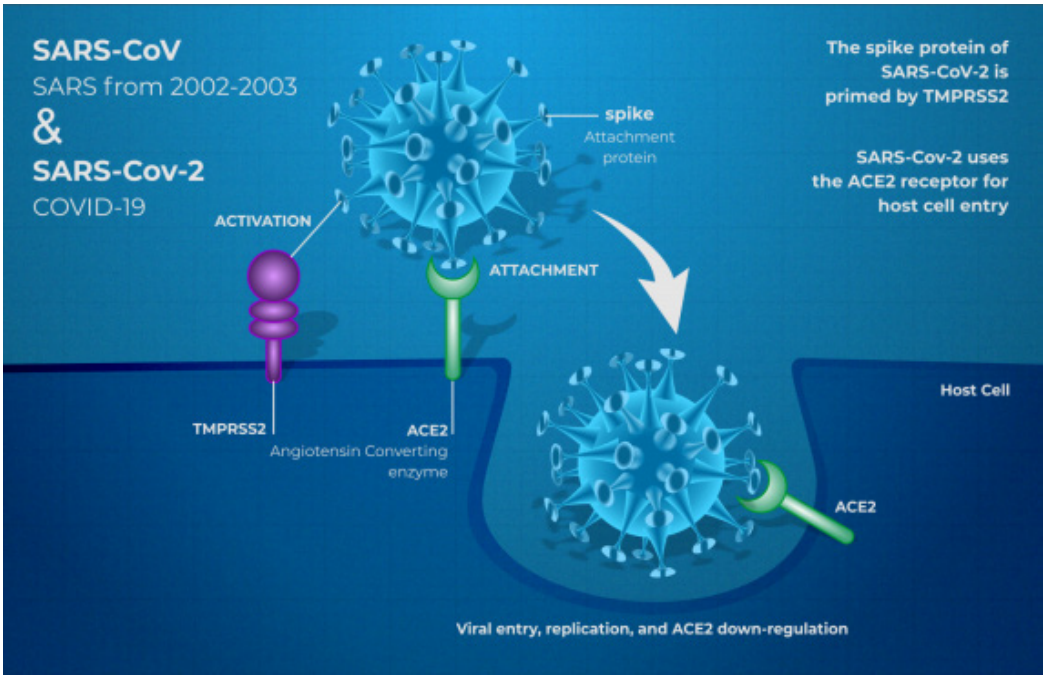

Figure 1 – *By means of its surface spike protein, SARS-CoV-2 binds to the human ACE-2 receptor following activation of the spike protein by TMPRSS2. SARS-CoV: severe acute respiratory syndrome coronavirus; SARS-COV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; ACE-2: angiotensin-converting enzyme-2; TMPRSS2: transmembrane protease, serine 2. Source: Costa IBSS, Brittar CS, Rizk SI, et al., 2020.*

of the renin-angiotensin system, such as systemic arterial hypertension (SAH), heart failure (HF), and atherosclerosis, by converting angiotensin II into angiotensin I-VII, which has a cardioprotective effect.

In addition to the heart and lungs, ACE-2 is expressed in the intestinal epithelium, vascular endothelium, and kidneys, providing a mechanism for multiple organ dysfunction, which can be observed in SARS-CoV-2 infection.

3- COVID-19 and Myocardial Injury

Increased troponin upon admission to the hospital has been associated with higher mortality in two studies involving patients hospitalized with COVID-19.[7-8]

One of these studies, which was conducted in a hospital at Wuhan University, evaluated a cohort of 416 patients hospitalized for COVID-19, with a mean age of 64 years, 50% of whom were female; the most frequent CVD was SAH (30.5%). Of the patients included, 82 (19.7%) had myocardial injury, defined as high-sensitivity troponin I above the 99th percentile. Patients with hypertension had more myocardial injury than those without hypertension (59% vs. 23%). The same was the case patients for patients with coronary artery disease (CAD) (29.3% vs. 6.0%); cerebrovascular disease (15.9% vs. 2.7%), and HF (14.6% vs. 1.5%) ($p < 0.001$ for all variables). The authors observed greater frequency of acute respiratory distress syndrome (58.5% vs. 14.7%, $p < 0.001$) and greater mortality among patients with myocardial injury (51% x 4.5%, $p < 0.001$).[7]

The second, a single-center retrospective study, evaluated a cohort of 187 patients with COVID-19. Mean age was 58 years; 35% had some CVD (SAH, CAD, or cardiomyopathy), and 43 patients progressed to death (23%). The authors observed increased troponin T in 27.8% of cases. Mortality rate was around 7% for patients without CVD and negative troponin T; this value was ten-fold when the presence of CVD was associated with the presence of cardiac injury.[7] It is worth underscoring that mortality in patients with CVD, who nonetheless had negative troponin T during infection, was not as expressive (13.3%) as mortality in those with increased troponin.[8]

Patients with increased troponin were more elderly. They had more comorbidities; higher levels of leukocytes, NT-pro-BNP, C-reactive protein, and procalcitonin; and lower lymphocyte counts.

Another study demonstrated that, on the fourth day after onset of symptoms, mean troponin levels were 8.8 pg/mL in patients who did not survive, in comparison with 2.5 pg/mL in those who survived. During follow-up, median troponin among survivors did not change significantly (2.5 – 4.4 pg/mL), while it rose to 24.7 pg/mL on the seventh day, 55.7 pg/mL on the thirteenth day, 134.5 pg/mL on the nineteenth day, and 290.6 pg/mL on the twenty-second day among patients who did not survive. Average time to death after onset of symptoms was 18.5 days (IQR 15 - 20 days).[9]

The increase in troponin was accompanied by an increase in other inflammatory biomarkers (D dimer, ferritin, interleukin-6 (IL-6), and lactate dehydrogenase), thus

increasing the chance that this reflects a cytokine storm or secondary hemophagocytic lymphohistiocytosis, rather than isolated myocardial injury.

Mechanisms of myocardial injury and COVID -19

The mechanisms of myocardial injury are not well established, but they probably involve an increase in cardiac stress due to respiratory failure and hypoxemia, acute coronary syndrome (ACS), indirect lesion from the systemic inflammatory response, direct myocardial infection by SARS-CoV-2, and other factors (Figure 2).[10]

Myocardial injury secondary to imbalance between oxygen supply and demand

Situations of severe physiological stress, such as sepsis and respiratory failure, which are present in patients with COVID-19, are associated with increased biomarkers of myocardial injury, leading to worse prognosis in some patients.[11]

The most likely mechanism is an imbalance between oxygen supply and demand, without rupture of the atheromatous plaque, consistent with diagnosis of type 2 myocardial infarction.[12,13]

These patients have higher rates of mortality when compared to those with type 1 myocardial infarction, likely as a result of a greater number of comorbities.[14]

Due to age and the comorbidity profile of patients hospitalized with severe COVID-19, it may be inferred that this population has a higher risk of underlying non-obstructive CAD and that the occurrence of type 2 myocardial contributes to increased troponin and worse outcomes.[7]

Microvascular injury

The likely mechanism of myocardial injury results from the formation of microthrombi in the myocardial vasculature, in the presence of a state of hypercoagulability as in disseminated intravascular coagulation (DIC). Changes in the coagulation and fibrinolytic systems are important in patients with COVID-19, and DIC has been observed in the majority patients who died.[15]

The mechanisms of DIC in the context of sepsis and acute respiratory distress syndrome present in these patients are complex; it is believed to be related to an exhaustion of the coagulation and fibrinolytic systems causing both bleeding and thrombosis.[16]

The increase in inflammatory cytokines, such as IL-6 and tumor necrosing factor-alpha (TNF-α), as well as endothelial injury, increase the expression of tissue factor, leading to a pro-thrombotic state.[17]

On the other hand, dysregulation of antithrombin III, plasminogen activator inhibitor type 1 (PAI-1), and protein C in significant situations of inflammation and sepsis promotes a state of anticoagulation.[18]

Furthermore, platelet activation also occurs in the context of sepsis and inflammation, changing the delicate balance of the coagulation system.[19]

In this manner, the presence of inflammation and the immune activation present in severe COVID-19 infection may lead to DIC, microvascular dysfunction, and myocardial injury.

Systemic inflammatory response

One of the likely mechanisms related to cardiac injury in patients with severe COVID-19 involves the intense systemic

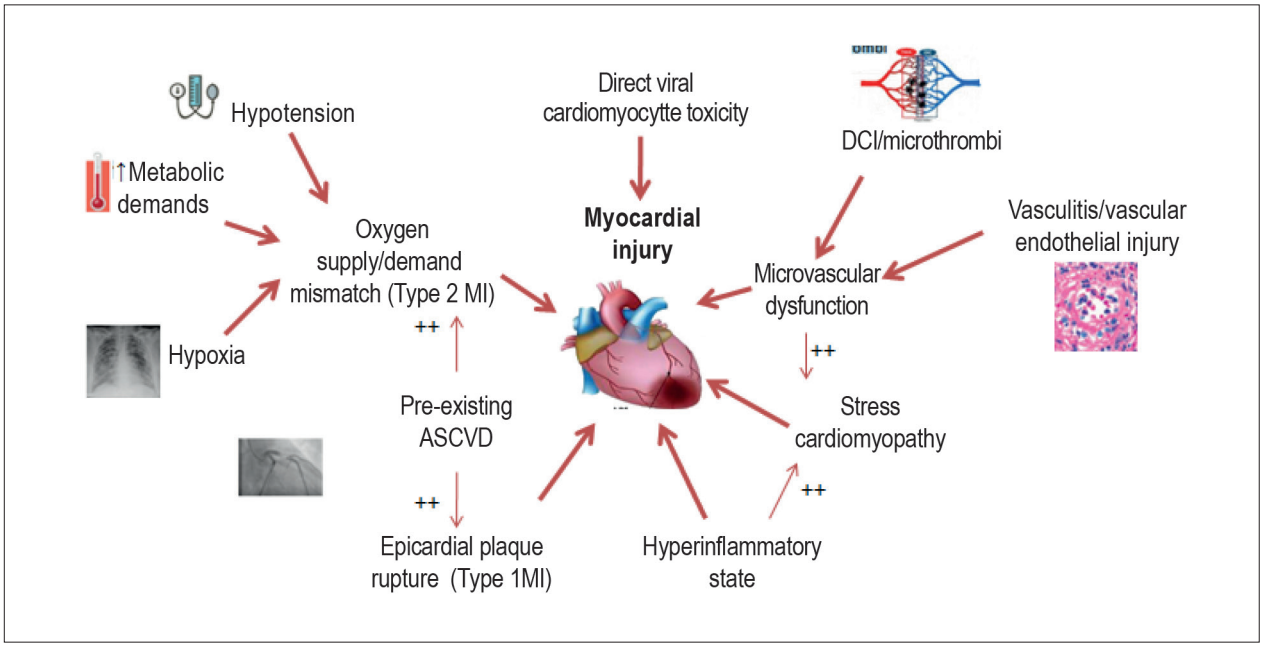

Figure 2 – *Potential mechanisms of myocardial injury in COVID-19. DIC: disseminated intravascular coagulation; MI: myocardial infarction. Source: Atri D, Siddidi HK, Lang J, et al. COVID-19 for the Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical Manifestations and Potential Therapeutic Strategies. JACC Basic Transl Sci. 2020 Apr 10. doi: 10.1016/j.jacbts.2020.04.002. [Epub ahead of print]*

inflammatory response. Initial reports demonstrate that extremely high levels of inflammatory biomarkers and cytokines, IL-6, C-reactive protein, TNF-α, interleukin-2R (IL-2R), and ferritin were associated with more severe manifestations of COVID-19 and worst outcomes.[20]

Several studies have demonstrated that cardiomyopathy in sepsis is partially mediated by inflammatory cytokines such as TNF-α, IL-6, IL-1β, INF-γ, and IL-2.[21,22]

Cultivated rat cardiomyocytes demonstrated reduced contractility when exposed to IL-6. The mechanism may be through modulated calcium channel activity with resulting myocardial dysfunction.[23]

It is furthermore believed that nitric oxide is a mediator of myocardial depression in states of intense inflammation, such as sepsis.[24]

More recently, observation of the role of mitochondrial dysfunction in septic states raised questions concerning the role of this entity in cardiomyopathy associated with sepsis.[25]

Patients with more severe forms of COVID-19 have multiple organ dysfunction with cytokine storms and immune dysregulation, which are likely mechanisms involved in the myocardial injury observed in these patients.[26]

Stress cardiomyopathy

The role of stress cardiomyopathy (takotsubo syndrome) in cardiac injury related to COVID-19 is still not well known, and there are few reports to date.[27-29]

It is, however, believed that several of the proposed mechanisms for cardiac injury related to COVID-19 that are detailed in this review are implicated in the pathophysiology of stress cardiomyopathy, especially microvascular dysfunction, cytokine storm, and sympathetic increase.[30]

The intense emotional stress and the respiratory infections caused by COVID-19 may represent potential triggers in this context. It is possible that stress cardiomyopathy may also play a significant role in the COVID-19 pandemic.

Non-obstructive acute coronary syndrome

Patients with COVID-19 may have more classical signs and symptoms of ACS, such as chest pain and electrocardiographic changes suggestive of myocardial ischemia or acute myocardial infarction, making this differential diagnosis difficult.[31]

The data published to date do not explain the incidence of ACS due to epicardial plaque rupture, as a mechanism for the cardiac injury observed in COVID-19.

Nonetheless, existing acquired knowledge demonstrates the association between infection and increased risk of ACS. Epidemiological studies have demonstrated that hospitalization due to pneumonia is associated with increased risk of atherosclerotic events.[32]

Studies evaluating influenza infection have demonstrated a temporal association between cardiovascular complications and ACS, and annual vaccination against influenza was associated with a 36% decrease in major adverse cardiovascular events in a meta-analysis of clinical trials evaluating this question.[33,34]

In this manner, viral infection is associated with an increased risk of coronary events, and prevention is associated with reduced risk. It is, therefore, plausible that ACS is also an important cause of acute cardiac injury in patients with COVID-19. There are several possible pathophysiological mechanisms whereby systemic viral infection (by influenza or SARS-CoV-2, for example) can lead to an increased risk of plaque destabilization and ACS. The role of inflammation in the development and progression of atherosclerosis is well established.[35-38]

The immune response to acute viral infection and the concomitant increase in cytokines and inflammatory mediators present in COVID-19 can lead to localized arterial inflammation, which may be more pronounced in coronary plaque.[39]

The entrance of viral products into systemic circulation, also known as pathogen-associated molecular patterns (PAMP), can lead to innate activation of the immune receptor, in turn leading to activation of immune cells residing in pre-existing atheroma, which may cause plaque rupture; furthermore, viral PAMP can activate the inflammasome, promoting conversion of pro-cytokines to biologically active cytokines.[40,41]

Finally, endothelial dysfunction resulting from infection and inflammation may lead to vessel constriction, with decreased coronary flow.[42]

All of these physiopathological alterations present in COVID-19 can lead to destabilization of pre-existing atherosclerotic plaque, thus triggering an acute coronary event.

Direct viral myocardial injury

Reports of cases of myocarditis in COVID-19 provide evidence of cardiac inflammation, but they do not determine the mechanism.

One of the proposed mechanisms behind the myocardial injury observed in COVID-19 is direct viral infection of the heart, with resulting myocarditis.

In fact, the human myocardium expresses the receptor used by COVID-19 to infect host cells, namely, ACE-2. Thus, without a doubt, in some cases, viral myocarditis may occur due to this agent.

The increase in troponin, however, appears to be omnipresent in patients who require intensive care, an indication of cardiac involvement, which is a marker of poor prognosis in many cases, as in many other circumstances.[41]

A murine model of lung infection, demonstrated with SARS-CoV-1, also precipitated myocardial infection dependent on ACE-2[42-43]. In human beings, during the SARS outbreak in Toronto, RNA of the SARS-CoV-1 virus was detected in 35% of autopsied hearts.[1] This increases the likelihood of direct viral damage to cardiomyocytes.[44]

In view of the host cell input receptor shared by SARS-CoV-1 and SARS-CoV-2, direct viral myocardial entry and the resulting injury is also plausible with SARS-CoV-2. SARS-CoV-2 may share the same mechanism with SARS-CoV-1, given that the two viruses have highly homologous genomes.[45,46]

To date, we have only one report of viral myocarditis due to SARS-CoV-2 confirmed by biopsy, with viral inclusions of viral DNA detected in myocardial tissue.[46] Viral particles, however,

were not present in cardiomyocytes, but only inside macrophages in the cardiac interstice.

Another hypothetical mechanism behind direct viral myocardial injury is due to infection-mediated vasculitis. The ACE-2 receptor is highly expressed in arteries and endothelial veins.[47]

There are pathological data on SARS-CoV-1, showing evidence of vasculitis with the infiltration of monocytes and lymphocytes, as well as endothelial cell injury in the heart.[48]

Direct viral entry in endothelial cells of the myocardium can trigger vasculitis, or the presence of the virus can lead to an indirect immunological response and consequent reaction of hypersensitivity.[49,50] This injury would be associated with myocardial injury and perhaps also with the myocardial dysfunction that is evident in COVID-19.

Even though ACE-2 is only slightly expressed in cardiomyocytes, it is highly expressed in pericytes. COVID-19 may attack pericytes, which are essential to endothelial stability, thus causing endotelial dysfunction, which leads to microcirculatory disorders. This explains why COVID-19 may cause cardiac injury, even though ACE-2 is only slightly expressed in cardiomyocytes.[51]

Autopsies have shown inflammatory infiltrates composed of macrophages and, to a lesser extent, T and CD4 + cells.[52,53]

These mononuclear infiltrates are associated with areas of cardiomyocyte necrosis, which, according to the Dallas criteria, define myocarditis.[54]

Real-time PCR analyses of post-mortem cardiac tissue from the SARS-CoV-1 epidemic detected the viral genome in 35% of patients who died of SARS-CoV-1. It is important to note that these hearts also showed decreased levels of ACE-2 and increased hypertrophy.[44]

Observing these data together, it is still not clear to what extent cardiac injury is attributable to direct viral infection versus indirect toxicity due to systemic infection. Furthermore, it has yet to be defined which cell populations in the myocardium are most vulnerable to infections and/or systemic inflammation. Levels of expression of ACE-2 may be important, but the implications of such differences are still debatable.

Inciardi et al.[55] described a patient with COVID-19 who presented with fatigue, increased troponin, increased BNP, electrocardiographic changes, changes in segmental contraction, pericardial effusion, and left ventricular dysfunction on echocardiogram, with normal coronary angiography approximately one week after having presented fever and dry cough; magnetic resonance demonstrated biventricular myocardial interstitial edema, and diffuse late gadolinium enhancement suggesting diagnosis of myocarditis. The patient required inotropic support, and she showed clinical and laboratorial improvement after one week after treatment.

Hu et al.[56] described a patient with chest pain and dyspnea for three days, as well as increased troponin and BNP, electrocardiographic changes, changes in segmental contraction, pericardial effusion, and left ventricular dysfunction, with normal coronary angiography. Upon admission, he had hypotension with clinical picture suggestive of fulminant myocarditis. He was treated with hemodynamic support (vasopressor and inotropic drugs) and methylprednisolone associated with human immunoglobulin. After three weeks of treatment, the patient evolved with complete recovery of ventricular function and normalized markers of myocardial injury.

In short, it seems clear that there is an association between the presence of myocardial injury, identified by increased troponin, and worse prognosis in patients with COVID-19. In relation to diagnosis of myocarditis, as defined by elevated markers, associated with a suggestive clinical picture and compatible alterations on cardiac imaging exams, some case reports have been described in patients with COVID-19, but without biopsy data confirming the cause of myocarditis.

In this manner, considering that SARS-CoV-1 and SARS-CoV-2 infect cells through ACE-2, a membrane protein present in myocardial cells, it is possible that this mechanism is also responsible for myocarditis in patients diagnosed with COVID-19. However, more evidence is needed to prove this association.

Conclusion

Myocardial and pericardial involvement (strokes/pericarditis) is common in severe phases of COVID-19. Acute myocardial involvement has been described as acute cardiac injury, induced by a possible "inflammatory cytokine storm," which may or may not cause cardiomyocyte necrosis.

Rare cases of mild inflammatory infiltrate and the presence of the virus in inflammatory cells of the cardiac interstice and the endothelial cells of coronary microcirculation have been precisely described, confirming the real histological presence of viral myocarditis, but, to date, the coronavirus has not been described inside the cardiomyocyte. The state of adrenergic response and myocardial inflammation may explain the occurrence of the phenotypic pattern of takotsubo syndrome.

In summary, high degree of clinical suspicion, characterized by chest pain, hemodynamic changes and/or changes in ST/Te arrhythmias (ECG), associated with morphofunctional abnormalities in cardiac imaging methods, and increased cardiac troponin, represent the pillars of clinical reasoning for the presence of acute myocardial aggression in the current coronavirus pandemic.

Furthermore, cardiac monitoring has become necessary for these patients, given that, in light of the current knowledge, we do not know whether or not they may progress with late myocardial dysfunction.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Figueiredo Neto JA, Marcondes F, Moura L, Rocha RM, Mesquita ET; Data acquisition: Figueiredo Neto JA, Marcondes F, Moura L, Figueiredo AMS, Figueiredo VMS, Rocha RM, Mesquita ET.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

This study is not associated with any thesis or dissertation.

References

1. A referência correta é: Guan WJ, Liang WH, Zhao Y, et al. China Medical Treatment Expert Group for Covid-19. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J. 2020 Mar 26; 2000547. doi: 10.1183/13993003.00547-2020 [Epub ahead of print].
2. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.
3. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv. 2020 Jan 26.
4. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25(6):291-4.
5. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112-6.
6. Costa IBSS, Bittar, CS, Rizk SI, Araújo Filho AE, Santos KAQ, Machado TIV, et al. The heart and COVID-19: what cardiologists need to know.. Arq Bras Cardiol. 2020 May 11. [Epub ahead of print].
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020. [Published online 2020 March 25] doi: 10.1001/jamacardio.2020 Mar 25. [Epub ahead of print].
8. Guo T, Fan Y, Chen M. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27. [Epub ahead of print].
9. 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. 2020;395(10229):1054-62.
10. Atri D, Siddidi HK, Lang J, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: a current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies. JACC Basic Transl Sci. 2020 Apr 10. [Epub ahead of print].
11. Sarkisian L, Saaby L, Poulsen TS et al. Prognostic impact of myocardial injury related to various cardiac and noncardiac conditions. Am J Med. 2016;129(5):506-14.e1.
12. Libby P, Loscalzo J, Ridker P, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in atherothrombosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2018;72(17):2071-81.
13. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
14. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, et al. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. Circulation. 2018;137(12):1236-45.
15. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.
16. Simmons J, Pittet JF. The coagulopathy of acute sepsis. Curr Opin Anaesthesiol. 2015;28(2):227-36.
17. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. Circulation. 2004;109(22):2698-704.
18. Green J, Doughty L, Kaplan SS, Sasser H, Carcillo JA. The tissue factor and plasminogen activator inhibitor type-1 response in pediatric sepsis-induced multiple organ failure. Thromb Haemost. 2002;87(2):218-23.
19. Cox D, Kerrigan SW, Watson SP. Platelets and the innate immune system: mechanisms of bacterial-induced platelet activation. J Thromb Haemost. 2011;9(6):1097-107.
20. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020 Mar 12. [Epub ahead of print].
21. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med. 1996;183(3):949-58.
22. Natanson C, Eichenholz PW, Danner RL, Eichacker PQ, Hoffman WD, Kuo GC, et al. Endotoxin and tumor necrosis factor challenges indogs simulate the cardiovascular profile of human septic shock. J Exp Med. 1989;169(3):823-32.
23. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004;363(9404):203-9.
24. Hobai IA, Edgecomb J, LaBarge K, Colucci WS. Dysregulation of intracellular calcium transportes in animal models of sepsis-induced cardiomyopathy. Shock. 2015;43(1):3-15.
25. Balligand JL, Ungureanu D, Kelly RA, Kobzik L, Pimental D, Michel T, et al. Abnormal contractile function due to induction ofnitric oxide synthesis in rat cardiac myocytes follows exposure to activated macrophage conditioned medium. J Clin Invest. 1993;91(5):2314-9.
26. Stanzani G, Duchen MR, Singer M. The role of mitochondria in sepsis-induced cardiomyopathy. Biochim Biophys Acta Mol Basis Dis. 2019;1865(4):759-73.
27. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall S, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
28. Meyer P, Degrauwe S, Van Delden C, Ghadri JR, Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. Eur Heart J. 2020;41(19):1860.
29. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, et al. Acute myocarditis presenting as a reverse TakoTsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J. 2020;41(19):1861-2.
30. Chazal HM, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(16):1955-71.
31. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-segment elevation in patients with Covid-19 — a case series. N Engl J Med. 2020 Apr 17. [Epub ahead of print].
32. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CCH, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015;313(3):264-74.
33. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013;310(16):1711-20.
34. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol. 2016;1(3):274-81.

35. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in atherothrombosis:JACC review topic of the week. J Am Coll Cardiol. 2018;72(17):2071-81.

36. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(9):2045-51.

37. Violi F, Cangemi R, Calvieri C. Pneumonia, thrombosis and vascular disease. J Thromb Haemost. 2014;12(9):1391-400.

38. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev. 2009;22(2):240-73.

39. Van de Veerdonk FL, Netea MG, Dinarello CA, Joosten LAB. Inflammasome activation and IL-1beta and IL-18 processing during infection. Trends Immunol. 2011;32(3):110-6.

40. Vallance P, Collier J, Bhagat K. Infection, inflammation, and infarction: does acute endothelial dysfunction provide a link? Lancet. 1997;349(9062):1391-2.

41. Libby P. The Heart in COVID19: primary target or secondary bystander? JACC Basic Transl Sci. 2020;5(5):537-42.

42. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol. 2004;203(2):622-30.

43. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.

44. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7):618-25.

45. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63(3):457-60.

46. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020 Apr 10. [Epub ahead of print].

47. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome(SARS): a report from China. J Pathol. 2003;200(3):282-9.

48. Hamming I, Timens W, Bulthuis MLC, Lely AT, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.

49. Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. Clin Exp Rheumatol. 2006;24(2 Suppl 41):S71-81.

50. Guillevin L. Virus-induced systemic vasculitides: new therapeutic approaches. Clin Dev Immunol. 2004;11(3-4):227–31.

51. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116(6):1097–1100.

52. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4),420-2..

53. 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(5):411-7.

54. Fung G, Luo H, Qiu Y, Yang D, McManus B. Myocarditis. Circ Res. 2016;118(3):496-514.

55. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020 Mar 27.

56. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J. 2020 Mar 16. [Epub ahead of print].

Physical Activity And Reducing Sedentary Behavior During The Coronavirus Pandemic

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Introduction

The novel coronavirus pandemic recently declared by the World Health Organization[1] has led several municipal and state health departments to issue decrees closing different spaces intended for practicing physical activity. Furthermore, the Ministry of Health[2] has prepared a manual with several initiatives to prevent the spread of the disease, in addition to making decisions suggesting social isolation and recommending that people remain at home. All of these measures have made it more difficult for the Brazilian population to practice physical activity.

On the other hand, the literature has consistently provided evidence regarding the diverse health benefits that physical activity promotes,[3] especially to the cardiovascular/metabolic[4] and immunological system.[5] More recently, the literature began to show evidence that health is related not only to regular practice of physical activity, but also to reduced sedentary behavior, in other words, time spent sitting, lying down, or reclining during the day, excluding sleep hours.[6]

Accordingly, there is an important need to continue practicing physical activity during the novel coronavirus pandemic; however, some measures should be observed in order to keep this practice safe. It is worth emphasizing that even in the city of Wuhan, China, the initial epicenter of the disease, it was recommended that people continue practicing physical activity inside their homes.[7] Furthermore, it has become important that the population be informed regarding the need to reduce sedentary behavior during this period of social isolation.

Thus, the objectives of this viewpoint are to emphasize the importance of these issues and to propose suggestions for continuing practice of physical activity and reducing sedentary behavior during the novel coronavirus pandemic in Brazil.

Keywords

Pandemics; Coronavirus; Exercise; Physical Activity; Leisure Activities; Screen Time; Population Dynamics; Cardiovascular Physiological Phenomena

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The important of practicing physical activity and health benefits

Physical activity and cardiovascular and metabolic health

The benefits of regular physical activity to cardiovascular/metabolic health have been widely published in the literature for a long time. Physical activity has been shown to be inversely associated with blood pressure levels, diabetes, lipid alterations, and other cardiovascular events.[4,8]

With respect to duration and intensity of physical activity required for these benefits to occur, a recent publication suggested that 180 to 300 minutes of moderate to intense activity weekly for men and 150 to 300 minutes of moderate to intense activity for women would be the most adequate measure for promoting cardiovascular and metabolic health benefits.[9] These recommendations are in agreement with the main physical activity guidelines published by international organizations.

Physical activity and the immune system

The immune system is an important defense mechanism of the body. It is capable of recognizing and eliminating a series of invasive microorganisms. The first line of defense is made up of leukocytes (neutrophils, eosinophils, basophils, monocytes), which are natural killer cells, acute-phase proteins, and enzymes. The second line of defense is made up of T and B lymphocytes and imunoglobulins.[5]

Practice of physical exercise modulates the quantity of these substances in the organism, both increasing and decreasing, and the magnitude depends on the intensity and duration of physical activity.

In relation to leukocytes, for example, during practice of physical activity, their concentration increases, and it is immediately reduced following physical practice, especially after exercise with long duration and high intensity that may lead to immunosuppression, according to the theory of the "open window," when there is a depression in the immune system after strenuous exercise, leaving the organism more susceptible to bacteria for a period of 3 to 72 hours. It is worth stressing that the period of immunosuppression is much shorter after light to moderate exercise without prolonged duration.[5]

The importance of reducing sedentary behavior and cardiometabolic health

Sedentary behavior is defined as activities characterized by low energy expenditure, not exceeding 1.5 metabolic

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equivalents, including the specific behaviors of sitting, reclining, or lying down to read, study, watch television, use the computer, etc., excluding sleep hours.[6]

A recent publication has demonstrated that reduced sedentary behavior is associated with beneficial effects on diverse variables that represent cardiometabolic health in adults.[10] In this same study, the authors also demonstrated that, when the reduction in sedentary behavior was associated with regular practice of physical activity, the benefits were maximized.

Suggestions for continuing practice of physical activity during the novel coronavirus pandemic

Places for practicing physical activity

Considering that Brazil is a country of continental dimensions, it is important to accompany decisions published by state or municipal health departments and by the Ministry of Health regarding restricted access to gyms, clubs, clinics, and other spaces intended for practicing physical activity and exercise.

In the event that these spaces are closed to the public, physical activity should, whenever possible, continue in open-air environments. In this case, people should prioritize individual activities, always taking care to avoid crowds or even small groups of people. If these conditions are restricted, physical activity should be continued at home, preferably with the assistance of technology, such as exercise videos, applications, or professional guidance online.

Types of Physical Activity/Exercise

When it is possible to practice physical activity outdoors, aerobic activities are recommended, especially individual activities; crowds should be avoided. At this moment, it is necessary to avoid practicing group sports, even in small groups.

In the event that it is necessary to exercise at home, muscle-strengthening exercises (squats, push-ups, sit-ups, and others), stretches, balancing exercises, and climbing up and down stairs are recommended, preferably with the assistance of technology, such as exercise videos, applications, and professional guidance online. It is, furthermore, worth emphasizing the importance of increased domestic physical activity, i.e., general housework, such as washing dishes, washing and ironing clothes, and similar activities.

Intensity of Physical Activity

During the coronavirus pandemic in Brazil, it is recommended that the intensity of physical exercise be light to moderate, given that very high intensity may lead to more accentuated immunosuppression, requiring longer recovery time.

Duration of Physical Activity

During the coronavirus pandemic in Brazil, it is recommended that the duration of each exercise session be approximately 30 to 60 minutes daily. It is suggested that total time not be too long due to the immune system depression with longer recovery time.

Suggestions for reducing sedentary behavior during the novel coronavirus pandemic

Considering that, in addition to regular practice of physical activity, it is very important to reduce sedentary behavior, the following are recommended:

1. Reduce sedentary behavior to a maximum of 6 to 8 cumulative hours daily.
2. Reduce to a maximum of 2 to 4 hours sitting in front of the screen daily.
3. Attempt to maximize the number of interruptions/pauses to sitting time, namely, for every hour spent sitting, stand up for at least 5 minutes.

Final considerations

Based on the studies consulted, the evidence confirms the importance of continuing to practice physical activities during the novel coronavirus pandemic, with light to moderate intensity and duration, preferably in outdoor environments or at home. In addition, it is also very important to emphasize reducing sedentary behavior, namely, time spent sitting, lying down, or reclining, excluding sleep hours, and time spent in front of the television, computer, and similar devices.

Author contributions

Conception and design of the research: Pitanga FJG; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Pitanga FJG, Beck CC, Pitanga CPS.

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References

1. World Health Organization. (WHO). Novel Coronavirus (2019-nCoV): Situation Report-19. [Cited in 2020 Mar 23]. Available at: https://www.who.int/docs/default-source/corona viruse/situation-reports/20200208-sitrep-19-ncov.pdf?sfvrsn=6e091ce6_2

2. Brasil.Ministério da Saúde do Brasil. O que você precisa saber o Corona Vírus. [Citado em 16/03/2020] Disponível em: https://coronavirus.saude.gov.br/

3. Blair SN, Kohl HW, Gordon NF, Paffenbarger RS Jr. How much physical activity is good for health? *Ann Rev Publ Health. 1992; 13*: 99-126.

4. Lin X, Alvim SM, Simoes EJ, Bensenor I, Barreto S, Schimidt M, et al. Leisure time physical activity and cardio-metabolic health: results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Am Heart Assoc. 2016; 5(6):003337.

5. Krinski K, Elsagedy H, Colombo H, Buzzachara C, Soares I, CamposW, et al. Efeitos do exercício físico no sistema imunológico. Rev Bras Med. Jul 2010;67(7).

6. Tremblay MS, Aubert S, Barnes JD, Saunders T, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN)—terminology consensus project process and outcome. Int J Behav Nutr Phys. 2017;14(1):75.

7. Chen P, Mao L, Nassis GP, Harmer P, Ainsworth BE, Li F. Wuhan coronavirus (2019-nCoV): The need to maintain regular physical activity while taking precautions. *J Sport Health Sci*. 2020;9(2):103–4.

8. Pitanga FJG, Matos SMA, Almeida MDC, Barreto SM, Aquino EML. Leisure-Time Physical Activity, but not Commuting Physical Activity, is Associated with Cardiovascular Risk among ELSA-Brasil Participants. Arq Bras Cardiol. 2018;110(1):36-43.

9. Pitanga FJG, Pitanga CPS Beck CC. Physical Activity for the Prevention of Cardiometabolic Diseases: how much is Required? Curr Res Diabetes & Obes J. 2019; 9(4):

10. Pitanga FJG, Matos SMA, Almeida MDCC, Patrão AL, Molina MDCB, Aquino EM. Association between leisure-time physical activity and sedentary behavior with cardiometabolic health in the ELSA-Brasil participants. *SAGE Open Med*. 2019;7:1-9.

QT Interval Control to Prevent Torsades de Pointes during Use of Hydroxychloroquine and/or Azithromycin in Patients with COVID-19

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Introduction

In December 2019, the first cases of the novel coronavirus disease (COVID-19) were reported in Wuhan, China.[1] Since the pandemic designation in March 2020 by the World Health Organization (WHO), with intercontinental spread of the disease, we are intensely seeking for a safe and effective treatment.[2]

In vitro studies have demonstrated some effect of chloroquine against the new coronavirus,[3] mediated by the glycosylation of SARS-CoV cell receptors and by increased endosomal pH, blocking cell invasion by the virus.[4] In addition to this antiviral activity, chloroquine, which is traditionally an immunomodulator, has shown to be promising for treatment of pneumonia that installs approximately one week after onset of symptoms.[5]

Hydroxychloroquine (HCQ), which is derived from chloroquine, has similar therapeutic effects, with fewer adverse effects, and it is widely used in autoimmune diseases. The first clinical trials with HCQ for treatment of COVID-19 reinforced an apparent benefit and encouraged its approval for clinical studies by national and international regulatory institutions.[6-8]

The macrolide azithromycin (AZ), due to a mechanism that is still unclear, has shown to be effective when initiated early in patients with severe respiratory infections.[9] Although these medications have an adequate safety profile in diverse clinical situations, both of them block the hERG potassium channel, which can prolong ventricular repolarization and cause torsades de pointes (TdP).[10,11]

The subgroup of the population with the highest risk of potentially fatal events are patients with multiple comorbidities or patients in intensive care, who will be exposed to drug interactions and/or electrolyte disorders, in addition to patients with congenital long QT syndrome, who may need treatment (1:2000 individuals).[12] Risk assessment before treatment and monitoring of the QTc interval during treatment are essential measures to preventing arrhythmic events.

Giudicessi et al.[13] published an institutional guideline from the Mayo Clinic for safety of patients receiving HCQ and/or AZ.[13] The American College of Cardiology suggested controlling the QT interval and preventing ventricular arrhythmias in patients participating in the HQC/AZ protocol for treating COVID-19.[14] The Arrhythmia Center of the Heart Institute of the University of São Paulo formulated an institutional protocol in order to contribute to the conscious use of these medications during the COVID-19 outbreak.

Definition

The QT interval is the measurement of the duration from the beginning of the QRS complex to the end of the T wave, which is modulated by heart rate (Figure 1). When the interval is prolonged, it is associated with a greater risk of polymorphic ventricular arrhythmias and TdP (Figure 2).[15] Measurement of the QT interval should be corrected by heart rate (QTc); in the adult population, ≤ 440 ms is considered normal in men, and ≤ 460 ms is considered normal in women.[16]

How to Measure the QTc Interval

The QT interval can be measured either by the tangent method (Figure 3) or visually (when the end of the T wave is easy to define), preferably in leads DII or V5.[17]

Heart rate correction can be done using Bazett's formula, considering the RR interval preceding the measured QT interval (QTc = QT interval / square root of the RR interval). This formula is available on website calculators (QTc calculator) or in applications (for example, EP Mobile or MedCalX).

Monitoring the QTc interval during treatment with HCQ/AZ

After evaluation of initial ECG, patients may be stratified by risk of developing TdP in the following manner: lower risk (green group), intermediate risk (blue group), intermediate to high risk (orange group), and high risk (red group).

Monitoring after the start of treatment can be done by conventional 12-lead ECG, ECG with limb leads only, telemetry, or other remote devices in order to minimize the exposure of health professionals and equipment to the virus during this particular pandemic situation. We recommend that the frequency of electrocardiographic monitoring and

Keywords

Coronavirus/complications; COVID-19, Pandemics; Torsades Pointes; Tachycardia,Ventricular; Hydroxychloroquine/therapeutic, use; Arrhythmias

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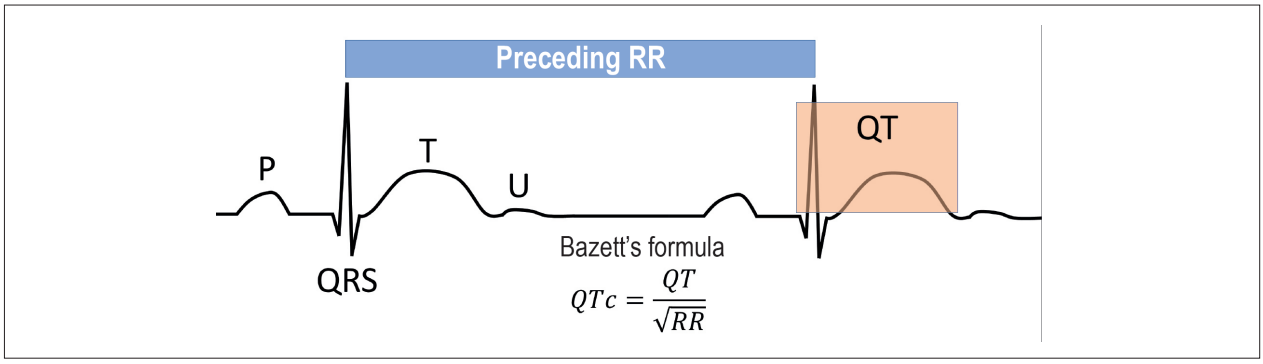

Figure 1 – *QT Interval Source: Collection, Heart Institute of the University of São Paulo (InCor HCFMUSP).*

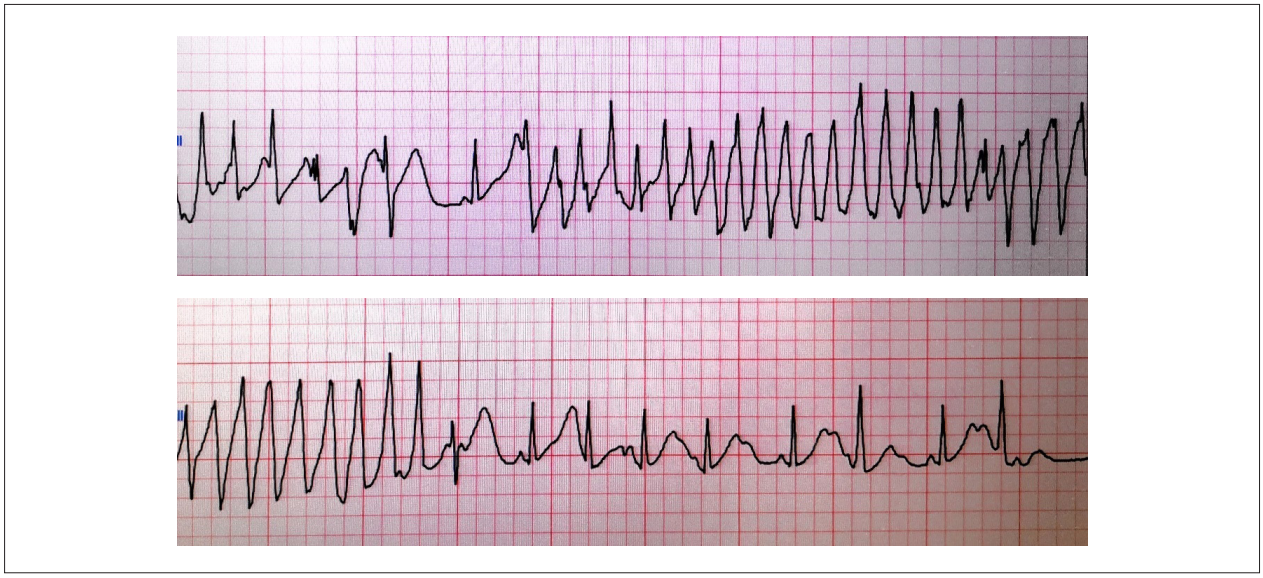

Figure 2 – *Long QT with torsades de pointes. Source: Collection, Heart Institute of the University of São Paulo (InCor HCFMUSP).*

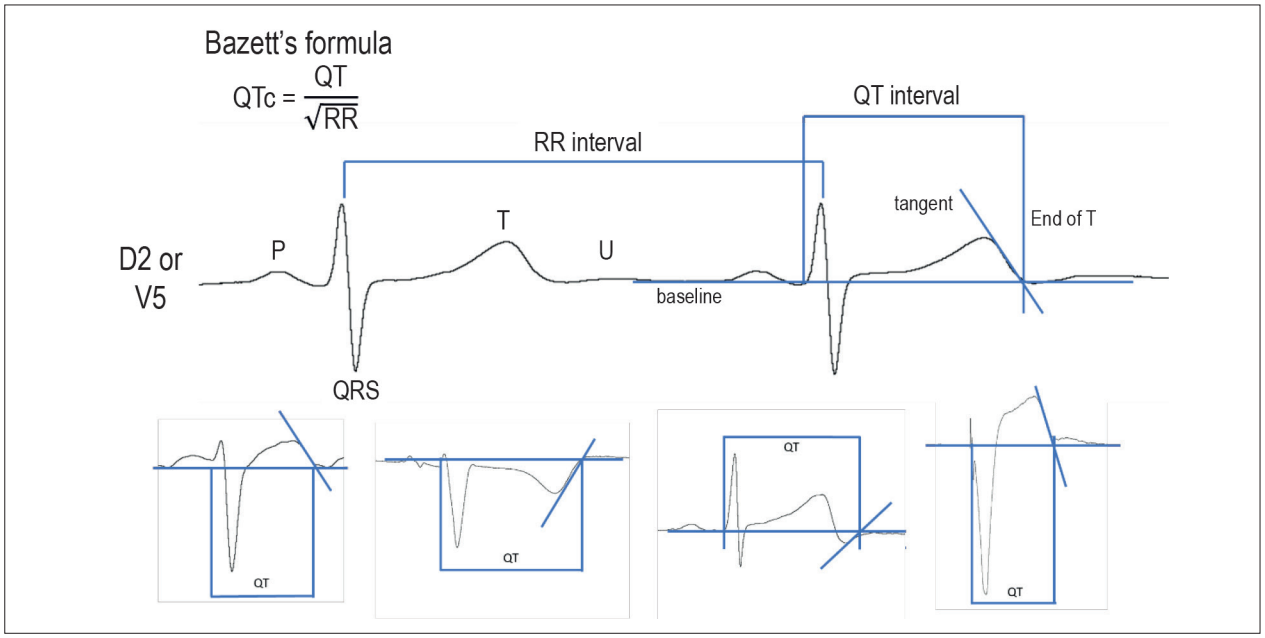

Figure 3 – *Examples of measurement of QT interval by the tangent method. Source: Collection, Heart Institute of the University of São Paulo (InCor HCFMUSP).*

the method (ECG, telemetry, or devices) be determined according to patients' risks, based on an initial QTc (upon admission to the hospital). Figure 4 outlines the proposed control model.

Initial risk assessment for treatment according to baseline QT measurement on 12-lead ECG:

QTc ≤ 450 ms	Approved for use
450ms < QTc ≤ 470 ms	Use with caution or only in the hospital
470ms < QTc < 500 ms	Avoid or only use in the hospital with telemetry
QTc ≥ 500 ms	Avoid, considering risk/benefit

In cases where doubts exist or in borderline measurements regarding greater risk throughout the treatment, it is possible to opt for isolated use of HCQ or AZ, or also for staggered use of HCQ, followed by AZ, under monitoring. It is recommended that a shared decision be reached with the hospital's cardiology or arrhythmia team.

When to repeat ECG during treatment in the hospital, according to previous QTc

QTc ≤ 450 ms	On day 2
450 ms < QTc ≤ 470 ms	On day 2
470 ms < QTc < 500 ms	On days 2 and 4
QTc ≥ 500 ms	4 to 8 hours after the first dose, then daily

Control should be intensified in the following conditions:

- If there are associated risk factors (Table 1).

- In the presence of cardiovascular complications, such as myocarditis and myocardial ischemia.

N.B.: Figures 5 and 6 show suggested models for pre-treatment and control checklists.

Warning signs

- Increase in QTc by > 60 ms and/or by more than 10% with respect to baseline ECG.

- QTc above 520 ms: evaluate suspending treatment after other drugs (those that are dispensable and that have a synergistic effect on QTc) have been suspended, or electrolyte disturbance.

- Need to add medications that prolong the QT interval, according to the patient's clinical evolution.

- Presence of ventricular arrhythmias and/or associated bradycardia -> Choose the drugs that can be suspended according to the risk-benefit ratio. In these situations, it is necessary to keep the patient on continuous telemetry.

Additional care measures for preventing TdP

Regarding electrolyte control upon hospital admission:

Measurements of calcium, potassium, and magnesium, which are essential for the stability of ventricular repolarization, should be carried out for all patients eligible for treatment with HCQ/AZ.

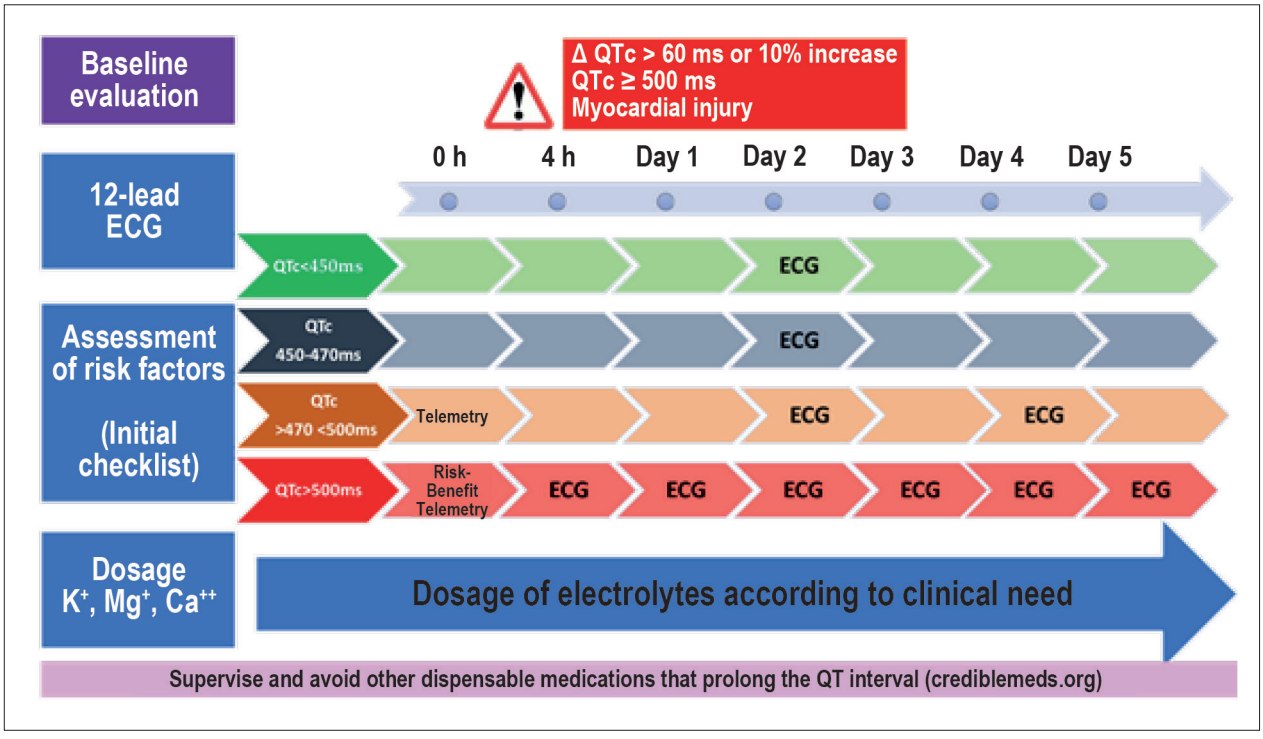

Figure 4 – *Suggested HCQ and / or AZ treatment control scheme.*

Table 1 – Risk factors for prolonged QT and TdP. (18)

- Age > 65 years
- Women
- Electrolyte disorders (hypocalcemia, hypokalemia, hypomagnesemia)
- Concomitant use of other medications that prolong QT (crediblemeds.org)
- Acute coronary failure
- Chronic heart failure or LVEF < 40%
- Bradycardia, branch block
- Hypertrophic cardiomyopathy
- Congenital long QT syndrome or other genetic susceptibility
- Diabetes mellitus
- Chronic renal failure on dialysis
- Anorexia or starvation
- Hypoglycemia
- Pheochromocytoma
- Recent post-cardiorespiratory arrest
- Post-subarachnoid hemorrhage, stroke, or traumatic brain injury (week 1).

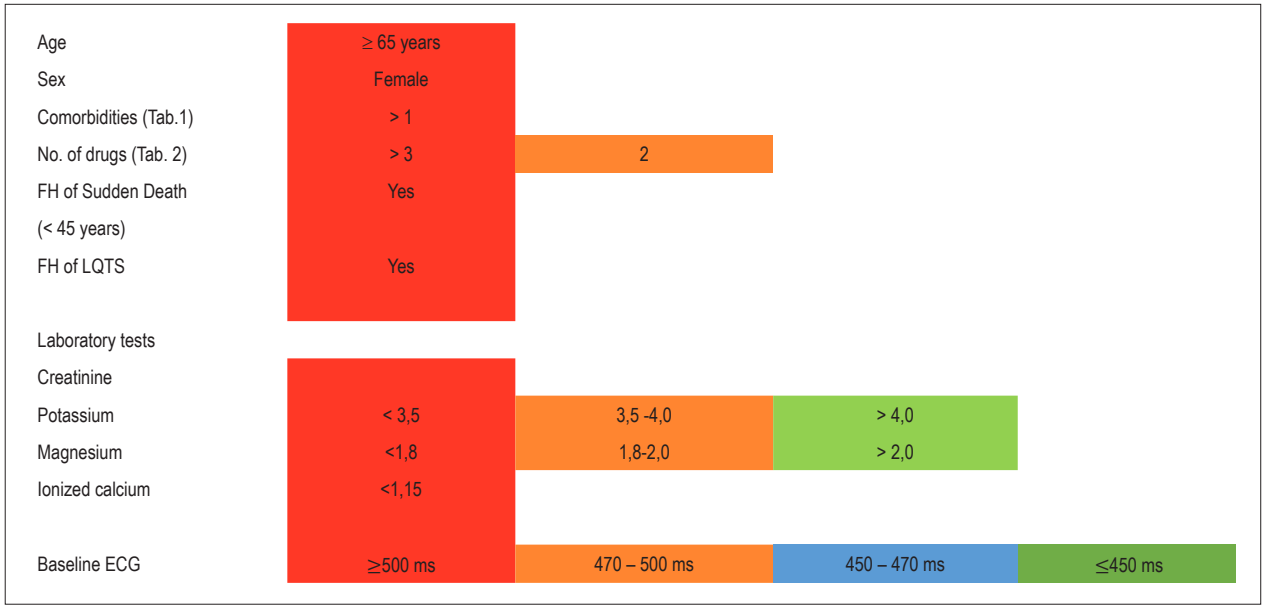

Figure 5 – *Pre-treatment Checklist: FH = family history; LQTS=long QT syndrome*
Red: special attention to conditions of risk; orange: moderate risk; green: low risk or desirable target

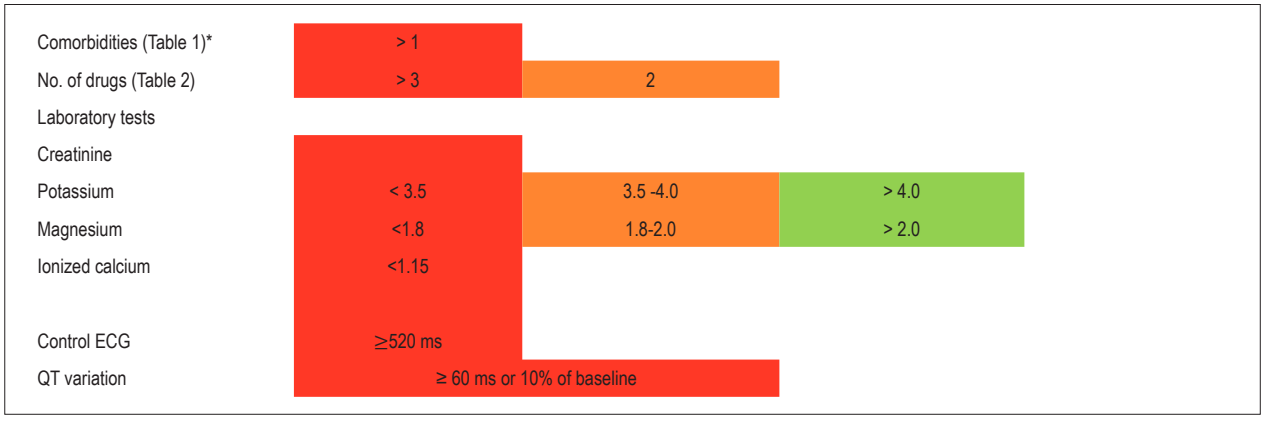

Figure 6 – *Control Checklist.*
** Clinical and metabolic conditions during clinical evolution: myocardial injuries, among others.*

- Maintain $K^+ > 4.0$
- Maintain $Mg^{++} > 2.0$
- Avoid hypocalcemia

N.B.: Even in patients with normal blood level, it is recommended to maintain empirical magnesium supplementation orally, except in those with renal failure (ClCr < 30 ml/min).

Regarding electrolyte control during patient progression:

Electrolyte monitoring routine should be determined at clinical discretion, whenever adjustments are needed to maintain ideal or desirable levels during treatment, especially in patients with an initial QTc interval > 470ms.

Regarding use of concomitant medications:

It is necessary to avoid prescribing other non-essential drugs that prolong the QT interval. Numerous drugs that are commonly used in hospitalized patients can block the hERG channel, prolong ventricular repolarization time, and facilitate the occurrence of TdP.[18] It is important to supervise use of medication whenever possible in order to guarantee patient safety.

Table 2 provides lists of low risk (green), possible risk (orange), and high risk (red) medications with respect to prolongation of the QT interval and occurrence of TdP. Therefore, whenever possible, additional low-risk medications should be preferred, as both HCQ and AZ are already listed as high risk for the occurrence of TdP.

Some medications can increase risk through other mechanisms or indirectly, as is the case of hypokalemia induced by diuretics. The complete list of drug interactions should be checked daily by the website crediblemeds.org.[19]

In the event of ventricular arrhythmia or TdP (Table 3): [20,21]

- Lidocaine is the antiarrhythmic drug of choice:
- Magnesium sulfate
- Isoprotenerol for TdP mediated by bradycardia
- Provisional pacemaker for bradycardic patients with recurrent TdP. Initial heart rate should be programmed to 90 bpm and adjustments should be made according to patient's clinical response.
- Immediately suspend the use of all medications with potential to prolong the QT interval.

Conclusion

The risk of fatal arrhythmias, increased with the use of HCQ and/or AZ, in patients with COVID-19, or in other daily situations, outside the pandemic, with medications that may potentially prolong the QT interval, can be minimized with the application of conduct protocols that help healthcare professionals decide on prescription and maintenance of treatment.

Table 2 – List of medications to avoid (red and orange)

	High risk	Moderate risk	Low risk or NC
Antiarrhythmic drugs	Amiodarone Sotalol	Propafenone	Lidocaine Propranolol Magnesium sulfate Isoproterenol
Antipsychotic drugs	Haloperidol Chlorpromazine Levomepromazine	Risperidone Quetiapine Promethazine Olanzapine	Benzodiazepine
Sedatives	Propofol	Dexmedetomidine	Midazolam Fentanyl
Antiemetic and prokinetic drugs	Ondansentron Domperidone Bromopride Cisapride	Cimetidine Granisetrone Metoclopramide	Dimenhydrinate
Antibiotics	Quinolones	Piperacillin/ tazobactam Sulfamethoxazole/ trimethoprim	Teicoplanin Vancomycin
Antifungal drugs	Fluconazol	Anfotericina Itraconazol Voriconazol	
Proton pump inhibitors		Pantoprazol Omeprazol Esomeprazol Lanzoprazol	
Antiallergic drugs		Promethazine Hydroxyzine Diphenhydramine	Fexofenadine Loratadine
Pandemic	Chloroquine Azithromycin		Oseltamivir
Bronchodilators		Salbutamol Fenoterol Formoterol Terbutalina	
Anticholinesterase drugs	Donepezil	Galantamine	
Antidepressives	Citalopram Escitalopram	Fluoxetine Paroxetine Mirtazapine Tricyclics Sertraline Venlafaxine	
Others	Cilostazol Methadone Tramadol	Loperamide	Phenytoin
Special precautions			
Diuretics	Precaution with spoliation of electrolytes		

NC – Not classified, i.e., absence of evidence of prolonged QT interval based on published studies.

Author contributions

Conception and design of the research and Data acquisition: Wu TC; Writing of the manuscript: Wu TC, Sacilotto L, Darrieux FCC, Pisani CF, Hachul DT; Critical

Table 3 – Pharmacological management of ventricular arrhythmia and/or TdP

Lidocaine
Loading dose: 1.0 to 1.5 mg/kg IV with repeated doses in bolus, 0.5 – 0.75 mg/kg in a bolus up to 3 mg/kg. Maintenance dose: 20 mcg/kg/min IV.
Magnesium sulfate
2 to 4 g IV
Isoprotenerol
Loading dose: 1 to 2 mcg IV. Maintenance dose: 0.15 mcg/min and titer up to 0.3 mcg/min according to clinical response or necessity.

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 02;382(8):727-33.
2. worldometers. https://www.worldometers.info/coronavirus/ [Cited in 2020, April 03] Available from: https://www.worldometers.info/coronavirus/.
3. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 03;30(3):269-71.
4. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005 Aug;2:69.
5. 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(11):1061-9.
6. U.S. Food and Drug Administration. (FDA) Coronavirus Disease 2019 (COVID - 19) [Cited in 2020 March 28]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020.
7. Agência Nacional de Vigilância Sanitária. Anvisa. Covid-19: liberada pesquisa com hidroxicloroquina. [Citado em 27 março 2020] Disponível em:http://portal.anvisa.gov.br/
8. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar:105949.
9. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. JAMA. 2015 Nov;314(19):2034-44.
10. Guo D, Cai Y, Chai D, Liang B, Bai N, Wang R. The cardiotoxicity of macrolides: a systematic review. Pharmazie. 2010 Sep;65(9):631-40.
11. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila). 2006;44(2):173-5.
12. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardi.ovasc Qual Outcomes. 2013 Jul;6(4):479-87.
13. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic potential of possible pharmacotherapies for (COVID-19). Mayo Clin Proc .xxx 2020: 1-9. [In Press]
14. Malviya A. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19. Indian Heart J. 2020 Apr 27 [Epub ahead of print]
15. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003 May;348(19):1866-74.
16. Johnson JN, Ackerman MJ. QTc: how long is too long? Br J Sports Med. 2009 Sep;43(9):657-62.
17. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev. 2014 Aug;10(3):287-94.
18. El-Sherif N, Turitto G, Boutjdir M. Acquired Long QT Syndrome and Electrophysiology of Torsade de Pointes. Arrhythm Electrophysiol Rev. 2019;8(2):122-30.
19. CredibleMeds. Quick search for drugs on the QTdrugs lists- [Cited in 2020 Apr 20]. [Available from: crediblemeds.org.
20. Panchal AR, Berg KM, Kudenchuk PJ, Del Rios M, Hirsch KG, Link MS, et al. 2018 American Heart Association Focused Update on Advanced Cardiovascular Life Support Use of Antiarrhythmic Drugs During and Immediately After Cardiac Arrest: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2018 12;138(23):e740-e9.
21. Sorajja D, Munger TM, Shen Win-Kuang S. Optimal antiarrhythmic drug therapy for electrical storm. J Biomed Res. 2015;29(1):20-34.

Acute Coronary Syndromes in the Current Context of the Covid-19 Pandemic

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Introduction

COVID-19, initially described at the end of 2019 in China, may present as atypical pneumonia and severe respiratory failure.[1] Classified in February 2020 as a pandemic[2] by the World Health Organization (WHO), COVID-19 has had major clinical, social, political and economic implications. Society as a whole has had to adapt to a new reality, forcing hospitals to rewrite their routine practices and clinical pathways. Specific measures have had to be put in place to prevent hospital transmission of the infection. Also, dedicated COVID units have been set up and infection control protocols implemented. Finally, additional human, material and financial resources have been allocated in order to provide patients with the best possible care, without compromising the safety of healthcare workers.

Social isolation as a way of containing the spread of the disease may have helped, in some places, to "flatten the curve", preventing the collapse of healthcare systems. However, the duration of the pandemic, as well as the precise risk of transmission are still largely unknown.

Typical symptoms of COVID-have been described[3,4] and most infected patients present with mild viral syndromes. As a result, and as part of social distancing measures, patients are recommended to seek hospital care only in case of severe symptoms. This policy has, on the other hand, has generated a widespread reluctance by the population to go to hospitals, for fear of being exposed to the virus in healthcare settings. As a result, diagnosis, treatment and prognosis of several other clinical conditions have been unintentionally impacted. This applies to cardiology and, particularly, to Acute Coronary Syndromes (ACS), a phenomenon described globally.[5]

Furthermore, individuals who are over 60 years old and those with previous cardiovascular or respiratory disorders are more likely to develop severe forms of COVID-19, with increased cardiovascular compromise during the infection course, such as myocarditis, type II infarctions and thromboembolic phenomena.[6,7]

International Experiences

Experiences shared from countries in which the COVID-19 infection wave preceded ours indicate important associations between COVID-19 and cardiovascular disease.

COVID-19 patients with established cardiovascular disease and those with hypertension and diabetes represent about 40% of the severe cases and have a worse prognosis.[8] These groups have a much higher fatality rate – 7.3-10.5% compared to 2.3% for the general population[9]. Cardiac manifestations attributed to COVID-19 have also been reported, with arrhythmias occurring in 16.7% and acute myocardial injury in up to 7% of hospitalized cases.[10,11]

In addition to these direct associations, the "side effects" of the COVID-19 pandemic in the care of acute coronary syndromes have generated concern. There was a sharp drop in the search for cardiac emergency room care by patients with ACS, possibly related to the fear of contracting infections in the hospital environment, which can result in underdiagnosis and inadequate treatment, with risk of death and long-term morbidity.[12,13] In addition, delays in primary angioplasty have been reported, with complications of late-presenting myocardial infarction having been described.[14]

National campaigns targeted to raise awareness of ACS symptoms have been put in place internationally, advising patients to seek help quickly in case of suspected cardiac emergencies.[15] Telemedicine is a facilitating tool for such complex COVID-19 circumstances, as it has the potential to allow the physician to remotely recognize suspected symptoms of acute coronary syndrome and guide the patient to seek care immediately. In addition, it allows pre-hospital diagnosis of

Keywords

Acute Coronary Syndrome/complications; Coronavirus; COVID-19; Pandemics; Acute Myocardial Infarction/prevention and control; Telemedicine/trends; Quarantine.

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acute ST-elevation myocardial infarction, enabling the rapid activation of catheterization laboratories and selection of the best myocardial reperfusion strategy using an individualized approach. It is possible to refer the patient directly to the heart attack center or catheterization laboratory, by-passing emergency departments, reducing hospitalization time and myocardial sequelae.[16,17]

Therefore, early training of cardiology teams with pathways that include the use of telemedicine is essential for the successful implementation of such tools.

Management of ACS *(protocols of care)*

The COVID-19 pandemic has impacted the management of acute coronary syndromes,[18] particularly the speed at which proven medical and interventional therapies can be implemented.[19] For instance, in STEMI cases, reperfusion is known to be most beneficial if implemented within the first few hours of symptom onset.[20] With early actions, there is a reduction of ventricular arrhythmias, reduced myocardial damage, lower incidences of reinfarction and greater preservation of ventricular function.[21] Unfortunately, late presentations of ACS have been reported worldwide. In New York, United States, there has been a reduction of up to 70% in the volume of emergency calls due to ACS and an increase of up to 800% in sudden deaths.[22,23]

Recommendations from several Medical Societies[19,20] highlight the cardiovascular clinical implications of coronavirus and call for attention to be paid to individual and populational risks.[20,21] In addition to public health strategies to prevent the spread of infection, such as influenza and pneumococcal vaccination, there is a warning of a very likely underreporting and lack of assistance for cases of acute myocardial infarction during the COVID-19 pandemic.[21,22] In this context, the creation of routes and flows aimed at the care of these patients need extensive structuring and dissemination. Figures 1 and 2

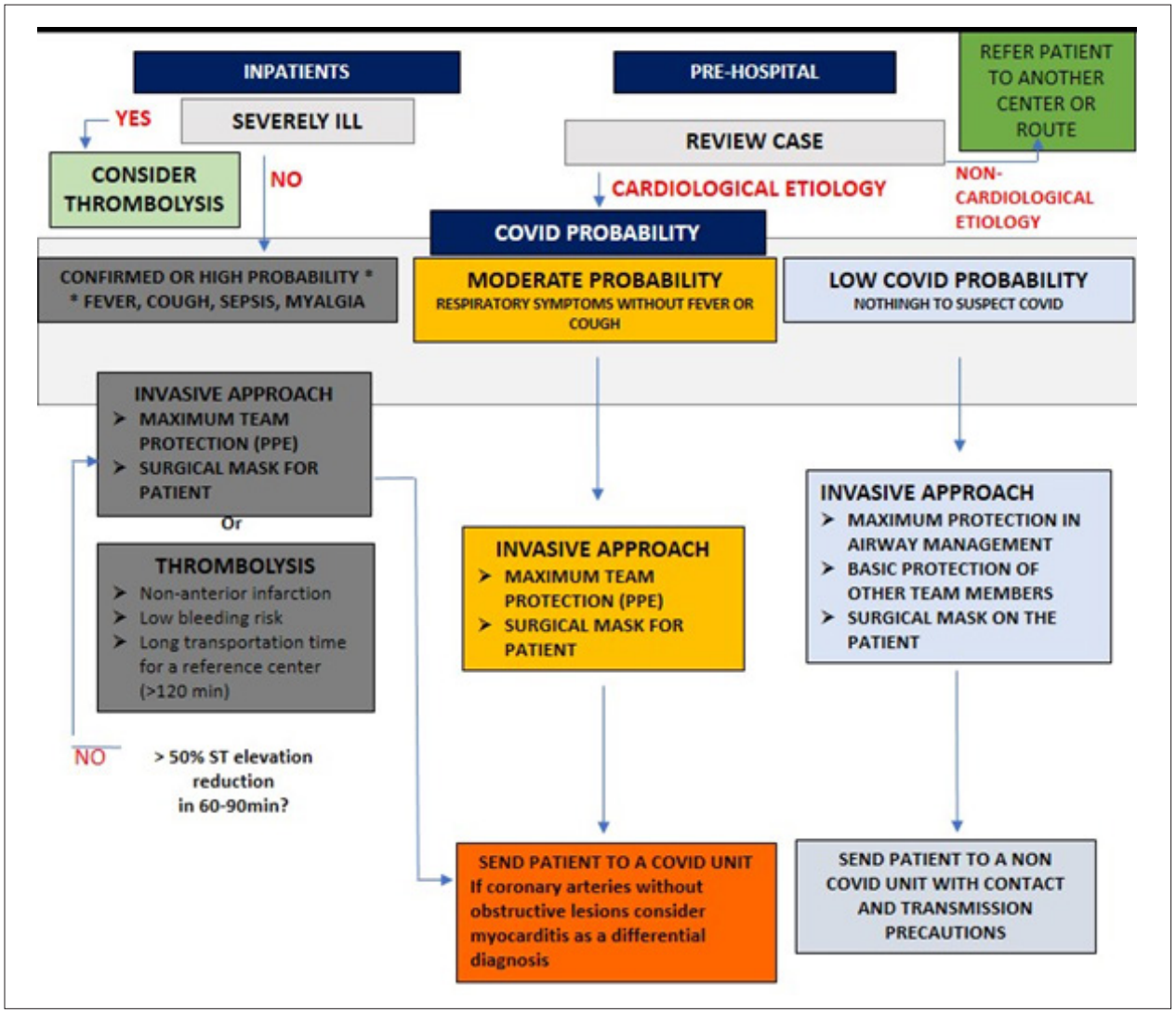

Figure 1 – *Acute ST elevation myocardial infarction in the COVID era.*

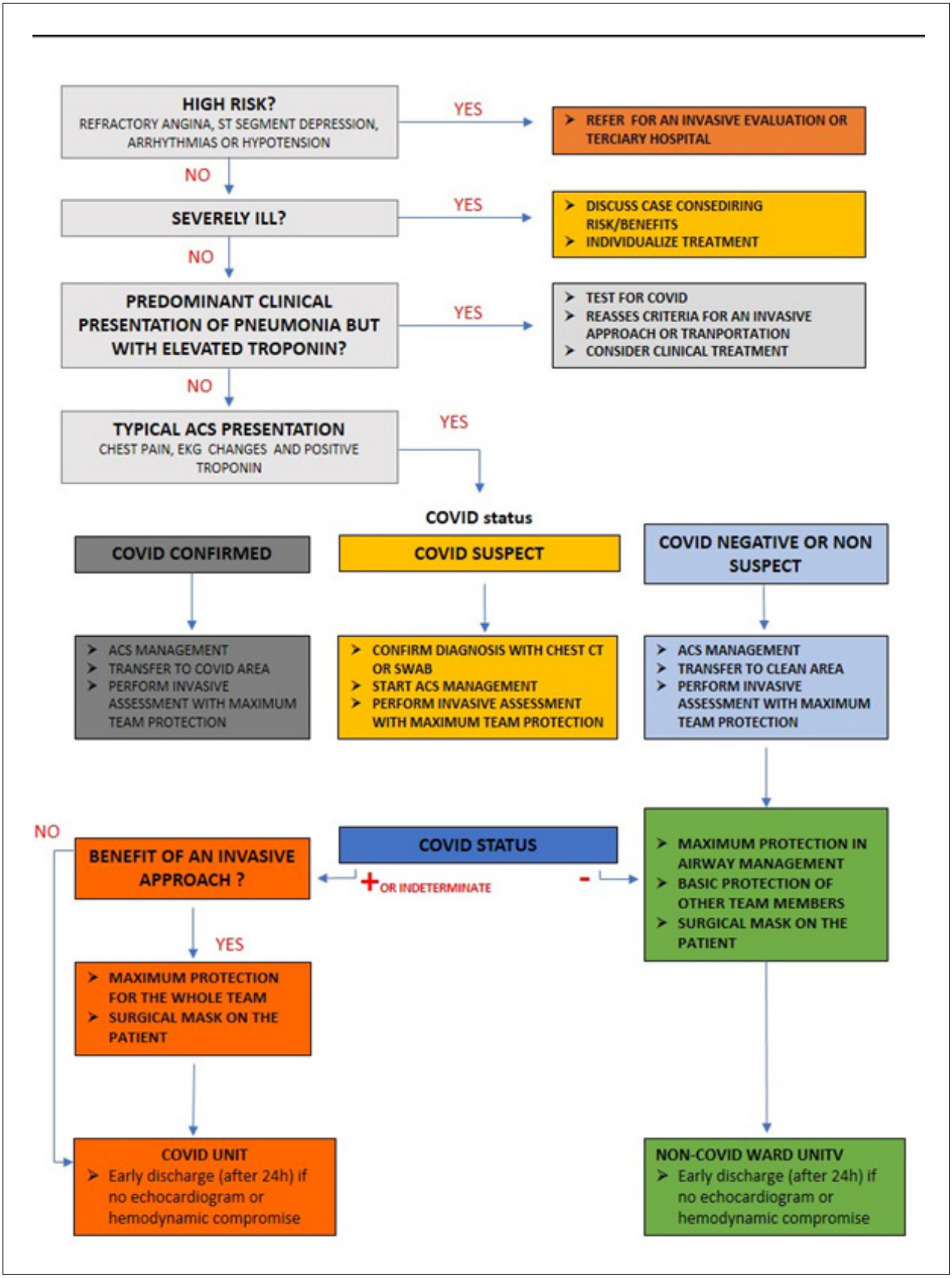

Figure 2 – *Unstable Angina/Coronary Syndrome Without ST elevation in the COVID era.*

depict suggestions of care pathways that can be adjusted to local hospital circumstances. For this purpose, personal protective equipment (anti-splash goggles, facial protectors, respirator masks, caps and waterproof aprons/gowns) should be available to the entire team with strict institutional routines for their use.

In addition, the creation of infarction networks, supported by telemedicine, can reduce mortality and length of hospitalization. The "Mission: Lifeline STEMI Systems Accelerator"[23] program observed the impact of the implementation of infarction networks in 167 hospitals, which treated 23,498 patients with acute ST elevation myocardial infarction. It documented key processes for improved care: pre-hospital catheterization laboratory activation (62% to 91%; P<0.001), single call protocol for external unit transfer (45% - 70%; P<0.001), and direct referral to the laboratory (avoiding delays in the emergency room) (48%- 59%; P=0.002). There was also a significant reduction in the time between the first medical contact and balloon inflation (88 minutes x 98 minutes; p<0.001). The LATIN[24-28] program connected 13 tertiary hospitals to 86 emergency care units (UPAs) in Brazil. It treated more than 6,000 patients with chest pain through telemedicine. The mean time for the diagnosis of infarction was 5 minutes. Primary percutaneous coronary intervention was used in 49% of these patients, reaching an average hospital mortality of 5%. In these networks, cases assisted early follow routes that avoid emergency care and lead the patient directly to the hemodynamics room, shortening the avoidable delays, which may even prevent the need for ICU, relieving the overload of the health care system.

Future Perspectives

The imminent economic recession caused by COVID-19 makes it challenging to maintain the population lockdown for long. This fact may theoretically imply a greater spread of the disease or the emergence of a second wave, with real chances of overcrowding and exhausting the health system. In this sense, providing a safe environment and adequate protocols for the treatment of patients with ACS is fundamental for coping with the pandemic, both in the public and supplementary health areas. The continuous review of institutional protocol management measures are fundamental for the management of patients with COVID-19 who have ACS, as well as for those without the co-existing infection. The medical staff should always be aligned and work as multidisciplinary teams, always alert to the potential cardiac side effects of the different drugs and therapies used to treat COVID-19. Training of the care team in relation to screening, biosafety, work routes, personal protective equipment, correct donning techniques, stringent observance of the doffing processes, patient care, isolation, hygiene measures, diagnostic adequacy and therapy avoiding the exposure of the health team will be imperative. Combined with all this preparation, it is urgent to warn the population that "myocardial infarction and heart diseases do not respect the quarantine". Dedicated campaigns such as *Coração Alerta* (https://coracaoalerta.com.br) sponsored by the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI), governmental, social and community actions and spaces for this purpose in the lay media and medical literature, as never before, can save lives.

A new way of living and providing care has emerged. The real final outcome of everything we are experiencing is not yet known, but what is certain is that this acute complicated situation will pass and cardiovascular pathologies, especially ACS, cannot be put in the background. Therefore, the best available management should always be available and offered. With science, wisdom and common sense we will come out stronger out of this serious situation with many teachings that will further help us to qualify our care activity for the greater good, which is the protection of life.

Author Contributions

Analysis and interpretation of the data and Writing of the manuscript: Guimarães RB, Falcão B, Costa RA, Lopes MACQ, Botelho RV, Petraco R, Sarmento-Leite R.

Potential Conflicts of Interest

Roberto Vieira Botelho is a shareholder of telemedicine companies. ITMS Telemedicine network and Conexa Saúde.

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This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Zhu N, Zhang D, Wang W, Xingwang Li, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8):727-33.
2. Siordia JA Jr. Epidemiology and clinical features of COVID-19: a review of current literature [published online ahead of print, 2020 Apr 10]. J Clin Virol. 2020; 127:104357.
3. Fang J, Deng L, Zhang L . Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545-9.
4. Paules CI, Marston HD, Fauci AS. Coronavirus infections — more than just the common cold. JAMA. 2020. Jan 23; doi 10.1001/jama 2020.0757 .
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the chinese center for disease control and prevention. JAMA 2020; 323(13):1239.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507-13.
7. Liu PP, Blet A, Smyth D . The science underlying COVID-19: implications for the cardiovascular system. Circulation. 2020 Apr 15; doi:1161/CIRCULATIONAHA.120.04715-49.
8. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, Li UL, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30; 382(18):1708-20.
9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020 Feb 24; doi:10.1001/jama/2020.2648 [Epub ahead print]
10. Wang D, Hu B, Hu C Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020 Feb 07;doi:10.1001/jama 2020.1585 [Epub ahead print]
11. Huang C, Wang Y, Li X Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497-506.
12. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. et al. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J. 2020 May 14; 41(19):1852-3.
13. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. 2020 Apr 9. J Am Coll Cardiol. Pii:S0735-1097(20_34912-5
14. Tam CF, Cheung KS, Lam S , Wong A, Yung A, Sze M, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. Circ Cardiovasc Qual Outcomes. 2020; 13(4):e006631.
15. American College Cardiology. American Heart Association. The new pandemic threat: people may die because they're not calling 911. https://newsroom.heart.org/news/the-new-pandemic-threat-people-may-die-because-theyre-not-calling-911. 2020 Apr 22.
16. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020 Apr 30;382(18):1679-81.
17. Waisman T, Botelho RV, Fernandez F, Mehta S, Oliveros E, Kostela JC. Telemedicine: the future of global STEMI Care. Interv Cardiol Clin. 2012; 1(4):623-9.
18. Strabelli TMV, Uip DE. COVID-19 e o coração: COVID-19 e o coração. ABC Cardiol Arq Bras Cardiol. 2020 Mar 20;pii:S0066-782X2020005005205
19. Yanamala CM, Bundhun PK, Ahmed A. Comparing mortality between fibrinolysis and primary percutaneous coronary intervention in patients with acute myocardial infarction: a systematic review and meta-analysis of 27 randomized-controlled trials including 11 429 patients. Coronary Artery Disease [Internet]. 2017;28(4):315-25.
20. Eisen A, Giugliano RP, Braunwald E. Updates on acute coronary syndrome: a review. JAMA Cardiol .. 2016; 1(6):718-30.
21. Writing Committee Members, Dehmer GJ, Badhwar V et al. 2020 AHA/ACC Key data elements and definitions for coronary revascularization: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing committee to develop clinical data standards for coronary revascularization). J Am Coll Cardiol. 2020 Apr 28; 75(16):1975-2088.
22. Angioplasty.Org – Cardiac arrest deaths at home in New York City have increased by a startling 800% . [Cited in 2020 Apr 30]. Available from: www.ptca.org.news/2020/
23. Dehmer GJ, Badhwar V, Bermudez EA, Cleveland JC Jr, Cohen MG, D'Agostino RS. 2020 AHA/ACC Key data elements and definitions for coronary revascularization. J Am Coll Cardiol. 2020;75(16):1975-2088.
24. Falcão B, Botelho R, Sarmento-Leite R, Marchese A, Tarantino AF, Rigattieri S, et al. Update on SBHCI positioning about COVID-19 pandemic. J Transcat Intervent. 2020; 28:1-5.
25. Welt FGP, Shah PB, Aronow HD Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from ACC's Interventional Council and SCAI. J Am Coll Cardiol. 2020 May 12;75(18):2372-5.
26. Tarantini G, Fraccaro C, Chieffo A, Italian Society of Interventional Cardiology (GISE) position paper for Cath lab-specific preparedness recommendations for healthcare providers in case of suspected, probable or confirmed cases of COVID-19. Catheter Cardiovasc Interv. 2020 Mar 29; doi:1002/ccd.28888
27. Fordyce CB, Al-Khalidi HR, Jollis JG, Roettig ML, Gu J, Bagai A. Association of rapid care process implementatioin on reperfusion times across multiple ST-segment-elevation myocardial infarction networks. Circ Cardiovasc Interv. 2017; 10(1):e004061.
28. Botelho RV, Mehta S. Editorial. Deconstructing STEMI Chaos. J Interv Cardiol. 2018;31(4):455-7.

COVID-19 and Acute Coronary Events – Collateral Damage. A Case Report.

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"On account of your fear, Sancho, you do not see or hear things correctly — said Don Quixote —, because one of the effects of fear is that it disturbs the senses and makes things seem not what they are."

Miguel de Cervantes, Don Quixote

A 49-year-old male patient, with dyslipidemia, 8-year-history of hypertension, and family history of coronary artery disease (His father had had an infarction at 60 years of age), had been using olmesartan 40 mg and rosuvastatin 10 mg daily until 10 days before being admitted to the hospital, having suspended use of olmesartan due to concern that the medication would facilitate SARS-CoV-2 infection.

On the morning of April 2, 2020, the patient had intense retrosternal chest discomfort and feeling of dyspnea. These symptoms were triggered by the slightest effort; they ceased while resting and recurred with decreasing intensity throughout the day. Concerned with the possibility of SARS-CoV-2 infection, he self-isolated, monitored his temperature, and self-administered paracetamol. He did not record a fever. The following day, chest pain recurred, radiating to his shoulders, in association with sweating and dyspnea. Due to the sweating, he became even more worried about the possibility of SARS-CoV-2, and he called an infectologist who instructed him to seek emergency medical care if the symptoms persisted or recurred. Throughout the day, the patient remained isolated and self-monitored his temperature. He reported that "only the possibility of coronavirus went through his mind."

On the morning of April 4, when the pain worsened, and the sweating was more intense, the patient decided to seek emergency medical care. The case was screened as possible acute coronary syndrome (ACS), but the patient refused to undergo tests, because he did not wish to remain in the sector where there were other patients, and he left against medical advice. On his way home, symptoms intensified, namely more profuse sweating and dyspnea; the patient changed course and came to our hospital, where he presented with sinus tachycardia (HR 108 bpm), SBP 176 mmHg, O2 saturation 98%, and temperature 36.4ºC. Electrocardiogram revealed ST segment elevation in V5, V6, D1, and AVL (Figure 1), indicating acute myocardial infarction with ST elevation (STEMI). The patient underwent coronary cineangiography and primary angioplasty in the middle third of the anterior descending artery, with a door-to-balloon time of 57 minutes (Figure 2). Echocardiogram showed mild systolic dysfunction, due to akinesia of the entire apical region and the middle segment of the anterior wall; ejection fraction was 45%, using the Simpson Method. Peak high sensitivity troponin I was 21,424 ng/L. The patient progressed without complications and was discharged after 3 days of hospitalization. Figure 3 shows the timeline of events up to diagnosis of acute STEMI.

Discussion

Considering the SARS-CoV-2 pandemic, quarantine periods have been declared in several cities in Brazil and worldwide, and people have been instructed to maintain social distancing in order to contain the rapid spread of the virus. Taken to the extreme, fear of becoming infected may result in typical symptoms of ACS being neglected or erroneously attributed to other less probable causes, delaying treatment and imposing avoidable risks to patients' lives. We report a typical case of ACS in a patient with risk factors for atherosclerotic disease, who, driven by panic related to COVID-19, was unable to recognize the nature of his symptoms, thus delaying his trip to the emergency room until the moment that chest pain became unbearable. Furthermore, also due to concerns related to SARS-CoV-2 infection, the patient suspended use of angiotensin receptor blocker (ARB). In spite of a door-to-balloon time of 57 minutes, as a result of prolonged ischemia time, the patient developed left ventricular systolic dysfunction, albeit asymptomatic.

Delayed recognition and medical care in acute myocardial infarction

Acute myocardial infarction (AMI) is the most lethal medical emergency worldwide, with an incidence of 43 – 144 per 100,000 people/year and a hospital mortality of 4% – 12%.[1] Primary angioplasty, especially when instituted within the first 12 hours after onset of symptoms, is considered the gold standard treatment.[1,2] Door-to-balloon time is an indicator of treatment quality in the context of AMI. It is equally important to minimize the time between onset of symptoms and arrival at a hospital. While time of

Keywords

ST Myocardial Infarction; Coronavirus; Pandemics; Panic; Fear; Cineangiography; Echocardiography/methods; Risk Factors.

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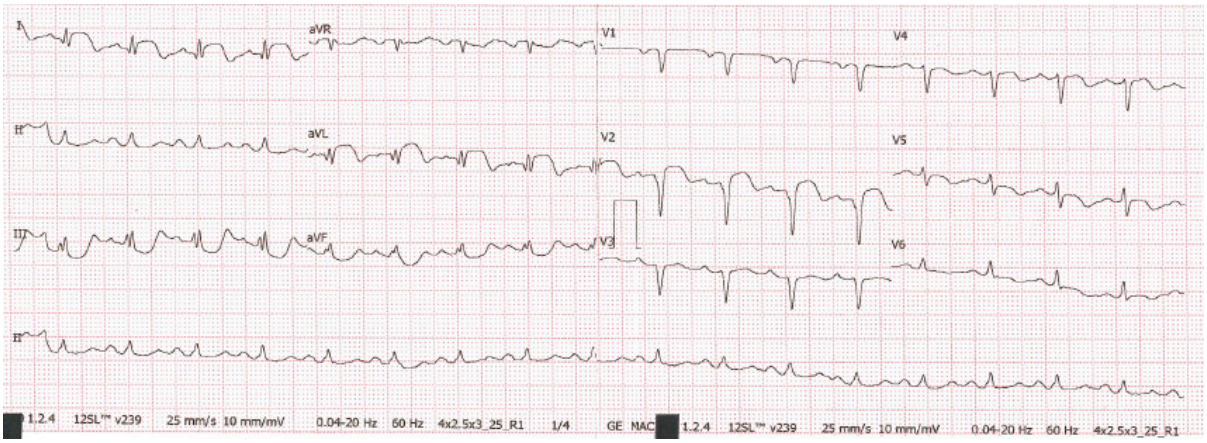

Figure 1 – *Electrocardiogram upon admission.*

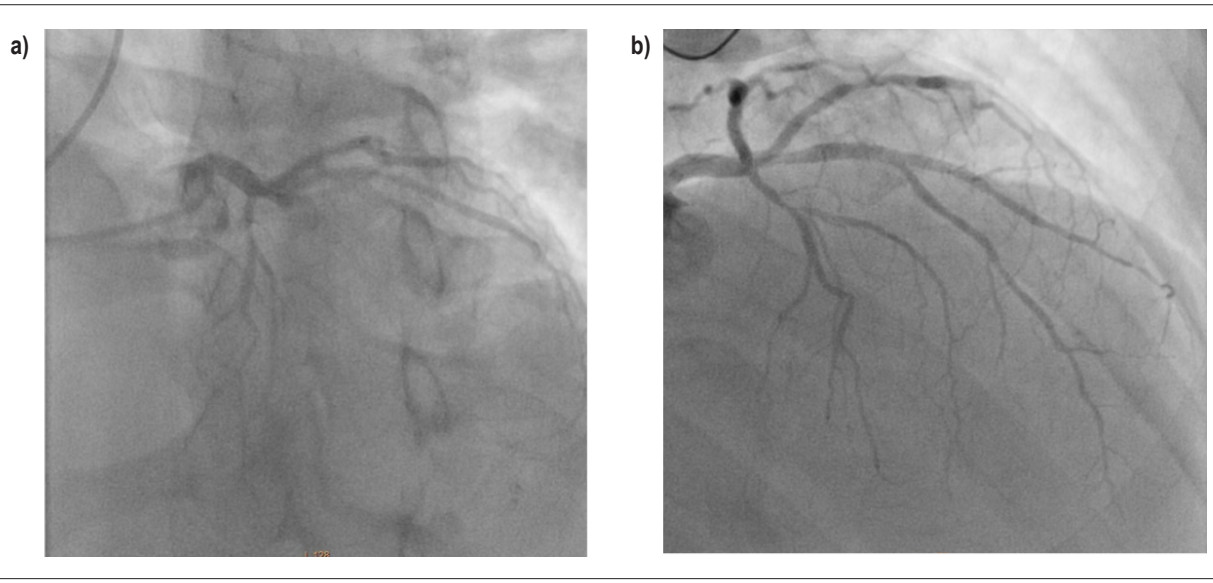

Figure 2 – *Coronary cineangiography representing: a) occluded anterior descending coronary artery and b) after primary angioplasty.*

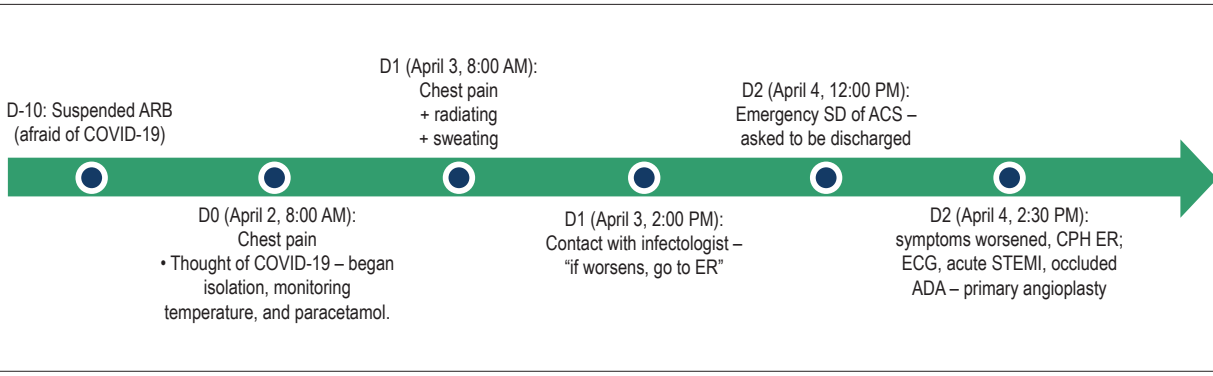

Figure 3 – *Timeline from onset of symptoms to diagnosis of myocardial infarction. ACS: acute coronary syndrome; ADA: anterior descending artery; ARB: angiotensin receptor blocker; CPH: Cardiopulmonary Hospital; ECG: electrocardiogram; ER: emergency room; SD: suspected diagnosis; STEMI: myocardial infarction with ST elevation.*

attendance upon arrival at the hospital may be optimized by internal movement and protocol, time to arrival at the hospital depends almost exclusively on patients' perception and evaluation of symptoms.

The SARS-CoV-2 pandemic has introduced other perspectives to this pathological approach, considering the potential risk of contamination in a hemodynamic environment, with procedures that may require more invasiveness, with inadequate environment for controlling the spread of the virus and guaranteeing the safety of healthcare professionals.[3] A recent publication from the epicenter of the pandemic weighs the possibility of thrombolytic therapy for confirmed cases with respiratory symptoms of the disease.[4]

The reported case illustrates another scenario within the SARS-CoV-2 pandemic, which is as concerning as the pandemic itself. Previously published studies during other viral epidemics have suggested an increase in the occurrence of myocardial infarction, with a greater propensity for inflammation and plaque instability,[5] and this also appears to be the rationale for SARS-CoV-2 infection.[6] Nonetheless, reports in different world centers point to a reduction in the frequency of hospital admission due to infarction, with an observational study indicating a 40% decrease in attendance for STEMI, with a slight increase in the rate of thrombolysis.[7] This paradoxical decline may be associated with a reduction in the number of patients seeking emergency care units, faced with fear generated by the pandemic, eventual doubts regarding symptoms associated with ACS and SARS-CoV-2 infection, and logistical issues related to healthcare caused by the collapse of the healthcare system. In our service, for instance, 21 patients were attended in the emergency room following the protocol for chest pain between March 20 and April 8, 2020; this is compatible with a 74% relative reduction with respect to the same period in 2019 and a 72% relative reduction with respect to the same period in 2018.

A case series from a single center for attending AMI in Hong Kong demonstrated a significant delay in providing care to these patients in comparison with a historical series from the previous year, with an increase in median time for all indicators of quality of care analyzed, especially time from onset of symptoms to first medical contact (318 minutes, IIQ 75 – 458 *vs.* 82.5 minutes, IIQ 32.5 – 195).[8]

Suspension of angiotensin converting enzyme inhibitors/ angiotensin receptor blockers and risk of events

The patient in question had suspended use of ARB of his own accord. Although we cannot define a causal nexus between this suspension and the occurrence of AMI, it is known that discontinuation of anti-hypertensive medications may contribute to greater occurrence of ACS.[9] The type 2 angiotensin-converting enzyme (ACE-2) appears to be involved in the internalization mechanism of SARS-CoV-2 on the tissue level. This information has led to speculation that users of angiotensin-converting enzyme inhibitors (ACEI) or ARB may have a greater likelihood of becoming infected due to ACE-2 upregulation. There are no published clinical data to prove this relationship apart from mechanistic observation, except the theoretical rationale.[10] Experimental models in animals have shown inconsistent effects of ACEI and ARB on levels of ACE-2 or its tissue activity.[11] Furthermore, cross-sectional studies in the fields of heart failure, atrial fibrillation, aortic stenosis, and coronary disease[12] resulted in similar ACE-2 plasma activity, regardless of whether ACEI and ARB were used or not. In addition to this, plasma levels of ACE-2 may not be reliable markers of the membrane-bound form, and there is a lack of evidence that modification of ACE-2 levels or tissue activity favor the penetration of SARS-CoV-2.

In this scenario, the world's leading cardiology societies have published informational updates, unanimously advising people to the maintain the use of these medications, given that the risk of rebound high blood pressure or decompensation of heart failure could lead to greater potential harm.[13] It is worth underscoring that some preliminary studies have even suggested that these medications may have a protective effect, reducing pulmonary inflammation.[14]

Conclusion

At this time, when everyone is concerned with the potential risks of the COVID-19 pandemic, we need to be aware and alert the population not to underestimate symptoms that are suggestive of cardiovascular events or risks related to delays in seeking emergency medical care. The direct harm of COVID-19 is at the center of media discussions and scientific publications, but the potential cardiovascular collateral damage related to delayed medical care in patients with acute vascular events should not go neglected.

Author contributions

Conception and design of the research: Ritt LEF, Viana MS, Darzé ES; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Ritt LEF, Viana MS, Feitosa GF, Oliveira AM, Souza FS, Darzé ES; Statistical analysis: Ritt LEF, Viana MS; Critical revision of the manuscript for intellectual content: Ritt LEF, Viana MS, Feitosa GF, Souza FS, Darzé ES.

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References

1. Ibanez B, James S, Agewall S, Antunes M, Ducci CB, Alida HB, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39(2):119-77.
2. Avezum Junior Á, Feldman A, Carvalho ACDC, Sousa ACC, Mansur AP, Bozza AEZ, et al. V Diretriz da Sociedade Brasileira de Cardiologia sobre Tratamento do Infarto Agudo do Miocárdio com Supradesnível do Segmento ST. *Arq Bras Cardiol*. 2015;105(2):1-105.
3. Driggin E, Madhavan M V, Bikdeli B, Chuich T, Laracy J, Zoccai GB, et al. et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Cardiol*. 2020;2019.
4. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. *Intensive Care Med*. 2020;75(18):2352-371.
5. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. *JAMA Cardiol*. 2016;1(3):274-81.
6. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol*. 2020;323(11):1061-9.
7. Rodríguez-leor O, López-palop R, Serrador A, Martin-Moreiras J, Rumoroso JR, Perez de Prado A. Impacto de la pandemia de COVID-19 sobre la actividad asistencial en cardiología intervencionista en España.REC Interv Cardiol.2020;82-9.
8. Tam C-CF, Cheung K-S, Lam S,wang A, Yung A, Sza M, et al. Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment–Elevation Myocardial Infarction Care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes*. 2020;13(4):e006631,2020 04.
9. Alharbi FF, Souverein PC, De Groot MC, Maitland-Van Der Zee AH, De Boer A, Klungel OH. Risk of acute myocardial infarction after discontinuation of antihypertensive agents: A case-control study. *J Hum Hypertens*. 2017;31(8):537-44.
10. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
11. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosniban AKB, Tallant A, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111(20):2605-10.
12. Ramchand J, Patel SK, Srivastava PM, Farouque O, Burrell LM. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. *PLoS One*. 2018;13(6):1-11.
13. Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. *JAMA Cardiol*. 2020;19(8):1965-74.
14. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-9.

Hypothermia-Induced Electrocardiographic Changes

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An elderly female patient was brought to the Emergency Department due to loss of consciousness. The past medical history was remarkable for hypercholesterolemia and essential hypertension. The patient was not treated with any negative chronotropic drug. At the admission, the patient's blood pressure was 90/60 mmHg, she had bradycardia (42/minute), and hypothermia (33ºC). Electrocardiogram (ECG) showed sinus bradycardia, 1st grade atrioventricular block, long corrected QT interval, and Osborn waves at the end of QRS complexes (Figure 1 A, arrowheads). Accordingly, these positive notching deflections were best seen in lateral precordial leads and disappeared after warming the patient to 36ºC (Figure 1B). The bradycardia, atrioventricular block, and QT prolongation were also resolved (Figure 1 B). During the inward stay, head computed tomography scan, 24-hour Holter, and laboratory analysis were unremarkable for pathological findings. Transthoracic echocardiogram only revealed degenerative aortic and mitral valve changes. This case is illustrative of hypothermia-induced electrocardiographic changes, namely prolongation of the PR, RR and QT intervals and particularly the presence of Osborn Waves.[1,2]

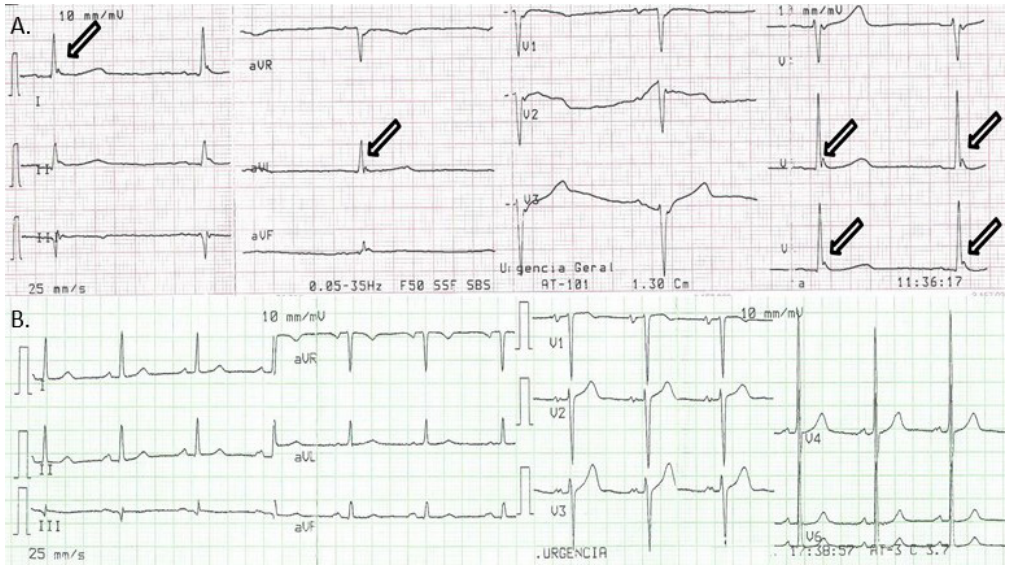

Figure 1 – *Panel A) Electrocardiogram (ECG) showing hypothermia-induced ECG changes: sinus bradycardia, 1st grade atrioventricular block, long corrected QT interval, and Osborn waves at the end of QRS complexes (arrowheads). Panel B) The ECG after warming the patient showing resolution of hypothermia-induced ECG changes.*

Keywords

Bradycardia; Atrioventricular Block; Electrocardiography/methods; Hypothermia; Osborn Waves.

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References

1. Alhaddad IA, Khalil M, Brown EJ Jr. Osborn waves of hypothermia. Circulation. 2000;101(25):E233-E244.
2. Doshi HH, Giudici MC. The EKG in hypothermia and hyperthermia. J Electrocardiol 2015; 48(2):203–8.

Position Statement: Cardiopulmonary Resuscitation of Patients with Confirmed or Suspected COVID-19 – 2020

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Note: These statements are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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	If, within the last 3 years, the author/collaborator of the statement:						
Names of statement collaborators	**Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this guideline**	**Spoke at events or activities sponsored by industry related to this guideline**	**Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry**	**Participated in normative committees of scientific research sponsored by industry**	**Received personal or institutional funding from industry**	**Wrote scientific papers in journals sponsored by industry**	**Owns stocks in industry**
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Content

Abstract

Care for patients with cardiac arrest in the context of the coronavirus disease 2019 (COVID-19) pandemic has several unique aspects that warrant particular attention. This joint position statement by the Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Society of Cardiology (SBC), Brazilian Association of Intensive Care Medicine (AMIB), and Brazilian Society of Anesthesiology (SBA), all official societies representing the corresponding medical specialties affiliated with the Brazilian Medical Association (AMB), provides recommendations to guide health care workers in the current context of limited robust evidence, aiming to maximize the protection of staff and patients alike.

It is essential that full aerosol precautions, which include wearing appropriate personal protective equipment, be followed during resuscitation. It is also imperative that potential causes of cardiac arrest of particular interest in this patient population, especially hypoxia, cardiac arrhythmias associated with QT prolongation, and myocarditis, be considered and addressed. An advanced invasive airway device should be placed early. Use of HEPA filters at the bag-valve interface is mandatory. Management of cardiac arrest occurring during mechanical ventilation or during prone positioning demands particular ventilator settings and rescuer positioning for chest compressions which deviate from standard cardiopulmonary resuscitation techniques. Apart from these logistical issues, care should otherwise follow national and international protocols and guidelines, namely the 2015 International Liaison Committee on Resuscitation (ILCOR) and 2019 American Heart Association (AHA) guidelines and the 2019 Update to the Brazilian Society of Cardiology Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Guideline.–

1. Introduction

Cardiopulmonary resuscitation (CPR) is perhaps the most extreme emergency procedure that can be required in a patient with coronavirus disease 2019 (COVID-19). In this setting, special caution is warranted, particularly regarding the increased risk of aerosol generation during chest compressions and ventilation, which poses a substantial hazard of rescuer contamination.

Considering the lack or inaccessibility of robust evidence on best practices in this novel scenario, the Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Society of Cardiology (SBC), Brazilian Association of Intensive Care Medicine (AMIB), and Brazilian Society of Anesthesiology (SBA), all official societies representing the corresponding medical specialties affiliated with the Brazilian Medical Association (AMB), have issued this position statement containing specific recommendations for the management of cardiac arrest in patients with confirmed or suspected COVID-19. In all other cases, the 2015 guidelines of the International Alliance of Resuscitation Committees (ILCOR), the 2019 American Heart Association (AHA) guidelines,[1] and the 2019 Update to the Brazilian Society of Cardiology Cardiopulmonary *Resuscitation* and Emergency Cardiovascular Care *Guideline*[2] apply.

2. Prevention of Cardiac Arrest

• All patients with suspected or confirmed COVID-19 who are at increased risk of acute deterioration or cardiac arrest should be appropriately flagged to the local rapid response team (RRT) or whichever other team has been designated to provide code response.[3-5] The use of severity scores and tracking systems, as well as the use of a "code yellow" system for identification of patients who are periarrest, allow early detection of critically ill patients and can optimize the care of cardiac arrest when it does occur;[2,5]

• Assessment of the potential difficulty of laryngoscopy/intubation must be performed on admission to the hospital and/or Intensive Care Unit (ICU) and recorded appropriately in the patient's medical record. Scores such as MACOCHA (*Mallampati, obstructive Apnea syndrome, reduced Cervical mobility, limited mouth Opening, Coma, severe Hypoxemia, and non-Anesthesiologist operator*) or mnemonics such as LEMON (*Look, Evaluate, Mallampati, Obstruction, Neck*) can assist in determination of the difficult airway, activation of appropriate support, and prompt a request for a difficult airway trolley or cart;[6,7]

• Considering that two therapies currently under evaluation as potential treatments for COVID-19, chloroquine and hydroxychloroquine, may prolong the QT interval in up to 17% of patients, it is essential to consider the risk of severe polymorphic ventricular arrhythmias – especially *torsades de pointes* – and consequent occurrence of cardiac arrest with shockable rhythms;[4,8-10]

• The patients most at risk of polymorphic tachycardias in this context are older adults; women; and those with COVID-related myocarditis, heart failure, liver or kidney dysfunction, electrolyte disturbances (particularly hypokalemia and hypomagnesemia), and bradycardia. Identification of patients who already have a prolonged (> 500 ms) corrected QT interval (QTc) at baseline is

paramount, and ECG monitoring should be performed daily as long as QT-prolonging drugs are used.[4,8-10]

3. Decision-making

• The decision of whether or not to initiate CPR must continue to be made on an individualized basis, be it during prehospital care, in the emergency department, or in the ICU. The potential benefits for the patient, the safety and exposure hazards of the code team, and the potential for futility of resuscitation maneuvers must be taken into account. Nevertheless, CPR should always be performed unless advance directives clearly state otherwise;[1,2]

• "Do not attempt CPR" (DNACPR) or "not for CPR" decisions/directives must be properly documented and communicated to the team. Palliative and end-of-life care should follow local and institutional policy.[1,2]

4. Guidance on Precautions

• Standard + aerosol precautions are recommended for all members of the code team in order to ensure adequate personal protection. Prompt availability of Personal Protective Equipment (PPE), e.g., by keeping PPE kits ready in every crash cart or trolley, minimizes the delay in initiating chest compressions and helps maintain continuity of care.[3,4,11-14] Each PPE kit must include an N95 filtering facepiece respirator, face shield, waterproof gown, cap, long-cuff disposable gloves, and goggles;

• The safety of the code team should be the utmost priority even if this means delaying chest compressions, and all those who respond to the code must first don appropriate PPE. In particular, CPR should not be started on any patient with suspected or confirmed COVID-19 until the code team is fully attired with appropriate PPE;[3,4,11-14]

• The number of team members at the site of the code (if it is an enclosed space such as a private room or cubicle) should be restricted;[2,4,15,16]

• Hand hygiene plays an important role in reducing the transmission of COVID-19. All team members must wash their hands with soap and water (only when visibly soiled) or use an alcohol-based hand sanitizer;[3,15]

• Adherence to all applicable federal (Ministry of Health) and local government guidelines is mandatory.

5. First Response

• Recognition of cardiac arrest should follow ILCOR/AHA and Brazilian Society of Cardiology guidelines. Assessment should start by checking for responsiveness, breathing (chest rise and fall), and presence of a central pulse;[1,2]

• In adults, CPR should begin with continuous chest compressions. If the patient does not already have an invasive or advanced airway (orotracheal tube or extraglottic airway device) in place, a mask delivering low-flow oxygen or a towel should be placed over the patient's mouth and nose before initiating compressions and kept in place until an invasive airway is secured,[8] as chest compressions can generate aerosols;

• In children, CPR should preferably consist of compressions and ventilation with a bag-valve-mask (BVM) coupled to a high-efficiency particulate arrestance (HEPA) filter until a definitive airway is established, since pediatric arrest is most commonly of respiratory etiology, and compression-only CPR is known to be less effective in this population.[3] If a BVM with HEPA filter is not available, compression-only CPR with a standard oxygen mask or towel covering the patient's mouth is a reasonable alternative;[17]

• Despite the guidance of some emergency medical services that prehospital care of cardiac arrest in the absence of a medical professional (lay rescuer CPR) should be limited to hands-only CPR, the recommendation that the patient's oral cavity be sealed to prevent aerosol generation as described above still stands;[4,8,9,14]

• Cardiac monitoring should be placed as soon as possible to ascertain whether there is a shockable rhythm, so as not to delay defibrillation if appropriate and provide guidance as to the optimal resuscitation algorithm to follow;[1,2]

• Defibrillation of a shockable rhythm should never be delayed to secure the airway or for other procedures;[1,2]

• If the patient already had a face mask in place to deliver supplemental oxygen before cardiac arrest occurred, it should be kept on until intubation, but delivering low-flow oxygen only (6–10 L/min at most); higher flow rates may be aerosol-generating;

• If the patient does not have any airway device in place, the rescuer should place a cloth or towel over the patient's mouth and nose and begin continuous compressions;

• Before considering termination of CPR, any reversible causes should be identified and addressed, with particular emphasis on hypoxia, acidemia, and coronary thrombosis – all cited as common causes of death in recent publications on COVID-19.[3] Additionally, polymorphic *torsades de pointes*-type ventricular tachycardia (associated with QT prolongation, which is known to be caused by drugs under investigation as potential COVID-19 treatments) and cardiac tamponade (associated with myocarditis), as well as ventilation-induced pneumothorax, have all been described as causes of cardiac arrest.

6. Airway Management

• BVM or bag-valve-tube (BVT) ventilation should be avoided, due to the high risk of aerosol generation and staff contamination.[3,15,18,19] If BVM ventilation is absolutely necessary, two rescuers should always be present to allow a two-handed mask seal, and an oropharyngeal (Guedel) cannula should be placed. In this case, 30 compressions and two breaths should be performed in adults and 15 compressions and two breaths in children until an invasive airway has been established, at which point the ratio should switch to continuous compressions and one breath every 6 seconds for adults and children alike. Placement of a HEPA filter between the mask and the bag is recommended (Figures 1 to 3);

• Considering that hypoxia is one of the main causes of cardiac arrest in patients with COVID-19, invasive airway access should be prioritized for isolation purposes, due to the lower likelihood of aerosol generation and, consequently, staff contamination, as well as the possibility of achieving better ventilation and oxygenation patterns.[15,16,19-21] During airway instrumentation, chest compressions should be halted to protect the code team. It is suggested that airway instrumentation be performed or attempted during pulse checks, to reduce hands-off time. It is

recommended that orotracheal intubation always be performed by the most experienced operator present;

• Videolaryngoscopy with a blade capable of providing a wide-angle view should be the first-line method of choice for quick, safe, and definitive airway management, ideally on first attempt, and always performed by the most experienced physician. In the event of intubation failure, the assistance of a second operator must be requested immediately. Videolaryngoscopy should again be prioritized for the second attempt;[16,20,21]

• For children, videolaryngoscopy with a blade suitable for the size of the patient is recommended; there is no particular need for a wider view angle;[20]

• If intubation fails again or is deemed impossible, an extraglottic device (laryngeal tube or laryngeal mask) should be placed. This will allow closed-circuit mechanical ventilation and capnography until conditions are present for establishment of a definitive (surgical) airway via tracheostomy or cricothyrotomy.[20,22] In children, a laryngeal mask suitable for the patient's weight and size is the extraglottic device of choice.[23] In Brazil, placement of extraglottic airway devices is within the scope of practice of both physicians and nurses, and can thus be an alternative for airway management in prehospital intermediate life support or limited advanced life support, as well as in nurse-led codes.[1,2] Nevertheless, endotracheal intubation is still recommended whenever possible, largely with the aim of reducing aerosol generation;

• When more than one extraglottic device is available, priority should be given whenever possible to that providing the best airway seal and the possibility of sequential placement of an orotracheal tube through the device lumen (Fastrach™ or other intubating laryngeal mask airway);

• Even after a patient has been intubated or has an extraglottic device in place, occlusion and sealing of the oral cavity is still important to reduce aerosolization; this can be done with towels, gauze packs, or a standard surgical mask;

• When cardiac arrest occurs in a patient already on mechanical ventilation, the patient should be connected to the ventilator through a closed ventilation circuit and the ventilator parameters set as follows (Chart 1):

Figure 1 – *Bag-valve-mask device fitted with HEPA filter. Source: Personal collection.*

○ Mode: volume assist-control ventilation (AC or ACV). Tidal volume (V_T): 6 mL/kg predicted body weight.

○ Fraction of inspired oxygen (FiO_2): 100%.

○ Respiratory rate (RR): approximately 10 breaths per minute; inspiratory time (Ti): 1 second.

○ Flow triggering: off; if triggering cannot be disabled, switch to pressure-triggering mode and adjust the triggering pressure to the least sensitive (i.e., lowest) possible threshold; this ranges from -15 to -20 depending on ventilator model.

Figure 2 – *Manikin simulation of an intubated patient being ventilated with a bag-valve-mask device fitted with a HEPA filter. Note surgical mask covering the nose and oral cavity. Source: Personal collection.*

Figure 3 – *Manikin simulation of a patient with an extraglottic airway device being ventilated. Note HEPA filter and surgical mask covering the nose and oral cavity. Source: Personal collection.*

○ Positive end-expiratory pressure (PEEP): zero.

○ Alarms: set tidal volume alarms to the minimum and maximum allowed by the ventilator and pressure alarms to 60 cmH_2O (maximum) and 1 or 0 cmH_2O (minimum). The high and low minute volume alarms should be set to the maximum and minimum allowed by the device. The respiratory rate alarm should be set to the maximum allowed by the device, and the apnea time, to 60 seconds.

• The exact same parameters apply in children;

Continuously assess whether the ventilator can maintain these parameters without auto-triggering, which leads to hyperventilation and air trapping with excessive pressures (systematically above 60 cm H_2O). In children, temporary disconnection from the ventilator may be necessary; in this case, BVM ventilation with a HEPA filter should be performed;

• Some ventilators provide a "CPR mode" function, which automatically adjusts the alarm limits and ventilator parameters as described above. For mechanically ventilated patients, it is recommended that a HEPA filter be placed in the ventilation circuit after the orotracheal tube and a second filter at the expiratory circuit;[16,20,21]

• To minimize aerosol generation, the tube should be clamped with a strong straight hemostat whenever there is a need to switch ventilator circuits (BVM to mechanical ventilator circuit, for instance);

• For the safety of the team and the patient, adhesive pads (which do not require disconnection from the ventilator) should always be preferred for defibrillation. If manual (paddle) defibrillation is needed, the ventilator should be placed in standby mode and the orotracheal tube disconnected from the ventilator, keeping the HEPA filter attached to the tube, only after the shock has been delivered.

7. Chest Compressions

• High-quality chest compressions should be performed, ensuring:

○ A compression rate of 100 to 120 compressions per minute.

○ In adults, a compression depth of at least 5 cm (compressions deeper than 6 cm should be avoided).

Chart 1 – Mechanical ventilator settings for cardiopulmonary resuscitation.

Volume assist-control ventilation mode; VT = 6 mL/kg PBW
Respiratory rate = 10 bpm
FiO2 = 100%
Flow trigger = disabled or sensitivity threshold -15 to -20
PEEP = 0
VT alarms = maximum and minimum allowed by device
Pressure alarms = 60 cmH_2O maximum, 1 or 0 cmH_2O minimum
High and low minute volume alarms = maximum and minimum allowed by device
Apnea time = 60 seconds

FiO_2: fraction of inspired oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; VT: tidal volume. Source: Personal collection.

○ In infants, compression depth should be one-third of the anteroposterior diameter of the chest; in children, it should be one-third of the anteroposterior diameter of the chest or at least 5 cm.

• Allow full recoil of chest after each compression; do not lean on the patient's chest;

• Minimize interruptions in chest compressions; pauses should be limited to 10 seconds at most (for two breaths). Consider performing CPR with the goal of the highest possible chest compression fraction, aiming at a minimum of 60% to 80%;

• Rotate out with another team member every 2 minutes to avoid rescuer fatigue, which can lead to poor compressions;

• If the patient is in the supine position, compressions should be performed in the center of the chest, on the lower half of the breastbone (sternum);

• Considering the need for PPE use to limit the risk of aerosol generation, the strenuous nature of resuscitation maneuvers, the potential for rescuer fatigue and exhaustion, and the need to minimize the number of team members present during resuscitation, use of a mechanical chest compression device is advised for adults whenever one is available.

8. Cardiopulmonary Resuscitation in the Prone Position

• If the patient is in prone position with no invasive airway in place, he or she should be quickly repositioned supine, CPR should be initiated, and an invasive airway device should be placed as soon as possible, preferably by orotracheal intubation;

• If the patient is already intubated and ventilated, it is recommended that CPR maneuvers be initiated with the patient still in prone position. The surface landmark for hand placement is the exact posterior projection of the site for chest compressions, i.e., in the interscapular region, at the T7-T10 level (Figure 4). Attempts to de-prone (i.e., return the patient to the supine position) should be performed with maximum care to avoid ventilator disconnection and minimize the risk of aerosolization. If adhesive defibrillator pads are available, they should be placed in an anteroposterior arrangement;[10,22,23]

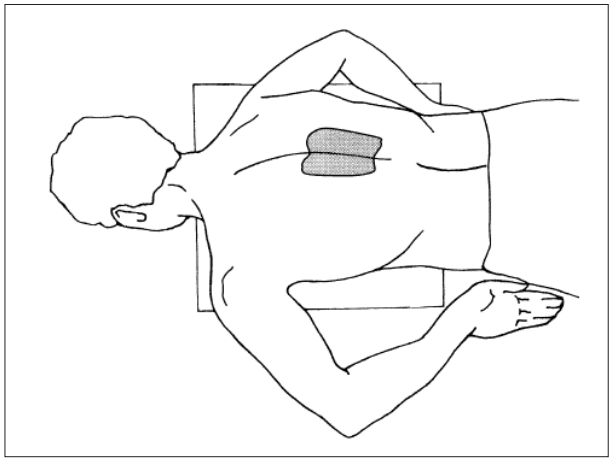

Figure 4 – Hand placement for compressions on a patient in the prone position.[23]

• If no adhesive pads are available, manual defibrillation can be attempted by placing the sternal paddle on the dorsal region and the apical paddle on the patient's flank (Figure 5). It is recommended that the effectiveness of CPR be assessed by end-tidal CO_2 monitoring (partial pressure of carbon dioxide > 10 mmHg) and invasive blood pressure monitoring (diastolic blood pressure > 20 mmHg). It bears stressing that evidence for this maneuver is still unclear and, whenever possible, the patient should be de-proned, as the supine position is best suited for high-quality CPR and adequate ventilation.

9. Post-cardiac Arrest Care

• If the patient is not already in intensive care, an ICU bed with respiratory isolation should be requested even before return of spontaneous circulation (ROSC) is achieved;[3,15,16]

• All equipment used during CPR should be disposed of or sanitized following manufacturer recommendations and institutional or local guidelines;[3]

• All surfaces onto which airway/resuscitation equipment was placed must also be cleaned as per local guidelines. Check that no airway management devices (including laryngoscopes and face masks) have been left on the bed. All equipment should be left on the intubation tray if possible;[3,18]

• After the code, team members should doff all PPE safely, avoiding self-contamination.[3,15] Particular attention is required during this step, which is when contamination of health care workers is most likely to occur (through contact with patient secretions and respiratory droplets).

10. Specific Guidance for Prehospital Care

• In the prehospital environment, CPR should never be attempted in patients with suspected or confirmed COVID-19 who present with obvious signs of death;[3]

• Prehospital care providers should follow standard + aerosol precautions when caring for patients with suspected or confirmed COVID-19;

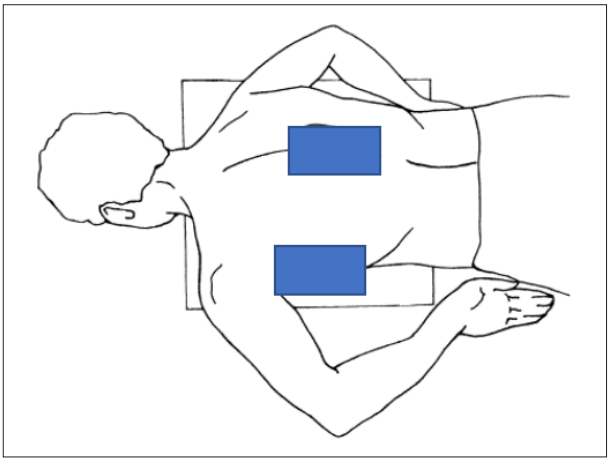

Figure 5 – Suggested paddle position for manual defibrillation of a patient in the prone position.[23]

• The population should be instructed to notify the dispatcher if the victim is suspected to have COVID-19 when calling an ambulance. This allows prehospital care providers to don appropriate PPE before arrival at the scene. Emergency medical service dispatchers and physician regulators/medical directors are strongly advised to conduct active case-finding of COVID-19 by inquiring about flu-like symptoms, fever, and dyspnea during calls;

• CPR should be limited to continuous chest compressions. Mouth-to-mouth ventilation, even with use of a pocket CPR mask, should never be performed for patients with suspected or confirmed COVID-19;[3]

• Considering that most out-of-hospital cardiac arrests occur at home, in pediatric out-of-hospital arrests, the lay rescuer will most likely be a parent, family member, or caregiver who will already be in close contact with the child and thus exposed to respiratory secretions. In this case, the lay rescuer should be instructed to perform compressions and consider mouth-to-mouth ventilation if he or she is able and willing to do so, since most pediatric arrests are secondary to respiratory causes;[23]

• Hands-only CPR is a reasonable alternative if the rescuer is unable or unwilling to provide mouth-to-mouth resuscitation or has not had close contact with the child before;[17]

• The rescuer should cover the victim's mouth and nose with a cloth or towel (or, if available, place a mask delivering low-flow oxygen) to prevent suspension of aerosols generated during CPR;

• Do not delay defibrillation. Early use of an automated external defibrillator (AED) significantly increases the odds of survival and does not increase the risk of COVID-19 transmission;

• Positive-pressure BVM ventilation should be avoided at all cost. If absolutely necessary, it must always be performed by two providers, one of whom will be exclusively responsible for sealing the mask to the patient's face, using the most suitable grip technique to avoid air leak. A BVM may only be used if a HEPA filter is available and has been placed at the bag-valve interface.

• In children, CPR should preferably consist of chest compressions and BVM ventilation (always with a HEPA filter);

• Otherwise, prehospital airway management should follow the aforementioned recommendations for in-hospital care – namely, ensuring that a BVM and any other ventilation devices are equipped with HEPA filters and that an advanced airway device (tracheal tube or extraglottic airway) is placed as early as possible;

• Open the rear doors of the transport vehicle and activate the heating, ventilation, and air conditioning (HVAC) system during any aerosol-generating procedures (do this away from pedestrian traffic);

• Family members or chaperones may not ride along in the ambulance in the same compartment as the patient. According to Ministry of Health recommendations, patients with suspected or confirmed COVID-19 are not allowed any chaperones who may be at risk of contamination. It is suggested that companions or chaperones be instructed to make their own way to the health facility;

• If the transport vehicle lacks an isolated driver compartment, the outside air vents in the driver's area should be opened and the rear exhaust fans turned on at the highest setting.

11. Training and Debriefing

• Perform debriefing at the end of each code to support team growth and improvement;[1,2]

• All health care workers involved in the care of patients with suspected or confirmed COVID-19 should undergo skills training in donning and, especially, doffing PPE as soon as possible, as well as participate in simulated code blue response;[15,16,20,21]

• Skills training and continuing medical education are paramount to protecting staff and improving safety in patient care. The use of moulages/vignettes, realistic simulation resources, and distance education resources is strongly recommended.

Following are the algorithms for PCR care of adult (Figure 6) and pediatric (Figure 7) patients with suspected or confirmed COVID-19.

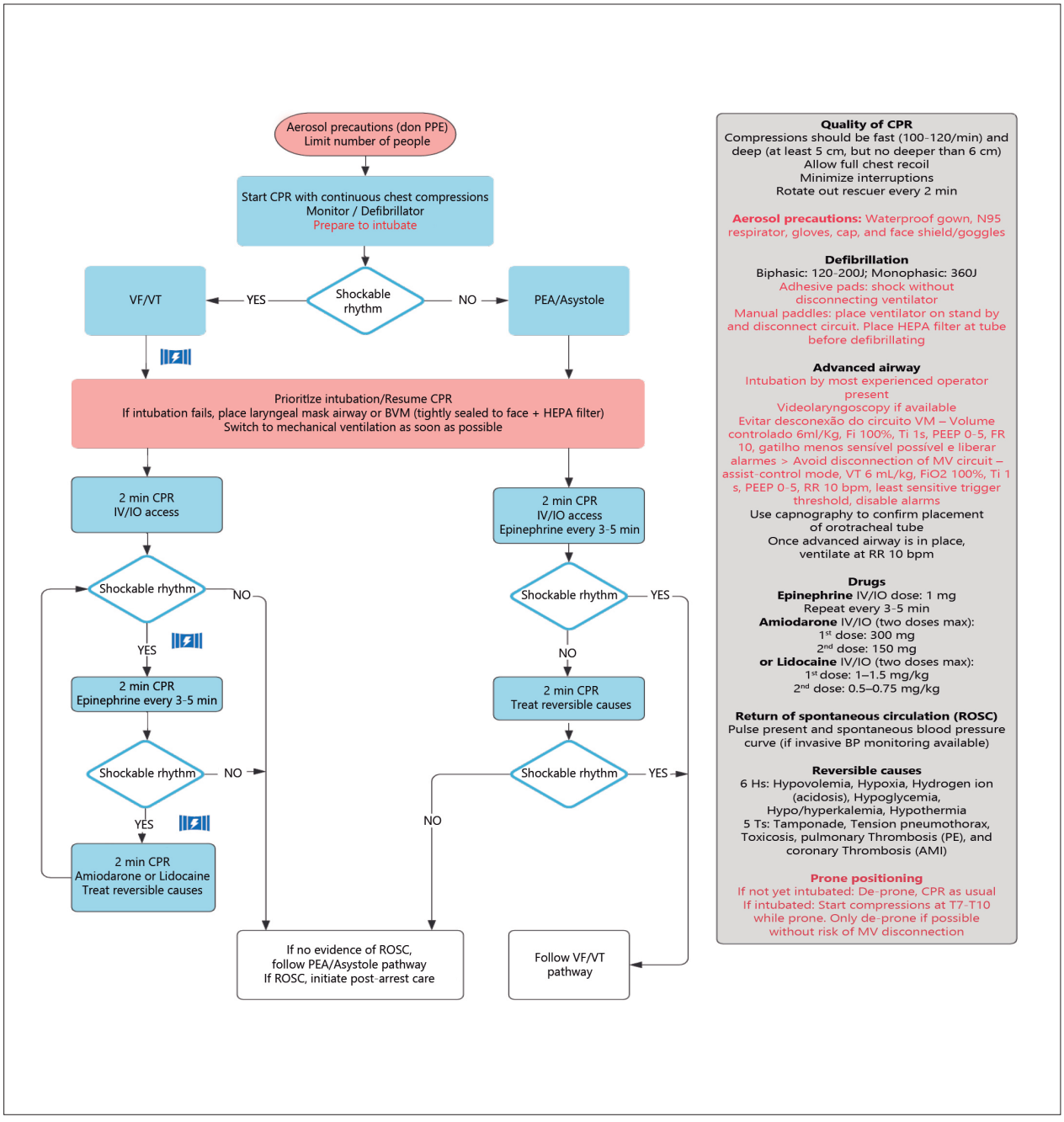

Figure 6 – *Algorithm for management of cardiopulmonary arrest in patients with suspected or confirmed COVID-19. AMI: acute myocardial infarction; BP: blood pressure; BVM: bag-valve-mask; CPR: cardiopulmonary resuscitation; Fi: inspired fraction; HEPA: high-efficiency particulate arrestance; IO: intraosseous; IV: intravenous; MV: mechanical ventilation; PE: pulmonary embolism; PEA: pulseless electrical activity; PEEP: positive end-expiratory pressure; ROSC: return of spontaneous circulation; RR: respiratory rate; Ti: inspiratory time; VF: ventricular fibrillation; VT: ventricular tachycardia.*

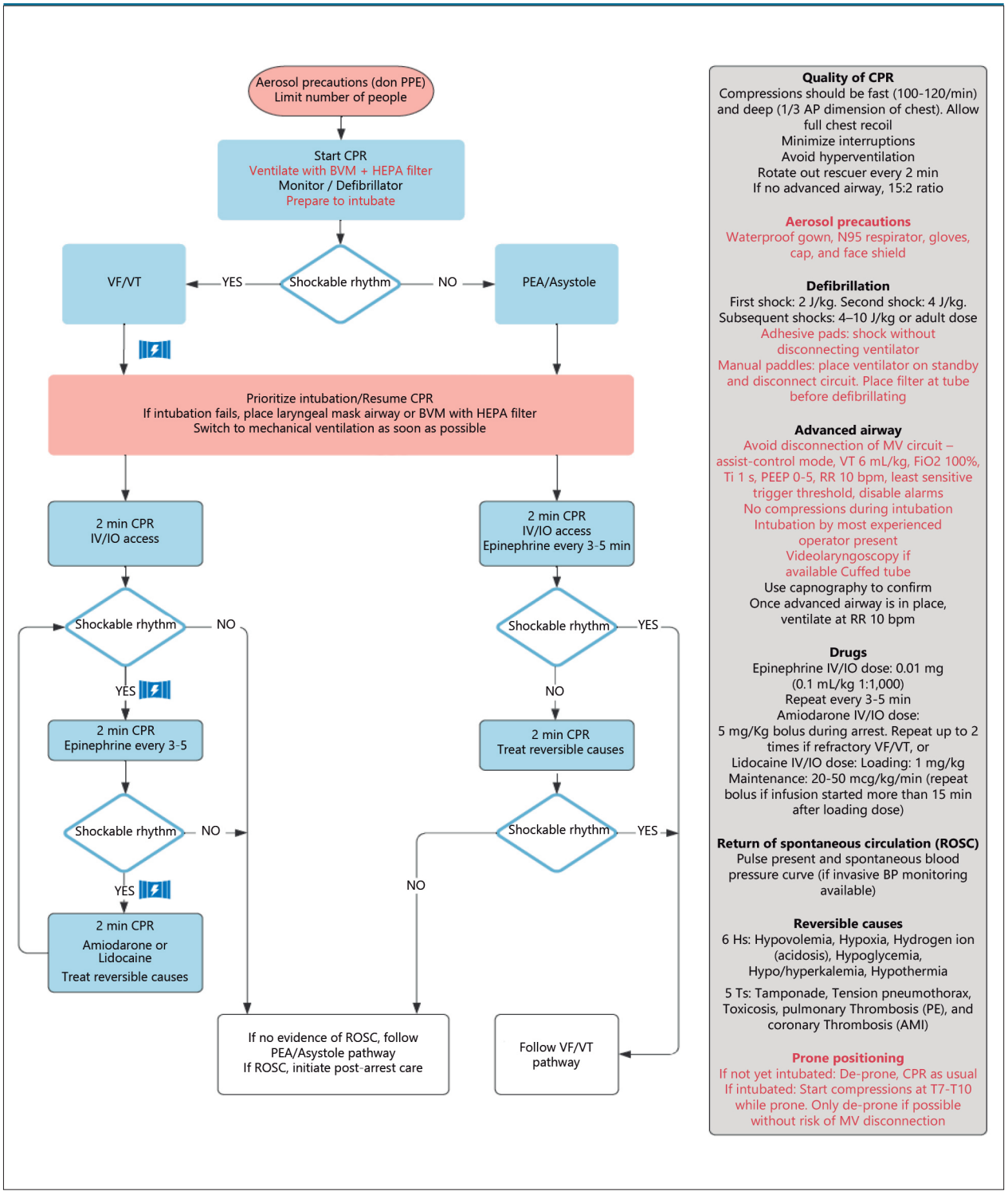

Figure 7 – *Algorithm for management of cardiopulmonary arrest in pediatric patients with suspected or confirmed COVID-19*
AMI: acute myocardial infarction; BP: blood pressure; BVM: bag-valve-mask; CPR: cardiopulmonary resuscitation; Fi: inspired fraction; HEPA: high-efficiency particulate arrestance; IO: intraosseous; IV: intravenous; MV: mechanical ventilation; PE: pulmonary embolism; PEA: pulseless electrical activity; PEEP: positive end-expiratory pressure; ROSC: return of spontaneous circulation; RR: respiratory rate; Ti: inspiratory time; VF: ventricular fibrillation; VT: ventricular tachycardia.

References

1. American Heart Association. Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. [Cited in 20 March 2020] Available from: Available from: https://eccguidelines.heart.org/wp-content/uploads/2019/11/2019-Focused-Updates_Highlights_PTBR.pdf.
2. Bernoche C, Timerman S, Polastri TF, Giannetti NS, Siqueira AWS, Piscopo A et al. Atualização da Diretriz de Ressuscitação Cardiopulmonar e Cuidados de Emergência da Sociedade Brasileira de Cardiologia – 2019. Arq Bras Cardiol. 2019; 113(3):449-663.
3. Resuscitation Council UK. Guidance for the resuscitation of COVID-19 patients in hospital. [Cited in 20 March 2020] Available from: http://resus.org.uk
4. World Health Organization (WHO). Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. Interim Guidance. [Cited in 20 March 2020] Available from: //https://www.who.int/emergencies/diseases/novel-coronavirus-2019
5. World Health Organization (WHO). Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. [Cited in 20 March 2020] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
6. De Jong A, Molinari N, Mongardon N, Arnal JM, Guitton C, Allaouchiche B, et al. Early identification of patients at risk for difficult intubation in the intensive care unit. Am J Respir Crit Care Med. 2013;187(8):832-9.
7. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalinguam G, Gale R, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018;120(2):323-52.
8. Resuscitation Council UK. Statement on COVID-19 in relation to CPR and resuscitation in first aid and community settings. [Cited in 24 March 2020] Available from: https://www.resus.org.uk/media/statements/resuscitation-council-uk-statements-on-covid-19-coronavirus-cpr-and-resuscitation/covid-community.
9. Jarman AF, Hopkins CL, Hansen JN, Brown JR, Burk C, Younqquist ST. Advanced Airway Type and Its Association with Chest Compression Interruptions During Out-of-Hospital Cardiac Arrest Resuscitation Attempts. Prehosp Emerg Care .2017;21(5):628-35.
10. Resuscitation Council UK. Guideline for Health care providers, to produce its management of cardiac arrest during neurosurgery in adults guidance. Accreditation is valid for 5 years from March 2015. [Cited in 24 March 2020]. Available from: http://www.resus.org.uk.CPR_in_neurosurgical_patients.pdf
11. Pan L, Wang L, Huang X. How to face the novel coronavirus infection during 2019-2020 epidemic: the experience of Sichuan Provincial People's Hospital. Intensive Care Med.2020;46(4):573-5.
12. Cheung JC, Ho LT, Cheng JV, Cham EYK, Lam KN. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med. 2020;8(4):e19.
13. Tran K, Cimon K, Seern M, Pessoa-Silva CL, Conl J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One. 2012;7(4):e35797.
14. Simonds AK, Hanak A, Cjhatwin M, Morrell M, Hall A, Parker KH, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess. 2010;14(46):131-72.
15. Xie T, Tong Z, Guan X, Du B, Chiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med. 2020; March 02. doi:10.1007/s00134-020-05979-7
16. Peng PWH, Ho PL, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. Br J Anaesth. 2020;124(5):497-501.
17. Edelson DP, Sasson C, Chan PS, Atkins DL, Aziz K, Becker LB, et al. Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting Organizations: American Association of Critical Care Nurses and National EMS Physicians. Circulation. 2020 Apr 09. doi: 10.1161/CIRCULATIONAHA.120047463 [Epub Ahead Print]
18. Hill C, Reardon R, Joing S, Falvey D, Miner J et al. Cricothyrotomy technique using gum elastic bougie is faster than standard technique: a study of emergency medicine residentes and medical students in an animal lab. Acad Emerg Med. 2010; 17(6):666-9.
19. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pnemonia in Wuhan, China: a single-centered, retrospective, observational sudy. Lancet Respir Med. Feb 24. pii:S2213-2600(20)30079-5 [Epub Ahead Print]
20. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anesth. 2020;67(5):568-76.
21. Brewster DJ. Consensus Airway Society principles of airway management and tracheal intubation of COVID-19 adult patients group. Med J Aust. 2020 May 1, doi:10,5694/mja2.50598 [Epub Ahead Print]
22. Cave DM, Gazmuri RJ, Otto CW, nadkarni VM, Cheng A, Brooks SC, et al. Part 7: CPR techniques and devices: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):5720-8.
23. Mazer SP, Weisfeldt M, Bai D, Cardinale C, Arora R, Ma C, et al. Reverse CPR: a pilot study of CPR in the prone position. Resuscitation. 2003;57(3):279-85.