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Continuation of the Revista Mexicana de Cardiología

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- The role of ANCAM in the prevention of cardiovascular diseases in Mexico
- Safe and effective early start of oral anticoagulant therapy in COVID-19
- Percutaneous MitraClip device in mitral regurgitation
- Bradycardia in patients with COVID-19 and triple therapy
- Unusual coronary thrombosis and interventricular septal rupture
- Severe hemoptysis and left pulmonary vein stenosis
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Editorial

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Letter from the presidency of ANCAM
The role of ANCAM in the prevention of cardiovascular diseases in Mexico. 2020-2022 biennium

Carta de la presidencia de ANCAM
El papel de la ANCAM en la prevención de las enfermedades cardiovasculares en México. Bienio 2020-2022

Gabriela Borrayo-Sánchez*

For more than 20 years, cardiovascular diseases (CVD) have been the leading cause of death in the world, and Mexico has not been the exception. Worldwide, only in 2019 more than 18.6 million deceases were documented from this cause, representing an increase of 53.7% from 1990, attributed in turn to the increase in the global burden of modifiable risk factors.[1] Still, the leading cause of death is ischemic heart disease with 8.9 million deaths, being also the second leading cause of disability-adjusted life years (DALYS). On the other hand, income influences life expectancy. For example, in 2016, this demographic parameter was 18.1 years lower in low-income countries (~ 62.7 years) than in high-income countries (~ 80.8 years).[2] The three main causes associated with premature death are ischemic heart disease, lung cancer, and suicide.[3]

The World Health Organization (WHO) informed that non-communicable diseases account for 70% of the causes of mortality, while CVD currently represent 16% of all deaths. These data point to the urgent need to drastically improve primary health care, in an equitable and comprehensive manner to carry out the fight against non- communicable diseases and manage its global epidemic.[4] Global investment is necessary for health systems, services, and workforce to develop sustainable objectives to prevent non-communicable diseases.[5]

Global health systems seek universal coverage rate of at least 95%, while the proportion of catastrophic health expenditures per capita should be less than 3%. Only between 33-49% of all countries have such health service covering. The proportion of the population that spends more than 25% of its personal budget on health care was 3% in 2015, while in 2000 it was 1.7%. By the end of 2020, about 1 billion (12.9%) people will use at least 10% of their budgets on health care.[6] In Mexico, the proportion of population spending out-of-the pocket on health care expenditure is more than 40%. Furthermore, in the country there is a delay in dealing with many health problems with opportunity due to the lack of economic possibilities and the poor supply and a low coverage from government health services (< 60%). As well, Mexico per capita expenditure in health is lower than the Organization for Economic Co-operation and Development (OECD) average (4,000 USD in OECD average against 1,150 USD in Mexico).[7]

Although Mexico continues to have a high mortality rate from acute myocardial infarction in those patients over 45 years of age (27.5 versus 6.9% in the OECD)[7] we have at least a history of success with the implementation of the so-called «Infarct Code», a protocol performed in emergency services and referral hospitals of the Mexican Institute Social Se-

* President of ANCAM.

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curity (IMSS), taking into consideration both the direct economic losses and the fact that CVD are the main cause of years of healthy life lost due to premature death and disability. With this protocol, it was possible to improve myocardial reperfusion from 34.9 to 71.4% ($p < 0.0001$), by increasing fibrinolytic therapy from 25.5 to 40.1% and incrementing primary percutaneous coronary intervention from 9.4 to 31.3% ($p < 0.0001$), reducing the time of care significantly and lessening mortality from 21.1 to 9.4% ($p < 0.0001$).[8] However, the great challenge still is to universalize this strategy in all segments of the national health system of our country, to reduce acute myocardial infarction mortality to levels closer to those of the OECD average.

The role of cardiological societies in the implementation of public health policies is of certain importance, especially when underline the need of a wider approach allowing the guarantee in the equitable provision of health care services, for example, in the elderly, which is a problem that continues to be neglected worldwide.[9]

The European Society of Cardiology (ESC) through a comprehensive model of care adapted to address multiple barriers in specific communities, attained substantial control rates of blood pressure, drug ministration, and adherence. During the 2019 ESC Congress, the results of several studies were shown revealing that the reinforcement of preventive interventions reduced cardiovascular risk indeed. In addition to hypertension and dyslipidemias, there are other factors such as low education, pollution, and poor nourishment that impact on cardiovascular risk, especially in low- and middle-income countries,[10] which highlights the importance of education and promotion of health in all populations.

However, in our country, this influence is rather limited, and it hardly impacts on the promulgation or modification of laws, regulations and norms related to health and prevention. Despite this, we must continue to insist on being a national benchmark to guide and support governmental and legislative decision-making, contributing with our knowledge and presenting the best scientific evidence in prevention strategies for non-communicable diseases, aimed to a high-risk population like ours. Of similar importance is to establish the appropriate guidelines for the diagnosis in the initial stages of the disease and the estimation of therapeutic goals, to reduce the probability of major cardiovascular events, such as acute myocardial infarction, cerebral vascular event, arrhythmias, and heart and kidney failure, to lessen the risk of premature death.

THE NATIONAL ASSOCIATION OF CARDIOLOGISTS OF MEXICO (ANCAM) CONSTITUTED ON JULY

21, 1984, in the City of Ensenada, Baja California, was initially called the National Association of Cardiologists graduated from the Mexican Institute of Social Security. On October 13, 1990, its denomination was changed to The National Association of Cardiologists of the Mexican Institute of Social Security, and finally, on November 8, 1994, its current name was approved. It is the cardiological association with the largest membership in our country, assembling more than 2,140 members due to its open and inclusive orientation. Its motto is «Prevent is our goal», which commits the entire membership to take actions towards cardiovascular prevention and to reduce the global burden of cardiovascular diseases in our country.[11]

ANCAM's strength comes from its statutes that facilitate the execution of its tasks and from its organic executive structure composed by a biannual board of directors and an advisory council that includes the last four former presidents, which allows to take the best decisions together, in addition to being self-sustained.

ANCAM's objectives are focused on promoting the development, research, diffusion, and continuing professional education of cardiology, promoting the study, research, teaching, exercise, and application of cardiology in its basic, clinical, and surgical areas, as well as in related sciences. Our association also provides scholarships to low-income students and associates, promoting the prevention, detection, diagnosis, treatment, rehabilitation and research of cardiovascular diseases, and their complications in our country. Also serves as a national consultant body in research and teaching related to cardiology, and at the same

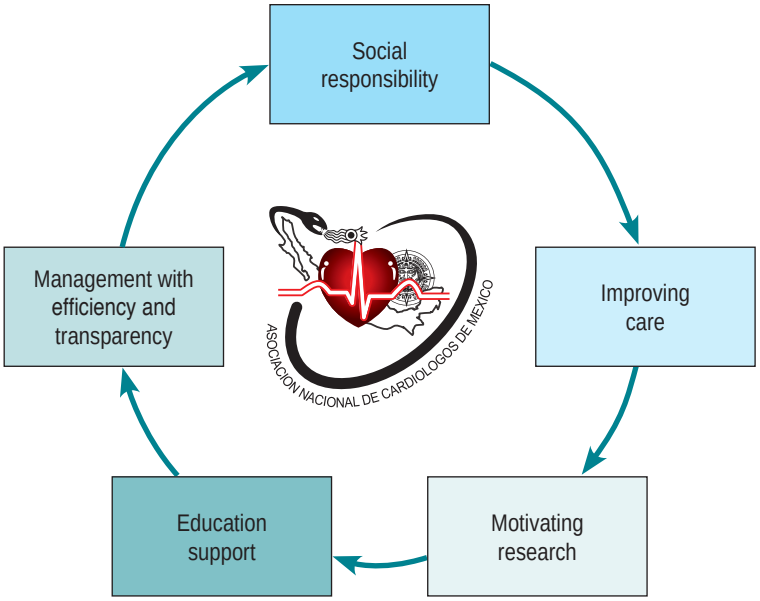

Figure 1: Axes of action of ANCAM to achieve cardiovascular prevention in Mexico.

time execute national health programs related to our discipline. Besides, the Association establishes necessary relationships with other national and international medical societies, which allows and stimulates scientific, cultural, and social exchange and development.

THE NEW PROPOSAL OF ANCAM FOR THE PREVENTION AND DETECTION OF CARDIOVASCULAR RISK FACTORS

The renewal of ANCAM began with the election, for the first time in our country, of a woman as vice president of a cardiologic association, where in general those positions are reserved for men. In addition, our association includes different age generations, institutions and geographical regions, for all united try to improve integrally Mexican cardiology through five axes focused on social responsibility, improving care, stimulation to research, supporting medical education, while having efficient and transparent management *(Figure 1)*.

1. Social responsibility

It is one of the most important and difficult to achieve axis which includes educating the population about the importance of cardiovascular diseases. A YouTube channel was created aimed at patients and the public to increase awareness and knowledge about cardiovascular diseases, how can they be detected early and treated; as well as how to participate with preventive and detection actions, in collaboration with state governments, especially in those populations affected by a limitation of health resources.

The recently created Initiative for the Women's Heart carries out actions to detect cardiovascular risk in women without access to institutional medical services, to identify those who have risk factors, and guide them to start appropriate treatment.

2. Improving care

The development of health care protocols yields to improve the nature of care through six dimensions of quality.[12] Quality care, for example, is included in the guidelines for the diagnosis and treatment of acute myocardial infarction as an indicator of the responsibility that health systems must assume.[13] Other transcendent action is the elaboration of statement positions, which can influence the improvement in detection and control of the main cardiovascular diseases. Therefore, ANCAM can be part of focus groups for cardiovascular diseases and participate with the Ministry of Health in better decision-making and public health policies.

3. Motivating research

It is important to stimulate and support high-quality research, allowing that basic and experimental knowledge migrate to clinical and healthcare practice. For this purpose, a new chapter on cardiovascular research was created. Furthermore, it is intended to organize a research committee, composed of highly recognized scientists to facilitate the members of ANCAM their participation in research programs and involve them in collaborative clinical studies. It is a priority that our associates involved in research produce their own results through clinical studies, mainly real- world studies that provide relevant information. We must participate in national and international multicenter studies on pertinent epidemiologi-

cal, clinical, and technological evaluations. In addition, courses of methodological support to clinical research will be developed.

Scientific production will be promoted by the ANCAM chapters, and the produced papers can be exposed in the pages of our Journal «Cardiovascular and Metabolic Science», which, in this way, will increase its scientific quality and will generate the possibilities of increasing the editorial impact, and national and international recognition.

4. Support in continuing medical education

The association will carry on with the promotion of continuous medical updating of specialists, cardiology residents and related subspecialties, professionals from areas related to cardiology, as well as undergraduate and general practitioners, through new communication technologies. The continuing medical education chapter was created, which, in collaboration with the coordinators of other chapters, the ARCAME (Association of Cardiology Residents of Mexico), institutions training professionals in cardiology and subspecialties, universities and medical societies will carry out specific programs for continuous medical updating *(Figure 2)*. Accreditation will be sought in those areas that require it, due to their assistance or technological complexity, to promote the high-quality clinical practice, based on standards and professional competencies sponsored by ANCAM, including bioethical aspects.

Clinical cardiology will be strengthened by the continuous presentation of clinical cases online, from national or international authors, which will allow us to challenge our knowledge and keep up to date on cardiovascular diseases and other specialties.

5. Management with efficiency and transparency

Undoubtedly an important pillar for ANCAM is to be an efficient and transparent organization. To improve the organizational management, a structure that seeks the good of the association will always be promoted, streamlining the resources, taking care of existing assets, and generating more wealth, through effective actions. The diverse functions of ANCAM leadership will be delimited, and resources will be used responsibly, attending the real needs of our members collectively. With all these actions ANCAM will continue being a self-sustaining organization. The spaces in our Heart's House «La casa del corazón», one of the most important assets of ANCAM, will be optimized, to remain the place of science and technology of national cardiology.

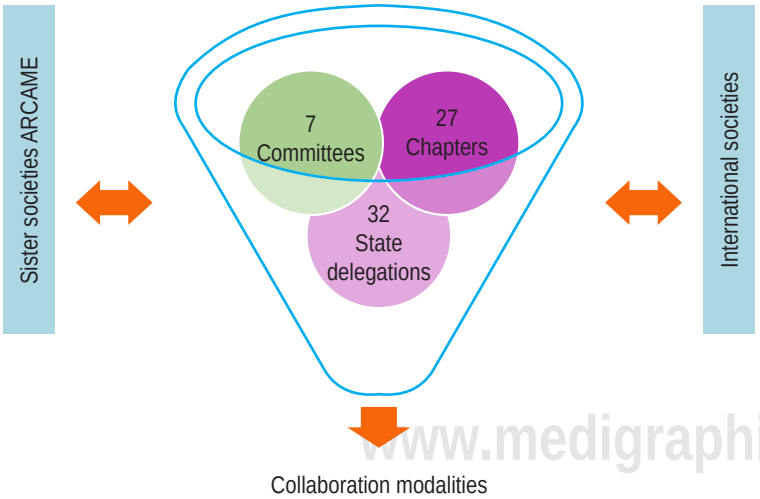

Figure 2: Collaboration between chapters, committees, delegations, and related societies for the 2020-2022 biennium.

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Original Research

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Safe and effective early start of oral anticoagulant therapy in ambulatory patients with COVID-19

Seguridad y efectividad de la terapia de anticoagulación temprana en pacientes ambulatorios con COVID-19

Samuel Chacek-Saslavsky,* Ana Luisa Hernández-Pérez,‡ Rafael Moguel,§ Ana Gabriela Gallardo-Hernández¶

Keywords:
COVID-19, oral anticoagulation, outpatient treatment.

Palabras clave:
COVID-19, anticoagulación oral, paciente ambulatorio.

ABSTRACT

The current pathophysiological knowledge of COVID-19 patients includes inflammation and micro-thrombus, so hospitalized patients receive low-molecular weight and unfractionated heparin, but not all patients can access these drugs. Our objective is to inform our experience with oral anticoagulants in different doses in ambulatory COVID-19 patients. **Material and methods:** This study presents a retrospective case series of COVID-19 patients, with confirmed PCR diagnosis. According to the disease burden criteria, every patient received supportive treatment plus rivaroxaban or apixaban on different doses and oxygen if needed. The team evaluated the clinical course of the disease, laboratory markers, imaging studies and the presence of complications. The statistical analysis was done with SPSS 21. **Results:** This study included forty-one patients with moderate to severe disease, from a universe of 300 patients with confirmed COVID-19 infection; the patients were allocated into one of three groups based on the severity degree and received intense anticoagulation, usual anticoagulation and usual anticoagulation plus platelet blockade. The median age was 50 years (30-75), 64% male. The D-dimer and ferritin were above normal levels in all patients. The group under intense anticoagulation had higher D-dimmer and ferritin, as well as lower lymphocyte count. This group had a shorter recovery time. **Conclusions:** In COVID-19 patients, the early initiation of oral anticoagulation at home was safe and effective, without the need for hospitalization. We found ferritin as the most important serum marker to define the patient's stage.

RESUMEN

*Los conocimientos fisiopatológicos actuales de los pacientes de COVID-19 incluyen la inflamación y la microtrombosis, por lo que los pacientes hospitalizados reciben heparina de bajo peso molecular y no fraccionada, pero no todos pueden acceder a estos medicamentos. Nuestro objetivo es informar nuestra experiencia con anticoagulantes orales en diferentes dosis en pacientes ambulatorios con COVID-19. **Material y métodos:** Este estudio presenta una serie de casos retrospectivos de pacientes de COVID-19, con diagnóstico confirmado. Cada paciente recibió un tratamiento de apoyo, además de rivaroxabán o apixabán en diferentes dosis y oxígeno si era necesario, según los criterios de carga de la enfermedad. El equipo evaluó el curso clínico de la enfermedad, los marcadores de laboratorio, los estudios de imagenología y la presencia de complicaciones. El análisis estadístico se hizo con SPSS 21. **Resultados:** Nuestra experiencia incluyó 41 pacientes con enfermedad moderada a grave, de un universo de 300 pacientes con infección por COVID-19 confirmada; los pacientes fueron asignados a uno de los tres grupos, de acuerdo con el grado de gravedad, y recibieron anticoagulación intensa, anticoagulación habitual y anticoagulación habitual más bloqueo plaquetario. La edad media fue de 50 años (30-75), 64% de hombres. El dímero D y la ferritina estaban por encima de los niveles normales superiores en todos los pacientes. El grupo bajo anticoagulación intensa tenía mayor dímero D y ferritina, así como menor cantidad de linfocitos. Este grupo tuvo un tiempo de recuperación más corto. **Conclusiones:** En los pacientes con COVID-19 la iniciación temprana de la anticoagulación oral en el hogar fue segura y eficaz, sin necesidad de hospitalización. Encontramos que la ferritina es el marcador sérico más importante para definir la etapa del paciente.*

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INTRODUCTION

The several clinical complications of COVID-19 are due to thrombosis and generalized inflammatory events.[1-3] The rapid progress of the COVID-19 pandemic has limited the ability to regulate the treatment in early stages of the disease, and most research directs towards seriously ill patients.[4,5] The RECOVERY trial[6] documented a significant decrease in 28-day mortality in critically ill patients, who received dexamethasone management.

Regarding thrombotic complications, the evidence is not clear yet. Forty percent of the infected patients develop mild symptoms with fever, cough, myalgia, arthralgia, onychophagia, fatigue, dyspnea, diarrhea, and headaches; 40% developed moderate symptoms with radiological evidence of pneumonia; 15% had severe pneumonia that requires supplemental oxygen; and 5% developed severe complications such as acute distress syndrome, thromboembolism, coagulation disorders and multiorgan failure.[7,8] The guidelines and recommendations for early outpatient management of COVID-19 patients establish only palliative measures such as: control of fever, rest and hydration without more effective prevention towards critical complications.[9]

There are significant restrictions to early stage anticoagulation therapy in the official outpatient management guidelines for COVID-19, including the National Institute of Health (NIH)[9] and the guidelines of the Secretary of Health of Mexico.[10] The WHO *(World Health Organization)* declared COVID-19 as a pandemic, on March 11, 2020, and 8 months after, one in every five infected patients progresses towards severe stages and need hospitalization.[11]

Many patients with moderate or even severe symptoms seek for outpatient care, due to lack of conclusive evidence, infodemics, hospital saturation, high costs and possible exposition to infection.[12,13]

Luca Carsana et al., in northern Italy, published their histopathological findings in lung SARS-CoV-2 specimens from 38 dead patients, with capillary congestion, interstitial edema, dilated alveolar ducts, hyaline membranes composed of fibrin and serum proteins, loss of pneumocytes, hyperplasia and atrophy of type II pneumocytes, proliferation of myofibroblasts, alveolar granulation tissue, obliterative fibrosis, and significant thrombosis of small blood vessels (diameter less than 1mm) in 33 autopsies.[12]

The critical COVID-19 patients develop pulmonary and systemic thrombosis in small

Table 1: Description the signs and symptoms clinic, laboratory and cabinet features.

Positive test PCR for SARS-CoV-2	Obtained by nasal swab • Mild sickness: focal areas with increased opacity, with a reticular pattern, ground glass with diffuse distribution
Lesions on radiographic film and/or simple chest tomography consisting of	• Moderate illness: consolidation patches associated with a reticular pattern, ground glass with subpleural distribution, associated with thickening of sedept. Interlobular and intralobular • Severe illness: frank airspace consolidations large areas of ground glass, with thickening interlobular sedept and cobblestone appearance, paving lesions and/or crazy paving
Clinical manifestations	Anosmia, respiratory distress, pharyngeal burning, decrease in capillary saturation values, dry cough, hyperthermia, myalgia, arthralgias, headache, abdominal pain or bloating, sickness, diarrhea
Laboratory	D dimer values, ferritin, DHL • Moderate increase in dimer D. Values from 500 to 800 mg/mL • Severe increase in D-dimer values. Values above 800 mg/mL • Ferritin > 300 mg/dL • Lymphocyte count

Table 2: Criteria for ambulatory anticoagulation.

Group	Findings	Management
7 Full anticoagulation	Present 2 or more of the following • Patients with 2 or more comorbidities • Basal saturation less than 90% • Markers of thrombosis or inflammation with severe increase • Severe injuries in radiology	Rivaroxaban 30 mg/day (15 mg every 12 hours) for 10 days (+)
6 Formal Antico-agulation more anti-aggregation	Presence of any of those previous • Comorbidities: 2 or more • Previous management with anticoagulation or anti-aggregation • Markers of thrombosis or inflammation with a moderate increase • Moderate injuries in radiology	Rivaroxaban 15 to 20 mg/day (+) or apixaban 10 mg/day for 15 days (+) more clopidogrel 75 mg or ASA 100 mg/day
5 Formal anticoagulation	Presence of 1 or more of those previous • Comorbidities: 1 or more • Markers of thrombosis or inflammation with a moderate increase • Previous anticoagulation and/or anti-aggregation management • Moderate injuries in radiology	Rivaroxaban 15 to 20 mg/day or apixaban 10 mg/day for 15 days (+)
4 Prophylactic anticoagulation and anti-aggregation	Presence of 2 or more of those previous • Comorbidities 1 or more • Previous separate management of prophylactic anticoagulation and/or anti-aggregation • Mild injuries in radiology	Rivaroxaban 5 to 10 mg/day or apixaban 2.5 mg every 12 hours more clopidogrel 75 mg/day or ASA 100 mg/day for 15 days (+)
3 Prophylactic anticoagulation	Presence of anyone • Comorbidities 2 or more • Minor injuries in radiology	Rivaroxaban 5 to 10 mg/day or apixaban 2.5 mg every 12 hours for 30 days
2 Anti-aggregation	Presence of • Comorbidities 1 or more	Clopidogrel 75 mg/day or ASA 100 mg/day for 30 days
1 Without drug	• Absence of comorbidities • Laboratories and radiology in normal ranges • Basal saturation greater than 90%	Without antithrombotic pharmacological management
Criteria for initial referral to other healthcare centers	• Patients with tachypnea, hemodynamic instability, intolerance to the oral route • Stroke in the past year • Known presence of vascular malformations • History of gastric ulcer, polyps, epistaxis, hypermenorrhea, or history of bleeding or hemorrhage in the last six months • History of seizures or psychiatric illness • Uncontrolled hypertension (SAT > 150 mmHg or TAD > 90 mmHg) • Previous management with vitamin K inhibitors • History of liver or kidney failure	
Criteria for suspending outpatient oral anticoagulant management	• Hemorrhage: major bleeding or presence of minor bleeding on 2 or more occasions • Hypertensive crisis: all patients were asked to have a digital manometer at home and to administer each dose of anticoagulant only if the previous pressure measurement was within normal ranges. In the case of high values, management with oral amlodipine 5 mg was indicated. If the pressure was controlled within the 1st hour, the anticoagulant intake was allowed to continue. Otherwise, the continuity of the study will be evaluated • Neurological or alertness disorders • Decision to transfer to the hospital due to clinical deterioration or request of the patient • Lack of attachment to driving • Loss to follow up • Express the patient's desire to discontinue the anticoagulant	

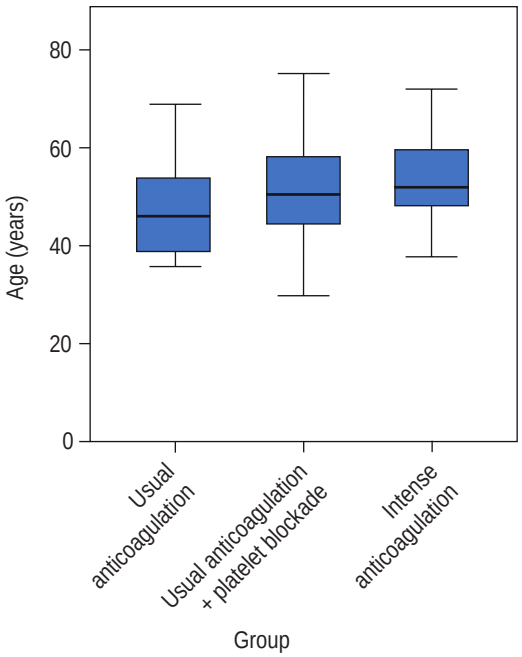

Figure 1: Age distribution between in groups.

vessels,[14,15] possibly related to the typical ground glass tomographic images,[16,17] that may lead to further complications or even death. These findings favour the decision to administer anticoagulants.[11]

The Massachusetts General Hospital[18] suggested measuring the D-dimmer in every in-hospital COVID-19 patient, with the recomendation for parenteral anticoagulation, when confirmed high levels. There are current indications for using oral anticoagulants, either that directly inhibit Factor Xa (rivaroxaban, apixaban), or thrombin (dabigatran).[5,13]

The EINSTEIN[19] and AMPLIFY[3] trials showed the safety and efficacy in the management of high doses of Factor Xa inhibitors in patients with acute pulmonary thromboembolism. The European Society of Cardiology (ESC) 2014[13] guidelines for the management of pulmonary thromboembolism, recommend therapies for up to 3 weeks with these oral anticoagulants, when hospitalization or parenteral drugs are not possible.[3,19]

Tang et al.,[20] documented a decrease in mortality of critical COVID-19 patients with previous coagulopathy, high D-Dimer and prophylactic anticoagulants?[21,22] Nonetheless, the treatment with drugs with supposed antiviral action over SARS-CoV-2, such as lopinavir, ritonavir, favipiravir, chloroquine and hydroxychloroquine, predominate, despite negative evidence of benefit.[23,24]

To date, there are no publications confirming the benefit of oral anticoagulants at different doses in patients with COVID-19. Treatment with enoxaparin is limited in our environment, due to high cost, parenteral application and high demand,[5,25,26] these problems make oral anticoagulants an alternative.

We inform our experience regarding oral anticoagulants, in different doses, in ambulatory COVID-19 patients, under the authors' criteria, based on the previous evidence for small vessels thrombosis and compassionate approach.

MATERIAL AND METHODS

The authors retrospectively analyzed ambulatory patients' clinical records with SARS-CoV-2, treated with rivaroxaban and apixaban at different doses, from May to September 2020.

Table 1 states the diagnostic criteria to confirm SARS-CoV-2, based on clinical, laboratory and cabinet information, subsequently followed through office consultation or by telephone,

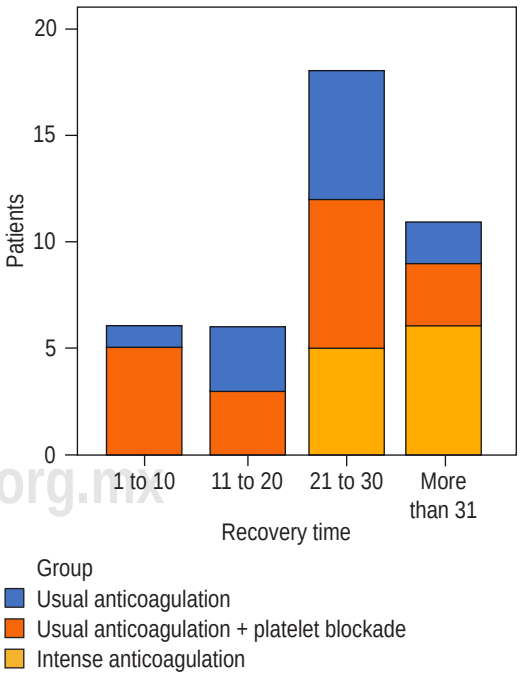

Figure 2: Recovery time in the groups.

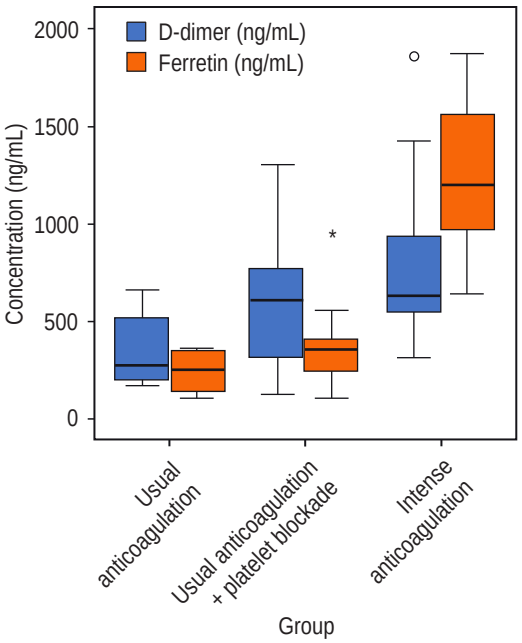

Figure 3: D-dimer and ferritin concentration in plasma in the groups.

emphasis the clinical progress, adherence to treatment, complications and adverse events.

The statistical analysis was done using SPSS 21 software and expressed in median ± standard deviation, frequency and percentages according to bivariate analysis with U Mann Whitney and χ^2.

According to the comorbidities and risk factors detected, as well as the results obtained in baseline and follow-up studies, management groups according to the original criteria, as discussed in *Table 2* classified the patients.

RESULTS

The analysis included 41 patients, from a group of 300 with a recent diagnosis of SARS-CoV-2 infection. The *Table 2* summarizes three different allocation groups: The group with intense anticoagulation consisted of 12 patients, the usual anticoagulation plus platelet blockade group with 18 patients, and in the usual anticoagulation group, with 11 patients; 92.6% of the patients received rivaroxaban and the rest apixaban.

All the patients received supplemental oxygen if needed, azithromycin 500 mg every 24 h for five days and intramuscular prolonged release dexamethasone 21-isonicotinate 8mg/day for five to seven days.

The median age was 50 years old (from 30 to 75) *(Figure 1)*, 64% men, middle socioeconomic status and most of them living in Mexico City.

The comorbidities were: overweight or obesity 21%, systemic arterial hypertension 12%, diabetes mellitus 5%, obstructive pulmonary disease 10%, history of venous thrombosis 5%, hypothyroidism 2.5%, dyslipidemia 5%, kidney disease 5%.

The *Figure 2* shows the recovery time in the different groups. All the patients received ambulatory treatment; all with moderate to severe disease, tolerated the oral anticoagulation and showed faster recovery; only one patient presented mild sub-conjunctival hemorrhage.

The laboratory disclosed elevated D-Dimer and Ferritin, but higher in the intense anticoagulation group *(Figure 3)*.

The lymphocyte count was normal in the usual anticoagulation and anticoagulation plus platelet blockade groups; below 1,100 mm^3 in the intense anticoagulation group *(Figure 4)*.

The 114 patients presented a mild or moderate form of COVID-19 and received

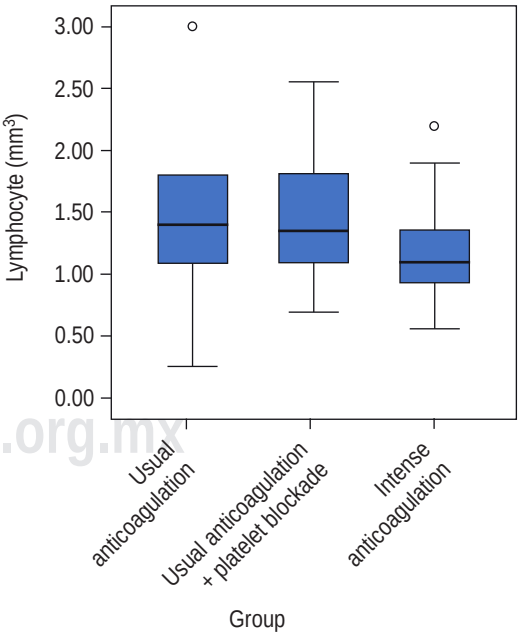

Figure 4: Level of lymphocyte in the groups.

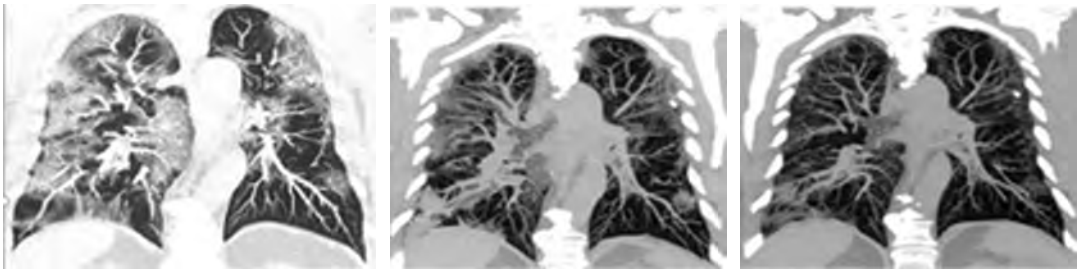

Figure 5: Tomographic course of a patient treated with maximum dose from left to right, the first picture documents pneumonia severe with what was needed in the initial consultation the following are days seven and 14 of the beginning of the outpatient treatment established in the protocol.

prophylactic anticoagulation plus platelet blockade. They had a positive PCR test for COVID-19 and mild or negative radiological imaging, especially ground glass and a mild reticular pattern *(Figure 5)*. The most frequent comorbidity was overweight and hypertension. All these patients continued ambulatory treatment without complications.

All the patients received an additional pharmacological scheme based on vitamin supplements (vitamins C and D), antioxidants (Quercetin and N-Acetyl cysteine) in addition to zinc.

DISCUSSION

The systemic inflammatory response and generalized microthrombosis result from COVID-19[11,12] infection. The current guidelines focused on the treatment of the inflammatory phase suggest concomitant management with enoxaparin in a hospital setting.

It is justified the extrapolation of the Factor Xa inhibitors, as described for the patients with acute pulmonary thromboembolism, on the European Society of Cardiology[13] treatment guide, to treat moderate to severe COVID-19 patients, in order to reduce the risk of thrombosis. The treatment was proven safe and effective, none of the treated patients required hospitalization, not even the patients with lymphopenia. Ferritin had a higher correlation than D-Dimer to clinical deterioration and severity of the radiological lesions. Therefore Ferritin can be used to determine if anticoagulation therapy should be indicated.

Our experience proved that oral anticoagulation therapy is safe and effective for ambulatory COVID-19 patients, even in severe cases.[21,25] The patient has to be educated to identify early sings of worsening, such as oxygen saturation and vital signs, and the need to report them to the physician to establish the need for a further clinical test to ensure the treatment's safety.

CONCLUSIONS

This study showed that oral ambulatory anticoagulation is safe and effective in COVID-19 patients, especially with thrombotic risk factors. Our results showed that both the elevation of ferritin levels and the decrease in the lymphocyte count correlate with the severity of the disease and may suggest the initiation of oral anticoagulation at high doses without increasing the risk of bleeding.

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Original Research

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Percutaneous MitraClip device in patients with symptomatic mitral regurgitation: results from three medical centers in Mexico

Dispositivo MitraClip percutáneo en pacientes con regurgitación mitral sintomática: resultados de tres centros hospitalarios en México

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Keywords:
Heart failure, mitral valve disease, severe mitral regurgitation, MitraClip.

Palabras clave:
Insuficiencia cardiaca, enfermedad valvular mitral, regurgitación mitral severa, MitraClip.

ABSTRACT

Objective: The aim of this study was to evaluate the experience of the use of the MitraClip device in terms of mortality, complications, mitral valve regurgitation reduction, and variations in left ventricle echocardiographic parameters. **Material and methods:** All patients included in the study were treated with the MitraClip device, assessed and considered to be high risk by the Heart Team. Follow-up was conducted 3-9 months after the procedure with transthoracic and transesophageal echocardiography. **Results:** Thirty-three patients were recruited from three medical centers in Mexico. After the procedure, 76% of patients were considered to have had a successful treatment, and during follow-up, 70% remained in this category, whereas only 6% of patients continued to experience mitral valve regurgitations still. Seven patients died, two of them during follow-up and five more dying from postoperative complications. The overall survival was 17.2 ± 1.3 months (CI 14.6-19.9). During the procedure, one detachment and one partial detachment of the device occurred. The procedural success was similar to the one reported in the EVEREST I study and the 2016 TVT registry. In this study, it was found that only one patient had a recurrence of severe MR. It has been described that The Society of Thoracic Surgeons (STS) risk scale and mortality had a strong relationship, which matched the results of this study. In this research, no complications were found, as seen in other trials, such as stroke or dialysis requirements. **Conclusions:** In this population, treatment with the MitraClip device improved the functional class and had few adverse events, signifying this treatment is an achievable option.

RESUMEN

El objetivo de este estudio fue evaluar la experiencia del uso del dispositivo MitraClip en términos de mortalidad, complicaciones, reducción de grado de insuficiencia mitral y las variaciones en los parámetros ecocardiográficos ventriculares izquierdos. ***Material y métodos:*** *Todos los pacientes del estudio fueron tratados con el dispositivo MitraClip, considerados de alto riesgo por el equipo de Cardiología. Se realizó un seguimiento entre 3-9 meses posterior al procedimiento, mediante ecocardiografía transtorácica y transesofágica.* ***Resultados:*** *Treinta y tres pacientes fueron reclutados de tres centros médicos en México. Después del procedimiento, 76% de los pacientes tuvieron un tratamiento exitoso y durante el seguimiento, 70% de ellos permanecieron en esta categoría, donde únicamente el 6% de los pacientes continuaron con regurgitación mitral valvular. Siete pacientes fallecieron, dos de ellos durante el seguimiento y los otros cinco por complicaciones durante el periodo postoperatorio. La supervivencia total fue de 17.2 ± 1.3 meses (IC 14.6-19.9). Durante el procedimiento, se presentó un desprendimiento y un desprendimiento parcial del dispositivo. El éxito del procedimiento fue similar al reportado en el estudio EVEREST I, así como en el registro TVT 2016. En este estudio, se encontró recurrencia de regurgitación mitral severa en un paciente. Se ha descrito previamente una fuerte relación entre la escala Society of Thoracic Surgeons (STS) y la mortalidad, lo cual coincide con estos resultados. En el presente estudio, no se hallaron complicaciones como las descritas en otros estudios publicados, tales como infarto o requerimientos de diálisis.* ***Conclusiones:*** *En esta población, el tratamiento con MitraClip mejoró la clase funcional disminuyendo eventos adversos, aumentando la factibilidad de este tipo de tratamiento.*

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INTRODUCTION

Heart failure has a wide range of etiologies, and mitral valve disease (MVD), together with ischemic heart disease and diabetes, are the leading causes of heart failure; in this context, valvular heart disease remains one of the leading causes of heart failure.[1] In the last fifteen years, due to the increase in life expectancy, there have been changes in the etiology of MVD, while rheumatic causes have diminished, degenerative diseases have increased. In the management of MVD with medical treatment in severe mitral regurgitation (MR), the mortality rate does not improve, only the symptoms. Reports indicated that for every patient who required surgical treatment for the aortic valve, four patients with severe MVD needed surgery, and approximately 6.4% of the population older than 65 years had moderate to severe MVD.[2]

International guidelines recommend treatment with a percutaneous mitral valve repair (pMVR) procedure with the MitraClip device for moderate or severe MR in patients who are not candidates for surgery, such as those with a high surgical risk, with a life expectancy greater than 12 months, who are symptomatic and receiving optimal medical treatment or who have severe MVD that was either degenerative or functional.[3,4]

The safety and viability of the MitraClip system were widely demonstrated in the EVEREST report with a success rate of 75% that diminished the degree of MR after the procedure;[5] on the other hand, the EVEREST II study showed that MitraClip was safer than surgery; however, the surgery was more efficient than the MitraClip.[6] During the four years of follow-up in the EVEREST study, it was found that the patients treated with MitraClip more commonly required surgery to treat residual MR compared to surgery alone. However, no differences were found in the patient mortality for moderate or severe MR.[7]

This research aimed to evaluate the mortality, complications, mitral valve regurgitation reduction and modifications in left ventricular echocardiographic parameters during the follow-up for the MitraClip device.

MATERIAL AND METHODS

Study population

This prospective cohort study of consecutive patients included 33 patients with severe MR (++++) who underwent pMVR with the MitraClip device (Abbot Vascular, Menlo Park, California) in three medical centers, National Medical Center "20 de Noviembre", ISSSTE, Doctors Hospital (in Monterrey) and Angeles Lomas Hospital, between September 2015 and December 2016 for severe primary and secondary MR.

The Heart Team assessed the decision for pMVR. All included individuals were considered to be symptomatic high risk patients (Society of Thoracic Surgeons [STS] mortality risk > 8%) according to the 2014 AHA/ACC Guidelines[3] and to have severe (++++) primary or secondary MR that could not be addressed with a traditional surgical procedure. The inclusion criteria were: symptomatic, New York Heart Association (NYHA) functional class

Table 1: Characteristics of the patients (N = 33).

	n (%)
Age-yr	67.7 ± 10.8
Gender	
Male	18 (54.5)
Female	15 (45.5)
Cardiovascular risk factor	
Hypertension	24 (73)
Diabetes mellitus type 2	9 (27)
Previous heart disease	
Coronary heart disease	21 (64)
Percutaneous coronary intervention	17 (52)
Cardiac resynchronization therapy	9 (27)
Revascularization surgery	5 (15)
Occluder for percutaneous left atrial appendage closure	4 (12)
TAVR	3 (10)
Hemoglobin	13.2 ± 1.8
Hematocrit	40.4 ± 5.6
Creatinine	1.2 ± 0.4

TAVR = Transcatheter aortic valve replacement.

Table 2: Mitral insufficiency modification after MitraClip (N = 33).

Severity of mitral insufficiency at baseline	n (%)
++++	33 (100)
After procedure	
≥ ++	25 (76)
≤ +	6 (18)
Died	1 (3)
Aborted procedure	1 (3)
Clinical follow-up	
≥ ++	19 (58)
≤ +	4 (12)
Died	6 (18)
Lost follow-up	4 (12)

III-IV or patients with NYHA II with at least two hospitalizations due to decompensated heart failure despite optimal medical therapy. Anatomical valve criteria were based on the echocardiographic measurements established in the EVEREST study[5] as follows: valve area > 3.5 cm^2, length of the posterior leaflet > 7 mm, coaptation depth < 10 mm. The exclusion criteria were myocardial infarction within the last 12 months, creatinine > 2.5 mg/dL, endocarditis, rheumatic valvular disease or a mean transvalvular pressure gradient (MVPG) > 3 mmHg. Severe primary MR was defined according to the AHA/ACC guidelines[3] based on the following echocardiographic characteristics: central jet MR > 40%, left atrium (LA) or holosystolic eccentric jet MR, vena contract area ≥ 0.7 cm, regurgitant volume ≥ 60 cc, regurgitant fraction ≥ 50%, and effective regurgitant orifice (ERO) ≥ 0.40 cm^2. Severe secondary MR was defined by ERO ≥ 0.20 cm^2 and regurgitant volume ≥ 30 cc. Mitral insufficiency was classified from mild to severe (+/++++).

Measurement of LV volumes and ejection fraction was performed according to the biplane Simpson's method.

Procedure and devices

The MitraClip was implanted with the usual technique.[6] Additional MitraClip implantations were performed if a moderate or severe residual lateral/medial MR was present.

Definitions

Successful treatment was considered to be a decrease ≥ ++ after the procedure, determined by transesophageal echocardiography.

Cardiac tamponade, intracardiac thrombus, major bleeding, partial or complete detachment were considered as complications during the procedure. Major bleeding was defined as a decrease in hemoglobin > 3 g/dL or the need for a blood transfusion. Partial detachment was defined as the complete loss of connection between a clip and one leaflet. Complete detachment was defined as the disconnection of the clip from both the anterior and posterior leaflets.

Follow-up

After the procedure, follow-up was conducted 3-9 months later with transthoracic and transesophageal echocardiography. In patients who were unable to be present, telephone interviews were conducted to establish their survival status. Transthoracic and transesophageal echocardiography were performed with ultrasound systems (ACUSON SC2000, Siemens Medical Solutions USA, Inc., and Phillips EPIQ 7, Royal Phillips Electronics, Amsterdam, the Netherlands) with the technique reported by Foster and collaborators.[8]

Hospitalization and any-cause of death were considered as events during follow-up.

Statistical analysis

The data were analyzed using Statistical Package SPSS for Windows version 20 (IBM, 2010). Variables were tested for normality with the Kolmogorov-Smirnov test. Parametric variables were expressed as the means (standard deviation). Categorical variables were described as absolute and relative frequencies. The overall change over time for repeated measures was analyzed with the Friedman test. A comparison between groups was determined with a Student's t-test. For the association between variables,

a Pearson correlation was used. A two-tailed p value of < 0.05 was considered significant. The overall survival rates and mean time were assessed by the Kaplan-Meier method. A multiple regression was performed to analyze any risk associated to death.

RESULTS

The general characteristics of the patients were determined *(Table 1)*. A total of thirty-three patients with severe MR (++++) were recruited for MitraClip device implantation in three medical centers in Mexico. The mean follow-up was 4.6 months.

All patients were considered high risk by the multidisciplinary heart team (mean STS mortality risk 8.2). And all of them signed a written informed consent for the procedure. Four patients with degenerative and 29 patients with functional MR.

In twenty-three patients, one clip was placed (70%); in seven patients, two clips were implanted (21%); and in three patients, three clips were deployed (9%).

Mitral insufficiency was compared with a Wilcoxon test immediately after the procedure ($n = 31$, $p \leq 0.001$) and during follow-up ($n = 23$, $p \leq 0.001$). After the procedure, 25 patients (76%) were considered to have successful results, and during follow-up, 19 patients (70%) were deemed to have successful results *(Table 2)*. Two patients (6%) during the follow-up continued to experience severe MVR.

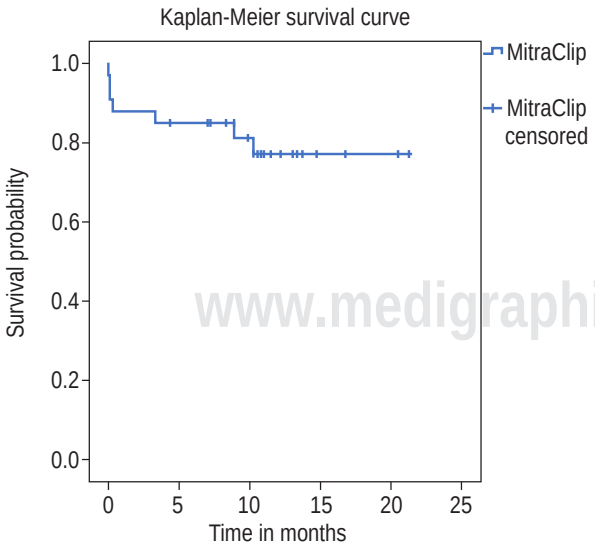

Figure 1:

Kaplan-Meier survival curve for death within 25 months.

Before the procedure, four patients were in NYHA class II (12%), twenty-one patients were in class III (64%), and eight patients were in class IV (24%); after the procedure, seven patients died, and one of them was lost to follow-up. In the remaining patients, the NYHA scale improved as follows: nine patients were in class I (27%), twelve patients were in class II 4 (36%), three patients were in class III (9%), and only one patient remained in class IV (3%); a Friedman test indicated statistical significance ($n = 25$, $p \leq 0.001$).

The overall mortality was seven patients (24%), including two who died during the follow-up, with one of them dying due to heart failure. Five patients died within the first ten days after the procedure, and the causes were pulmonary embolism, hemothorax, esophagus perforation, acute pulmonary edema, and cardiogenic shock. A Pearson correlation was used to determine the association between mortality and hemoglobin (rho = -0.373, p = 0.042), hematocrit (rho = -0.387, p = 0.034) and STS score (rho 0.463, p = 0.11). Kaplan-Meier *(Figure 1)* analysis revealed a median overall survival of 17.2 ± 1.3 months (CI 14.6-19.9).

Echocardiographic parameters were compared with a Student's t-test *(Table 3)*. We found differences in the left ventricle diastolic diameter and the systolic pulmonary pressure *(Table 3)*. A postprocedural mean transvalvular gradient < 5 mmHg was the most predominant measurement in 16 patients (49%), a gradient of 6 mmHg was found in three patients (9%) and a gradient of 7 mmHg was found in 2 patients (6%); the data were lost for 10 patients (30%), 7 patients died and in 3 patients were lost during follow-up. Furthermore, the correlation between postprocedural gradient and mortality was not significant (rho = .065, p = .767), and all of the patients who had a postprocedural gradient ≥ 6 survived during the follow-up, but the correlation with NYHA exhibited only a slight correlation (rho = .446, p = .026) *(Table 3)*.

Major bleeding was recorded in two patients (6%); two patients required rehospitalization during the follow-up due to heart failure. One of them died, which was secondary to a

Table 3: Echocardiographic measurement.

Variable	Before	After	p
LVEF (%)	36.6 ± 11.7 (n = 27)	38.8 ± 15.6 (n = 27)	0.387
LVDD* (mm)	61.2 ± 9.4 (n = 25)	56.8 ± 9.5 (n = 25)	0.027
LVSD (mm)	49.1 ± 10.7 (n = 25)	53.9 ± 38.4 (n = 25)	0.624
LVDV (mL)	169.0 ± 53.9 (n = 25)	174.1 ± 59.6 (n = 25)	0.829
LVSV (mL)	109.2 ± 48.3 (n = 25)	111.7 ± 58.7 (n = 25)	0.448
SPAP* (mmHg)	48.0 ± 17.9 (n = 22)	45.1 ± 15.0 (n = 22)	0.001

LVEF = left ventricle ejection fraction; LVDD = left ventricular diastolic diameter; LVSD = left ventricular end systolic diameter; LVDV = left ventricular diastolic volume; LVSV = left ventricular systolic volume; SPAP = systolic pulmonary artery pressure.
* $p < 0.05$.

left atrial thrombus found during the echocardiography. During the procedure in one patient, he had a complete detachment, and eventually, the patient died of a pulmonary embolism; another patient had partial detachment without clinical consequences. Additionally, one of the patients required repeat MitraClip therapy due to significant recurrent mitral regurgitation.

Logistic regression analysis showed no relationship between mortality and age, sex, diabetes, hypertension, ischemic cardiomyopathy, left ventricular ejection fraction or previous heart surgery.

DISCUSSION

To the best of the knowledge of the heart team, this is the first report on the use of MitraClip in Mexico and in Latin America. The procedural success in these institutions (75%) was similar to the success rate reported in the EVEREST I (74%)[9] trial and the 2016 TVT registry (86%). However, during follow-up, this rate decreased to 54% but was not related to the EVEREST I rate, which remained constant. The following mechanisms could explain this discrepancy: progression of the underlying cardiomyopathy or loss of leaflet insertion into the clip caused by insufficient leaflet grasping, which predisposes the clip to leaflet tear or perforation.[10]

Taramasso and colleagues[11] found that severe pulmonary hypertension and restricted posterior leaflet motion increased the risk of recurrence or persistent MVR after MitraClip implantation in cases of functional mitral regurgitation (FMR). In this study, it was found that only one patient (3%) had a recurrence for severe MR. Since he had functional MR and presented a gradual decrease in the diastolic diameter of the left ventricle (88 mm to 66 mm), it was suspected that he had a loss of leaflet insertion; nevertheless, this patient did not have a negative prognostic impact in terms of survival or symptoms since his NYHA functional class and LVEF presented a slight variation compared to the baseline.

It has been established that STS risk and mortality have a strong relationship,[12] which is consistent with the results presented; nevertheless, in the present study, the association between LVEF < 30% and mortality previously reported in TRAMI[13] did not agree with said results because, in this study, this association was not significant (rho = - 0.234). Although five of the seven patients who died had an LVEF < 30%, this outcome could be explained because the sample was small.

The essential periprocedural morbidity reported was single leaflet device detachment, which was identified in 1.4% of patients by the previous reports;[14] in this study, it was observed that 3% of patients had that detachment type. No complications were found as seen in other trials, such as stroke or dialysis requirements.

The increase in postprocedural MVPG is a significant event predictor for poorer long-term outcomes (2 years) and increased all-cause mortality.[15] Our study showed that patients with increased MVPG did not currently have any clinical deterioration; nevertheless, we could expect a different outcome from a longer follow-up. It was found that implantation of ≥ 2 clips was not associated with higher gradients during follow-up.

Other predictors of 1-year mortality in TRAMI[13] were NYHA class IV, anemia, previous aortic valve intervention, renal failure with serum creatinine ≥ 1.5 mg/dL, peripheral artery disease, left ventricular ejection fraction < 30%, and severe tricuspid regurgitation. In this study, only an association between hemoglobin and hematocrit was found, as previously reported.

This research had some limitations. The data were from an observational study of the

feasibility of the MitraClip device. This study was not a randomized trial and did not have a medically treated control group for comparison. In addition, follow-up was limited, and data during the follow-up could not be obtained. Nevertheless, all the echocardiography was performed with the same echocardiography protocol, which limited the results' variation, and such results are similar to those of more extensive studies.

CONCLUSIONS

The medical heart team can conclude that treatment with the MitraClip device seems viable and safe in a preselected high-risk population. Improvements in the functional class and few adverse events make this treatment a feasible option.

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Early bradycardia in patients with COVID-19 and triple therapy

Bradicardia temprana en pacientes con COVID-19 y triple terapia

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Keywords:
Bradycardia, COVID-19, hydroxychloroquine, azithromycin, lopinavir-ritonavir drug combination.

Palabras clave:
Bradicardia, COVID-19, hidroxicloroquina, azitromicina, combinación de fármacos lopinavir/ritonavir.

ABSTRACT

Because there is still no effective medical treatment for COVID-19, off-label drugs have been used such as hydroxychloroquine or chloroquine, lopinavir/ritonavir and/or azithromycin, whose safety information is limited with the risk of developing potential cardiac adverse effects. In order to contribute with the safety information about combined drugs used in COVID-19, we used the CARE Guidelines: Consensus based Clinical Case Reporting Guideline Development by EQUATOR Network (Enhancing the Quality and Transparency of Health Research) to present four patients, without known cardiac pathology or evidence of cardiac rhythm disorders, who developed early sinus bradycardia, 1 to 3 days after the concomitant use of triple therapy with hydroxychloroquine, lopinavir/ritonavir and azithromycin, which solved after the suspension of one or more of the mentioned medications. These cases contribute to improving the awareness of safety concerns about the past use of off-label drugs for COVID-19. The risk of bradycardia with the triple therapy presented should be considered.

RESUMEN

Debido a que aún no hay un tratamiento médico efectivo para la COVID-19, se han utilizado medicamentos fuera de indicación como la hidroxicloroquina o cloroquina, lopinavir/ritonavir y/o azitromicina, cuya información de seguridad es limitada con el riesgo de la presencia de efectos adversos cardiacos potenciales. Con la finalidad de contribuir con la información de seguridad del uso de combinación de medicamentos para COVID-19, seguimos la Guía «Consensus based Clinical Case Reporting Guideline Development» desarrollada por la Red EQUATOR (Enhancing the Quality and Transparency of Health Research) para presentar cuatro pacientes, sin patología cardiaca conocida o evidencia de trastornos del ritmo cardiaco, que desarrollaron bradicardia sinusal temprana uno a tres días posteriores al uso concomitante de la triple terapia con hidroxicloroquina, lopinavir/ritonavir y azitromicina, la cual remitió tras la suspensión de uno o más de los medicamentos mencionados. Estos casos contribuyen a mejorar el conocimiento de los problemas de seguridad sobre el uso pasado de medicamentos no aprobados para la COVID-19. Se debe considerar el riesgo de bradicardia con la triple terapia presentada.

INTRODUCTION

In the absence of an effective treatment against the infection by the new SARS-CoV-2 coronavirus, multiple pharmacological options that over the years have shown effectiveness for the management of other viral infections have been evaluated. For example, the combination lopinavir/ritonavir (L/R) is used in patients with HIV/AIDS infection. It has been shown to have inhibitory activity *in vitro* against the virus that causes Severe Acute Respiratory Syndrome (SARS) in humans.[1] Hydroxychloroquine (HCQ), known for its immunomodulatory properties, has shown *in vitro* its potential beneficial effect by limiting the entry of the virus into cells and its replication,[2] likewise, an experimental study reported that the combination of HCQ with azithromycin, macrolide antimicrobial with immunomodulatory properties, has the ability to decrease viral loads more quickly.[3]

The American Heart Association (AHA) has listed HCQ among the agents that can cause direct myocardial toxicity or exacerbate underlying myocardial lesions.[4] While the CredibleMeds database, an online resource

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that promotes the safe use of medications, classify azithromycin and HCQ in the category of drugs with known risk, and to L/R as a possible risk, in relation to the ability to prolong the QT interval.[5]

The term bradycardia refers to a heart rate less than 60 beats per minute. Its etiology can be intrinsic (ischemic heart disease, acute myocardial infarction, acute and chronic coronary disease, sick sinus syndrome, radiotherapy, myocarditis, among others) or extrinsic (endotracheal aspiration by vasovagal reflex, β-blockers, digoxin, blockers of calcium channels, class I to IV antiarrhythmic, hypothyroidism, sleep apnea, hyperkalemia, etc.).[6] Only some patients present symptoms such as fatigue, exercise intolerance, dizziness, syncope, worsening of cardiac pathologies or cognitive deceleration,[6] which require interventions for their correction.

Recently, it has been reported that there is a tropism of SARS-CoV-2 for cardiac tissue, and viral load and particles have been found in the myocardium of infected patients.[7]

Until now, only potential cardiac rhythm disturbances derived from the combination of HCQ and azithromycin as part of the treatment for patients with SARS-CoV-2 infection have been reported in the literature, without mentioning the association of these drugs with L/R. Using the CARE Guidelines: Consensus based Clinical Case Reporting Guideline Development by Equator Network, we present the case of four patients with confirmed COVID-19 infection, in whom sinus bradycardia was identified during the first week, after exposure to the triple therapy based on HCQ, L/R and azithromycin.

RESULTS. PRESENTATION OF CASES

I. Patient information

a) Demographic and clinical information of the cases *(Table 1)*
b) Medical, family and psychosocial history including relevant genetic information

Case 1:

- Family history: genetic load for DM2.
- NPPI: recent immunizations: influenza and pneumococcus in November 2019.
- PPI: traumatic: Fracture of the 5th metatarsal 30 years ago, conservative treatment. Previous hospitalizations: in 2019, with a

Table 1: Demographic and clinical information of the cases.

Variable	Case 1	Case 2	Case 3	Case 4
Age (years)	55	54	67	73
Sex	Male	Male	Female	Male
Non cardiac comorbidity	No	DM2 Hypertriglyceridemia	DM2	No
Cardiac comorbidity	No	No	No	No
BMI category (BMI kg/m^2)	Normal (23.5)	Overweight (29.6)	Overweight (28.3)	Normal (22.8)
Bradycardia onset after use of HCQ, azithromycin and L/R (days)	2	1	3	3
Corrected QT interval on bradycardia day by Bazett (ms)	s/d	429	490	365
Tisdale score on bradycardia day	9/moderate	10/moderate	11/high	11/high
Length of hospital stay (days)	65	49	46	79
Survivor	No	Yes	No	No

BMI = body mass index, DM2 = type 2 diabetes mellitus, HCQ = hydroxychloroquine, L/R = lopinavir/ritonavir, ms = milliseconds.

diagnosis of influenza pneumonia. Smoking: suspended 30 years ago, positive for 10 years at the rate of 3 cigarettes per day. Smoking index (SI): 1.5 packages a year.

Case 2:

- Family history: mother: alive, 82 years old, diagnosed with breast cancer, DM2 under treatment. Father: 83 years old deceased, due to acute myocardial infarction, history of chronic obstructive pulmonary disease. Four living siblings, two with a diagnosis of DM2 and systemic arterial hypertension (SAH).
- NPPI: immunization against influenza in November 2019. Exposure to chemical dusts and/or solvents for 30 years.
- PPI: DM2 for 12 years, on treatment with insulin NPH 15 IU in the morning and 25 IU at night, metformin 850 mg every 8 hours, in apparent good control. Familiar hypertriglyceridemia being treated with 400 mg bezafibrate every 24 hours. Allergies: penicillin. Surgical: strabismus correction at age 9, without complications.

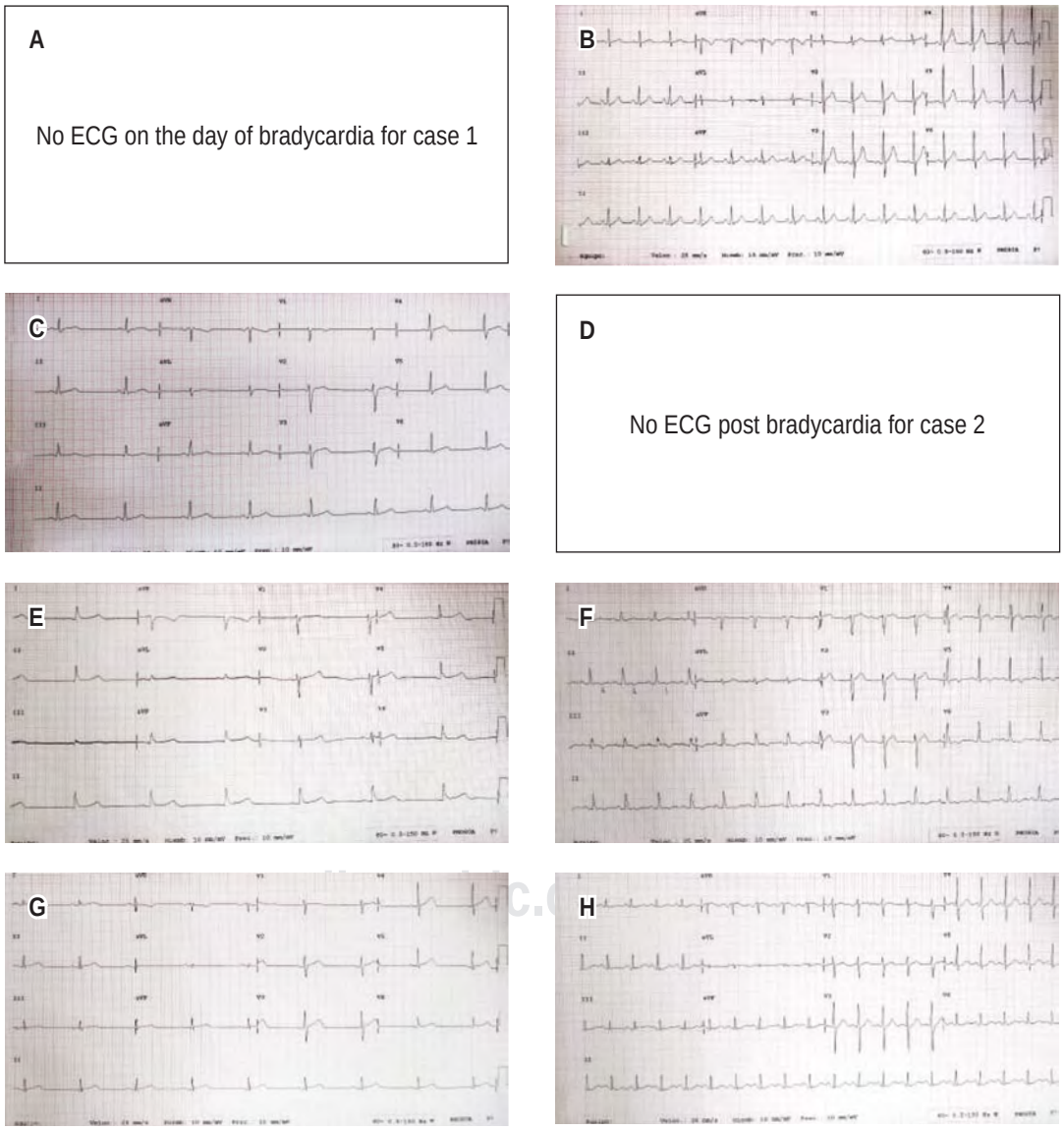


Figure 1:

Electrocardiograms (ECGs) of the cases. Electrocardiograms (ECGs) are shown for each case. The left column represents ECGs at the day of the event (bradycardia), and the right column represents ECGs days after the event (bradycardia). **A, B:** Case 1. **C, D:** Case 2. **E, F:** Case 3. **G, H:** Case 4.

Case 3:

- Family history: father died at 68 years old with history of SAH and DM2. Mother died at 71 years old due to complications of DM2 with history of SAH as well. Five living siblings, diagnosed with DM2 and SAH (systemic arterial hypertension). Five children alive, apparently healthy.
- NPPI: denies immunization against influenza.
- PPI: diagnosis of DM2 for 18 years, with regular adherence to unspecified oral treatment. Second hand smoking, by her husband, suspended 15 years ago.

Case 4:

- Family history: unknown.
- NPPI: contact with a co-worker with a diagnosis of COVID-19.
- PPI: smoking: positive from 20 to 60 years old at the rate of 20 cigarettes a day. SI: 40 packages a year. Rest denied.

II. Admission diagnostics

Case 1. Septic shock of pulmonary origin. Community acquired pneumonia (CAP) of atypical presentation. SARS-CoV-2 infection.

Case 2. CAP due to SARS-CoV-2. Uncontrolled DM2.

Case 3. SARS-CoV-2 infection. Multisegmental CAP of viral etiology by SARS-CoV-2. DM2.

Case 4. Pulmonary focus septic shock. Moderate acute respiratory distress syndrome. Atypical pneumonia due to SARS-CoV-2. Type 1 respiratory failure.

III. Clinical findings and timeline

To determine the medications used concomitantly that prolong the QT interval, we considered that in approximately seven half lives (t ½) the totality of the drug is eliminated from the body, and therefore, the following times were established:[8]

- Azithromycin t ½: 72 hrs, approximately in 21 days the drug is eliminated from the body.
- Hydroxychloroquine t ½: 40 days, approximately in 9 months.
- Lopinavir t ½: 6 hrs and ritonavir t ½: 5 hrs, approximately in 2 days.
- Dexmedetomidine t ½: 3 hrs, approximately in 21 hrs.
- Furosemide t ½: 2 hrs, approximately in 14 hrs.

IV. Diagnostic evaluation

a) Electrocardiograms (ECGs) of the cases at the day of the bradycardia (on the left) and days after the bradycardia (on the right) in *figure 1*.
b) Diagnosis

Sinus bradycardia confirmed by ECG (all cases).

V. Therapeutic intervention

The intervention in all cases was the suspension of some of the medications involved, see the suspension dates on the pharmacotherapy timeline in *Figures 2 to 5*.

VI. Monitoring and results

a) Clinical results

For all cases, the sinus bradycardia was transient, with spontaneous resolution within 1 to 5 days after discontinuation of some of the suspected medications.

b) Follow-up of important diagnostic tests or other

Follow-up ECG.

c) Discharge diagnosis

Case 1. Acute myocardial infarction. Acute respiratory illness due to SARS-CoV-2.

Case 2. Severe acute respiratory illness due to SARS-CoV-2. Remitted acute respiratory distress syndrome. Tracheostomy status. Remitted acute kidney injury AKI III. DM2.

Case 3. Severe acute respiratory illness due to SARS-CoV-2. Severe acute respiratory distress syndrome. Septic shock. DM2. Acute kidney injury.

Case 4. Severe acute respiratory illness due to SARS-CoV-2. Severe acute respiratory distress syndrome. Septic shock. Ventilator associated pneumonia. Acute kidney injury. DM2.

DISCUSSION

a) Strengths and limitations of case management

The strength of the study lies in the fact that no patient had a history of previous cardiovascular disease or electrolyte imbalances during bradycardia that could explain it. Likewise, the heart rhythm disorder reversed after the suspension of some of the medications involved.

The main limitation identified is that during the approach it was difficult to carry out complementary diagnostic studies for the intentional search for silent cardiovascular disease, as well as the lack of measurement of other variables because the patients were not enrolled in a research protocol and the number of patients involved.

b) Discussion of relevant medical literature

As a result of the limited scientific evidence on the efficacy and safety profiles of the use of drug combinations such as L/R, HCQ and azithromycin, some authors emphasize the role that identification of adverse events plays through spontaneous notification systems in pharmacovigilance to ensure the safety of new therapeutic options or those redirected for COVID-19.[9]

This report included four critical patients, three men and one woman, without known

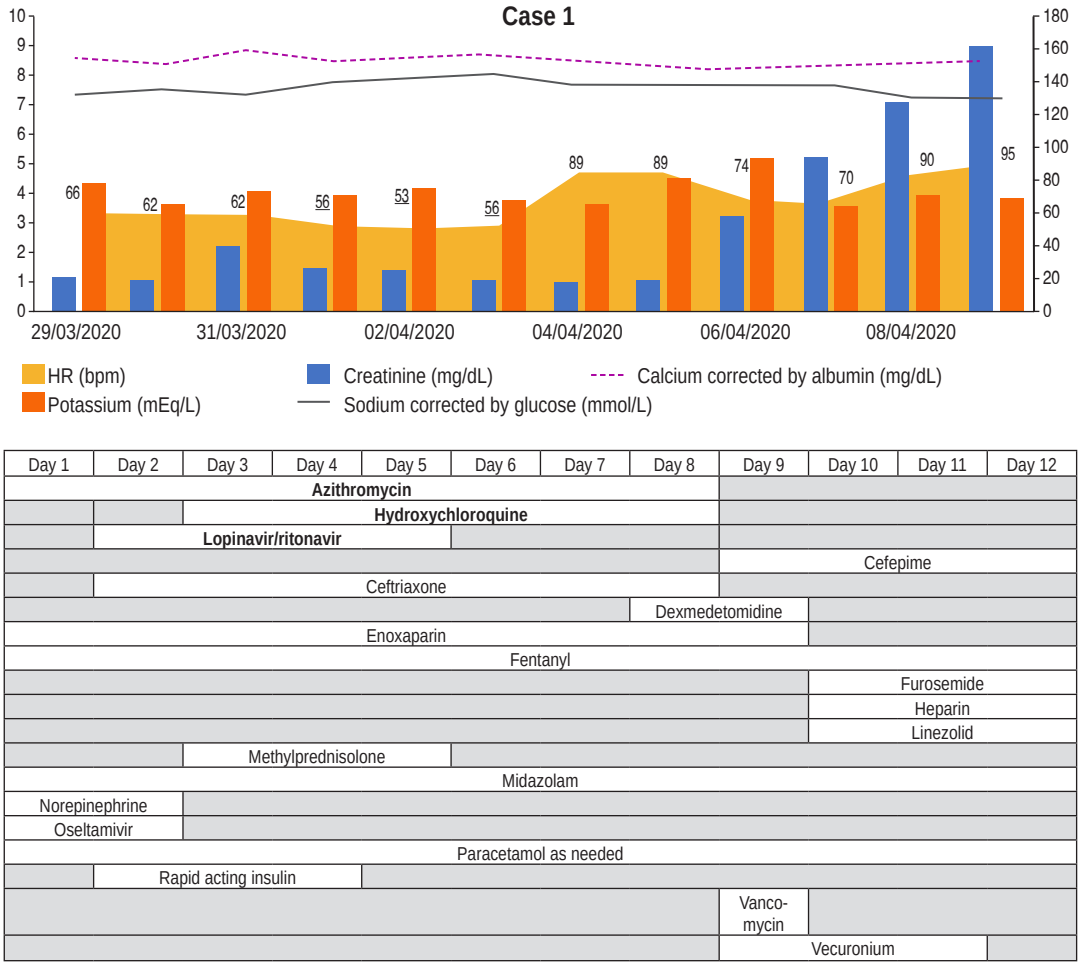
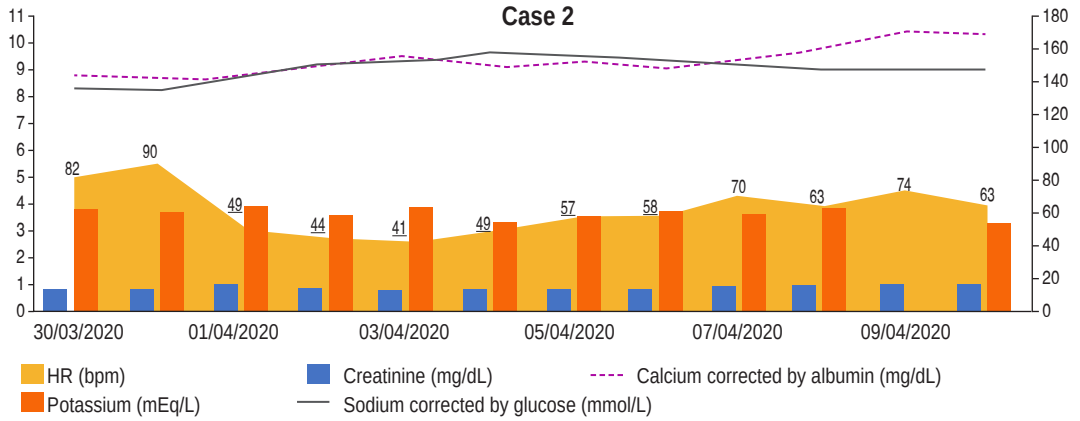


Figure 2:

Relevant clinical variables and pharmacotherapy timeline. Represents clinical variables (heart rate, creatinine, potassium, calcium corrected by albumin and sodium corrected by glucose) and drugs used in the first 12 days of hospitalization to observe their evolution before, during and after the development of bradycardia of each case. Case 1. For each case, the heart rate (HR) is represented in beats per minute (bpm) and underlined those with bradycardia.



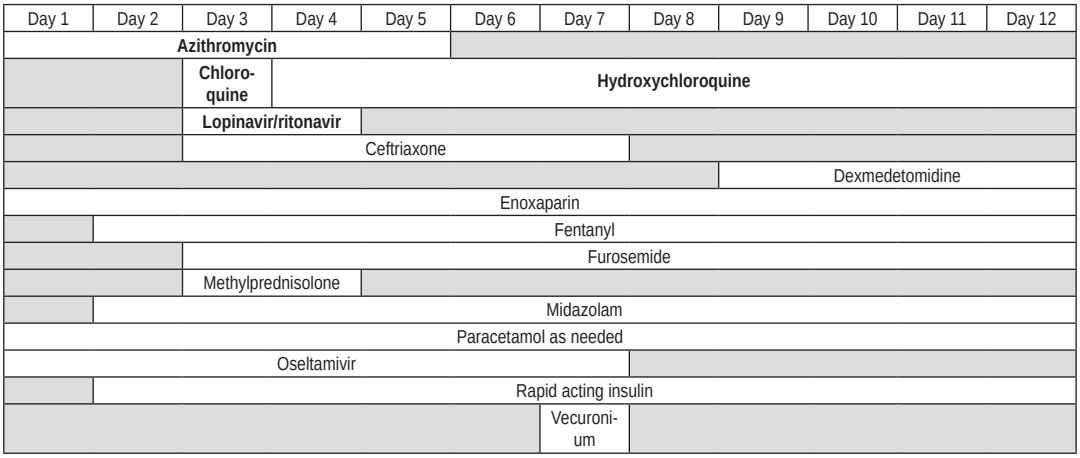


Figure 3:

Case 2.

heart disease or evidence of heart rhythm disorders upon admission who developed sinus bradycardia. Although there are no reports that describe the type of arrhythmia,[10] they were present in 16.7% of a Chinese cohort of 138 hospitalized patients with COVID-19, and they were more frequent in critical patients than in non critical patients (44.4 vs 6.9%).[11]

The time interval since the triple therapy was started and the development of bradycardia was between 1 to 3 days. However, it must be taken into consideration that, due to the half-life of the medications involved, it is expected to find plasma concentrations in the body after their suspension, with the risk of triggering potential drug interactions.[12] Among the medications with a potential negative chronotropic effect, it was identified that all patients had fentanyl-based analgesia, and only one patient was being administered dexmedetomidine at the time of bradycardia onset.

Because there was not enough evidence about the efficacy of triple therapy, and when the benefit-risk balance of its continuity was evaluated, especially concerning potential cardiovascular events, it was decided to stop the administration of one or more of the medications involved, observing in all patients a return to normal heart rate in an average of 4 days (2, 5, 4 and 5 days respectively for each case).

Amaratunga et al. suggest that the development of bradycardia in this group of patients could be a manifestation directly related to COVID-19 due to alterations in the pacemaker cells' heart rhythm dynamics or due to limiting their response capacity derived from the pro-inflammatory cytokine cascade,[13] while Hu et al. attribute bradycardia to the inhibitory effect of the virus on the activity of the sinus node.[14] However, the temporality among the event (bradycardia) and the medication exposure,

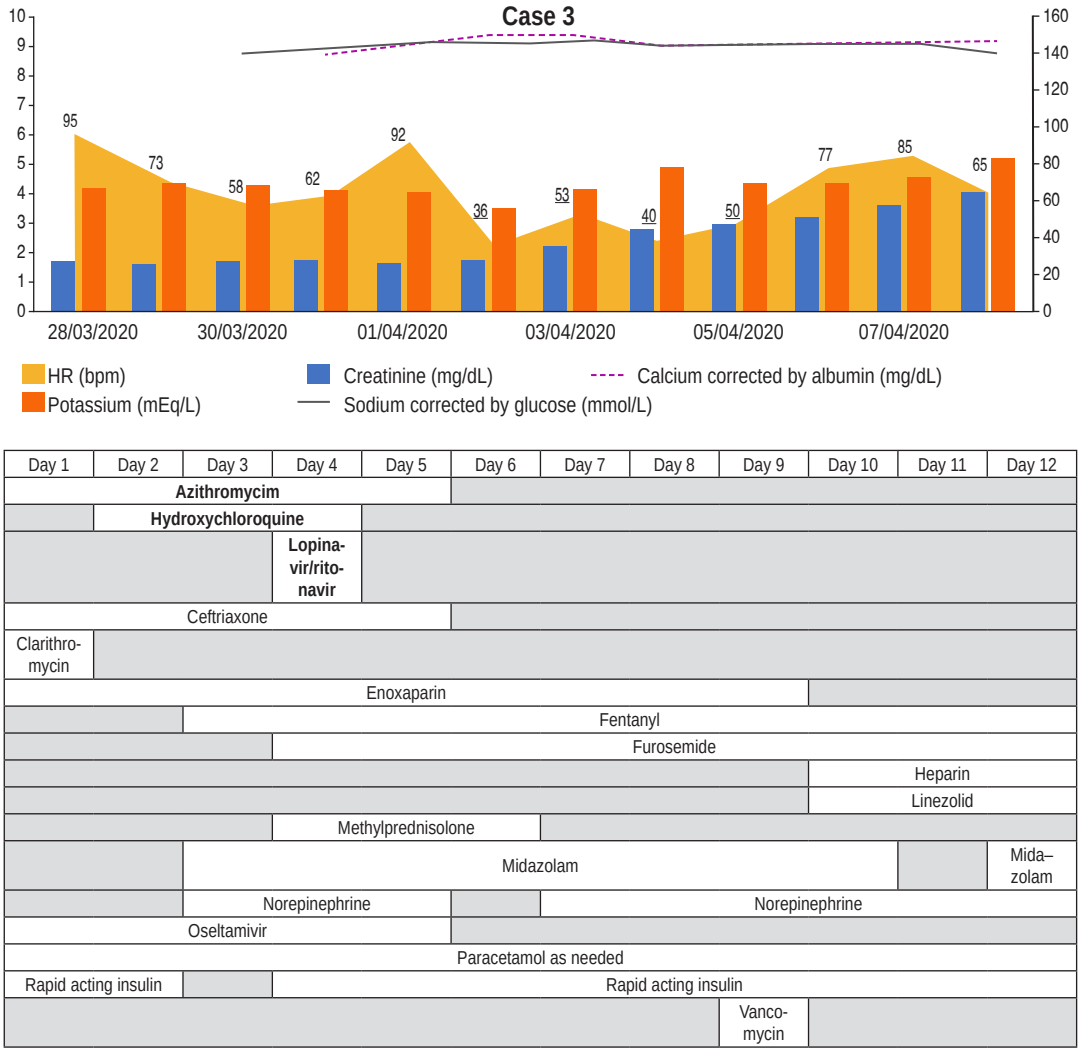


Figure 4:

Case 3.

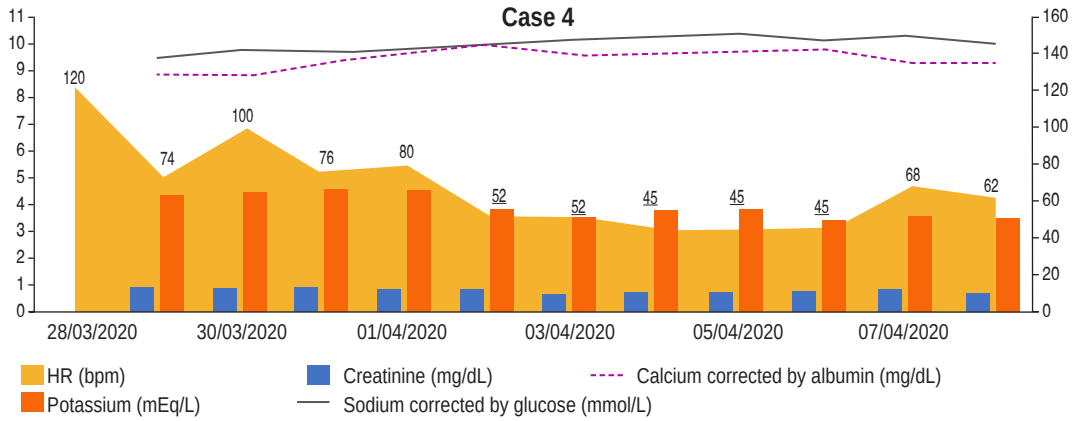
the response to its discontinuation and the knowledge of its arrhythmogenic potential, are three of the Bradford Hill causality criteria that strongly support the establishment of the causal relationship between medications and bradycardia.

Evidence from studies in patients who usually use HCQ for autoimmune diseases such as lupus or rheumatoid arthritis, report that the observed heart rhythm disturbances, prolongation of the QT interval/torsades de pointes (TdP), are attributed to azithromycin more than to the combination of azithromycin and HCQ or HCQ alone (lower value of the 95% CI of the proportional reporting ratio 3.80 vs 1.80 vs 1.29),[9] likewise, Lane et al. suggest that the use of HCQ is safe as they do not find an increased risk of serious adverse events after 30 days of use, including myocardial infarction, stroke, transient ischemic attack, cardiac arrhythmias, among others, however, when azithromycin was added to HCQ treatment, an increased risk of cardiovascular mortality was observed after 30 days of use (HR 2.19 [95% CI 1.22-3.94]), chest pain/ angina (HR 1.15 [95% CI 1.05-1.26]), and heart failure (HR 1.22 [95% CI 1.02-1.45]), thus suggesting that the increased risk of cardiovascular mortality with the combined therapy could arise through the synergistic effect (drug interaction) for the induction of lethal arrhythmias (TdP) or as an adverse effect of azithromycin alone, however

the design of the afore mentioned study did not allow this evaluation.[15]

Some authors even recommend serial ECG for patients who require a combination of medications with proarrhythmic risks, such as HCQ, favipiravir, L/R, macrolides, fluoroquinolones and/or piperacillin/tazobactam; however, it is reported that drug interactions are usually underestimated when drugs are used off label for the treatment of new diseases.[12] A preliminary report showed that the maximum change in the QT interval in patients diagnosed with COVID-19 treated with HCQ and azithromycin occurred between 3 and 4 days,[16] so in an environment with limited resources, this monitoring could be carried out every 3-4 days.[12] Among the patients involved in the present report, the QT interval was only prolonged in case 3 at the time of the development of bradycardia.

Finally, only one patient (case 1) presented fever during the reported bradycardia event. On days 6 and 7 the patient had relative bradycardia, having heart rate (HR) < 100 bpm despite fever (38-38.5 ºC), but on day 8 the relative bradycardia remitted since the patient had HR > 100 bpm during fever. On day 5, lopinavir/ritonavir was suspended, continuing with azithromycin and hydroxychloroquine, and by day 8 the bradycardia had already remitted, so it continued meeting causality criteria



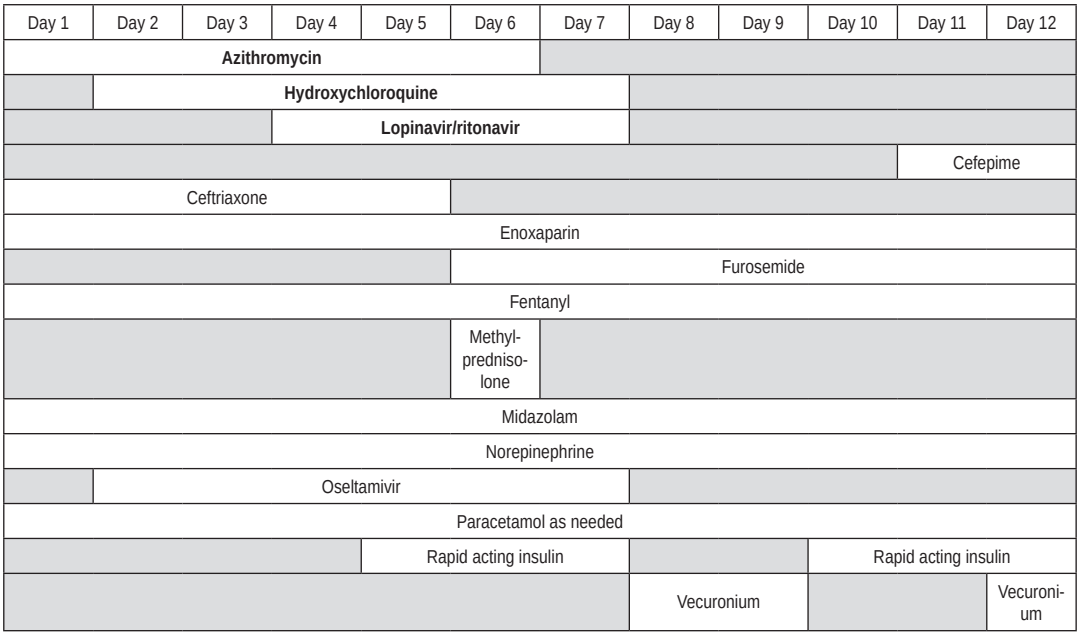


Figure 5:

Case 4. For each case, the heart rate (HR) is represented in beats per minute (bpm) and underlined those with bradycardia.

between bradycardia and exposure to drugs, such as the appearance of the event after the beginning of the medications and the response to stopping one of them.

CONCLUSIONS

Efficacy and safety of COVID-19 treatment are still evolving, so it is important to provide information, in this case regarding the use of triple therapy with HCQ, L/R and azithromycin, where no information was found.

Multiple factors could contribute to the development of sinus bradycardia in addition to the triple therapy for COVID-19, such as sedation or the probable presence of viruses in the myocardium, so the monitoring of the patients' heart rate should be strengthened during treatment of severe COVID-19 pneumonia and do not forget to consider the presence of relative bradycardia to identify it correctly.

It is recommended to establish early monitoring guidelines for patients to assess the benefit-risk of treatments in conditions where there are no established pharmacological guidelines with an evaluation of the efficacy and safety and even more when the pharmacokinetics of these medications in Mexican people with COVID-19 is still unknown.

The main lesson learned from this case report is that the risk of bradycardia with triple therapy (HCQ, L/R, and azithromycin) should be considered to improve the awareness of safety concerns about the past use of off-label drugs for COVID-19.

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Multi-vessel coronary thrombosis and interventricular septal rupture post myocardial infarction with ST elevation, unusual presentation

Trombosis coronaria multivaso y ruptura septal interventricular postinfarto de miocardio con elevación del ST, presentación inusual

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Keywords:
Coronary thrombosis, multivessel coronary disease, interventricular septal rupture, acute myocardial infarction, coronary angiography.

Palabras clave:
Trombosis coronaria, enfermedad coronaria multivaso, ruptura septal interventricular, infarto agudo de miocardio, angiografía coronaria.

ABSTRACT

Multivessel thrombosis is an uncommon finding in coronary angiography. Ventricular septal rupture is a mechanical complication with high mortality rate in acute myocardial infarction, requiring an invasive emergency treatment. The association of these entities has not been reported in the medical literature. This paper presents the case report of a patient with acute myocardial infarction, that underwent thrombolysis, coronary angiography, percutaneous coronary intervention and emergency surgery due to simultaneous coronary thrombosis of anterior descending artery and right coronary artery with interventricular rupture, refractory cardiogenic shock and death.

RESUMEN

La trombosis multivaso es un hallazgo poco común en la angiografía coronaria. La ruptura septal ventricular es una complicación mecánica con alta mortalidad en el infarto agudo de miocardio, siendo necesario un tratamiento invasivo de emergencia. La asociación de estas entidades no ha sido reportada en la literatura médica. Este artículo presenta el caso clínico de un paciente con infarto agudo de miocardio sometido a trombólisis, coronariografía, intervención coronaria percutánea y cirugía de urgencia por trombosis coronaria simultánea de descendente anterior y coronaria derecha con rotura interventricular, choque cardiogénico refractario y muerte.

INTRODUCTION

ST-elevation myocardial infarction is one of the leading causes of death worldwide, caused by the thrombotic occlusion of a coronary artery, called «culprit artery».[1]

Myocardial infarction involving two or more culprit arteries is uncommon in patients undergoing primary percutaneous coronary intervention, and is associated with high mortality.[2] This entity is difficult to diagnose from 12-leads electrocardiography, it has been postulated that the presence of a diffuse inflammatory process, caused by occlusion of the first artery, brings about thrombosis of the others.[3,4] Not practice guidelines are available for the treatment of this complication.

On the other hand, postinfarction ventricular septal rupture (PIVSR) is a mechanical complication that usually appears in the first 24 hours or three to seven days after infarction,[5,6] with an incidence of 0.17-0.31%[6] and a near mortality of 100% without surgery or transcatheter closure device.

The association of these pathologies is not mentioned in large retrospective studies.[2,3,5,7-10] This paper presents a clinical case report of a patient with multivessel coronary thrombosis in hospital, complicated by inter-

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ventricular septal rupture after a successful percutaneous intervention.

CASE REPORT

A 50 year old male, smoker during 35 years (8.75 pack-years), with negative past medical history, presented to the emergency department of a secondary care hospital 3 hours after sudden chest pain grade 8/10, accompanied by cough, nausea and vomiting. He was in Killip class II, electrocardiogram showed anterior ST-segment elevation *(Figure 1)*, biomarkers: creatine kinase -MB 639.9 mg/dL (0-24 mg/dL), total creatine kinase 5,019 mg/dL and iTn 8.59 ng/mL (0-0.40 ng/mL). Anterior ST-elevation myocardial infarction was diagnosed, thrombolysis was performed using alteplase with door-to-needle time of 15 minutes, decreasing the ST 50%, but due to hemodynamic instability and persistent angina he was transferred to tertiary care hospital.

On arrival vital signs: BP 80/50 mmHg, SaO_2 78%, T 37 ºC, HR 113 bpm, RR 34 rpm. Jugular venous distention was recognized. Cardiac auscultation revealed rhythmic heart sounds, no murmurs. Lungs revealed crackling rales. No limb edema. He was intubated and vasopressors/inotropic infusion were set. Electrocardiogram showed J point elevation in DII, DIII, AVF and V1-V5 with anterior leads T wave inversion *(Figure 2)*. Chest X-ray revealed cephalization of the pulmonary vessels, Kerley B lines, peribronchial cuffing, «bat wing» pattern, patchy shadowing with air bronchograms, and increased cardiac size *(Figure 3)*. Coronary angiography demonstrated thrombotic occlusion of the left anterior descending and thrombotic suboclusive lesion of the right coronary artery. The patient underwent percutaneous coronary

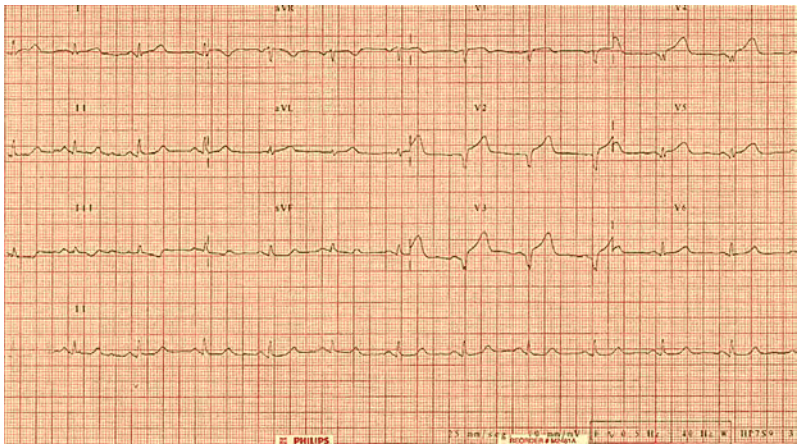

Figure 1:

Initial electrocardiogram: ST segment elevation in V2-V5 precordial leads.

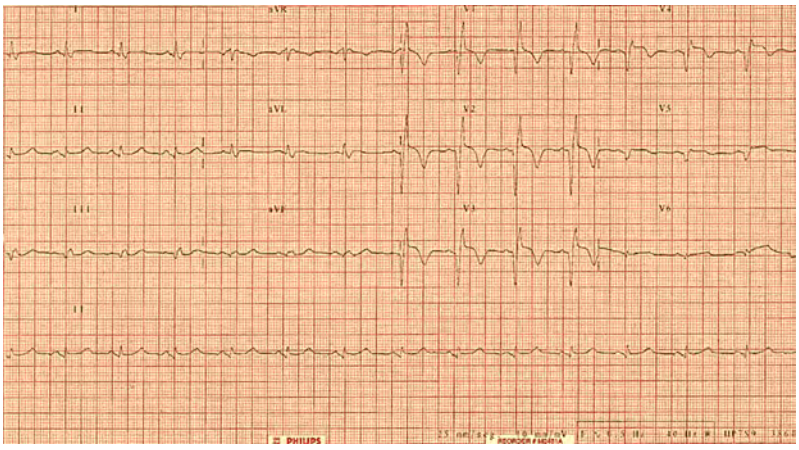

Figure 2:

Electrocardiogram with inverted T waves from V1 to V4 and biphasic in V5.

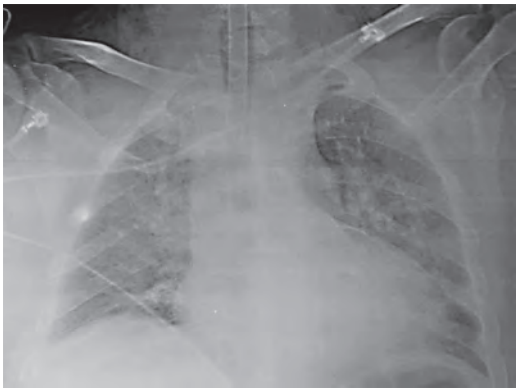

Figure 3: Chest radiograph consistent with pulmonary edema.

intervention of the left anterior descending with four drug-eluting stents and two drug-eluting stents in the right coronary artery, antegrade flow was restored to TIMI 3 *(Figure 4)*.

Ten hours later, he had holosystolic murmur grade III/VI without thrill at the left inferior parasternal border. The echocardiogram showed an interventricular septal rupture of 5 × 3 mm at the apical level with speed of 4.4 m/s, maximum gradient 77.6 mmHg, QP/QS 1.4, pulmonary artery systolic pressure 43 mmHg, anterior, inferior and septal wall akinesis, apex dyskinesia, without pericardial effusion, intracavitary thrombus or vegetation *(Figure 5)*. Intra-aortic balloon counterpulsation was placed due to cardiogenic shock and, 48 hours later, the septal rupture was repaired with a bovine pericardial patch *(Figure 6)*. Post-surgical echocardiogram revealed a residual defect 3 mm in size, with a speed of 2 m/sec. He died from refractory cardiogenic shock, before percutaneous closure with transcatheter device.

DISCUSSION

In percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI), the main finding is thrombotic occlusion of a coronary artery, due to rupture or erosion of atherosclerotic plaque,[1] known as the «culprit artery». Simultaneous thrombosis of two main coronary arteries is uncommon.[2,3] It is defined as STEMI associated with angiographic visualization of two or more thrombi that cause partial or complete occlusion of at least two epicardial coronary arteries.[3] The incidence is 2.5% in PCI and 50% in autopsies of patients with sudden cardiac death,[11] with hospital mortality of 2 to 5%.[2,3] Risk factors include: male sex, smoking and systemic arterial hypertension, with an average age of presentation of 59 years. Cardiogenic shock is the clinical presentation in 40% of cases and up to 38% requires an intra-aortic balloon pump (IABP).[3]

Diagnostic approach includes the search for thrombosis causes (hypercoagulable states,[12] unusual coronary anatomy,[13] drug-induced coronary vasospasm,[14] endocarditis of the mitral or aortic valve), when they are not identified, it has been postulated that the diffuse inflammatory process of an occluded artery leads to the thrombosis of another;[3,4] also, multiple plaque rupture secondary to coronary panarteritis,[15,16] as well as an increase in catecholamines with platelet activation are other proposed theories.[17]

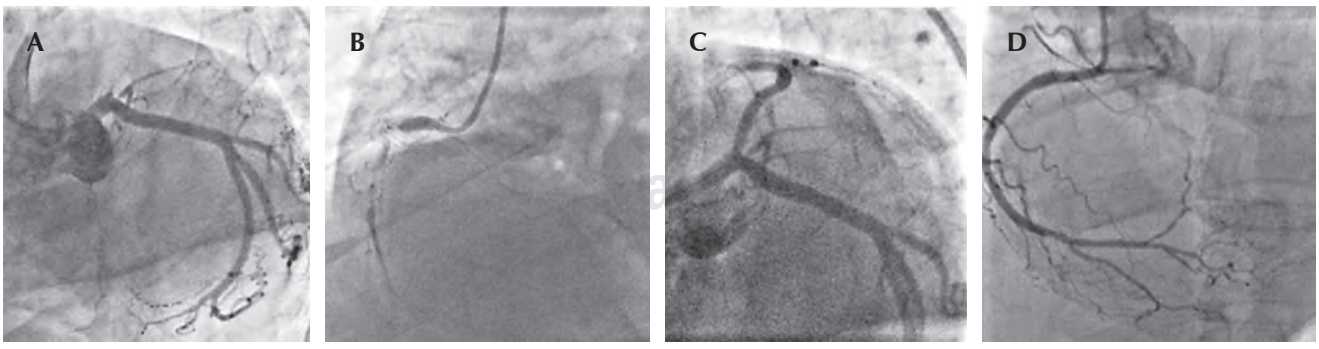

Figure 4: Coronary angiography: **A)** acute occlusion in the left anterior descending artery and **B)** in the right coronary artery. **C)** TIMI III flow return from the left anterior descending artery and **D)** from the right coronary artery.

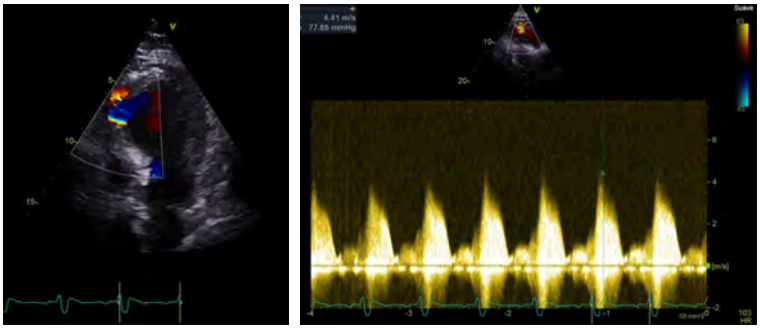

Figure 5: Echocardiogram shows a defect of the interventricular septum at the apical level with a speed of 4.4 m/s and a maximum gradient of 77.6 mmHg.

By electrocardiogram, acute multi-vessel involvement cannot be determined; this patient had ST elevation in anterior leads, but in retrospective studies 29% had elevation in inferior leads, 21% in anterior leads, and 41% in two territories (inferior plus anterior leads),[3] so the standard diagnosis is ICP. Coronary angiography of the patient showed occlusion of the right coronary artery plus the anterior descending one; 50% of the cases have this combination.[3] He was treated with a direct stent, but thrombus aspiration and the implantation of 2 V-stents are also options with good results.[18]

On the other hand, post infarction interventricular septal rupture (PIVSR) is a mechanical complication that causes pulmonary overcirculation and biventricular failure,[6] it can occur within 24 h to several days after myocardial infarction,[5] the incidence is 0, 17-0, 31% in STEMI, 49.7% due to inferior infarction and 41.1% anterior infarction,[5,7,19] without having reported patients with multivessel thrombosis who developed it. The diagnostic standard is transthoracic Doppler echocardiography, with a sensitivity and specificity of 100%, but it can underestimate the size of the rupture, since many are complex (thin, akinetic, greater in systole or diastole).[20] Cardiac magnetic resonance imaging provides transverse plane imaging to estimate the size of the defect;[21] in this patient, it was not performed due to hemodynamic instability.

Early surgical closure is the standard of care despite the high mortality (56 ± 23%) and postoperative residual shunts (up to 20%),[20] in part due to the high hemodynamic instability of the patients and the friable tissue that surrounds the PIVSR. There is the alternative of delaying surgical closure until the myocardial tissue has healed to better hold the sutures, although it is generally reserved for more stable patients. The interventional approach with a transcatheter occlusion device is considered a definitive treatment, or as a bridge to surgery (hybrid closure) with a 90% success rate in delivery, but the frequency of the residual shunt is unknown.[8,22] One limitation is the anatomical complexity of the rupture, not appropriate if the size is ≥ 15 mm.[22]

The treatment of the patient was according to the procedures established in international guidelines; since he did not present improvement with medical treatment, intra-aortic balloon contrapulsation was placed, although the cardiogenic shock for which he was taken to surgery persisted, which did not improve his hemodynamic status in part due to residual shunt that was attributed to the friable tissue around the PIVSR. It was proposed to close with a percutaneous device; however, due to biventricular failure, he suffered a sudden death.

The 2017 European Society of Cardiology guidelines promote early surgery when there is no improvement with pharmacological treatment (vasodilator, diuretic) and the IABP does not stabilize patients; it may be delayed in patients who respond well to aggressive

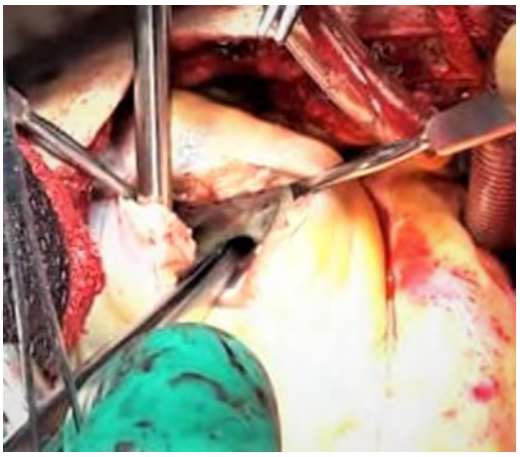

Figure 6: Interventricular septal rupture (surgeon's view).

therapy for heart failure.[23] The same guidelines mention that there is no consensus on the optimal time for surgery. Therefore, to obtain better results, the hemodynamic status of the patient, the anatomical complexity of the defect, and the availability of devices for percutaneous closure as well as a surgical team with experience in these types of complications should be evaluated.

The coexistence of both pathologies has not been reported previously (at least explicitly) in the medical literature. Probably, this association represents a subgroup with extreme mortality, and the lack of autopsy in all cases provides no help to identify them.

CONCLUSIONS

Multivessel coronary thrombosis is an uncommon angiographic finding in an acute myocardial infarction with ST-segment elevation. At this time, not practice guidelines are available for optimal treatment strategy; but restoration of coronary blood flow with thrombolysis or primary PCI, should always be the goal. The presence of PIVSR in this subgroup has not been reported or studied, due to the scarcity of cases; therefore, the gold standard management is not clearly defined, and suitable timing for surgery remains controversial. The present clinical case exposes the medical needs to clarify facts which lead to a reduction of mortality with efficient and scientific supported clinical practice guidelines.

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Severe hemoptysis as a debut form of left pulmonary vein stenosis

Hemoptisis grave como forma de debut de una estenosis de venas pulmonares izquierdas

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Carmen María Acosta Gutiérrez,¶ María Teresa Río Ramírez¶

Keywords:
Percutaneous ablation, atrial fibrillation, complications, hemoptysis, lung edema.

Palabras clave:
Ablación percutánea, fibrilación auricular, complicaciones, hemoptisis, edema pulmonar.

ABSTRACT

Atrial fibrillation is the most common arrhythmia. This pathology carries high healthcare cost and impairs the quality of life of the patients. Percutaneous pulmonary vein ablation is a consolidated therapy to treat it and several studies have shown that long-term recurrence and mortality is lower compared to those who are treated with antiarrhythmic medication. We present the case of a 48-year-old non-smoker man with a clinical history of a difficult-to-control incessant atrial tachycardia that presented to the emergency department with hemoptysis. The clinical picture was due to a complete occlusion of the distal segment of the left pulmonary veins as a complication of a previous percutaneous pulmonary vein ablation. Pulmonary vein stenosis is a rare complication of ablation for atrial fibrillation, being an early diagnosis esential to improve prognosis.

RESUMEN

La fibrilación auricular es la arritmia más común. Es una patología que conlleva un alto coste sanitario y perjudica la calidad de vida de los pacientes. La ablación percutánea de las venas pulmonares es una terapia consolidada para su tratamiento y varios estudios han demostrado que la recidiva a largo plazo y la mortalidad es menor en comparación con pacientes tratados con medicación antiarrítmica. Presentamos el caso de un varón de 48 años, no fumador, con antecedente de taquicardia auricular incesante de difícil control que acude a urgencias por hemoptisis. El cuadro clínico se debió a una oclusión completa del segmento distal de las venas pulmonares izquierdas como complicación de una ablación percutánea previa. La estenosis de la vena pulmonar es una complicación poco común de la ablación para tratar la fibrilación auricular, siendo un diagnóstico precoz fundamental para mejorar el pronóstico.

INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia. More than 90% of the underlying ectopic foci of electrical activity originate in the pulmonary veins.[1]

Percutaneous ablation of the left pulmonary vein (LPV) is a therapeutic alternative in the management of symptomatic recurrent AF and several studies have shown that long-term recurrence and mortality is lower compared to those who are treated with antiarrhythmic medication.[2] It's a first-line treatment of patients with symptomatic paroxysmal AF refractory to antiarrhythmic drugs, and offers improved quality of life, although in the case of long-standing persistent AF, percutaneous ablation is more complex and laborious and usually requires more than one intervention.

It is a safe technique but, like any procedure, even in experienced hands it is not exempt from complications, with a rate between 0.8 and 16.3%.[3] Complications can be severe, such as cardiac perforation or stroke, or milder, such as those related to the catheter access point.

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CASE PRESENTATION

We present the case of a 48-year-old non-smoker man, chronically anticoagulated due to a difficult-to-control incessant atrial tachycardia. He had required 5 ablation procedures perfomed in a different hospital: 4 radiofrequency ablations (RFA) and a surgical one. The first four were RFA, which were not effective. The patient was highly symptomatic, describing shortness of breath, anxiety and palpitations due to the AF, reason why he finally undertook a minimal invasive surgery. During the surgery, an Atriclip exclusion device was inserted. He also had suffered from a bradycardia-tachycardia syndrome and was a DDDR pacemaker carrier.

He presented to the emergency department with a 15-day history of hemoptysis and flu-like symptoms the previous month. Sixty milliliters were measured during the first 24 hours at the hospital. On admission, the physical examination was normal and no analytical alterations were observed. The chest X-ray was unremarkable.

During the first hours of hospitalization, hemoptysis increased and the expectoration was more than 150 mL/hour. An emergency bronchoscopy was performed, showing edematous and friable left bronchial tree mucosa with very intense bleeding with the touch of the bronchoscope *(Figure 1)*. Instillation of adrenaline was required. The microbiological and pathological analyses of the samples were negative. A chest computed tomography angiography (CT-angiography) was performed, showing both left pulmonary veins (LPV) originated from a common ostium, an occlusion of it and left interstitial edema *(Figure 2)*. Our patient had a relevant medical history of cardiac procedures, which was a risk factor to develop this kind of complications.

Given the potential severity of the clinical picture, the patient was referred to another hospital with Cardiac Surgery Department. Once there, a hybrid approach was performed. During the surgery, under extracorporeal circulation, normal drainage of the right pulmonary veins was confirmed in the left atrium. However, the common ostium was completely blocked. Retraction and fibrosis after radiofrequency ablation seemed the etiopathogenic mechanism, without any relation to the appendage exclusion surgical device. Angioplasty was carried out and weeks later, a stent in the common ostium was placed in a percutaneous procedure with optimal results.

DISCUSSION

The pulmonary veins carry oxygenated blood from the lungs to the heart. The anatomy of the pulmonary veins is variable among patients, with several noteworthy variant and anomalous patterns, including supernumerary pulmonary veins, a common ostium, anomalous pulmonary venous return, and levoatriocardinal veins.[4] Under normal conditions, four pulmonary veins carry oxygenated blood from both lungs and drain into the left atrium. The right superior pulmonary vein drains the upper and middle lobes, the left superior pulmonary vein drains the upper lobe and lingula, and the two inferior pulmonary veins drain the lower lobes.[5]

The two most common PV anomalies are the presence of a right middle PV and common left trunk.[6] Our patient not only had a common ostium, but also developed a complete obstruction of it due to previous procedures.

Radiofrequency ablation is an efficacious alternative in patients with symptomatic atrial fibrillation who do not respond to or are intolerant to at least one class I or class III antiarrhythmic drug. Although it is a safe technique,

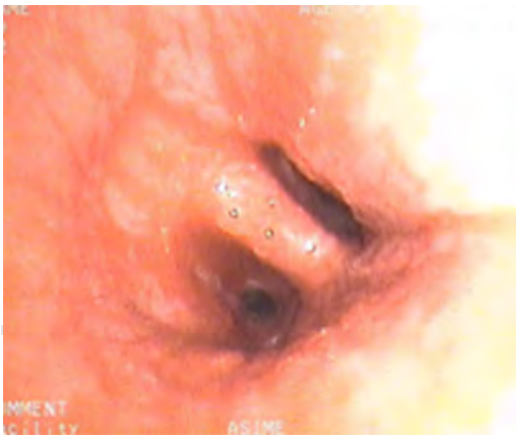

Figure 1: An edematous and inflamed mucosa was observed in the left upper lobe. It tended to bleed with the touch of the bronchoscope.

pulmonary veins stenosis are still described and it usually occurs about three months after ablation. The severity of PPV stenosis is classified according to the diameter reduction. It is considered slight if the reduction is < 50%, moderate between 50 and 70%, and severe if it is ≥ 70%, requiring this last urgent intervention.[7] Luckily, the incidence has decreased over the last years to between 0.32 and 3.4%.[8]

Patients are usually asymptomatic until they have severe stenosis, as the case we describe.

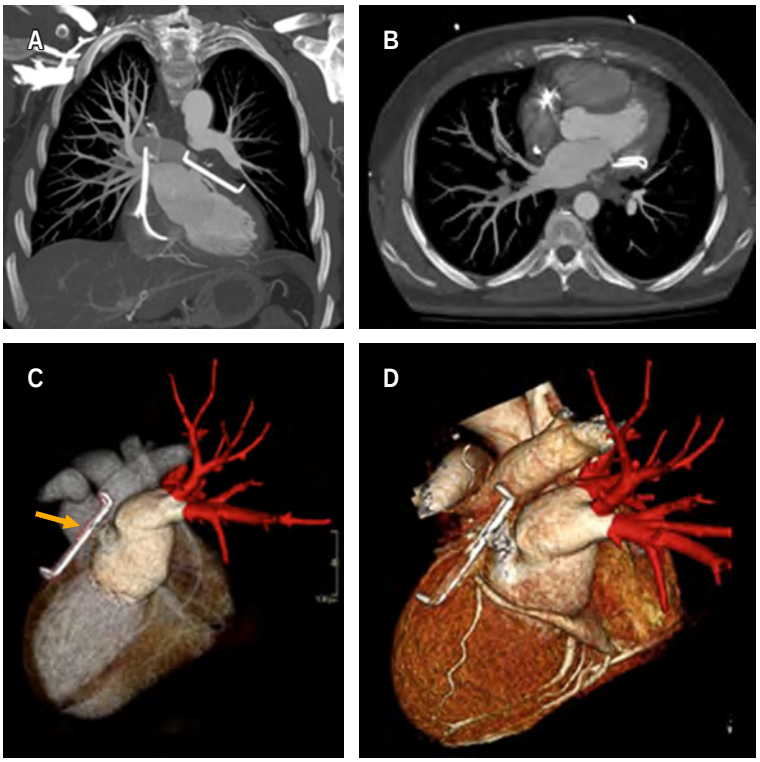

Figure 2: Images corresponding to a computed tomography angiography with intravenous contrast in systemic arterial phase. The greatest contrast opacification can be seen in the pulmonary venous tree and in the systemic arteries. **A)** Axial MPR image with a thickness of 40mm showing the asymmetry of the pulmonary vascularization, as well as the absence of left pulmonary veins draining into the left atrium. **B)** MPR with a thickness of 40 mm showing the same findings as in **A)**. Metal clip on the left appendage. **C)** 3D image of the cardiac volume. Posterior view of the heart. Transparency of cardiac chambers. Left atrium colored white. Right pulmonary veins colored red. Lack of visualization of left pulmonary veins due to its obstruction and therefore absence of contrast within it. Clip on left appendage indicated by arrow. Ascending aorta and pulmonary arteries in gray. **D)** 3D image similar to the previous one. Volumetric reconstruction of the cardiac surface. Posterior view of the heart.
MPR = multiplanar reconstruction.

They often debut in the form of dyspnea or cough from unilateral pulmonary edema or even chest pain. However, hemoptysis is infrequent, as in the previously cited study published by Fender EA et al, where it was only described in 27% of patients with severe stenosis, where pulmonary infarctions can also be observed.[9]

The management is different, depending on the grade of the stenosis. When a 50-70% stenosis is seen, follow-up in 3-6 months is recommended. If it is above 75%, another CT in three months is recommended, unless the stenosis is > 90%, when urgent treatment is required.[10]

Our patient presented with severe hemoptysis, which also needs an urgent approach. Hemoptysis develops due to pulmonary venous hypertension. As the resistance of the venous drainage to the left atrium increases, a pulmonary congestion is triggered, moving the plasma fluid from the pulmonary capillaries towards the interstitial spaces and alveoli. That generates pulmonary edema.[11]

CONCLUSIONS

Pulmonary vein stenosis related to radiofrequency ablation is becoming a less frequent complication, which makes it sometimes hard to diagnose. Our patient had a medical history of AF ablations and surgical cardic procedures. This should be always taken into account in order to be able to suspect this pathology soon and avoid unnecessary delay in the diagnosis.

Although it is a well described complication, it is rare and physicians that do not usually work in that area are frequently unaware of it. Moreover, since symptoms are not specific, they could be mistaken.

Hemoptysis, therefore, may be the first manifestation of a large number of diseases, and not only lung ones. Medical history may be the key to focus the diagnosis.

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Cardio-Oncology Cardiovascular toxicity and antineoplastics

Cardio-Oncología Toxicidad cardiovascular y antineoplásicos

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Keywords: Cardiotoxicity, chemotherapy, cardio-oncology, anthracycline cardiotoxicity, radiotoxicity.

Palabras clave: *Cardiotoxicidad, quimioterapia, cardio-oncología, cardiotoxicidad por antracíclicos, radiotoxicidad.*

ABSTRACT

The last century has witnessed record-high life expectancy, mainly related to decreasing infectious disease as the cause of mortality, paralleled with this tendency there has been a shift in mortality towards non-infectious causes, mainly cardiovascular disease and cancer. With new antineoplastic therapies there is now a large number of long term cancer survival population. It is now known that specific cancer therapies increase the risk of cardiovascular disease, and in the last 20 or 30 years, we have observed an increased prevalence of heart failure, ischemic heart disease, arrhythmias, and hypertension in cancer patients survivors. In this article, we review general aspects related to antineoplastic therapy, including action mechanism of most common used anti-cancer agents, also, issues over tyrosine-kinase inhibitors nomenclature, and classification of cardiotoxicity. The variety of anti-cancer agents is increasing every day, and we will briefly summarize the description of different antineoplastic drugs, including traditional and new targeted and immune-oncological therapeutic agents and how they relate to cardiovascular toxicity. Classic clinical cardiovascular risk factors are known predictors of potential cardiotoxicity, and together with cardiac biomarkers and imaging techniques facilitate the early diagnosis of cardiotoxicity in the subclinical/asymptomatic stage that permits implement preventive measures. There have also been therapeutic advances in the symptomatic stage that will be disclosed. This area is in continuous evolution, and it is convenient to involve the general cardiologist mind in this relatively new topic, understanding that in not all the world there are specialized cardio-oncology units, but equally, as cardiologist, we have to collaborate with the oncologist in the treatment of patients with cancer.

RESUMEN

El último siglo ha sido testigo de un incremento sin precedentes en la expectativa de vida, principalmente por la disminución en las enfermedades infecciosas como causa de mortalidad. En forma paralela, se ha observado un cambio en la mortalidad hacia causas no-infecciosas, como enfermedad cardiovascular y cáncer. Con las nuevas terapias antineoplásicas se ha incrementado la población de sobrevivientes de cáncer a largo plazo; ahora se sabe que algunas de estas terapias incrementan el riesgo de enfermedad cardiovascular, ya que en los últimos 20 a 30 años se ha observado una mayor prevalencia de insuficiencia cardiaca, cardiopatía isquémica, arritmias e hipertensión arterial en sobrevivientes de cáncer. En este artículo revisamos aspectos generales relacionados a terapia antineoplásica, incluyendo mecanismos de acción de los agentes anticancerosos de uso más común, además de aspectos sobre la nomenclatura de inhibidores de tirosina quinasa y clasificación de cardiotoxicidad. La variedad de agentes anticáncer se incrementa día a día y de manera breve hacemos una descripción de diferentes drogas antineoplásicas, incluyendo agentes terapéuticos tradicionales y los nuevos que afectan blancos terapéuticos específicos, agentes inmunooncológicos y su relación con toxicidad cardiovascular. Los factores de riesgo cardiovascular clínicos clásicamente conocidos son predictores de potencial cardiotoxicidad, y junto con biomarcadores y técnicas de imagen han facilitado el diagnóstico temprano de cardiotoxicidad en estadios subclínicos/asintomáticos, lo cual permite implementar medidas preventivas. Ha habido también avances terapéuticos en la fase sintomática que serán discutidos. Esta es un área en evolución continua y es conveniente involucrar la mente del cardiólogo general en este, relativamente nuevo, tópico, en el entendido de que no en todas partes existen unidades especializadas de cardio-oncología; sin embargo, como cardiólogos debemos colaborar con oncólogos en el tratamiento de pacientes con cáncer.

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INTRODUCTION

Since the past century, several chemical compounds known as chemotherapy agents together with radiotherapy have been a mainstay for treatment of cancer, as a result of these therapies, there is an increasing population of childhood cancer survivors. After ten years, the risk of progression/recurrence of the original cancer is very small. Unfortunately, the long term follows up of cancer survivors have disclosed that the cumulative mortality after 30 years since a cancer diagnosis is still 30 or 40 percent higher than non-cancer patients, and this mortality is not cancer related. After cancer diagnosis and treatment, there is a gradual and progressive increase in cardiovascular morbidity and mortality.[1] In the '70s of past century, observations where done related to cardiac toxicity of anthracycline compounds[2,3] since then, as knowledge of extracellular and intracellular signalling pathways in cancer has increased, also treatment modalities have expanded. Unfortunately, cardiotoxicity has been associated with several different groups of these anti-cancer agents *(Figure 1)*.

The different group of anti-cancer therapies associated with cardiotoxicity include: 1. Classical chemotherapeutic agents, 2. Specific target humanized antibodies, 3. Small molecule tyrosine-kinase inhibitors (TKI), 4. Immune checkpoint inhibitors (ICI), 5. CAR T cell therapy, 6. Radiotherapy and others.

In this review, we will discuss anthracyclines as one of the first chemotherapeutic agents associated with cardiotoxicity. We will also describe other chemical compounds involved in cardiac damage, including new antineoplastics that target specific signalling tyrosine-kinase pathways such as monoclonal antibodies and TKI. There are new oncology agents such as ICI that together with CAR T cell therapy are involved as immune-oncological agents for specific neoplastic disease, also with well described cardiovascular toxicity. Radiotherapy associated cardiac toxicity has also been documented. In the diagnostic section, we will describe clinical aspects, electrocardiography, biomarkers and imaging techniques such as echocardiography, magnetic resonance and computed tomography and others, all very useful for early diagnosis of cardiotoxicity in the subclinical/asymptomatic stage and decision making concerning the implementation of preventive and therapeutic measures.[4]

How do antineoplastic drugs act? Basics

Cancer molecular aspects and antineoplastics action mechanisms are complex and difficult to cover by a non-biologist or oncologist. Briefly, in this review we will describe some of the most common anti-cancer drugs, and how they affect cardiovascular function.

Anthracyclines

Topoisomerase 2B (TOP2B) alters the tension of DNA during replication and transcription by breaking, twisting and resealing DNA sustaining in this way its integrity. Anthracyclines intercalate between DNA strands inhibiting its synthesis, also forms a complex with TOP2B inhibiting its activity, leading to p53 activation, decreasing mitochondrial biogenesis and function, resulting in the death of cardiomyocytes, mitochondrial DNA injury is an essential mechanism of cardiotoxicity and has been related to the long term risk of anthracycline myocardial damage *(Figure 2)*. There is also the generation of reactive oxygen species (ROS) that damage DNA, part of ROS generation induced by doxorubicin is iron mediated[5] and this results in lipid peroxidation and protein carbonylation that causes cellular dysfunction and death.[1,6,7]

Targeted anti-cancer therapies

Targeted therapies have been a breakthrough in cancer treatment. Knowing the specific target mutation involved in neoplastic cellular replication has been followed by therapies directed at such mutation. Several malignant neoplasms have mutations that overexpress growth factors regulated by tyrosin kinases of the human «Kinoma».

The «Kinoma» of an organism is the set of protein-kinases in our body. Human genome has 518 protein kinases, and kinases are enzymes that catalyze the transfer of a phosphate

group from ATP to aminoacids/proteins, and by this phosphorylation it modifies its action, subcellular location, and stability. There are three groups of kinases: a) kinases that phosphorylate the aminoacids serine and threonine (serine-threonine kinases), b) kinases that phosphorylate tyrosin (tyrosin kinase), and c) some kinases that phosphorylate both. About 90 of the 518 humane kinase are tyrosin kinase.

There are two major types of tyrosine-kinase: a) RTKs (receptor tyrosine-kinase), anchored in the cell membrane with an extracellular domain that attaches the soluble extracellular ligand and an intracellular domain with kinase activity responsible for the signalling process, and b) NRTKs (non-receptor tyrosine-kinase): localized inside the cell *(Figure 3)*.[8] There is a growing number of anti-cancer agents based on inhibition of these tyrosine-kinase, and several of them are involved in cardiotoxicity that we will describe in next sections.

Immune checkpoint inhibitor

During normal immune system development, T cells in our body acquire the capacity to react and eliminate foreign elements through the interaction of antigen presenting cells (APC)/Major Histocompatibility Complex (MHC), with T cell receptor (TCR) and other co-stimulatory signals such as CD80/B27 in the APC and CD28 in the T cell. APC and T cells have inhibitory signals that induce immune tolerance, balancing this immune stimulation, with less reactivity against host cells, so they act as co-inhibitory signals and by this mechanism downgrades immune response, including T cell response against cancer cells. Cytotoxic Lymphocyte Antigen-4 (CTLA-4) from T cell interacting with CD80/B7 on APC, and Programmed Death-1 of T cells are two of those T cell immune response inhibitors *(Figure 4)*. It is known in cancer biology that several

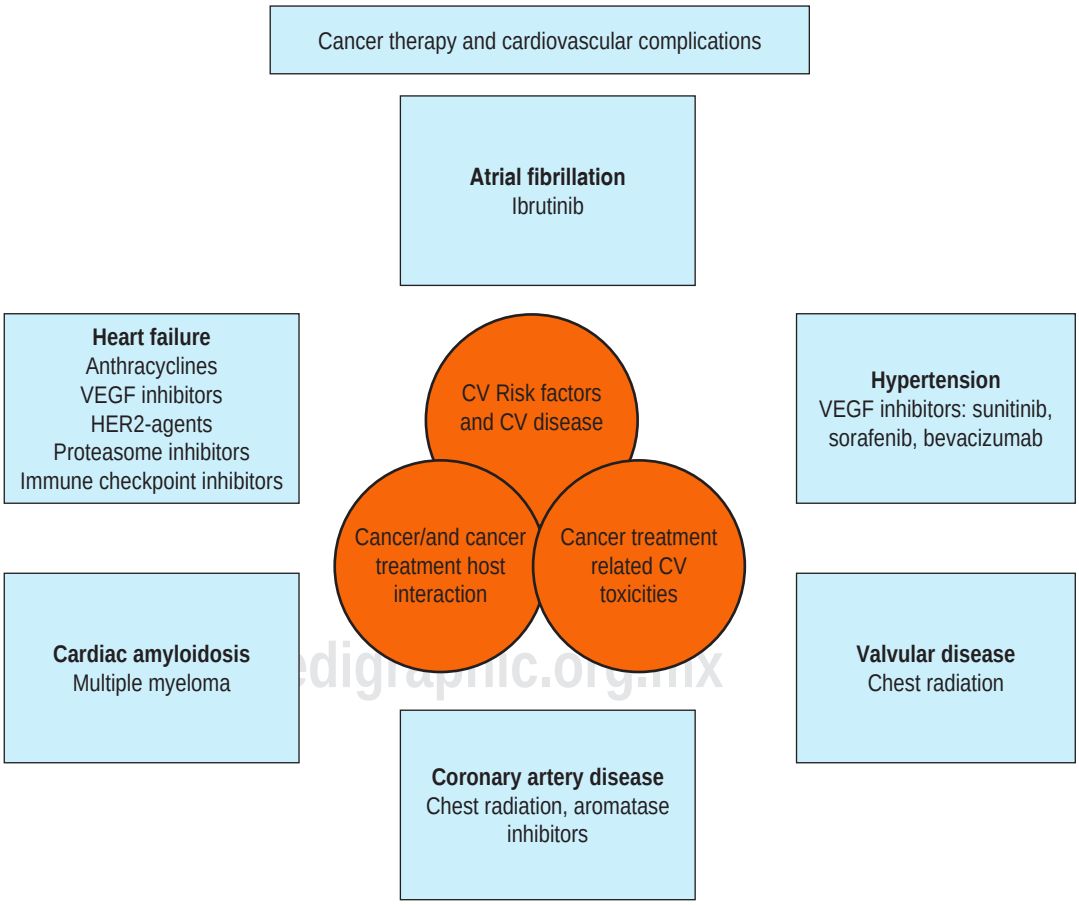


Figure 1:

Interaction between several host factors, different antineoplastic agents administration modes and expressions of cardiotoxicity. CV= Cardiovascular, VEGF = vascular endothelium growth factor, HER2 = human epidermal growth factor receptor-2.

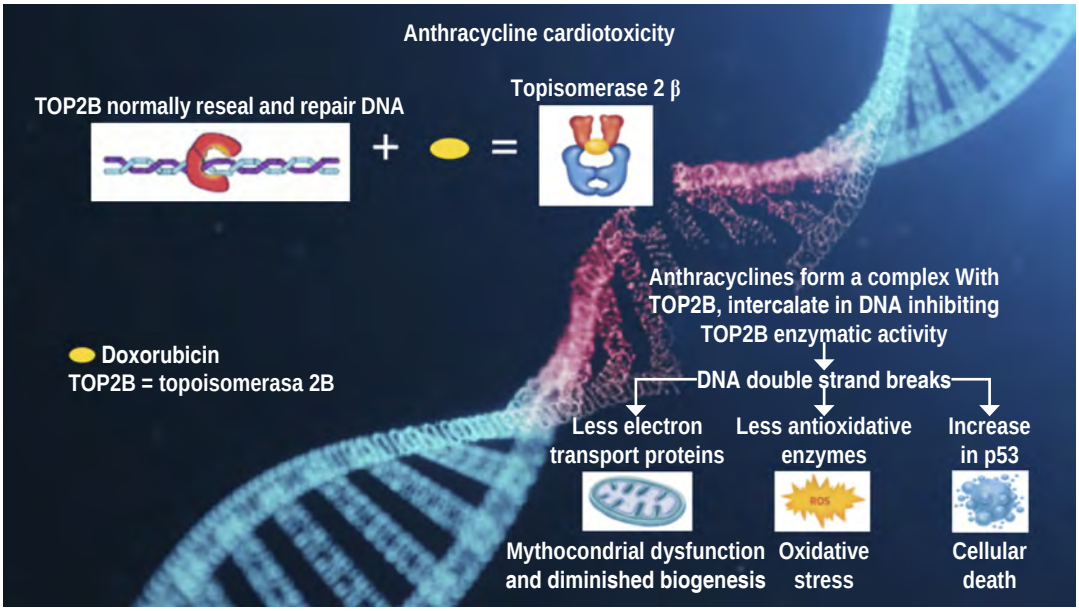


Figure 2:

Anthracycline interacts with topoisomerase 2B and intercalates in DNA altering its repairing properties. The consequences are increased p53 and oxidative stress and diminished mitochondrial bioenergetics and biogenesis that results in cell death.

tumours express different molecules that may act as an antigen, and if we inhibit T cell repression by CTLA-4 and PD-1 and mount a strong immune/active response against tumour antigens, it may have a favorable antineoplastic effect. Several studies have corroborated this, and immune checkpoint inhibitors (ICI) are current anti-cancer therapies in common use these days.[9] In September 2017, there were 940 immune based anti-cancer therapies in clinical development,[10] at the same, time there are more than 3,000 clinical trials evaluating efficacy in almost 600,000 patients. As much as 46.6% of patients with cancer in 2018 were considered eligible for ICI. More than 50% of the research & development of pharmaceutical companies is in the area of immuno-oncology.[11]

Chimeric antigen receptor T

The Chimeric antigen receptor T (CAR T) is an *in-vitro* engineered therapy where autologous T cells are obtained/drew from the patient, and usually with a lentivirus vector, genetic material is introduced into the patient T cell, this genetic material codifies for a receptor directed against a specif antigen or protein of tumoral cells. The in-vitro engineered T cells are re-injected into the patient causing tumoral lysis. Recently anti-CD19 CAR T cell therapy has shown efficacy in patients with B cell neoplasms; also, promising results have been observed in patients with melanoma.

Knowing new antineoplastic drugs nomenclature

We will witness the development of a large number of new therapies in cancer, most of them targeted TKI, it may be useful to disclose some aspects related to its «nomenclature». As previously stated, we have larger molecule monoclonal antibodies acting over extracellular receptor tyrosine-kinases (RTKs) or its ligand, and small molecule non-receptor tyrosine-kinase (NRTKs) that act mainly over intracellular tyrosine-kinases (TK). The therapeutic monoclonal antibodies may be murine, humanized, or mixed. The more humanized and less murine antibodies are associated with less antigenicity. The antibodies that act on RTK all end with de suffix «mab», and depending on if it is completely murine, partially, or completely humanized we complete suffix as:

1. Murine (0% human) = omab,
2. Chimeric (65% human) = ximab,
3. Humanized (> 90% human) = zumab,
4. Completely human (100% human) = umab.

For small NTRKs whose main action is intracellular, the suffix is «nib».[12]

How to classify different aspects of cardio-oncology and cardiotoxicity?

Cancer is a very complex disease with several diverse aspects such as mechanism of malignant cell proliferation, mutations/genetics, external chemical or viral etiological issues, host aspects, including the immune system that may predispose to perpetuate cancer or maybe eliminate neoplastic cells. Treatment of cancer is also a very complex issue with a variety of host cells and patient response to antineoplastic therapies, this, together with the many diverse action mechanism of antineoplastic therapies affecting the tumour, and that cardiac injury is usually related to more than one single mechanism of damage makes the classification of cardiotoxicity difficult.

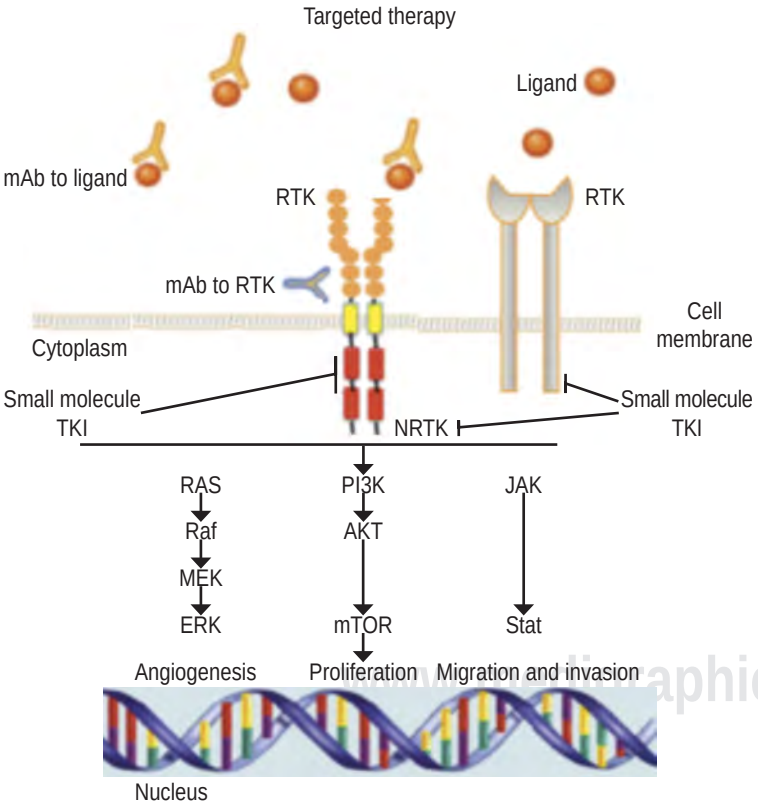


Figure 3: Monoclonal antibodies and non-receptor tyrosin-kinase inhibitors. mAb = Monoclonal antibodies, TKI = Tyrosin-kinase inhibitors, RTK = Receptor tyrosin-kinase, NRTK = non-receptor tyrosin-kinase.

Initially, cardiotoxicity was classified as type I: non-reversible damage associated with cell loss (necrosis/apoptosis) and progressive cardiovascular disease (doxorubicin) and, type II: reversible, associated with cellular dysfunction (mitochondrial/protein), with normalization of cardiovascular function after discontinuation of the antineoplastic drug (trastuzumab).[13,14] Recently, in a review article from Mayo Clinic, they classified cardiotoxicity in three subtypes based on pathophysiology and mechanism of tissue injury:

- Type I: direct cardiomyocyte toxic lesion (anthracycline drugs),
- Type II: non-direct toxic effect over cardiomyocyte, with cardiac damage mediated by a different mechanism (vasospasm, ischemia), and,
- Type III: inflammatory damage with the expression as myocarditis (Immune checkpoint inhibitors, ciclophosfamide).[7]

ANTINEOPLASTICS

Conventional chemotherapy *(Table 1)*

Anthracycline induced cardiac dysfunction

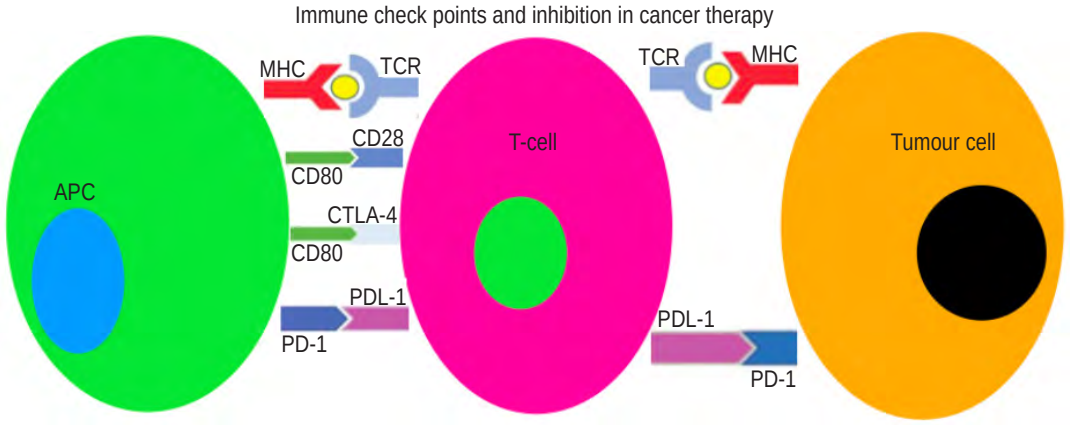
- Doxorubicin, epirubicin, liposomal doxorubicin

Non anthracycline chemotherapy and Cardiac dysfunction *(Table 1)*:

- Alkylating agents: cyclophosphamide, isosfamide, busulfan, melphalan.
- Antimetabolites: 5-Fluouracil, capecitabine, gemcitabine, cytarabine.
- Microtubule agents: docetaxel, paclitaxel, vinblastine, vincristine.
- Platinum agents: cisplatin, oxaliplatin.
- Antibiotics: bleomycin.
- Immunomodulatory drugs: thalidomide, lenalidomide.

Targeted anti-cancer therapies *(Table 2)*

- Monoclonal antibodies: trastuzumab, pertuzumab, rituximab, bevacizumab and several others.



Approved immune check point inhibitors

Anti-CTLA4: ipilimumab
Anti-PD1: novolumab, pembrolizumab, cemiplimab
Anti-PDL1: atezolizumab, durvalumab, avelumab.

Figure 4: The immune system reacts to foreign and tumoral antigens with co-stimulatory signals to eliminate such antigens. Cancer induced checkpoint inhibitory signals PD1, PDL-1 and CTLA-4 cause immune tolerance and permits a proliferation of neoplastic cells. Inhibition of these check points PD1, PDL-1, and CTLA4 restores immune co-stimulatory signals eliminating in this way neoplastic cells.
APC = antigen presening cells, MHC = major histopatibility complex, TCR = T cell receptor, CD = cluster differentiation, CTLA-4 = cytotoxic T lymphocyte antigen-4, PD-1 = programmed death-1, PDL-1 = programmed death ligand-1.

- Tyrosin kinase inhibitors (TKI): Imatinib, dasatinib, nilotinib, erlotinib, sunitinib, pazopanib, lapatinib, ibrutinib.
- Proteasome inhibitors: bortezomib, carfilzomib.
- HDAC (histone deacetylase) inhibitors: panobinostat, romidepsin, vorinostat.
- CDK4/CDK6 (cycline dependent kinase) inhibitors: abemaciclib, ribociclib.
- mTOR (mammalian target of rapamycin) inhibitors: everolimus, temsirolimus.

Immuno-oncologic therapeutic agents *(Table 3)*

- Immune checkpoint inhibitors (anti CTLA-4, anti PD-1): ipilimumab, nivolumab, pembrolizumab, others.
- CAR T cell therapy.

CARDIOVASCULAR TOXICITY

Direct cardiotoxicity

Anthracyclines

Doxorubicin is probably the most common conventional chemotherapy drug used. Acute toxicity is rare and occurs in less than 5% of patients. Chronic cardiotoxicity is seen in 0 and 16% of users, depending on the population studied, dosing regimen, and years of follow up. The risk of subclinical cardiotoxicity can be as high as 57% of childhood cancer survivors.[16] Patients with anthracycline related cardiac toxicity may have reduced left ventricle (LV) function, heart failure, high grade ectopic ventricular beats with 8.2 increased risk of sudden death even 25 years after they received cancer treatment.[17] Risk factors for anthracycline cardiotoxicity are cumulative dose, extremes of age, female gender, cardiovascular comorbidities, adjuvant chemotherapies and thoracic radiotherapy.[18]

Non-anthracycline chemotherapy

Cyclophosphamide can cause hemorrhagic myocarditis. Platinum based monotherapy cardiotoxicity is rare with unknown prevalence. All-transretinoic acid has been associated in some cases with hipotension and myocardial depression.

Tyrosin kinase inhibitors

Trastuzumab, blocks signalling through NRG1/ERBB2 (HER-2) pathway involved in breast

cancer cell proliferation and apoptosis inhibition, this same HER-2 pathway is responsible for cardiomyocyte survival/cellular proliferation/apoptosis inhibition and if it is blocked by trastuzumab may result in cardiotoxicity.[9] 20% of breast cancer patients are HER2 positive and have an excellent response to trastuzumab therapy. Unfortunately, a high percentage of patients develop myocardial dysfunction and usually discontinue a useful cancer medication. Adverse events are more common in the real world than those observed in the clinical trials. Cardiac toxicity can develop as early as two weeks after beginning HER2 inhibitor, and this suggests it does not represent a cumulative dose-dependent issue.[9,19,20] The opening article in the first edition of the new specialized cardio-oncologic journal from the American College of Cardiology on September 1, 2019 was related to this topic, and showed that when cardiologist prescribed ACE inhibitors and betablockers it may be possible to prevent myocardial dysfunction and complete the full trastuzumab cycle without interruption.[21] Several small molecule tyrosine kinase inhibitors (TKI), most commonly sunitimib may be responsible for myocardial dysfunction, occurring in between 1-27% of patients.

Immune checkpoint inhibitors

Immune checkpoint inhibitors have increased overall survival in otherwise very aggressive forms of cancer such as melanoma, renal cell carcinoma, non-small lung cancer and Hodgkin disease. Unfortunately, these immune based therapies are often associated with adverse immune based side effects in more than 50% of patients. Cardiovascular toxicity related to ICI includes myocarditis, *tako-tsubo*, arrhythmias, pericarditis, coronary artery disease/vasculitis and hypertension.[10] Myocarditis that occurs as a consequence of ICI is the most common cardiovascular adverse effect and has a bad prognosis with major adverse cardiac effects (MACE) in 50% and mortality in 17% of cases. Clinically, it may express itself with dyspnea, palpitations, acute heart failure and cardiogenic shock. Myocarditis May occur in 1.3% of patients treated with the anti-PD1 pembrolizumab, and 0.6% treated with nivolumab. Anti-CTLA-4 (ipilimumab) combined with anti-PD1 increases the percentage of myocarditis to 2.4%.[22-24]

CAR T-cell therapy

The main adverse effect after infusion of CAR T-cells is the cytokine release syndrome with

Table 1: Conventional chemotherapy.

	Arrhythmia	Cardiomyopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapy							
Anthracyclines (doxorubicin, epirubicin)		+					
Alkylating agents (cyclophosphamide, melphalan)	+	+	+				
Antimetabolites (5 fluoruracilo, capecitabina cytarabine)		+	+			+ cytarabine	
Microtubule binding agents (paclitaxel)	+		+				
Platinum based therapy (cisplatinum)			+		+		
Antibiotics (bleomycin)			+	+			
Immunomodulatory drugs (thalidomide)	+						

Table 2: Targeted therapy agents.

Target agents	Arrhyth-mia	Cardio-myopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Proteasome inhibitors (bortezomib, carfilzomib)		+	+		+		
HDAC inhibitors (vorinoztat)	+						
CDK4/CDK6 inhibitors (ribociclib)	+						
mTOR inhibitors (target of rapamycin) (everolimus)	+	+	+		+		
HER2 inhibitors (pertuzumab, trastuzumab)	+						
VEGF inhibitors (bevacizumab, sunitinib)		+	+		+		
BCR-ALB1 inhibitors (dasatinib, nilotinib, ponatinib)	+		+	+ Dasatinib			
BTK inhibitors (ibrutinib)	+						
ALK inhibitors (alectinib, nilotinib, ponatinib)	+		+				
BRAK inhibitors (dabrafenib)	+	+					
MEK inhibitors (MAPK/ERK kinase) (binimetinib, cobimetinib, trametinib)	+	+		+			

the liberation of interferon-gamma, granulocyte macrophage colony-stimulating factor, interleukin-6, and interleukin-10.[25]

Arrhythmias

Conventional chemotherapy

Atrial fibrillation has been described in 8% of patients on melphalan or busulfan and < 2% of patients on paclitaxel, mostly in the elderly, but also, it has been described in several cases of young patients without risk factors.[26] Paclitaxel and thalidomide have been associated with bradycardia. Arsenic trioxide used in some leukemias blocks repolarizing K currents (Ikr and Iks) and causes QTc prolongation above 500 ms in 65% of patients according to Bazzet QT corrective formula and 24-32% using Fridericia's. This latter formula is preferred in cancer patients because fewer overcorrection occurs at high heart rates, the issue that could lead to inappropriate cancer treatment interruption.[27] Torsade de Pointes usually does not occur in patients on Arsenic trioxide (probably because it also activates repolarizing K-ATP dependent current) unless there are electrolyte abnormalities, sudden death is infrequent.[28]

Tyrosin kinase inhibitors

Ibrutinib, an inhibitor of Bruton tyrosine-kinase (BTK) is used for chronic lymphocytic leukemia, it is associated with atrial fibrillation and ventricular arrhythmias, also sinoatrial arrest and asystole have been reported.[29] (BTK) is a regulator of PI3K-Akt signalling pathway and BTK inhibition by Ibrutinib is the postulated mechanism of the 8% risk of atrial fibrillation with this TKI.[30]

Another pro-arrhythmia related issue is QTc prolongation. Several small molecule TK inhibitors may increase QTc, especially in the context of K, Ca or Mg abnormalities, so these should be corrected before initiating these drugs. Some of the several TKI that may cause

QTc prolongation include lapatinib, sunitinib, nilotinib, sorafenib, vandetanib, the list is long and surely it will increase in the near future.

Immune check point inhibitors

Ventricular arrhythmias ocurrs in patients on ICI and these finding can increase mortality to 40%. Other forms of cardiac toxicity are AV or other conduction defects observed in 10% of patients and are associated with 50% mortality. These arrhythmias have been related to inflammatory cell infiltration of the myocardium and may be one of the manifestations of myocarditis.[22,31]

Vascular toxicity

Myocardial ischemia

Some antimetabolites, such as fluoropyrimidines may cause myocardial ischemia through coronary vasospasm even in the absence of angiographic disease.[32] 5-fluorouracil may cause coronary vasospasm in 1 to 68% of cases and capecitabine in 3-9% of patients.

Several new molecular agents signaling VEGF may cause vascular toxicities/arterial ischemia such as myocardial infarction, stroke, and/or limb ischemia.[33]

Platinum compounds are agents that may induce vascular toxicity and have been associated with hypertension, myocardial infarction, stroke, peripheral artery disease, and Raynaud phenomenon.[34,35] Chest pain may occur in 38% of testicular cancer patients treated with combination therapy that includes cisplatin, vinca alkaloids and bleomycin.[36]

Hypertension

Angiogenesis/VEGF (vascular endothelium growth factor) inhibitors: several VEGF inhibitors through vascular/capillary rarefaction and increased vascular resistance induce systemic hypertension. A relatively common used VEGF inhibitor used is bevacizumab.[37,38]

Radiotherapy induced cardiotoxicity

More than 50% of patients with cancer receive radiotherapy during some part of there treatment. Vascular structures are susceptible to radiation-induced injury, and it may cause endothelial dysfunction and inflammatory cells infiltration.[39] The cardiomyopathy observed after radiation therapy is often restrictive and manifests as heart failure with preserved ejection fraction. Patients with Hodgkin disease or breast cancer who recieved thoracic radiation may have premature atherosclerosis.[40] Long term radiation effect on the heart are heterogenous and include coronary heart disease (especially ostial/proximal disease), valvular heart disease, myocardiopathy with systolic and more commonly diastolic dysfunction and conduction defects. Also observed are pericardial and valvular fibrotic disease with calcification in the long term.[41-47]

DIAGNOSIS

Clinical syndrome

Cardiac toxicity may be asymptomatic, so, according to risk factors and specific antineoplastic therapy, we need to monitor potential toxicity issues as disclosed in next sections.

Table 3: Immunotherapies and other agents.

	Arrhythmia	Cardiomyopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Immunotherapies							
Immune check point inhibitors	+	+	+	+		+	
CAR T cell therapy	+	+	+	+		+	
Other therapies							
Radiotherapy	+	+	+	+		+	+

Patients may refer data related to heart failures such as dyspnea, pulmonary or systemic venous congestion, palpitations or dizziness/syncope related to arrhythmia/conduction defects, chest pain caused by ischemia/pericarditis, or data of acute heart failure/cardiogenic shock.

Electrocardiogram

The electrocardiograma is a very useful, inexpensive and available instrument to monitor patients under cancer treatments. Arrhythmias and conduction defects may be detected. Anthracycline cardiotoxicity occurs with ECG changes in 20-30% of patients, arrhythmias in 3% such as sinus tachycardia, supraventricular tachycardia, heart block and ventricular arrhythmias.[15] Also, it is necessary to monitor QTc and modify (QTc>450 ms) or temporal suspensión (QTc>500 ms) of antineoplastic treatment that increases QTc. Small progressive declining R wave amplitude voltage may be an indication of pericardial fluid accumulation related to pericarditis.

Biomarkers

Cardiac troponin (cTn) is an extremely useful biochemical marker of cardiac injury. It is elevated in 94% of established ICI myocarditis cases, and also it has important positive predictive value for potential left ventricular dysfunction in the setting of anthracycline therapy. Several years ago, a well done study measured cTn before, 72 hours, and one month after anthracycline therapy and showed that cTn elevation after this antineoplastic drug correlated with left ventricular (LV) dysfunction in the future. Also, the same study demonstrated the protective effect of angiotensin converting enzyme (ACE) inhibition in patients receiving this chemotherapic drug.[48,49] Brain natriuretic peptide (BNP) or amino-terminal pro-brain natriuretic peptide (NT-pro-BNP) also have value as a prognostic biomarker of myocardial injury.

Imaging

Echocardiography has an important role in monitoring the cardiotoxicity of antineoplastic drugs. In patients with previous cardiac risk factors or established heart disease, it is important to obtain a baseline echocardiogram. This study might influence to decide for potential chemotherapy drugs in the case of abnormal cardiac structure/function. The follow-up timing of subsequent echocardiographic studies will depend on clinical characteristics and risk factors of the patient, pre-existent cardiac abnormalities, chemotherapy chosen and cumulative drug dose. In general, chemotherapy related left ventricular dysfunction is classically defined as LV ejection fraction declines of more than 10% compared with baselines studies, or if it goes under 50% after chemotherapy cycles. Lately, strain/deformation myocardial imaging has significantly contributed to earlier detection of LV dysfunction, even before a fall in LV ejection fraction occurrs. Echo studies should include evaluation of different strain modalities such as global longitudinal (GLS), radial and circumferential. A GLS relative change above 15% represents subclinical left ventricular dysfunction. Echo is also excellent in the evaluation of pericardial disease, including effusion or hemodynamic compromise related to the pericardial fluid.

Multigated acquisition (MUGA) based left ventricular functional studies are used less often now, and have been widely substituted by echo imaging.

Magnetic resonance (MR) is actually the gold standard for the non-invasive evaluation of myocardial structure and function. Unfortunately, it is expensive, may be time consuming, and more critically or claustrophobic patients may not tolerate it. These logistical reasons make it also inappropriate for repeating follow up studies. Anyway, we might need MR studies in cancer patients on chemotherapy, it is extremelly useful when we suspect drug related myocarditis. It may provide diagnostic clues in favor of myocarditis or alternative diagnosis, it also gives us cardiac related prognostic information measuring extracellular matrix expansion of myocardium. A recent article provides excellent information related to MR to detect cardiovascular effects of cancer therapy and describes useful diagnostic sequences:[50]

1. Anatomical sequences, cine-volume and function,
2. T2 sequences-Edema,
3. Native T1 and T2 mapping-Edema/fibrosis,
4. Early Gadolinium Enhancement-Edema/ Late Gadolinium Enhancement-Fibrosis,
5. Post-Contrast T1 mapping/ECV-Fibrosis

Computed tomography (CT) or PET/CT: useful for detection of cardiac structure, coronary disease, cardiac primary/secondary neoplasm, it has an unwanted side effect: ionizing radiation.

PREVENTION

Screening is an important part of prevention, anticipating/early detection of declines in LV.

The American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACI) recommend in anthracycline-based therapy assess left ventricular ejection fraction (LVEF), GLS, and cTn after therapy and six months, and if the cumulative doxorubicin dose is above 240 mg/m^2 repeat LVEF, GLS and cTn before each additional dose of 50 mg/m^2. For non-anthracycline therapies, the ASE/EACI recommendation is to repeat these measurements every three months during therapy. Patients on TKI or vascular endothelium growth factor (VEGF) inhibitors should be evaluated at one month.

Modifying cardiovascular risk factors, including exercise and statins, is an established way to reduce susceptible patients for cardiac toxicity. In high-risk patients of developing cardiotoxicity, there is evidence of certain beta-blockers as carvedilol that also has antiapoptotic and antioxidant effects[51] and nebivolol as a measure to prevent LV functional decline. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are also useful,[21,48] in part through lowering blood pressure and potential overload mediated myocardial damage, and also inhibiting angiotensin II inducing NADPH oxidase oxidative stress. One study showed that the combination of the ACE inhibitor enalapril plus carvedilol prevents decline in LV ejection fraction.[52]

In the setting of anthracycline cardiotoxicity, dose reductions, prolonged infusions rates of doxorubicin instead of bolus and/or use of liposomal formulations reduces cardiac toxicity.

If trastuzumab is indicated, avoid concomitant anthracycline. Desraxozane, an iron chelator that interacts with topoisomerase IIb has been used successfully to prevent anthracycline myocardial injury,[7,53] but such preventive therapy is infrequently used in several countries because it is usually unavailable and economic issues.

Patients with pre-existent AV or other conduction defects usually also have other structural heart disease or cardiac risk factors, they might be at increased risk of bradycardias or heart blocks with antineoplastics drugs such as crizotinib, paclitaxel, thalidomide, and pazopanib. In such a situation, avoid, or if needed, carefully monitor non-dihydropyridine calcium antagonist as verapamil or diltiazem, beta-blockers, and digoxin.

In case of radiotherapy, especially in mediastinal or left breast cancer, reduction of dose exposure is the best intervention, use of protective shielding, specific positioning, or proton beam may be helpful measures to prevent radiation-induced cardiac toxicity. Some experimental studies have suggested statins and ACE inhibitors to prevent radiation-induced cardiotoxicity, unfortunately, not clinically proven.

TREATMENT

For LV dysfunction, follow guideline-based treatments, including betablockers as carvedilol, ACE inhibitors, ARB, and spironolactone. Sometimes it may be necessary to reduce or stop anticancer therapy, or modify administration protocol, or switch to less cardiotoxic regimes.

In the case of vascular induced cardiac toxicity (type II cardiotoxicity) by 5-FU or capecitabine that act as vasoconstrictors, the treatment is with vasodilators, nitrates may be useful on epicardial coronaries, and long acting nifedipine is a better strategy at the coronary microvascular level.

As previously disclosed VEGF inhibitors are associated with the development of hypertension, no specific quidelines are indicating the best antihypertensives in these situations. But we should have a target blood pressure less 130/80. In general terms, it is better to avoid the

calcium antagonist verapamil or diltiazem because potential drug-drug interaction through CYP3A4, better to use ACE inhibitors or the dihydropyridine amlodipine.[54]

Immune checkpoint inhibitors/myocarditis

ICI inhibitors related to myocarditis or ventricular tachycardia/fibrillation are life treating and require stopping the antineoplastic drug and initiate immunosuppressive agents. Also, AV block and conduction defects might be expressions of myocarditis, these, together with pericarditis or coronary vasculitis related to ICI is a clear indication to begin immunosuppressive therapy, the most common immunosuppresive therapy used are steroids. It is important to begin early immunosupression, ideally, before 24 hours of myocarditis diagnosis, patients recieving treament after 72 hours have the worst prognosis, and high dose corticosteroids are associated with the best outcomes. These indicate that myocardial damage may improve with early and intensive corticosteroid therapy.[55] If after initial evaluation the patient is asymptomatic and has only mild abnormal screening test, it may be appropriate to resume ICI under close monitoring. If the patient is symptomatic, we have to suggest to discontinue ICI permanently. If mildly symptomatic, oral prednisone 1-2 mg/kg/day may resolve toxicity. If severe cardiotoxicity symptoms develop it is necessary to progress to IV methylprednisolone 1 g/day for 3-5 days and then continue oral steroid until the cardiac function returns to baseline, then, taper over 4-6 weeks. Manage arrhytmias as needed. The intensive and rapid escalation of immunosuppressants are often required and may include intravenous immunoglobulin, thymocyte anti-globulin, anti-TNF (infliximab), mycophenolate mofetil or tacrolimus. Plasmapheresis has been used (eliminates the drug and autoreactive antibodies). It may be particularly useful to eliminate chemotherapic drugs that have long half-lives (14.5 days ipilimumab, 25 days pembrolizumab, and 27 days for atezolizumab).[7,56,57] Sometimes, and if neoplastic relatedlLife expectancy is favorable, advanced heart failure management, including support with ventricular assist devices may be indicated.

CONCLUSIONS

Half a century ago, in the 1970s began the relation between oncology and cardiology with the recognition of the cardiotoxicity of the antineoplastic drug doxorubicin. Since then, there have been significant advances in both areas, oncology and cardiology. As a result, we have witnessed increased life expectancy in cancer patients and longer lives in cardiac patients. The increased survival in cancer patients brought with it the recognition of the short and long term effects of several of the different modalities of anticancer therapy, and now, it is common to see in a general cardiology practice several cancer patients survivors, many of them with cardiac pathology. In the late part of the XX century cardio-oncology units appeared in the world, mainly in the setting of large academic/university-based hospitals.

There will not be special cardio-oncology units all around the globe, so, it will be necessary to include this area in cardiology teaching programs, acquire skills, and training cardiologist in this important issue so they will be able to collaborate with the oncologist in the management of the cardiovascular aspects of these patients.

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Anticoagulantes orales directos
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Síndromes coronarios agudos
Trombólisis en el IAM
Antiagregantes plaquetarios en SICAS
Muerte cardiaca súbita en atletas
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Epidemiología de la EAC
Nuevos paradigmas en el tratamiento de las dislipidemias
Diabetes, hipertensión arterial y EAC
Imagen cardiovascular
Obesidad y aterosclerosis coronaria

Director del curso

Dr. Alberto Unzueta Montoya
E-mail: aunzuetam@gmail.com

Valor curricular

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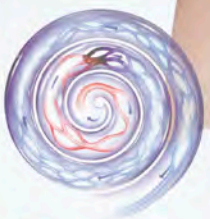

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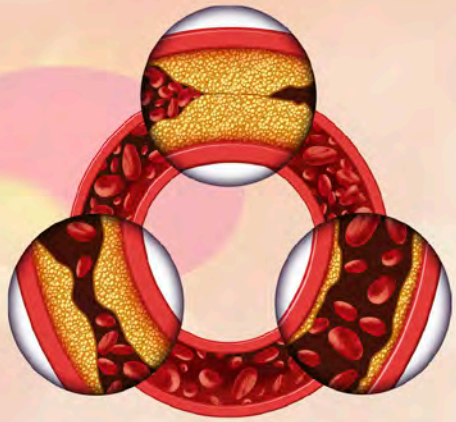

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