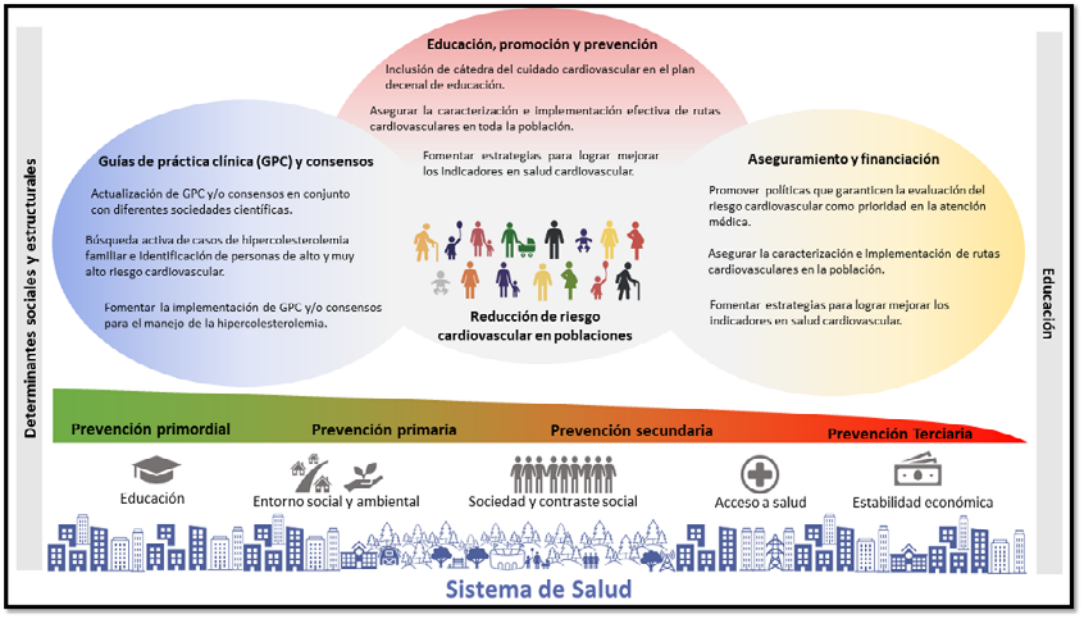
Revista Colombiana de
Cardiología

Volume 30 Issue 6 November / December 2023
ISSN: 2938-1525
Indexed in: Scopus, DOAJ and EBSCO Essentials™
www.rccardiologia.com
www.revcolcard.org



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EDITORIAL

Acute myocardial infarction in young people

Infarto agudo de miocardio en personas jóvenes

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Cardiovascular diseases are the main cause of death in Colombia, regardless of age. In the document titled "Basic health indicators for 2022"[1], the five main causes of death in men and women between the ages of 45 and 64 were: infectious diseases and parasites, ischemic heart diseases, assault, cerebrovascular diseases, diabetes mellitus, and breast cancer; thus, this topic is very important from a local and global point of view[1].

The age cut-off for describing young patients varies widely depending on the literature; some authors refer to age under 45 years and others to those under 55; this editorial will take a cut-off point equal to or less than 50 years when referring to myocardial infarction in young people[2,3].

It is estimated that more than one million hospital admissions in the United States from 2001 to 2010 were due to acute myocardial infarction in patients between 30 and 50 years old. The Framinghan Heart Study article, with a 10-year follow-up, indicated an incidence of myocardial infarction (MI) of 12.9, 38.2 and 71.2 per 1,000 men and 2.2, 5.2 and 13.0 per 1,000 women in the 30-34, 35-44 and 45-54-year age ranges, respectively[2].

Premature coronary disease has a high recurrence rate and mortality, which significantly impacts people's health and productivity. Therefore, the challenge is early diagnosis along with determining its pathophysiology and related risk factors, and thus offer early, comprehensive treatment and provide recommendations to prevent recurrence.

Young patients may have an MI associated with obstructive atherosclerotic coronary disease as well as non-obstructive atherosclerotic coronary lesions; therefore, understanding the pathophysiology of the acute events as much as possible would help determine the treatment.

The main abnormality is atherosclerotic plaque rupture, which would explain 60 to 65% of the MI cases in young people. This is generally related to a large lipid-rich necrotic nucleus with a thin fibrous cap (< 65 μm), few smooth muscle cells, and risk factors like smoking, hypercholesterolemia, diabetes mellitus, and arterial hypertension[2]. This is the pathophysiology in 57% of men and 47% of women under the age of 50 with ST elevation acute myocardial infarction (STEMI)[3].

The second mechanism is erosion of eccentric plaque which is rich in smooth muscle cells and proteoglycans, with a small necrotic nucleus, associated with smoking as the main risk factor. This mechanism explains the disease in 35% of men and 47% of women under the age of 50 with STEMI[3,4]. It is the most common in premenopausal women and the most frequent presentation is non-ST elevation acute myocardial infarction (NSTEMI)[5].

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Date of reception: 14-06-2023
Date of acceptance: 23-07-2023
DOI: 10.24875/RCCARE.M23000061
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):313-315
www.rccardiologia.com

When a young person is hospitalized with acute coronary syndrome (ACS), other, non-atherosclerotic causes should be considered, such as spasms, vasculitis, emboli and thromboses associated with risk factors like smoking, substance abuse (cocaine, amphetamines, marihuana, anabolic steroids) and hypercoagulability syndrome. Approximately one out of eight young patients with acute myocardial infarction behaves like a myocardial infarction with non-obstructed coronary arteries (MINOCA)[3]. Spontaneous dissection is an important cause of myocardial infarction in young women, especially in the peripartum period.

The risk factors in young people with MI with obstructive atherosclerotic disease are the same as those of older patients, but with a different prevalence. Studies have shown that smoking, lipid disorders and a family history of premature coronary disease are more prevalent in young people, while risk factors like diabetes and arterial hypertension are less frequent[3,6]. In a population of 206 patients under the age of 45, Marín et al. reported that the most important risk factors for atherosclerotic coronary disease and ACS were smoking and dyslipidemia[7].

Smoking is the most prevalent risk factor in young people (70 to 95%), and smoking cessation is the intervention with the best results, with a more than 50% reduction in mortality. Data from the Mass General Brigham YOUNG-MI Registry showed the significant impact of smoking cessation on the long-term prognosis[2,3,8]. Therefore, the Sociedad Colombiana de Cardiología and Fundación Colombiana del Corazón are working to promote smoke-free spaces as a smoking reduction strategy, which will have an impact on preventing coronary disease in young people.

It is also advisable to look for a history of substance use, such as cocaine use, as this is associated with hypertension, thromboses, spasms, accelerated atherosclerosis and an increased coronary plaque burden. Studies have reported cocaine and/or marihuana use in almost 11% of patients under the age of 50, associated with increased cardiovascular and all-cause mortality[9].

Dyslipidemias of the hypercholesterolemia variety should be diagnosed and treated in young people with obstructive and non-obstructive atherosclerotic coronary disease. Approximately 10 to 20% of patients with coronary disease have been reported to have heterozygous familial hypercholesterolemia. Other disorders found include low HDL cholesterol levels and high non-HDL cholesterol levels. Lipoprotein (a) is described as a cause of premature coronary disease; lipoprotein (a) levels over 50 mg/dl are associated with a three times greater likelihood of ACS in those under the age of 45[10].

There is no difference in the clinical signs and symptoms of ACS in young people and older patients. Chest pain is the most common symptom in men (90%) and women (88%) under the age of 50 who have an MI. However, young women may have non-cardiac symptoms like dyspnea, palpitations and fatigue. If a young patient with no clear symptoms is seen in the emergency room, diagnostic errors may be made, and the patient may be discharged while experiencing an ACS.

In fact, some studies have reported that two-thirds of young patients present with NSTEMI; in others, STEMI is more prevalent. In the Mass General Brigham YOUNG-MI Registry, 55% of men and 46% of women with an MI had STEMI[2,3,8].

Other characteristics related to the involvement of coronary arteries include less extensive coronary disease when compared to older people; approximately half of the patients have single vessel disease, with the anterior descending artery being the most often involved, and rarely the left coronary trunk (< 5%). Young women have a higher likelihood of MINOCA[6,11].

Cardiac magnetic resonance imaging, intravascular ultrasound and optical coherence tomography (OCT) are useful in the differential diagnosis and to evaluate the pathophysiology. In special cases where microvascular disease or vasospasm is suspected, function testing with adenosine and acetylcholine is recommended[3,12,13].

In patients with STEMI, the guidelines for percutaneous coronary intervention (PCI) and early reperfusion should be followed, together with dual antiplatelet therapy, high-intensity statins, beta blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Smoking should be stopped, and all risk factors strictly controlled. If coronary bypass surgery is required, arterial grafts are recommended. For non ST-elevation acute coronary syndrome (NSTE-ACS) cases, the secondary prevention guidelines and strategies must be followed. Young patients with heterozygous familial hypercholesterolemia and infarction are considered to be very high risk, and the LDL goal should be less than 55 mg/dl (less than 40 mg/dl in cases of recurrence); diet, statins, ezetimibe and PCSK9 inhibitors are recommended for its control[14]. If embolic events or antiphospholipid syndrome are found, anticoagulation should be prescribed. When vasospasm or cocaine-induced infarction is suspected, beta blockers are not recommended, with calcium antagonists preferred.

Acute myocardial infarction in young people is a disease that must be considered in the emergency room to avoid discharging patients experiencing an infarction, especially if there is a normal or non-diagnostic electrocardiogram. There is no consensus on whether the most frequent presentation is acute infarction with or without ST elevation. Coronary angiography can help determine if it is obstructive atherosclerotic coronary disease (80-90%). In the event of non-obstructive coronary artery myocardial infarction (10-20%), atherosclerotic and non-atherosclerotic causes must be ruled out, like spasms, emboli or thromboses. In this group, risk factors like smoking, familial hypercholesterolemia and the use of substances like cocaine, along with, in some cases, thrombogenic disorders (factor V Leiden, prothrombin gene polymorphism, antiphospholipid syndrome and hyperhomocysteinemia) must be evaluated.

Spontaneous coronary artery dissection is a frequent cause of infarction in young women, requires a high degree of suspicion, especially in the peripartum period, and warrants a specific approach and treatment.

For young patients, smoking cessation is the secondary prevention measure with the greatest impact.

Emergency rooms should have clinical pathways for treating chest pain, including an early electrocardiogram, high-sensitivity troponins and good clinical judgement to avoid overlooking an ACS in young patients.

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SPECIAL ARTICLE

Colombian Cholesterol Roadmap. National roundtable on cholesterol in Colombia. Call to action

Ruta colombiana del colesterol. Mesa redonda nacional sobre el colesterol en Colombia. Llamado a la acción

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Abstract

Atherosclerotic cardiovascular diseases (including myocardial infarction, stroke, and peripheral artery disease) continue to be a leading cause of premature death, disability, and healthcare expenditures worldwide. Therefore, preventing the vascular accumulation of atherogenic cholesterol-containing lipoproteins is crucial in averting major cardiovascular events. The Colombian Cholesterol Roadmap update is the outcome of a meeting held during the 2023 National Cardiology Congress, with the support of the World Heart Federation and a panel of clinical and thematic experts, along with representatives from various institutions involved in the management of dyslipidaemias in Colombia. The present update of this Cholesterol Roadmap provides a conceptual framework to describe the findings and achievements derived from working groups focused on identifying barriers that hinder the appropriate treatment of hypercholesterolemia in Colombia. It also outlines proposed actions adjusted to the local context, aiming to develop national policies and approaches within our healthcare systems. Furthermore, it reaffirms the commitment to intersectoral collaboration to achieve the cardiovascular health goals set for the year 2030.

Keywords: *Dyslipidemia. Hypercholesterolemia. Atherosclerotic cardiovascular diseases. Health goals. World Heart Federation.*

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Date of reception: 25-09-2023
Date of acceptance: 12-11-2023
DOI: 10.24875/RCCARE.M23000069
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):316-320
www.rccardiologia.com

Resumen

La enfermedad cardiovascular aterosclerótica (infarto de miocardio, accidente cerebrovascular y enfermedad arterial periférica) continúa siendo la causa más importante de muerte prematura, discapacidad y gastos en atención médica en todo el mundo. Por lo tanto, evitar la acumulación vascular de lipoproteínas aterogénicas de colesterol es fundamental para prevenir los eventos cardiovasculares mayores. La actualización de la ruta colombiana del colesterol, Colombian Cholesterol Roadmap, es el resultado de la reunión realizada en el Congreso Nacional de Cardiología 2023, con el apoyo de la Federación Mundial del Corazón y una mesa de expertos clínicos, temáticos y representantes de diferentes instituciones relacionadas con el manejo de las dislipidemias en Colombia. Este documento tiene como objetivo ser un marco conceptual para describir los hallazgos y logros obtenidos en las mesas de trabajo relacionadas con la identificación de barreras que limitan el tratamiento adecuado de la hipercolesterolemia en Colombia, y las acciones que fueron propuestas ajustadas al contexto local, que buscan desarrollar políticas nacionales y enfoques en nuestro sistema de salud. Así mismo, confirma el compromiso del trabajo articulado intersectorial para lograr las metas en salud cardiovascular propuestas para el año 2030.

Palabras clave: *Dislipidemia. Hipercolesterolemia. Enfermedad cardiovascular aterosclerótica. Metas de salud. Federación Mundial del Corazón.*

Introduction

According to national statistics, cardiovascular disease (CVD) is the leading cause of death and disability in Colombia[1-5]. Despite this, challenges remain in positioning CVD as a public policy priority and in following healthcare professionals' recommendations for managing risk factors. The World Heart Federation and the Sociedad Colombiana de Cardiología y Cirugía Cardiovascular (SCC) [Colombian Society of Cardiology and Cardiovascular Surgery] are committed to improving cardiovascular health in the world. By 2030, they have set the ambitious goals of reducing premature deaths from CVD, preventing major cardiovascular events, improving access to treatment, promoting healthy lifestyle habits and raising public awareness of this type of disease.

Materials and method

In 2017, the World Heart Federation and SCC, together with the Ministry of Health and civil society and academia representatives, gathered to determine decisive actions to impact on the incidence of acute myocardial infarction and its associated mortality. As a result of this work, a manifesto was published for acute myocardial infarction prevention, which was signed by all parties[6]. To continue this process, a roundtable was held on March 18, 2023, made up of a select group of professionals, clinical experts and representatives from the main associations related to cardiovascular health care in Colombia. The objective of this work group was to identify barriers to the appropriate treatment of hypercholesterolemia in Colombia and propose joint, efficient and achievable actions within the local context. It also aimed for commitment and coordinated intersectoral work to achieve the proposed goals for cardiovascular health.

This meeting, held during SCC's Thirteenth International Cardiology and Cardiovascular Surgery Symposium, was the platform for discussing the most relevant topics on hypercholesterolemia worldwide and in the local setting. Three thematic pillars were established, and three work groups were created to discuss them, distributed as follows:

– Education, promotion and prevention
– Clinical practice guidelines and consensuses
– Insurance and funding

Once the proposed topics had been discussed, a general roundtable was held to consolidate the contributions and comments related to each of the topics of interest, seeking innovative and effective solutions to combat hypercholesterolemia and improve the population's cardiovascular health.

Results

Reducing the burden of atherosclerotic cardiovascular disease requires different approaches and strategies to overcome the gaps and barriers that hinder the proper treatment of hypercholesterolemia in Colombia. Below, we describe the main discussion points and most relevant actions to contribute to the development of strategies in each of the three thematic pillars.

Group 1. Education, promotion and prevention

Objective: to generate a significant impact on cardiovascular health education and promotion, benefiting the entire population. The proposal to accomplish this is to foster broader and more effective cardiovascular health education to empower the general population in preventing the most common cardiovascular risk factors

and knowing how to avoid them, and promote knowledge of their personal cardiovascular risk profile.

Awareness raising campaigns are particularly important in different settings like mass media, schools, universities and workplaces. Other strategies are also considered, such as mandatory inclusion of health care curricula within the 10-year education plan (schools and universities), the use of social networks to disseminate knowledge, and a call to action through the commissioning of cardiovascular health ambassadors.

The need for certification and mandatory courses on the assessment and treatment of cardiovascular risk factors was discussed, as well as training health promoters.

Group 2. Adherence to clinical practice guidelines and controlling cardiovascular risk factors

Objective: to promote the implementation of clinical practice guidelines and/or consensuses for managing hypercholesterolemia. To accomplish this, simple pedagogical tools should be created to make them easier to apply.

The economic impact of cardiovascular diseases represents the highest economic burden for the Colombian healthcare system. The direct costs of medical care for cardiovascular diseases in Colombia account for approximately 10% of the country's total healthcare expenditure. Direct costs, like hospitalizations, procedures, medications and clinical follow up are just the tip of the iceberg[7,8]. These cardiovascular diseases also affect the patients' productivity and quality of life, with a significant indirect cost in terms of disability and lost opportunities, leading to an additional economic burden for the families and society in general[9,10].

Although there are national documents with recommendations for the prevention, diagnosis and treatment of dyslipidemias in Colombia, they are obsolete (year 2013)[11]. Therefore, to deal with this problem, these documents on the prevention, diagnosis and treatment of dyslipidemias in Colombia must be updated, with a holistic approach to cardiovascular prevention and as a user-friendly risk assessment tool with clear roadmaps and algorithms established for simple and effective use.

Likewise, it is essential to harmonize the risk assessment tools and establish efficient ways of screening to actively search for cases of familial hypercholesterolemia, identify people with high and very high cardiovascular risk who require cholesterol-reducing medications indefinitely and, ultimately, reduce the risk of major adverse cardiovascular events, thus achieving a significant reduction in the economic and human costs associated with CVD[8].

Group 3. Insurance and funding

Objective: to optimize the use of resources and prioritize the tasks that represent the greatest health gains for the general population, and use different strategies to improve the cardiovascular health indicators achieved to date. Among the proposed alternatives, the cardiovascular risk profile and demographics of the population must be understood in order to prioritize and assign resources differentially to manage cardiovascular risk factors.

Nonmedical professionals must be trained to deal with this problem in the far-flung areas of Colombia. In addition, economic incentive systems should be used with the insurance agencies to produce better cardiovascular health outcomes.

In this context, primary prevention and the control of risk factors are essential in reducing the incidence of CVD in Colombia and lowering the associated healthcare costs[8]. To accomplish this, the risk factors (like arterial hypertension, high cholesterol, smoking, obesity and diabetes mellitus) must be identified and controlled. Healthy lifestyles must also be promoted, along with cardiovascular health education, to prevent the onset of CVD and improve Colombians' quality of life.

To ensure the continuity of medical treatment, effective strategies must be devised to guarantee the continuity of medications after hospitalization in high- and very high-risk patients, such as the "Meds-to-Beds" strategy, which consists of medications being delivered directly to the patient's bedside prior to discharge from the hospital. This program has proven to be effective in decreasing the rate of hospital readmissions and in improving adherence to medical treatment[12]. Additionally, cardiovascular clinics specializing in the control of cardiovascular risk factors can be created to offer healthy lifestyle education, medical exams to monitor risk factors, medication prescriptions and ongoing follow up of patients' cardiovascular health.

However, for these strategies to be effective, a pilot should be implemented to fine-tune the flow charts and roll out the various strategies at local and national levels. This will allow the problem of cardiovascular diseases in Colombia to be dealt with effectively and improve the population's health and quality of life.

Discussion

The World Heart Federation's Cholesterol Roadmap strategy, with national roundtables, has been adopted in several countries around the world.

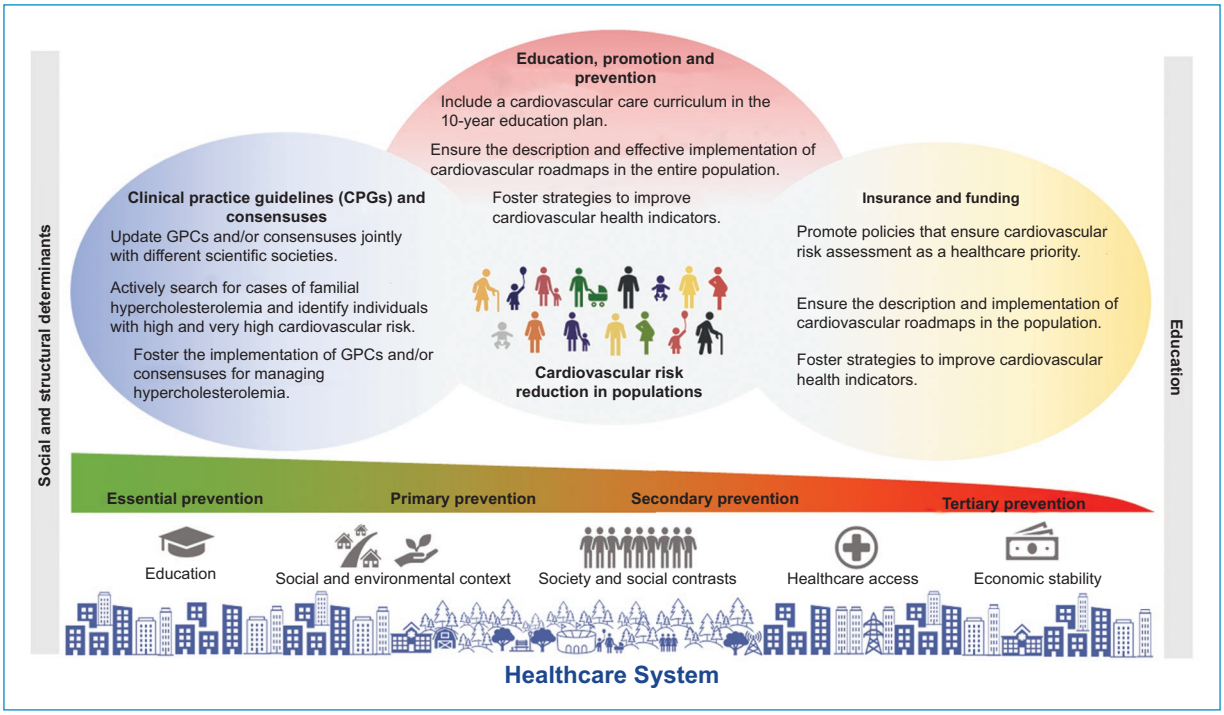

Figure 1. Implementation challenges: thematic axes and strategies.

Figure 2. The participants. Taken from archives. Colombian Society of Cardiology. XIII International Symposium of Cardiology and Cardiovascular Surgery of the Colombian Society of Cardiology 2023. Cartagena, Colombia.

The previous Colombian roadmap was developed in November 2017, with a roundtable set up by the SCC in cooperation with the World Heart Federation, the Ministry of Health, academia and civil society. The "Colombian Manifesto Against Heart Attacks" was a product of this meeting, with the goal of preventing 7,000 heart attacks per year by 2025. To achieve this goal, three priority actions were agreed upon for interinstitutional implementation: the creation of a National Colombian Infarct Registry - Red Flag Program; restructuring cardiac rehabilitation in all healthcare institution programs; and priority implementation of clinical guidelines on cholesterol

for managing high-risk patients in all healthcare service institutions in the country. The main healthcare system actors committed to fostering public policy to reduce cholesterol-related deaths in Colombia, not only to decrease mortality, but also to improve the patients' quality of life and the healthcare system's sustainability[6].

Various cholesterol roadmaps have been published in collaboration with the World Heart Federation in countries like Saudi Arabia, with the Saudi Heart Association in 2017; the Philippines, with the Philippine Heart Association in 2018; and Belgium, with the Belgian Heart League in 2021[6]. These publications have sought to identify priority solutions to improve education, prevention, screening and national dyslipidemia guideline updating. In general, the cholesterol roadmaps have emphasized the need for simplified and easily implemented CVD guidelines, adapting risk identification to specific regions, and optimizing community health worker training on risk assessment, especially in low and middle-income countries. They have also emphasized the need to conduct public health awareness raising campaigns aimed at increasing society's understanding of the causes and prevention of CVD, and thus overcome disinformation about treatment[13].

There is sufficient evidence of the adverse effects of the cumulative exposure to LDL cholesterol and apo B-containing lipoproteins and the consequent development of CVD. Implementing various preventive strategies aimed at effectively dealing with atherosclerosis in different stages throughout human life, along with health policies, lifestyle changes and, when necessary, pharmacological treatment to preserve health, will help prevent atherosclerosis and avoid adverse health effects[14,15].

In line with this, the different cholesterol roadmaps have identified a series of viable solutions covering five areas: a) improving awareness; b) implementing population-based approaches to prevent atherosclerotic CVD and reduce cholesterol exposure in the population throughout life; c) reinforcing risk assessment for atherosclerotic CVD and population screening to reduce the underdiagnosis of genetic dyslipidemias; d) implementing approaches aimed specifically at high-risk individuals; and e) establishing national/regional surveillance of cholesterol and the outcomes of CVD (Figs 1 and 2)[6,13].

Conclusions

The desired outcome of this expert discussion and action plan is to improve the prevention and treatment of CVD in Colombia, where these priority actions will be carried out jointly between different institutions. First, a multisectoral work group will be established to implement and monitor the proposals arising from this forum. Likewise, LDL cholesterol will be agreed upon as the etiological factor of CVD, and clinical practice guidelines and/or consensuses will be implemented using updated evidence for managing high-risk patients throughout the country, emphasizing LDL cholesterol control. This agreement represents the commitment of the healthcare system actors to incentivize public policy to reduce cholesterol-related deaths in Colombia, improve the quality of life of at-risk patients, and achieve greater healthcare system sustainability.

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Revista Colombiana de Cardiología
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ORIGINAL ARTICLE

Real-life effectiveness and safety of fixed amlodipine/irbesartan in hypertension management in Latin America: the PARCERIA study

Eficacia y seguridad en la vida real de amlodipino/irbesartán en combinación fija en el tratamiento de la hipertensión en América Latina: estudio PARCERIA

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Abstract

Introduction: *Latin American population-based studies have shown suboptimal blood pressure control rates. Fixed-dose anti-hypertensive combinations are associated with improved convenience, adherence and effectiveness compared with monotherapy.* **Objective:** *to assess the real-life effectiveness and safety of a fixed amlodipine/irbesartan combination in long-term management of hypertension in Argentina, Chile, Colombia, Guatemala, and Mexico.* **Materials and method:** *this was a 48-week, prospective, observational, single-cohort study, which included adults with uncontrolled hypertension treated with a fixed-dose amlodipine/irbesartan combination per the treating physician's judgment, were followed in routine care. Target blood pressure was < 140/90 mmHg (< 130/80 mmHg for patients with diabetes or renal disease).* **Results:** *509 patients (57.6% females) were included. The mean (SD) age and 10-year Framingham risk score were 60.6 (12.5) years and 9.9 (8.78), respectively. Over 48 weeks, 97.4% of patients took ≥ 80% of prescribed doses. Statistically significant and clinically important blood pressure improvements (- 25.7/-13.5 mmHg; p < 0.001) were observed. Control was achieved by 62.7% of patients. Treatment compliance was one of the significant (p < 0.05) predictors of target blood pressure achievement. Eighty-seven (17.1%) patients experienced 117 treatment-emergent adverse events, including 7 serious events by 5 (1.0%) patients. Adverse events were generally mild (75.2%) and judged not to be treatment-related (76.1%). The most common adverse events were peripheral edema (3.9% of patients) and dizziness (1.0%). Based on Kaplan-Meier estimates, the mean (SE) time to adverse event-related discontinuation was 32.85 (0.08) weeks.* **Conclusion:** *Treatment with the fixed-dose combination of irbesartan/amlodipine demonstrated clinical effectiveness, with a significant improvement in blood pressure values and a higher rate of achieving the treatment goal in those who adhered to the regimen. The treatment was well-tolerated, with a low percentage of treatment-related adverse events, and few severe events. The fixed-dose combination is an important tool in the management of arterial hypertension.*

Keywords: *Hypertension. Amlodipine/irbesartan. Effectiveness. Safety. Latin America.*

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Date of reception: 11-01-2023
Date of acceptance: 02-05-2023
DOI: 10.24875/RCCAR.23000001
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):321-329
www.rccardiologia.com

Resumen

Introducción: *los estudios basados en la población latinoamericana han demostrado tasas de control de la presión arterial subóptimas. La combinación de medicamentos antihipertensivos en dosis fijas se asocia con mayor comodidad, adherencia y efectividad en comparación con la monoterapia.* **Objetivo:** *evaluar la efectividad y seguridad en la vida real de la combinación fija de amlodipino/irbesartán en el tratamiento a largo plazo de la hipertensión en Argentina, Chile, Colombia, Guatemala y México.* **Materiales y método:** *estudio prospectivo, observacional, de cohorte única de 48 semanas, en el que incluyeron adultos con hipertensión no controlada, tratados con una combinación fija de amlodipino/irbesartán según criterio médico y fueron seguidos en la consulta ambulatoria habitual. La presión arterial objetivo fue < 140/90 mmHg (< 130/80 mmHg para pacientes con diabetes o enfermedad renal).* **Resultados:** *se incluyeron 509 pacientes (57.6% mujeres). La edad media (DE) y la puntuación de riesgo de Framingham a 10 años fueron 60.6 (12.5) años y 9.9 (8.78), respectivamente. Durante 48 semanas de seguimiento, 97.4% de los pacientes tomaron ≥ 80% de las dosis prescritas. Se observó mejoría en la presión arterial estadísticamente significativa y clínicamente importante (-25.7/-13.5 mmHg; p < 0.001). Se logró control en 62.7% de los pacientes. El cumplimiento del tratamiento fue uno de los predictores significativos (p < 0.05) de la presión arterial objetivo. Ochenta y siete (17.1%) pacientes experimentaron 117 eventos adversos emergentes del tratamiento, incluidos 7 eventos graves en 5 (1.0%) pacientes. Los eventos adversos fueron generalmente leves (75.2%) y se consideró que no estaban relacionados con el tratamiento (76.1%). Los acontecimientos adversos más frecuentes fueron edema periférico (3.9% de los pacientes) y mareos (1.0%). Según las estimaciones de Kaplan-Meier, el tiempo medio (SE) hasta la interrupción del tratamiento por acontecimientos adversos fue de 32.85 (0.08) semanas.* **Conclusiones:** *El tratamiento con irbesartán/amlodipino en combinación de dosis fijas mostró efectividad clínica, con mejoría significativa de las cifras de presión, y mayor llegada a la meta en quienes cumplieron con el tratamiento. El tratamiento fue bien tolerado, con un bajo porcentaje de eventos adversos relacionados con el tratamiento, y pocos eventos graves. La combinación en dosis fija es una importante herramienta en el tratamiento de la hipertensión arterial.*

Palabras clave: *Hipertensión. Amlodipino/irbesartán. Efectividad. Seguridad. Latinoamérica.*

Introduction

Hypertension is the leading cause of premature death and cardiovascular disease worldwide[1]. In 2010, a collaborative report by the World Bank and the World Health Organization showed that hypertension was the main single risk factor for the global burden of disease[2]. In 2000, a pooled analysis of available national and regional data estimated the worldwide prevalence of hypertension at 972 million individuals, the majority of whom (67.5%) resided in developing countries[3]. In Latin America, up to 40% of the adult population is affected by hypertension[4].

Randomized clinical trials have demonstrated that hypertension can be controlled and cardiovascular risk markedly reduced by changes in modifiable risk factors and the use of antihypertensive therapy[5]. In hypertensive patients, the primary goal of treatment is to achieve maximum blood pressure (BP) reduction while maintaining a good quality of life. However, despite improvements in the development of hypertension medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and thiazide-type diuretics[6] that are efficient in reducing BP in clinical trials, the real-life effectiveness of marketed treatments is suboptimal. BP control rates remain low at 21% among hypertensive patients[7], which is far below the Panamerican Health Organization (PAHO) target of 35% established for 2019[8]. Complicated treatment regimens and algorithms, inadequate patient follow-up, and poor adherence to therapy represent barriers to effective treatment delivery[9,10].

Due to the multifactorial cause of hypertension[11] and based on meta-analyses and review studies[12-15], several BP management guidelines acknowledge the necessity of combination therapy for the majority of patients[16-18]. Fixed-dose combinations of anti-hypertensives are regarded as a suitable alternative for hypertension management since they have been associated with patient convenience, improved adherence and compliance with treatment, as well as higher effectiveness in achieving BP control compared with separate agents and monotherapy[19-21].

Fixed-dose amlodipine/irbesartan, a combination of an angiotensin II receptor blocker with a calcium channel blocker, has been approved for the treatment of hypertension as a first-line or subsequent regimen. Irbesartan is an orally active angiotensin II type 1 receptor antagonist whose pharmacological profile differs significantly from those of many other compounds of the same class. In particular, according to its pharmacokinetic and pharmacodynamics profile, irbesartan has a high bioavailability,

a long duration of action, and a small potential for pharmacological interactions due to the nature of the enzymatic pathway involved in its metabolic process[22]. Amlodipine, on the other hand, is a calcium channel blocker with comparable effectiveness to that of irbesartan in reducing BP when considered as monotherapy[23].

Even though combination therapy with antihypertensive agents having complementary mechanisms of action is reportedly more effective than monotherapy with the individual components, the efficacy observed in controlled clinical trials does not translate to real-life effectiveness in routine clinical care. This is mainly because regional variations in the patient profiles, cultural influences, access to care, as well as variations in physician decision-making and practice patterns are rarely considered in controlled clinical trials. The design and performance of studies that take into consideration regional needs and treatment gaps are therefore required for the adequate assessment of approved treatments.

The aim of this study was to assess the real-life effectiveness and safety of a fixed amlodipine/irbesartan combination in the long-term management of hypertension in Latin America, as well as to describe patient compliance and to identify determinants of response to treatment.

Materials and method

This was a 48-week, prospective, observational, single-cohort study conducted in Argentina, Chile, Colombia, Guatemala, and Mexico. Adults with uncontrolled hypertension treated with a fixed-dose combination of amlodipine/irbesartan as per the judgement of the treating physician were followed as per routine care (see complete admission criteria in supplementary data 1). Although there was no fixed study visit schedule imposed, the investigators were asked to collect data for study endpoint assessments after 4, 8, 24 and 48 weeks of treatment with a fixed-dose combination of amlodipine/irbesartan, provided this was in line with their clinical practice. During the study, office BP was to be measured at each visit. The patient was to remain in the sitting position for at least 5 minutes before any office BP readings were recorded. Two BP measurements with a 5-minute interval were to be obtained and the average of the two measurements was to be reported. These measurements were to be taken as part of routine clinical care, using the same standardized equipment throughout the study. Uncontrolled hypertension was defined as grade II hypertension (systolic blood pressure [SBP] ≥ 160 mmHg and/or diastolic blood pressure [DBP] ≥ 100 mmHg), or grade I hypertension (SBP 140-159 mmHg and/or DBP 90-99 mmHg) and two or more cardiovascular risk factors (tobacco use, obesity, physical inactivity, dyslipidemia, diabetes mellitus, microalbuminuria or estimated glomerular filtration rate < 60 ml/min, age [older than 55 for men, 65 for women], and a family history of premature cardiovascular disease [men under age 55 or women under age 65]). Patients were responsible for acquiring the study treatment. This study was approved by all required regulatory agencies and Independent Ethics Committees and was conducted in accordance with local regulations.

The primary effectiveness outcome was the absolute change in SBP and DBP from baseline to 48 weeks of treatment. Secondary effectiveness outcomes were: the proportion of patients achieving target BP defined as SBP/DBP < 140/90 mmHg for patients with no target organ damage and no associated clinical conditions, and SBP/DBP < 130/80 mmHg for patients with diabetes or renal disease; the patient-reported treatment adherence as assessed by the ratio of treatment doses taken in relation to prescribed doses and treatment compliance, with patients with an adherence rate ≥ 80% considered compliant. The safety outcomes were the incidence of treatment-emergent adverse events (TEAEs) and the proportion of patients who discontinued due to TEAEs occurrence during the 48-week study period.

Effectiveness analyses were conducted on patients who had a baseline assessment, had taken at least one dose of study medication and had a minimum of one post-baseline assessment, while the safety analyses were conducted on patients who were administered any amount of the study drug. All treated patients had a post-baseline assessment, therefore the two populations overlapped.

Changes in SBP and DBP from baseline to 48 weeks were assessed with a two-sided one sample t-test with the null hypotheses of –5.0 mmHg and –3.0 mmHg, respectively. In addition, repeated measure analysis using general linear models was used to assess the change of SBP and DBP over time. Target BP achievement was descriptively assessed using an intent-to-treat approach where the denominator was the number of patients included in the analysis population regardless of data availability and the 99% confidence interval (CI) around the point estimate was calculated based on the normal approximation method.

Descriptive statistics were used to assess the patient-reported adherence and compliance with treatment at each visit and during the overall follow-up period.

A logistic regression model was built to identify determinants of response to treatment with fixed-dose

combination amlodipine/irbesartan, where the dependent variable was the target BP achievement at 48 weeks (yes vs. no) and pre-selected potential determinants were the overall cumulative compliance with treatment (≥ 80% vs. < 80%), the baseline dose of the fixed-dose combination of amlodipine/irbesartan (150/10 mg, 150/5 mg and 300/10 mg vs. 300/5 mg) and the country of residence (Argentina, Chile, Guatemala and Mexico vs. Colombia). Potential confounders, including country of residence, sex, age, and cardiovascular risk factors (body mass index [BMI], waist circumference, tobacco and alcohol consumption, diet, stress exposure, physical activity, family history of premature cardiovascular disease, co-morbid conditions [dyslipidemia, diabetes mellitus, microalbuminuria], Framingham score, fasting triglyceride levels, total cholesterol, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol) were assessed for statistical significance with Fisher's exact/Chi-square test for categorical variables and the t-test for continuous variables. Only statistically important ($p < 0.15$ when comparing patients who did and did not achieve BP at 48 weeks) and clinically important (a more than two-fold difference between patients who did and did not achieve the target BP at 48 weeks) confounders were considered in the multivariate logistic regression model.

All adverse events (AE) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The proportion of patients who experienced an AE during the treatment period was summarized by body system and preferred term. Descriptive statistics were used to assess the proportion of patients who discontinued due to an AE, while Kaplan-Meier survival analysis was used to determine the time to discontinuation due to an AE occurrence.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Figure 1 summarizes the patient disposition in the study. Five hundred forty-four (n = 544) patients were screened, of which 528 were enrolled in the study and 509 met the analysis population definition. Among the latter, 447 (87.8%) patients completed the 48-week follow-up period and 62 patients (12.2%) were discontinued prematurely due to losses to follow-up (n = 29; 5.7%), protocol deviations (n = 5; 1.0%), administrative problems (n = 5; 1.0%), adverse events (n = 4; 0.8%), withdrawal of consent (n = 3; 0.6%), death (n = 2; 0.4%), lack of effectiveness (n = 1; 0.2%) and other reasons (n = 13; 2.6%).

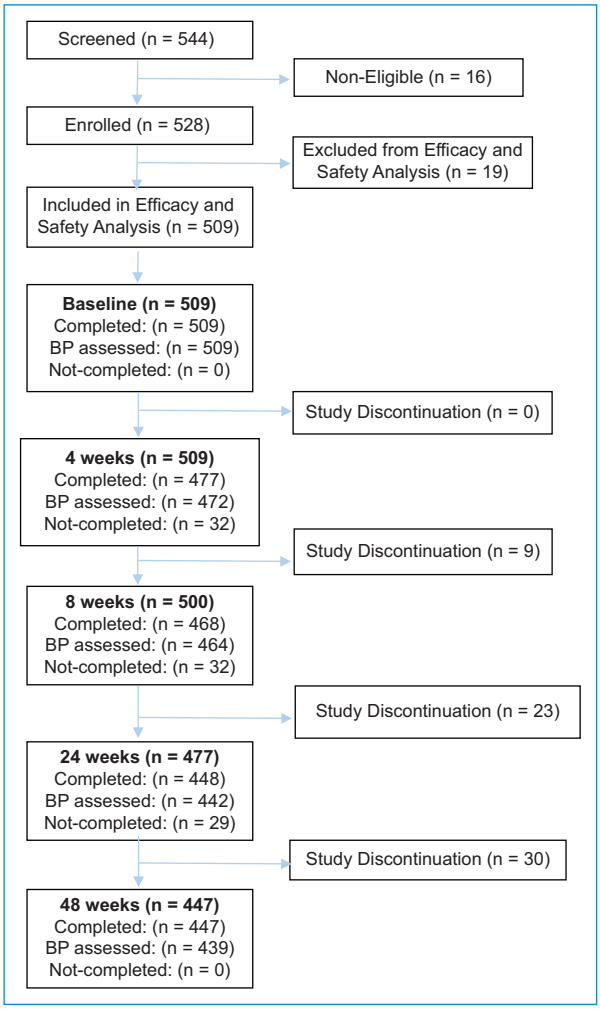

Figure 1. Patient disposition.

The baseline patient characteristics and cardiovascular risk factors are presented in table 1. The mean (SD) age was 60.6 (12.5) years, and 57.6% (n = 293) of patients were female. Patients were mainly from Colombia (n = 175; 34.4%), Argentina (n = 105; 20.6%) and Mexico (n = 101; 19.8%), while 85 (16.7%) were from Guatemala and 43 (8.4%) from Chile.

The mean (SD) 10-year Framingham risk score was 9.9 (8.78). Physical inactivity was reported by 76.8% (n = 391) of patients, 43.2% (n = 220) had comorbid dyslipidemia, 24.8% (n = 126) had ever smoked (5.9% current), and 19.3% (n = 98) were alcohol consumers.

At baseline, the mean (SD) SBP/DBP was 159.6 (14.61)/92.1 (93.0) mmHg. The results of a repeated measure analysis assessing the change in BP over time from baseline through follow-up are presented in figure 2. Statistically significant and clinically important

Table 1. Baseline characteristics and cardiovascular risk factors

Parameter	Analysis population (n = 509)
Age, years, mean (SD)	60.6 (12.5)
Sex, n (%) Male Female	 216 (42.4%) 293 (57.6%)
Country of residence, n (%) Argentina Chile Colombia Guatemala Mexico	 105 (20.6%) 43 (8.4%) 175 (34.4%) 85 (16.7%) 101 (19.8%)
Use of tobacco, n (%) Smoked in last 3 months Ex-smoker Never smoked	 30 (5.9%) 96 (18.9%) 383 (75.2%)
Alcohol user, n (%)	98 (19.3%)
BMI, kg/m^2, mean (SD)	29.0 (5.01)
Waist circumference, cm, mean (SD)	97.7 (12.83)
Use of salt at meals, n (%)	256 (50.3%)
Physical inactivity (less than 150 minutes of exercise per week), n (%)	391 (76.8%)
Daily hassles, n (%) Never Occasionally Frequently	 78 (15.3%) 275 (54.0%) 156 (30.6%)
Respond to stress with anger, n (%) Never Occasionally Frequently	 150 (29.5%) 289 (56.8%) 70 (13.8%)
Feeling tense or anxious, n (%) Never Occasionally Frequently	 89 (17.5%) 294 (57.8%) 126 (24.8%)
Family history of premature cardiovascular disease, n (%)	67 (13.2%)
Dyslipidemia, n (%)	220 (43.2%)
Total cholesterol level, mg/dl, mean (SD)	204.6 (53.34)
HDL level, mg/dl, mean (SD)	46.8 (15.83)
LDL level, mg/dl, mean (SD)	118.6 (41.17)
Triglyceride level, mg/dl, mean (SD)	172.1 (90.29)
Microalbuminuria, n (%)	21 (4.1%)
Diabetes mellitus, n (%)	69 (13.6%)
Framingham 10-year score, mean (SD)	9.9 (8.78)

improvements in BP were observed as early as four weeks into treatment (ΔSBP [99% CI]: –21.7 [–19.9, –23.4] mmHg; ΔDBP [99% CI]: –11.2 [–10.3, –12.2] mmHg) which were further enhanced over 48 weeks (ΔSBP [99% CI]: –26.2 [–24.3, –28.1] mmHg; ΔDBP [99% CI]: –13.7 [–12.6, –14.9] mmHg). In terms of BP control, target BP was achieved by 62.7% of patients (99% CI: 57.5%, 68.6%) at their last available visit after the baseline (Fig. 3). More specifically, the proportion of patients who achieved target BP increased from 45.6% (99% CI: 43.2%, 55.1%) at 4 weeks to 58.0% (99% CI: 61.4%, 73.0%) at 48 weeks.

Adherence to treatment remained high during the study, with mean (SD) rates at 4 and 48 weeks of 97.8 (9.4) and 98.5 (8.39), respectively, and cumulative adherence during the total follow-up period of 97.7 (8.29). Overall, 97.4% of patients reported taking ≥ 80% of prescribed doses and were therefore considered compliant with fixed-dose combination amlodipine/irbesartan treatment.

On multivariable analysis, country of residence (p = 0.001), treatment compliance (p = 0.035), and absence of diabetes (p < 0.001) were found to be significant predictors of target BP achievement (Table 2). More specifically, patients compliant with treatment were ≅ 7 times more likely to achieve BP control than non-compliant patients (OR = 6.86; 95% CI: 1.15, 41.09) while patients with comorbid diabetes were less likely to achieve it (OR = 0.26; 95% CI: 0.14, 0.48).

Table 3 shows an overview of the study safety analysis. There were 117 TEAEs experienced by 87 (17.1%) patients, including 7 serious TEAEs experienced by 5 (1.0%) patients. TEAEs were generally mild (75.2% of TEAEs) and judged not to be related to fixed-dose amlodipine/irbesartan combination (76.1% of TEAEs). Most of the TEAEs ended in patient recovery (77.8% of TEAEs) without any action taken (38.5% of TEAEs) or with the addition of a new concomitant medication (41.0% of TEAEs). The most frequently reported TEAEs (≥ 1% of patients) were peripheral edema (3.9%) and dizziness (1.0%) (Table 4). There were 6 (1.2%) patients who discontinued due to an AE. Of these, two died during the study, more specifically due to cardiac tamponade and myocardial infarction, neither of which was judged to be related to amlodipine/irbesartan, and the remaining four patients experienced peripheral edema. Based on the Kaplan-Meier analysis, the mean (SE) time to discontinuation due to an AE was 32.9 (0.1) weeks.

Discussion

In this real-life assessment of a fixed-dose combination of amlodipine/irbesartan in the management of uncontrolled hypertension in Latin America, statistically

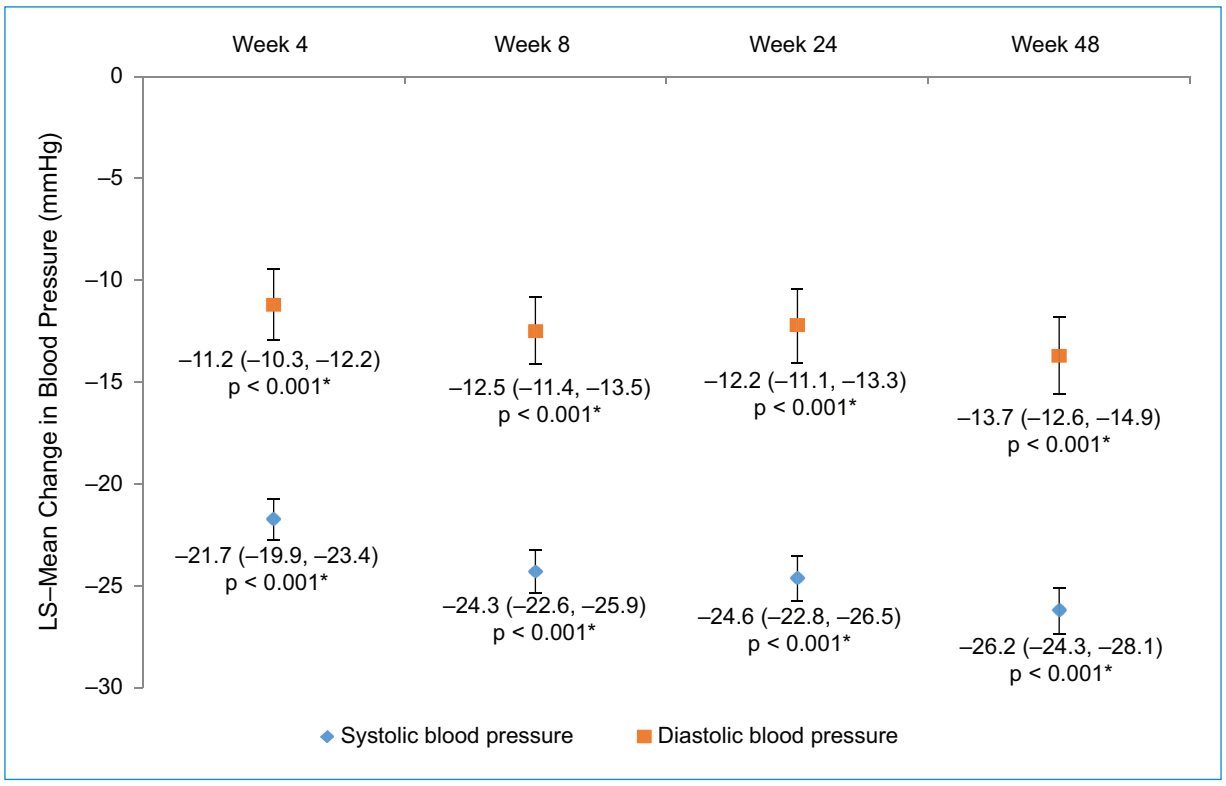

Figure 2. Repeated measure analysis for blood pressure change over time from the baseline. Error bars represent the 95% CI of the mean change in blood pressure.
*Compared to baseline values based on repeated measure analysis.

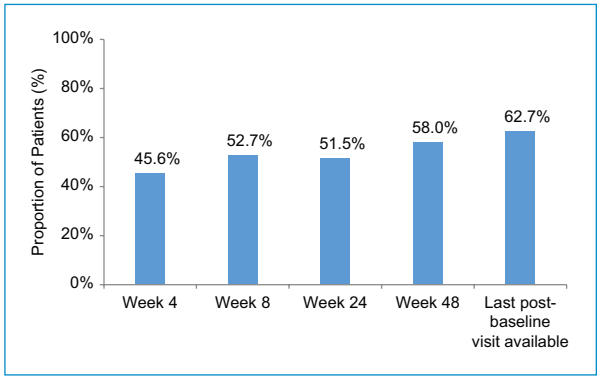

Figure 3. Blood pressure control rates over time. Target blood pressure control was defined as SBP/DBP < 140/90 mmHg for patients with no target organ damage and no associated clinical conditions; and SBP/DBP < 130/80 mmHg for patients with diabetes or renal disease. Percentages based on the total number of patients in the analysis population (n = 509).

significant and clinically important improvements in both SBP (–25.7 mmHg; p < 0.001) and DBP (–13.5 mmHg; p < 0.001) were observed over 48 weeks. The present findings are superior to those observed in two Phase III randomized clinical trials, I-ADD and I-COMBINE, which included patients inadequately controlled with amlodipine or irbesartan monotherapy. In the I-ADD and I-COMBINE studies, after 5 and 10 weeks of fixed-dose combination therapy, the mean (SD) SBP/DBP significantly decreased by –10.8 (1.0) / –3.8 (0.6) (p < 0.001) and –17.9 (1.2) / –7.7 (0.7) mmHg (p < 0.001), respectively.[24,25] Furthermore, the proportion of patients who achieved BP control over the treatment period was 62.7% (99% CI: 57.5%, 68.6%), which is close to the PAHO target of 70% established for treated patients for 2019[8]. The results observed in the current study are consistent with the results of the PARTNER study that demonstrated high therapeutic effectiveness of a fixed-dose combination of amlodipine/irbesartan combination for the management of hypertension.[26]

Over 48 weeks, 97.4% of patients reported taking ≥ 80% of prescribed doses and were therefore considered compliant with treatment. The high compliance with treatment reported in our observational study is consistent with previous studies showing that fixed-dose combinations of antihypertensives are associated with

Table 2. Multivariate logistic regression assessing predictors of target blood pressure achievement

Covariate	Odds ratio†	95% CI	p-value
Number of drinks per day*	0.909	0.749, 1.103	0.332
Country‡			**0.011**
Argentina vs. Colombia	1.567	0.518, 4.747	
Chile vs. Colombia	1.286	0.469, 3.528	
Guatemala vs. Colombia	0.227	0.090, 0.574	
Mexico vs. Colombia	0.920	0.434, 1.948	
Baseline dose (mg)‡			0.230
150/10 vs. 300/5	3.817	0.343, 42.537	
150/5 vs. 300/5	1.925	0.994, 3.727	
300/10 vs. 300/5	1.855	0.555, 6.198	
Cumulative compliance (≥ 80% vs. < 80%)‡§	6.862	1.146, 41.090	**0.035**
Regular use of salt at meals (yes vs. no)*	1.356	0.761, 2.417	0.301
Presence of diabetes mellitus (yes vs. no)*	0.257	0.138, 0.476	**< 0.001**
BMI (kg/m^2)*	0.959	0.888, 1.037	0.295
Triglyceride test (mg/dl)*	1.001	0.998, 1.005	0.524
Waist circumference (cm)*	1.000	0.968, 1.032	0.977

*Statistically important ($p < 0.15$) or clinically important (more than two-fold difference) variables identified in univariate analysis.
†Mutually adjusted.
‡Pre-selected covariates.
§Defined as the ratio of cumulative doses taken vs. prescribed using available data.
Statistical significance denoted by bold p-values.

Table 3. Overview of treatment-emergent adverse events

TEAE	Safety population (n = 509)		
	n of events	n of patients*	% of patients
Total			
TEAE	117	87	17.1
Serious TEAE	7	5	1.0
Severity			
Mild	88	69	13.6
Moderate	24	19	3.7
Severe	5	4	0.8
Relationship to amlodipine/irbesartan			
Not suspected	89	74	14.5
Suspected	28	23	4.5

*A patient may have reported more than one TEAE. TEAE: treatment emergent adverse events

Table 4. Most frequent (≥ 1% of patients) treatment-emergent adverse events by preferred term

PT of TEAE	Safety population (n = 509)		
	n of events	n of patients*	% of patients
Peripheral edema	22	20	3.9
Dizziness	5	5	1.0

*Two patients reported more than one TEAE. TEAE: treatment emergent adverse events; PT: preferred term.

improved adherence to and compliance with treatment and may explain the improved outcomes observed in our study compared to those of controlled clinical trials and PAHO[19-21,24,25].

Country of residence was identified as an independent predictor of BP control, which may be explained by differences in local patient management or by health care access[27]. Alternatively, although difficult to confirm, patient compliance may differ between countries despite what the patients may have reported. Increased treatment compliance and the absence of diabetes mellitus were also identified as significant determinants of target BP achievement, in line with the results of previous studies[28-30]. These findings highlight the need for additional initiatives for improving BP control, in addition to the use of fixed-dose combination treatments[15], such as patient programs to improve stress management and salt intake[31-36].

With respect to safety, treatment was generally well tolerated, as only a minority of patients experienced a TEAE. The most common TEAE was peripheral edema

(3.9% of patients) and the safety profile was in agreement with the product monographs[37,38].

The results should be interpreted in light of the study limitations. Although observational studies allow the assessment real-life effectiveness, this study design is prone to prescription bias. Furthermore, the assessment of treatment compliance may have been biased, as this was based on self-reported patient information. A strength of this study is the generalizability of the findings, since patients from various Latin American countries were included. Moreover, due to the observational nature of the study, the results are representative of the real-life long-term management of hypertension.

Conclusions

The findings of this study advocate the use of combination blood pressure-lowering therapy among patients with uncontrolled hypertension in Latin America. Improved effectiveness is expected, namely due to the high adherence associated with fixed-dose combination therapy. In addition, a favorable safety profile supports the administration of the fixed-dose combination amlodipine/irbesartan regimen. Future studies assessing fixed-dose combination amlodipine/irbesartan therapy may be performed in additional countries to further examine differences between countries regarding hypertensive patient profile as well as the effectiveness and safety of fixed-dose combination amlodipine/irbesartan.

In conclusion, the results of the current study support the real-life effectiveness of fixed-dose combination amlodipine/irbesartan in the long-term management of patients with hypertension. BP control rates close to the PAHO target were observed despite significant regional variability. Compliance with treatment was further shown to be independently associated with target BP achievement.

Novelty and significance

What is new?

– Among Latin American patients with uncontrolled hypertension, 62.7% achieve blood pressure control after 48 weeks of fixed-dose combination amlodipine/irbesartan treatment.
– Country of residence, treatment compliance, and diabetes presence are significant predictors of target blood pressure achievement.

What is relevant?

– Over 48 weeks of fixed-dose combination amlodipine/irbesartan therapy, 97.4% of patients were compliant with treatment.
– Fixed-dose combination therapy and a favorable safety profile are associated with high treatment effectiveness in hypertension management.

Acknowledgments

Sanofi sponsored the study with medical writing and manuscript development assistance provided by Julie Vaillancourt, M.Sc. and Angela Karellis, M.Sc., from JSS Medical Research, and Diego Funes, who was a Sanofi employee when the study was conducted and contributed to data analysis. JSS Medical Research conducted the data analysis.

Funding

This work was supported by Sanofi.

Conflicts of interest

Dr. Álvaro J Ruiz is a speaker for Amgen, Abbott, Pfizer, Sanofi, Valentech, and Lafrancol, and receives financial support for research projects from Sanofi, Amgen, Abbott, Colciencias, and Pontificia Universidad Javeriana. Dr. Marco Antonio Ramos Corrales is a speaker for Sanofi and Siegfried Ingelheim. Dr. Omar Alonzo serves as a speaker for Bayer and Sanofi. Diego Funes was a Sanofi Argentina employee when the study was conducted. Thais Cocarelli declares that he was a Consultoria Estatistica employee providing services for Sanofi Brasil when the study was conducted.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of

generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Supplementary data

Supplementary data are available at DOI: 10.24875/RCCAR.23000001. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Aortic challenges in Marfan syndrome, is the management of the aortic root enough?

Compromiso aórtico en síndrome de Marfan ¿es suficiente el tratamiento de la raíz aórtica?

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Abstract

Introduction: *the survival of patients with Marfan syndrome and aortic root involvement has increased over the past decades due to the introduction of valve-sparing aortic root replacement techniques.* **Objective:** *to identify and characterize the short- and long-term outcomes of patients with Marfan syndrome managed with aortic root replacement with aortic valve reimplantation (Tirone David procedure).* **Materials and method:** *a case series of patients diagnosed with Marfan syndrome who underwent the surgical procedure between 2002 and 2020. Kaplan-Meier curves were created to evaluate aortic reintervention-free time and survival.* **Results:** *18 patients were included, with an average age of 29 years; disease progression was identified in 35.3%, determined by reintervention in five patients, three patients had type B aortic dissection, two had severe aortic insufficiency, and five had chronic thoracic or abdominal aneurysms. There were three deaths, not directly related to disease progression.* **Conclusions:** *in patients with Marfan syndrome and aortic root disease, aortic root replacement with aortic valve reimplantation is the ideal technique due to its results in avoiding the need for reintervention and improving survival and quality of life. However, surgery does not resolve distal aortic involvement, which is the main factor in disease progression.*

Keywords: *Marfan syndrome. Aortic aneurysm. Dissecting aneurysm. Aortic valve regurgitation. Thoracic surgery.*

Resumen

Introducción: *la sobrevida de pacientes con síndrome de Marfan y compromiso de la raíz aórtica ha aumentado debido a la introducción de técnicas de reemplazo de raíz aórtica con preservación valvular.* **Objetivo:** *identificar y caracterizar desenlaces a corto y largo plazo de pacientes con síndrome de Marfan intervenidos con la técnica de reemplazo de la raíz aórtica con reimplante de la válvula aórtica (procedimiento de Tirone David).* **Materiales y método:** *serie de casos de pacientes con síndrome de Marfan sometidos al procedimiento quirúrgico de Tirone David entre 2002 y 2020. Se generaron curvas de Kaplan-Meier para evaluar el tiempo libre de reintervención aórtica y la sobrevida.* **Resultados:** *se incluyeron 18 pacientes, con edad promedio de 29 años. Se identificó progresión de la enfermedad en el 35.3%, determinada por reintervención en 5 pacientes, disección aórtica tipo B en 3 pacientes, insuficiencia aórtica grave en 2 pacientes y aneurismas crónicos torácicos o abdominales en 5 pacientes. Se identificaron 3 muertes no relacionadas directamente con la progresión de la enfermedad.*

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Date of reception: 31-10-2022
Date of acceptance: 23-05-2023
DOI: 10.24875/RCCARE.M23000071

Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):330-336
www.rccardiologia.com

Conclusiones: *en pacientes con síndrome de Marfan y patología de raíz aórtica, el procedimiento de reemplazo de la raíz aórtica con reimplante de la válvula aórtica es la técnica ideal por sus resultados en libertad de reintervención, sobrevida y calidad de vida. Sin embargo, la cirugía no resuelve el compromiso aórtico distal, el cual es el principal factor en la progresión de la enfermedad.*

Palabras clave: *Síndrome de Marfan. Aneurisma de la aorta. Aneurisma disecante. Insuficiencia de la válvula aórtica. Cirugía torácica.*

Introduction

Marfan syndrome is an autosomal dominant genetic connective tissue disorder, with a clinical presentation ranging from isolated characteristics to severe and progressive disease with cardiovascular, ocular, musculoskeletal and pulmonary effects[1,2]. Aortic disease is characterized by aneurysmal dilation (Fig. 1), aortic regurgitation and dissection, with this being the main cause of morbidity and mortality. The survival of patients with Marfan syndrome has improved significantly over the years, mainly due to the introduction of heart surgery[3].

Over the last 20 years, the technique described by Tirone David has become one of the most important aortic valve-sparing procedures due to its high rate of success, with a 15-year reintervention rate of only 5% and good long-term results. It is the technique of choice for treating young patients with aortic root aneurysms, one-third of whom have Marfan syndrome[4].

There are no studies available in Colombia focusing on patients with Marfan syndrome who undergo aortic root replacement with aortic valve reimplantation. This paper seeks to identify and characterize the short and long-term outcomes of patients diagnosed with Marfan syndrome who underwent surgery with this technique from 2002 to 2020 in our institution.

Surgical technique

Valve-sparing aortic surgery is a procedure developed to treat aortic root aneurysms, in which the aneurysmal sinuses are removed, and the native aortic valve is reimplanted within a tubular Dacron graft[5].There are different procedures designed to preserve the native aortic valve; the two most frequently used are aortic valve reimplantation, described by Tirone David, and aortic root remodeling, described by Sir Magdi Yacoub. The procedure described by Tirone David achieves greater stabilization of the root components, and therefore was the technique chosen for the patients included in the study[6-8].

Aortic valve reimplantation begins with preparing the coronary buttons and then resecting the aneurysmal sinuses, except for a few millimeters of arterial wall which remain adhered to the aortoventricular junction[5]. Subsequently, the root is replaced with a tubular Dacron graft over which the aortic valve is reimplanted. The cusps are examined to ensure proper coaptation, above the nadir of the aortic ring. Leaflet plication is also performed, if necessary. Finally, the coronary ostia are reimplanted, and the reconstructed aortic root is sutured to the ascending aorta[6] (Fig. 2).

Materials and method

This is a case series of 18 patients diagnosed with Marfan syndrome who underwent aortic root replacement with aortic valve reimplantation between January 2002 and December 2020. Patients over the age of 18, with a diagnosis of Marfan syndrome based on the Ghent criteria or genetic studies were included. Moreover, patients with a history of prior aortic root surgery and those who underwent aortic root surgery with another technique were excluded.

This study was approved by the institutional ethics committee at La Cardio, and informed consent was obtained in 100% of the telephone follow ups.

A descriptive analysis of the data was performed; continuous variables are expressed as averages and standard deviation or medians and interquartile range. Overall survival, defined as the time elapsed between the surgical procedure and the date of death from any cause, was analyzed with the Kaplan-Meier method, as was the reintervention-free time, defined as the time elapsed between the surgical procedure and the date of a new intervention on any part of the aorta. Disease progression was determined as an accelerated increase in the aortic diameter (> 5 mm per year or 5%), a descending thoracic aorta diameter > 55 mm, and symptoms of functional class deterioration. All analyses were processed using STATA® version 15.0 (StataCorp LP, College Station, TX, USA).

Results

Eighteen patients were included, with an average age of 29 years; 72% were men and 94% had an NYHA

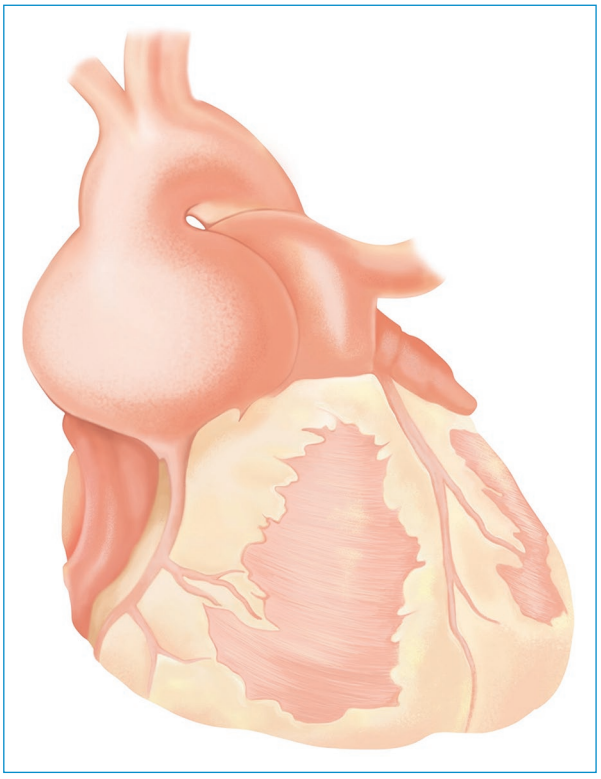

Figure 1. Aneurysmal dilation of the aortic root.

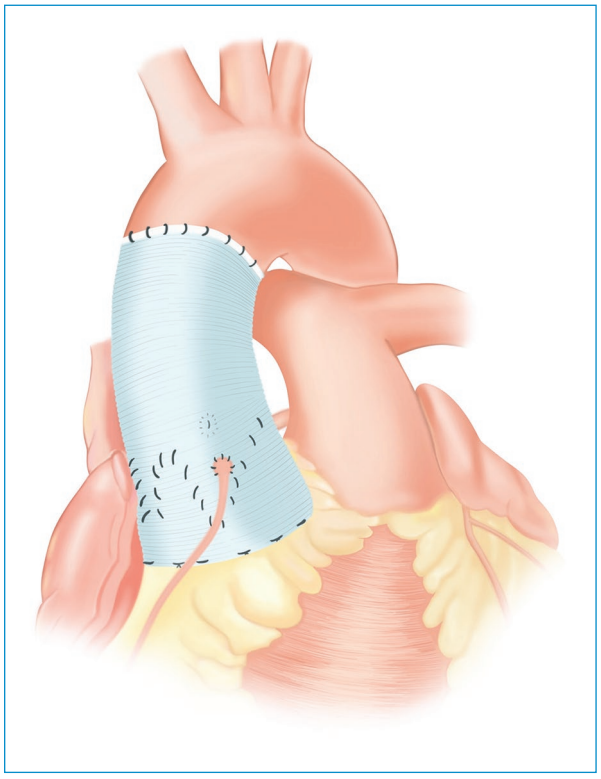

Figure 2. Aortic root replacement with aortic valve reimplantation.

functional class ≥ 2. The surgical indication was dissection in five cases (27.8%) and 60% of these were Stanford type A dissections. Altogether, 55.5% had aortic regurgitation ≥ 2, and 22% were bicuspid valves. The median aneurysmal diameter was 53 mm, the repair extended to the aortic arch in 33%, and there were no surgical site infections or cases of surgical mortality. Table 1 describes the demographic, clinical, echocardiographic and surgical characteristics of the patients.

Clinical, imaging or telephone follow up was conducted with 94.4% of the patients over a mean of 6.1 years (SD 4.8/interquartile range between 0.9 and 7.3). Clinical and imaging follow up was accomplished in 93% (14 patients), while clinical follow up alone was done in 7% (4 patients). Patients with a history of aortic dissection or pre-existing aneurysms had more frequent follow up. This study's follow up closed on December 31, 2020.

Reintervention

Four patients required reintervention due to bleeding in the 30 days after surgery, representing 22.2% of the sample. Of the 18 patients, 29.4% underwent reintervention. Two patients required aortic valve reintervention, while the other three required intervention in the descending or thoracoabdominal aorta. None of the patients who were reintervened died during follow up. The time free from the first aortic reintervention was 46.4 months, with a percentile ranging from 15.2 to 94.2.

Transfusions

A total of seven patients required blood product transfusions (packed red blood cells, fresh frozen plasma, platelets), representing 38.9%.

Hospital stay

The length of ICU stay after surgery ranged from one to three days, and the total hospital stay was six to 14 days.

Aortic dissection

Prior to the aortic root surgery, three patients had Stanford type A and four patients had Stanford type B dissections. During follow up, three patients developed

Table 1. Demographic, clinical, echocardiographic and surgical characteristics of the patients

Variable	n = 18
Demographic and clinical	
Male	13 (72)
Age in years	29.4 ± 10.5
Arterial hypertension	5 (27.8)
Dyslipidemia	4 (22.2)
Cerebrovascular event	1 (5.6)
Peripheral vascular disease	2 (11.1)
NYHA	
I	1 (5.6)
II	16 (88.9)
III	1 (5.6)
Family history	
Marfan syndrome	7 (38.9)
Aortic dissection	4 (22.2)
Echocardiographic variables	
Aortic regurgitation	
Trivial	1 (5.6)
Mild	6 (33.3)
Moderate	2 (11.1)
Severe	8 (44.4)
LVEF	55 ± 8.3
Aneurysmal diameter	53 (50-56)
Aortic valve morphology	
Bicuspid	4 (22.2)
Tricuspid	14 (77.8)
Mitral regurgitation	
Trivial	1 (5.6)
Mild	2 (11.1)
Moderate	3 (16.7)
Tricuspid regurgitation	
Trivial	1 (5.6)
Mild	3 (16.7)
Atrial septal defect	1 (5.6)
Surgical indication	
Aortic aneurysm	13 (72.2)
Aortic dissection	5 (27.8)
Stanford classification	
A	3 (60)
B	2 (40)
Intraoperative variables	
Graft diameter	
28	4 (22.2)
30	7 (38.9)
32	5 (27.8)
34	2 (11.1)
Aortic valve plication	9 (50)
Gore-Tex reinforcement	6 (33.3)
Concomitant procedures	
Aortic arch replacement	6 (33.3)
Congenital defect repair	1 (5.6)
Mitral valve repair	2 (11.1)
Coronary artery bypass	1 (5.6)
Extracorporeal circulation time (min)	184 (169-271)
Aortic clamping time (min)	159 (148-191)
Postoperative events	
Reintervention due to bleeding	4 (22.2)
Blood product transfusion	7 (38.9)
Hospital stay	
ICU	1 (1-3)
Total hospitalization	4.5 (6-14)

The data are presented as numbers and percentages (%), medians and 25th percentile – 75th percentile, or as averages ± standard deviation. LVEF: left ventricular ejection fraction. NYHA: New York Heart Association; ICU: Intensive Care Unit.

Stanford type B aortic dissection within a follow up period of 18 years, representing 17.7% of the cases. In addition, 33.3% had chronic thoracic or abdominal aneurysms.

Aortic regurgitation

Five patients were found to have developed aortic regurgitation, three cases of which were trivial and two were severe and required reintervention.

Mortality

There were three late deaths, representing 16.6% of the sample. One patient died from infective endocarditis of the aortic valve in the year after surgery, following a dental procedure in which he only received medical management. One patient died from an acute myocardial infarction and another from a massive hemothorax. The Kaplan-Meier survival analysis estimates an 80.9% survival probability (Fig. 3).

During follow up, one patient with a history of arterial hypertension and an infrarenal aneurysm had two cerebrovascular events with no neurological sequelae.

Discussion

The survival of patients with Marfan syndrome has improved significantly over the years due to the introduction of aortic root surgery. The introduction of the Bentall procedure increased life expectancy by preventing proximal aortic dissections, and this was the treatment of choice until aortic valve-sparing techniques were developed[4]. There are different procedures designed to preserve the native aortic valve; however, the two most

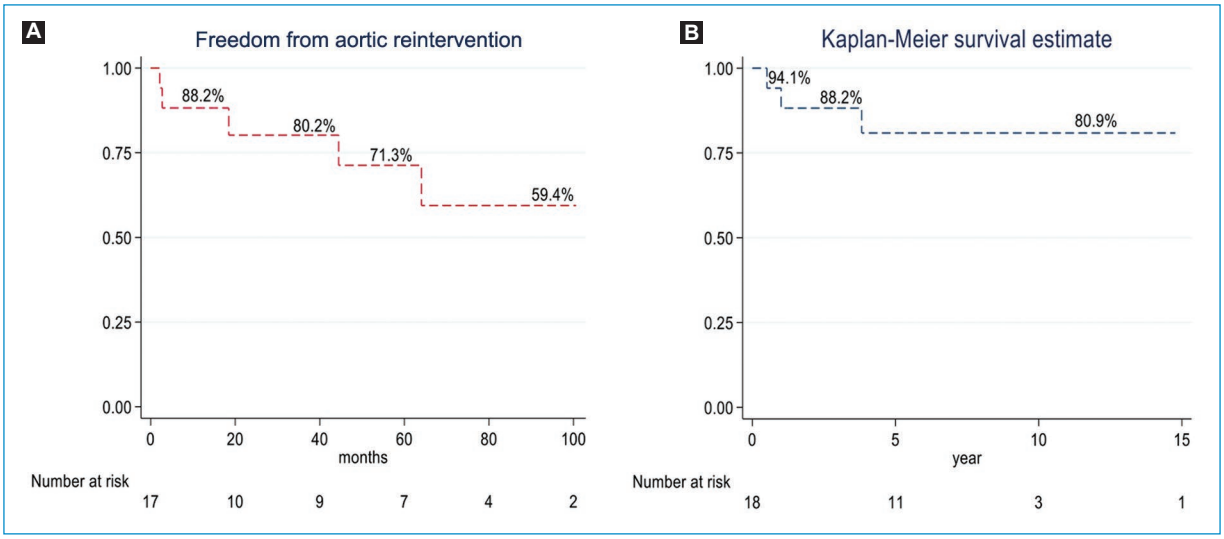

Figure 3. Freedom from re-operation and survival of patients with Marfan syndrome undergoing valve-sparing surgery with the Tirone David technique. **A:** freedom from surgery at 12 months 88.2% (95% CI = 60-97); **B:** 81% 10-year survival (95% CI = 51-93).

frequently used are aortic valve reimplantation, described by Tirone David, and aortic root remodeling, described by Sir Magdi Yacoub.

In these patients, aortic valve reimplantation has proven to have better outcomes than remodeling, because the aortoventricular junction continues to dilate after remodeling and, over time, they may develop aortic regurgitation. Also, with Tirone David's procedure, patients do not require long-term anticoagulation, and when surgery is performed at an early age, the cusps preserve their normal morphology and aortic regurgitation is due to annuloectasia or dilation of the sinuses of Valsalva[8-10]. In patients with Marfan syndrome, aortic root aneurysm surgery is indicated when the cross-sectional diameter of the root reaches 50 or 45 mm, when there is a family history of aortic dissection, or when pregnancy is planned[4].

This study seeks to identify the signs of disease progression, considering the characteristics of the Colombian population, in order to conduct a focused clinical follow up aimed at preventing long-term complications. Disease progression will be defined as the need for reintervention, type B aortic dissection, moderate or severe aortic regurgitation and the presence of aneurysms on follow up, as outlined in table 2. In addition, it is important to know the rate of perioperative complications such as revision due to postoperative bleeding, cardiac tamponade or cardiac arrest, transfusions, arrhythmias and postoperative deaths.

Table 2. Disease progression

Clinical follow up	n = 17
Disease progression	6 (35.3)
First reintervention	5 (29.4)
Second reintervention	2 (40)
Site of the first aortic reintervention	
Aortic valve ascending aorta	2 (11.8)
Descending aorta	1 (5.9)
Thoracoabdominal aorta	2 (11.8)
Abdominal aorta	2 (11.8)
Stanford B dissection	3 (17.7)
Aneurysm	6 (35.3)
Aortic regurgitation	
Trivial	3 (17.7)
Vere	2 (11.8)
Endocarditis	1 (5.9)

The data are presented as numbers and percentages (%), medians and 25th percentile -75th percentile, or as averages ± standard deviation.

The scientific literature reports that the 15-year rate of aortic root reintervention reaches 5%, the 10-year aortic dissection rate is 16 to 20% with no elevation at 15 years, the 15-year aortic regurgitation rate is 8 to 11%, and the estimated 15-year survival is 93%[4,11,12]. Likewise, the most significant short-term complications

have been reported to be remissions due to postoperative bleeding, cardiac tamponade and cardiac arrest. Blood product transfusion is done in approximately 43% and cardiac arrhythmias occur in 11% of the cases[4].

In our series of 18 patients with Marfan syndrome undergoing aortic root replacement with aortic valve reimplantation, disease progression was found in six, representing 35.3% of the sample.

Progression is seen in that five patients required reintervention within the first six years after surgery, accounting for 29.4% of the sample. Throughout the entire follow up, 88% were free from a first aortic reintervention at 16 months, which decreased to 59.4% at 10 years. Of the reintervened patients, three had type B aortic dissection, two had severe aortic regurgitation, and all five had chronic thoracic or abdominal aneurysms. In addition to the intervened patients, one patient had an abdominal aneurysm that has not required surgical intervention to date. These results show that the main factors affecting disease progression are chronic thoracic or abdominal aneurysms and Stanford type B dissections. An observational study by Hartog et al. in 600 patients with Marfan syndrome evaluated the cause of distal aortic dissections, which occurred in 54 patients. The authors speculated that ascending aorta replacement with a Dacron graft may cause high pulsatile pressures in the aortic arch and the proximal descending thoracic aorta, increasing the risk of distal complications[13].

No intraoperative or short-term mortality was found in the study. Three deaths were reported throughout the entire follow up, representing 16.6% of the sample. None of these were related to disease progression. One of the causes of death was secondary to a surgical complication and the other two occurred due to endocarditis and acute myocardial infarction. These figures establish the efficacy and durability of the surgical procedure.

It may be specified that follow up decreased over the years; during the first year, 94.1% of the patients received follow up; however, this decreased to 29.4% after eight years of follow up. Fifty percent of the patients had 14 to 94 months of follow up.

Surgical procedures that preserve the aortic valve have significantly reduced morbidity and mortality in patients with Marfan syndrome. However, in light of the percentage of patients affected by disease progression, it is important to emphasize that aortic root surgery does not resolve aortic problems long-term, especially distal aortic complications. Thus, a multidisciplinary team is needed focused on strict patient follow up, to promptly identify disease progression and carry out the necessary interventions. The current guidelines recommend imaging follow up of the aorta one, three, six and twelve months after dissection, and then annually, using computed tomography or magnetic resonance imaging[14,15]. Therefore, the data from this study suggest that patients could benefit from clinical follow up every six months by a multidisciplinary group implementing protocols aimed at early detection of distal aortic complications.

Conclusions

In patients with Marfan syndrome, aortic valve reimplantation should be the technique of choice, as it does not require long-term anticoagulation and has favorable, long-lasting outcomes. Considering the natural course of the disease, monitoring its progression should be the main pillar of long-term follow up, to improve patients' quality of life, morbidity and mortality.

Study limitations

One of the study limitations is that it was carried out at a single center, providing a small sample. In addition, as a descriptive study, it is an initial approach to patients' surgical outcomes, with no comparative studies. Furthermore, the patients' clinical follow up was not homogenous due to difficulties in the national healthcare system.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This study received funding from the Department of Cardiovascular Surgery at La Cardio.

Ethical disclosures

Human and animal protection. The authors declare that no experiments were conducted in humans or animals for this study.

Data confidentiality. The authors declare that they have followed their workplace protocols for publishing patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Recommendations for treatment and follow-up in patients with transthyretin-mediated hereditary amyloidosis

Recomendaciones de tratamiento y seguimiento en pacientes con amiloidosis hereditaria mediada por transtirretina

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Abstract

Introduction: *Transthyretin-mediated hereditary amyloidosis is an autosomal dominant disease with progressive systemic involvement that affects the function of multiple organs and is associated with high morbidity and mortality. Patients present neurological, cardiac, autonomic, ophthalmological and renal involvement, among others, related to the patient's genotype. These alterations affect quality of life and are directly related to early mortality. Peripheral neuropathy is an early marker of the disease. Its identification allows early treatment with disease-modifying therapies aimed at stabilizing disease progression, which, along with adequate follow-up, has a positive impact on patients' quality of life and prolongs life expectancy.* **Objective:** *To structure a series of recommendations appropriate to the local setting on treatment and follow-up in patients with hereditary transthyretin-mediated amyloidosis.* **Materials and method:** *Delphi methodology was used, and a cut-off point of 75% favorability was established.* **Results and conclusions:** *A series of recommendations were presented based on the available evidence and international recommendations, applicable to the local setting, on diagnostic methods that facilitate early detection of the affected patient and the parameters for initiation of treatment and follow-up that improve the quality of life, decrease complications, and increase the life expectancy of these patients.*

Keywords: *Hereditary amyloidosis. Transthyretin (TTR). Hypertrophic cardiomyopathy. Cardiology.*

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Date of reception: 22-02-2023
Date of acceptance: 16-06-2023
DOI: 10.24875/RCCARE.M23000062

Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):337-344
www.rccardiologia.com

Resumen

Introducción: *La amiloidosis hereditaria mediada por transtirretina es una enfermedad autosómica dominante, con compromiso sistémico y progresivo, que altera la función de múltiples órganos, y se asocia con una alta morbilidad y mortalidad. Se presenta compromiso neurológico, cardiaco, autonómico, oftalmológico y nefrológico, entre otros, que se relacionan con el genotipo del paciente. Estas alteraciones afectan la calidad de vida y tienen una relación directa con la mortalidad temprana en estos pacientes. La neuropatía periférica es un marcador temprano de la enfermedad. Su identificación permite un tratamiento temprano con terapias modificadoras de la enfermedad, en busca de la estabilización de la progresión de la enfermedad, lo cual, acompañado de un seguimiento adecuado, tiene un impacto positivo en la calidad de vida de los pacientes y una prolongación de la expectativa de vida.* **Objetivo:** *Estructurar una serie de recomendaciones adecuadas al entorno local sobre el tratamiento y seguimiento en pacientes con amiloidosis hereditaria mediada por transtirretina.* **Materiales y método:** *Se utilizó la metodología Delphi y se estableció como punto de corte un 75% de favorabilidad.* **Resultados y conclusiones:** *Se plantearon una serie de recomendaciones basadas en la evidencia disponible y las recomendaciones internacionales, aplicables al entorno local, sobre métodos diagnósticos que faciliten la detección temprana del paciente afectado y los parámetros de inicio del tratamiento y el seguimiento que mejoren la calidad de vida, disminuyan las complicaciones y aumenten la expectativa de vida de estos pacientes.*

Palabras clave: *Amiloidosis hereditaria. Transtirretina (TTR). Miocardiopatía hipertrófica. Cardiología.*

Introduction

Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, progressively debilitating and fatal disease caused by a pathogenic transthyretin (TTR) mutation[1-4]. It has a global prevalence of 5 to 10,000 cases worldwide, with endemic areas[5]. Approximately 150 TTR mutations or pathogenic deletions[6] have been reported to date, with genotype-phenotype variability and incomplete penetrance[7,8].

Genotypic characterization of the patients allows treatment and follow-up to be individualized, given its high phenotypic variability[9,10] and the association of certain mutations with specific phenotypes[11-13]. The most common mutation in the world is *p.Val50Met*, which occurs with endemic regional variations and is characterized by polyneuropathy with autonomic and ocular involvement[14,15]. On the other hand, patients with *p.Leu78His, p.Leu78Arg, p.Lys90Asn, p.Ile104Ser, p.Ile127Val* and *p.Tyr134His* variants have carpal tunnel syndrome as their first symptom[14], while those with *p.Asp38Asn, p.Val40Ile, p.Pro44Ser, p.Ala65Thr, p.Ala65Ser, p.His76Arg, p.Gly77Arg, p.Ile88Leu, p.Ala101Thr, p.Ala101Val, p.His108Arg, p.Glu112Lys, p.Arg123Ser, p.Leu131Met* and *p.Val142Ile* genotypes develop cardiomyopathy without peripheral neuropathy[14]. There is another subgroup of hATTR patients who present the following genotypic variations: *p.Leu32Pro, p.Asp38Gly, p.Ala45Thr, p.Val50Gly, p.Ala56Pro, p.Gly73Glu, p.Gly73Ala, p.Phe84Ser, p.Tyr89His* or *p.Tyr134Cys*[14], and these patients accumulate amyloid in the leptomeningeal membranes and blood vessels of the subarachnoid space.

Transthyretin is mainly synthesized in the liver, with less synthesis in the choroid plexuses and retinal pigment epithelium[8,16-18]. It circulates as a tetramer and is involved in vitamin A-retinol and thyroxin transport[19,20]. Transthyretin mutations result in an unstable protein which dissociates into monomers, misfolds and aggregates in amyloid fibrils[21,22] that accumulate in the extracellular space of organs and tissues[1,3]. Amyloid deposits cause organ damage with manifestations like bilateral sensory and motor polyneuropathy, autonomic dysfunction, infiltrative cardiomyopathy and cardiac dysautonomia[1,3,8,23-33].

The age of symptom onset varies; once instated, the disease progresses relatively rapidly in its neuropathic presentation[9], and, therefore, three to five years after symptoms begin, patients begin to need assistance for walking, and they can lose that function within five to ten years if not treated[9]. Death occurs approximately 4.7 years after diagnosis, and patients with heart disease have a life expectancy of 3.4 years[9].

Despite the genotypic-phenotypic variability reported in these patients, heart disease and polyneuropathy occur in most[12,34-36]. From a neurological perspective, patients with hATTR have mixed axonal polyneuropathy with sensory and motor symptoms[9], with peripheral neuropathy being an early marker of the disease. In some cases and genotypes, the neuropathy may be compressive, in which case carpal tunnel syndrome is the most common manifestation[9]. The symptoms derived from neurological complications include pain, paresthesia, difficulty walking, balance disorders and difficulty with fine motor movement in the hands. Some negative signs are related to loss of the sensory function, such as hypoalgesia and/or anesthesia to pain in the lower extremities, areflexia, apallesthesia in the feet and muscular weakness, such as bilateral foot drop[9]. From a cardiac perspective, the

patients have sympathetic and parasympathetic involvement with secondary cardiac dysautonomia[8,9], which manifests with orthostatic hypotension and heart rate variability (standard deviation of the R-R interval variability on a Holter monitor or electrocardiogram)[9,37,38]. Cardiomyopathy usually occurs in those over 50, with symptoms suggesting congestive heart failure, like dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, jugular distention, lower extremity edema, fatigue, abdominal distention, exertional tachycardia, syncope, low exercise tolerance or weight gain[9,39].

In addition, patients may develop intravitreal amyloid deposits with secondary eye problems, kidney dysfunction, weight loss, nausea and fatigue. All of these abnormalities secondary to amyloid deposits naturally have a negative impact on the quality of life[9].

Disease modifying therapies include TTR tetramer stabilizers, gene silencing therapies and antisense therapies[8,9,35,36,40-42]. There is evidence that these therapies halt disease progression and, in some cases, improve its clinical signs and symptoms[8,9]; therefore, early initiation of these therapies is vital, given the rapid progression associated with the disease.

Index case family testing is important, as it can identify presymptomatic patients, and thus provide them with adequate management and follow-up[43]. In addition, a multidisciplinary approach to these patients is essential for correct data interpretation, genetic counseling and specific disease management[43].

Likewise, patients should be followed after diagnosis to determine the course of the disease and response to treatment[8].

In summary, in light of the available evidence, multidisciplinary management of patients with amyloidosis, preceded by a prompt diagnosis with early treatment and adequate follow-up, are vitally important aspects.

This article proposes a series of locally adapted recommendations regarding diagnostic methods, parameters for beginning treatment, and follow-up in different areas of amyloidosis patient treatment, such as genetics, neurology, cardiology, ophthalmology and nephrology. Their implementation is expected to have a positive effect on the quality of life of these patients and reduce their morbidity and mortality.

Materials and method

Panel creation

A multidisciplinary panel of experts was selected, composed of 41 specialists in different fields of medicine (cardiology, pulmonology, physiatry, genetics, nephrology, ophthalmology, neurology and imaging). The experts were selected based on their knowledge and experience in managing hereditary transthyretin-mediated amyloidosis.

Method description

Once the available evidence was reviewed by the experts in the previously mentioned specialties, they gathered to develop their proposed recommendations in each of these areas. All participants in the Position Statement meeting received the available bibliography on the disease and its treatment, including clinical practice guidelines.

An on-site meeting was held during which one or two experts from each area presented a summary of the concepts derived from the review of the literature on the disease, its diagnosis, treatment and follow-up. Then they presented the recommendations drafted for each area, and these were voted on. The Delphi method was used, with 75% favorability established as the cut-off. If this favorability threshold was not reached, the arguments in favor and against were presented by the panel of experts, the recommendation was restructured according to the discussion, and it was presented for a second vote. Once the recommendations were accepted, minor adjustments were made in their wording and content, based on the participants' opinions.

Recommendations

1. The role of genetics in hATTR

Recommendation 1

The following studies are recommended for diagnosing hATTR[3,34]:

- Complete sequencing of the TTR gene to diagnose the index case
- Point mutation in the pedigree study

Recommendation 2

Molecular studies[8,44] are recommended for:

- Symptomatic patients
- Immediate relatives of the index case
  - Over the age of 18
  - Patients who state that they wish to have the test

  This point should be individualized for each case.

Recommendation 3

All patients should be referred to genetics for a family study and genetic counseling[44].

2. Neurological follow-up in symptomatic patients

Recommendation 4

Treatment for hATTR[45,46] should be started when there is evidence of:
- Objective clinical and/or neurophysiological symptoms of polyneuropathy and/or pathological evidence of amyloid deposits
- Patients in stage I or II of the Polyneuropathy Disability (PND) scale[47]

Recommendation 5

The following scales and clinical criteria are recommended to be included in patient follow-up[1,48-52]:
- The neuropathy scale in diabetic polyneuropathy (PND) to stage the disease. It should be applied every three to six months.
- These follow up scales are recommended: a) Neuropathy Impairment Score (NIS), b) Neuropathy Impairment Score in the Lower Limbs (NIS-LL), c) Neuropathy Impairment Score plus seven components (NIS+7) and d) the Norfolk Quality of Life (Norfolk-QOL) questionnaire, as follows:
  - Asymptomatic patients: every year
  - Symptomatic patients: every three to six months

Follow-up should be done by neurology and/or physiatry and/or a specialist with appropriate training in the disease.

Recommendation 6

Neurophysiological follow-up is recommended[8]:
- With the following frequency:
  - Every 12 months for asymptomatic carriers
  - Every six to twelve months for symptomatic patients
- Including bilateral nerve conduction tests:
  - Motor (median, ulnar, peroneal and tibial)
  - Sensory (median, ulnar, sural and superficial peroneal)
  - F waves of the lower extremities
  - Sympathetic skin response (SSR) in the foot and hand.

Recommendation 7

Disease progression should be considered in light of any of the following findings[48,49]:
- Worsening by at least one stage, measured qualitatively
- A more than 10-point increase on the NIS scale
- An increased PND score
- A decrease of more than 50% from the baseline amplitude of the composite motor and sensory score
- Absent sympathetic skin response in the foot and hand score, when it was previously present

3. Complementary tests in patients with hATTR and carpal tunnel syndrome

Recommendation 8

In patients with hATTR and mild carpal tunnel syndrome, the following is recommended:
- Begin conservative treatment immediately, keeping in mind the clinical and paraclinical findings[23,24,53]
- Consider surgical management in severe or moderate cases that do not respond to conservative management

Recommendation 9

In patients with hereditary transthyretin-mediated amyloidosis with carpal tunnel syndrome, the following are recommended:
- Electromyography and nerve conduction tests of the upper extremities[23,24,53] at baseline and every 6 to 12 months
- Clinical follow-up every 6 to 12 months, using questionnaires such as the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and Boston Questionnaire
- Neurophysiological follow-up every 6 to 12 months with electromyography and nerve conduction tests of the upper extremities

4. Complementary autonomic nervous system assessments in patients with hATTR

Recommendation 10

We recommend:
- Clinical follow-up of autonomic symptoms using the Composite Autonomic Symptom Score-31 (COMPASS-31) at diagnosis and every six months[54,55]
- Paraclinical follow up with a tilt-table test and RR interval every 12 months, according to clinical judgement[9]

Recommendation 11

Clinical follow-up of neuropathic symptoms is recommended with the Norfolk-QOL scale at diagnosis and every six months[9,56,57]

Complementary tests

Recommendation 12

– Quantitative sensory testing (QST) is recommended (when the technology is available) at the time of diagnosis[27,58-60]
– To evaluate progression (the onset of new sensory impairment), QST is recommended every 12 months (when the technology is available) for patients with hATTR with no previously documented sensory impairment[27,58,60]

5. Cardiology assessment in patients with hATTR

Recommendation 13

The following clinical, paraclinical and imaging tests are recommended for cardiological assessment of patients with transthyretin-mediated amyloidosis to determine the disease's stage and prognosis[13] (every 6 to 12 months, depending on the tool used[61]):

– Clinical parameters: hospitalizations for heart failure, functional class (based on the New York Heart Association [NYHA] classification), six-minute walk test, functional tests, and quality of life (EQ-5D)
– Paraclinical tests: N-terminal pro-brain natriuretic peptide (NT-proBNP), electrocardiogram, troponin, NAC scale
– Imaging: transthoracic echocardiogram with global longitudinal strain

Recommendation 14

Disease progression should be determined when any of the following parameters are present[62,63]:

– From a clinical or functional perspective:
  • The need to be hospitalized for heart failure
  • Functional class deterioration
  • Decreased scores on quality of life questionnaires (KCCQ/EQ-5D)
  • A 30 to 40-meter reduction in the six-minute walk
– From a biomarker perspective:
  • A 30% increase in natriuretic peptide, starting from the NT-proBNP cut-off point of 300 pg/ml
  • A 30% increase in troponin I
  • An advanced NAC stage
– From a cardiovascular imaging perspective[62,64-66]:
  • A 2 mm increase in wall thickness
  • Increased degree of diastolic dysfunction
  • A change in some of the echocardiographic parameters (> 5% reduction in LVEF, > 5% reduction in stroke volume, > 1% increase in global longitudinal strain)
  • EKG: onset of a new conduction disorder

6. Nephrological follow-up in patients with hATTR

Recommendation 15

The following paraclinical tests should be ordered for the nephrological assessment of patients with or without transplant[67-70]:

– Baseline tests and at the beginning of treatment and for follow up (every 6 to 12 months):
  • Creatinine
  • Urinalysis
  • Albumin/creatinine ratio (if > 300 mg/g, order 24-hour protein)

Recommendation 16

A nephrology assessment is recommended in patients with amyloidosis[9]:

– Before beginning treatment, to establish their baseline kidney status
– The frequency of the assessment should be based on the grade of renal involvement:
  • Grades 1 and 2: every 12 months
  • Grades 3A and 3B: every 3 to 6 months, depending on the stability
  • Grades 4 and 5: these patients have a high degree of progression to end stage renal disease, and therefore must adhere to the high-cost care coverage policies in Colombia, in the nephroprotection program, for follow-up and the paraclinical test panel stipulated by nephrology at a national level

Recommendation 17

A kidney biopsy is recommended if the patient is a candidate for liver transplant, to determine if he/she requires a kidney transplant[67,71].

7. Ophthalmological treatment of patients with hATTR

Recommendation 18

An ophthalmological exam is recommended at the following times[70,71]:

– When making the genetic diagnosis
– A biannual exam in asymptomatic carriers

– An annual exam in symptomatic patients

In addition, quarterly follow-up of retinal microangiopathy is recommended, along with biannual follow up of:

– Amyloid deposits in the iris
– Irregular pupils
– Chronic glaucoma
– Treated or monitored vitreous opacities

Recommendation 19

Regarding patients' ophthalmological management, this should be divided according to symptomatology:

– Asymptomatic patients
  • Biannual follow-up
  • Look for symptoms
– Symptomatic patients
  • Monitor glaucoma
  • Use lubricants for dry eyes
  • Pay close attention to the onset of opacities and retinal changes
  • Use tacrolimus/cyclosporine

Conclusions

Hereditary transthyretin-mediated amyloidosis is a rare, progressive and fatal disease that requires early diagnosis, appropriate treatment and close follow-up to improve patients' quality of life and reduce their morbidity and mortality. It is important to emphasize that patients with hATTR may have neurological involvement from the initial stages, although not always with the typical symptoms; therefore, it must be diagnosed promptly and treated appropriately.

The above recommendations are intended to be a guide for clinicians in diagnosing and following patients with hATTR, and they help monitor the disease and determine when to begin treatment and the follow-up needed by the different specialties to provide patients with comprehensive management.

Glossary

– NAC Scale (United Kingdom National Amyloidosis Centre Staging System): An easily applied scale that requires knowing the level of NT-proBNP and glomerular filtration rate (GFR), with which patients are classified in three stages, and helps determine the mortality prognosis. Patients in NAC stage I (NT-proBNP less than 3,000 ng/L and GFR greater than 45 ml/min) have an average survival of 69.2 months; patients in NAC stage III (NT-proBNP greater than 3,000 ng/L and GFR less than 45 ml/min) have an average survival of 24.1 months, and patients in stage II (those who do not meet the criteria for stages I and III) have a survival of 46.7 months[72].
– NT-proBNP: N-terminal pro-brain natriuretic peptide.
– PND: polyneuropathy disability.

Funding

PTC Therapeutics covered the cost of medical writing services for this article.

Conflicts of interest

Dr. Jennifer Garay has been a scientific advisor for PTC Therapeutics. Dr. Juan D. López-Ponce de León has been a scientific advisor for PTC Therapeutics, Pfizer and Sanofi. Dr. Maria Juliana Rodríguez has been a scientific advisor for PTC Therapeutics, Boehringer Ingelheim, Abbot, Pfizer, Sanofi and Novartis. The rest of the authors report no conflicts of interest.

Ethical disclosures

Human and animal protection. The authors declare that no experiments were performed on humans or animals for this study.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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ORIGINAL ARTICLE

Validation in Colombian Spanish of the Duke Anticoagulation Satisfaction Scale (DASS)

Validación al español de Colombia de la escala DASS (Duke Anticoagulation Satisfaction Scale)

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Abstract

Introduction: *assessing the quality of life of anticoagulated patients is important; there is currently no Spanish validation of the Duke Anticoagulation Satisfaction Scale (DASS). The Duke Anticoagulation Satisfaction Scale (DASS).* **Objective:** *to conduct a linguistic validation and preliminary psychometric properties estimation in Colombian Spanish of the DASS for assessing quality of life in patients anticoagulated with vitamin K antagonists.* **Materials and method:** *a validation study of a qualitative scale conducted in a private university hospital in Bogotá, Colombia. This validation had three phases: translation and cultural adaption by a bilingual panel; pilot testing including initial application, a cognitive interview with patients (n: 5), and a clinical review by experts (n:10); and internal consistency assessment of the scale (n: 100).* **Results:** *the study yielded a version of DASS in Colombian Spanish that was technically and conceptually equivalent to the English version. The domains of limitations in patient activity, discomfort produced by anticoagulation, and psychological impact had a Cronbach's alpha of 0.9. According to expert opinion, most questions had the right relevance (Aiken's V coefficient: 0.67-0.87).* **Conclusion:** *this is the first version of the DASS published in Spanish. The translation and cultural adaptation process resulted in a scale equivalent to its original version. The internal consistency analysis showed a highly consistent but not redundant scale.*

Keywords: *Quality of life. Anticoagulation. Warfarin. Psychometrics. Spanish.*

Resumen

Introducción: *Evaluar la calidad de vida de los pacientes anticoagulados es importante; no existe en la actualidad una validación al español de la escala de satisfacción con la anticoagulación de Duke (DASS).* **Objetivo:** *realizar una validación lingüística y una estimación preliminar de las propiedades psicométricas en español colombiano de la escala de satisfacción de anticoagulación de Duke (DASS) para evaluar la calidad de vida en pacientes anticoagulados con antagonistas de la vitamina K.* **Materiales y método:** *estudio de validación de una escala cualitativa realizado en un hospital universitario privado de Bogotá, Colombia. La validación tuvo tres fases: traducción y adaptación cultural por un panel bilingüe; prueba piloto que incluye aplicación inicial, entrevista cognitiva con pacientes (n: 5) y revisión clínica por expertos (n: 10); valoración de la consistencia interna de la escala (n: 100).* **Conclusiones:** *esta es la primera versión de la DASS publicada en español.*

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Date of reception: 07-03-2023
Date of acceptance: 11-08-2023
DOI: 10.24875/RCCARE.M23000063

Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):345-350
www.rccardiologia.com

El proceso de traducción y adaptación cultural resultó en una escala equivalente a su versión original. El análisis de consistencia interna mostró una escala altamente consistente, pero no redundante.

Palabras clave: *Calidad de vida. Anticoagulación. Warfarina. Psicometría. Español.*

Introduction

Anticoagulation is the treatment of choice in different clinical situations like venous or arterial thromboses or diseases with a high embolic risk.

In 2016, the estimated global prevalence of atrial fibrillation was 43.6 million[1], and the annual incidence of pulmonary thromboembolism and deep vein thrombosis is 39-115 and 53-162 per 100,000 inhabitants, worldwide[2]. In many of these cases, the patients require indefinite anticoagulation.

Although direct oral anticoagulants are prescribed with increasing frequency due to their safety profile[3] and proven effectiveness for various specifications, warfarin continues to be the most used anticoagulant in the world[4].

The quality of life of patients on anticoagulation is affected not only by the burden of disease, but also by the treatment, due to several factors like potential bleeding, diet restrictions, high-impact physical activity restrictions and the need for periodic laboratory tests[5-7].

The impact on quality of life may reduce treatment adherence and persistence; therefore, the objective assessment of quality of life is a useful tool for identifying patients who would benefit from intensified education and strict follow up to ensure treatment continuity.

One of the tools created to evaluate quality of life in patients anticoagulated with warfarin is the Duke Anticoagulation Satisfaction Scale (DASS), which consists of 25 items dealing with the negative impacts of anticoagulation (limitations, inconveniences and burdens) and its positive impacts (confidence, peace of mind and satisfaction). This scale was created and validated in the United States, with a study including 262 patients on warfarin anticoagulation. The study showed that each component of the scale had high internal consistency, proving it to be a tool that produces valid, reliable and sensitive results in measuring these patients' quality of life[8]. These results have been consistent in its validation in other languages[9-11].

Considering the importance of having a validated tool for clinical practice and research on quality of life in anticoagulation in Colombia, the objective of this study was to validate the DASS in Colombian Spanish, in order to facilitate its use as a tool for evaluating the quality of life of patients anticoagulated with vitamin K antagonists.

Materials and method

This was a test validation study to determine the accuracy and psychometric properties of measurement tools. The DASS validation process consisted of three stages: scale translation, interviews to evaluate its face and content validity, and assessment of its psychometric properties.

For the second and third phases, patients over the age of 18 who were hospitalized or seen in the outpatient department and were being followed by the anticoagulation clinic team and were included in the anticoagulation registry at Hospital Universitario San Ignacio, in Bogotá, Colombia, who were on warfarin anticoagulation for any reason, and had received it for at least four months, were included. Patients with a life expectancy of less than three months or who had received anticoagulation for less than four months were excluded.

The study was approved by the Ethics and Research Committees at Hospital Universitario San Ignacio and Pontificia Universidad Javeriana, in Bogotá. Verbal informed consent was requested from the participants to be included in the study. In addition, permission was requested from the author of the original scale to perform the validation process.

Translation and back translation were used for the first phase, consisting of an initial bilingual panel responsible for producing the first Spanish version of the scale. This panel was made up of two local individuals, with no professional clinical practice background in the medical field, whose native language was Spanish and who were fluent in English. The second panel translated the scale from Spanish into English and consisted of two local individuals whose native language was English and who had a good command of Spanish. Once the definitive translation was obtained, the document with the translators' comments was sent by email to the author of the original scale, Dr. Greg Samsa, for approval.

For the second phase, in order to evaluate the applicability, relevance, comprehensibility, and semantic and technical equivalence of the Colombian Spanish version, face-to-face cognitive clarification interviews were conducted with five patients. In these interviews, the interviewees filled out the questionnaire, while an

investigator used the "think aloud" technique and asked about any questions that might arise from each of the items. The participants were also asked about their understanding of some concepts in the scale items (What does…mean for you?)

A clinical review by experts selected based on their anticoagulation experience (a general practitioner, four internal medicine specialists, a hematologist, a rheumatologist, a nurse in the anticoagulation program and a patient on warfarin anticoagulation for more than 20 years) was conducted using a virtual questionnaire, to evaluate the relevance of each item as a source of content validity evidence. The argumentation coefficient (K coefficient)[12] was calculated for all expert panel participants, except for the patient.

Finally, to determine its internal consistency as a source of reliability evidence, the Colombian Spanish version underwent psychometric evaluation through a single application of the scale with 100 patients who met the inclusion criteria, randomly selected from the anticoagulation registry.

For the descriptive analysis, the normality of the variables was tested using the Shapiro-Wilk test; averages and standard deviations were used for normally distributed numeric variables and medians and interquartile range for those with a non-normal distribution.

Internal consistency was evaluated by calculating Cronbach's α, keeping in mind that a value greater than 0.70 indicates satisfactory internal consistency and an appropriate relationship between the items.

The relevance of the scale items assigned by the experts was evaluated with Aiken's V. Scores equal to or greater than 0.70, as well as confidence intervals that do not include 0.50, indicate that the item is relevant.

The sample size for estimating internal consistency was determined based on the results of the study by Bujang et al.[13], with an $\alpha = 0.05$ and a $\beta = 0.1$, estimating that 15% of the questionnaires would have missing data. The calculated sample size was 100 patients.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS).

Results

The participants on the first bilingual panel considered that both the instructions as well as most of the questions were clear and easy to translate. Alternative translations for each item were discussed until a consensus was reached, as an indicator of conceptual equivalence.

The second bilingual panel also considered that most of the questions were understandable and discussed translation alternatives until a consensus was reached.

Once the two-panel consolidated version was obtained, cognitive clarification interviews were conducted with five hospitalized patients (three men and two women), who took an average of eight minutes to complete the survey. A difficulty was found in understanding Item 3g ("Anticoagulant treatment is a burden for you"). Discussion within the research group led to an adjustment in the translation ("To what degree do you feel that your anticoagulant treatment is a burden for you or requires a significant effort from you?").

Content validity was evaluated through expert opinion. The results of the assessment are presented in table 1. The items in bold type are those that did not achieve a score of 0.70 or had confidence intervals that included 0.50.

A total of 100 patients were included in the psychometric evaluation, whose characteristics are shown in table 2. Most of the patients were women, with a median age of 54 years; the main reasons for anticoagulation were atrial fibrillation and deep vein thrombosis.

The scale's internal consistency was measured with Cronbach's alpha for each of the items, with an average value of 0.93 (Table 3).

The knowledge coefficient (Kc) was calculated based on the professional's own evaluation on a scale from 0 to 100 (expert self-appraisal test) and multiplied times 0.01. Each expert (except for the patient) was requested to indicate on a scale from 1 to 100 the degree of knowledge he/she had regarding anticoagulation with vitamin K antagonists.

The argumentation coefficient (Ka) was calculated by adding the sources that influenced the level of knowledge and argumentation regarding anticoagulation with vitamin K antagonists of each of the experts, except the patient[14]. The standard value was assigned to each of the sources[14].

Table 4 shows the results of the estimated level of competence of the participating experts.

Discussion

This study carried out the first translation, cultural adaptation and psychometric validation of the DASS for Colombian Spanish. Adequate internal consistency and content validity were found, achieving psychometric equivalence with the original scale. These results allow

Table 1. Aiken's V coefficient in the evaluation of the relevance of each of the questions

Question	Average	Aiken's V	95% CI
1a	4.4	0.85	0.7092-0.9293
1b	**3.6**	**0.65**	**0.495-0.7786**
1c	4.1	0.775	0.6249-0.8768
1d	4.2	0.8	0.6524-0.895
1e	4.2	0.8	0.6524-0.895
2a	4	0.75	0.598-0.8581
2b	**3.7**	**0.675**	**0.5201-0.7991**
2c	4.3	0.825	0.6804-0.9125
2d	3.9	0.725	0.5716-0.8389
3a	3.8	0.7	0.5456-0.8192
3b	4.4	0.85	0.7092-0.9293
3c	4.3	0.825	0.6804-0.9125
3d	**3.6**	**0.65**	**0.495-0.7786**
3e	3.8	0.7	0.5456-0.8192
3f	**3.5**	**0.625**	**0.4703-0.7577**
3g	4.6	0.9	0.7694-0.9604
4h	4.5	0.875	0.7388-0.9454
4a	5	1	0.9123-1
4b	4.3	0.825	0.6804-0.9125
4c	4.8	0.95	0.8349-0.9861
4d	4.5	0.875	0.7388-0.9454
4e	**3.7**	**0.675**	**0.5201-0.7991**
4f	4.2	0.8	0.6524-0.895
4g	4.4	0.85	0.7092-0.9293
4h	4.3	0.825	0.6804-0.9125

Items in are bold those that did not achieve a score of 0.70 or had confidence intervals that included 0.50.
CI: confidence Interval.

Table 2. Sociodemographic characteristics of the participants

Variable	n = 100
Age, years, median (SD)	54 (21.81)
Sex, n (%)	
Female	54 (54)
Male	46 (46)
Occupation, n (%)	
Self-employed	20 (20)
Employee	33 (33)
Household duties	35 (35)
Student	6 (6)
Unemployed	6 (6)
Schooling, n (%)	
Graduate studies	6 (6)
College	28 (28)
Technical/technological	17 (17)
Basic primary (1st - 5th)	19 (19)
High school (10th - 13th)	27 (27)
None	3 (3)
Marital status, n (%)	
Cohabiting	23 (23)
Widowed	8 (8)
Single	16 (16)
Separated or divorced	6 (6)
Married	47 (47)
Reason for anticoagulation, n (%)	
Atrial fibrillation	24 (24)
Deep vein thrombosis	23 (23)
Antiphospholipid syndrome	22 (22)
Prosthetic valve	13 (13)
Chronic PTE	8 (8)
Hereditary thrombophilia	4 (4)
Atrial flutter	3 (3)
Acute PTE	3 (3)

SD: standard deviation; PTE: pulmonary thromboembolism.

this tool to be recommended for use in evaluating the quality of life of patients anticoagulated with vitamin K antagonists in our setting.

In the semantic evaluation, comprehensibility was adequate, overall; only one question (3g) required a revised translation to improve patients' understanding.

Most of the questions had adequate relevance (K coefficient: 0.87) and adequate pertinence, except for five (1b, 2b, 3d, 3f, and 4e). These data suggest the need to evaluate whether these items should remain in the scale. Questions 1b, 2b and 3d evaluate limitations in activities relevant to daily life; therefore, we consider that, from a clinical perspective, it is important to keep them, along with Question 4e, which evaluates the fear of negative consequences of the disease which is being treated. However, Question 3f addresses the pain caused by the medication; as warfarin is an oral medication, the need for this item in the questionnaire is debatable.

Future studies may determine the need to keep or remove these questions.

Internal consistency, measured with Cronbach's coefficient, was adequate for each of the items, similar to other previous validation studies in other languages, with Cronbach's α results greater than 0.7[15].

As this is the first validation of the scale in Colombian Spanish, the main strength of the study is the ability to fill a knowledge gap, contributing a tool for clinical and

Table 3. Internal validity of the scale through a calculation of Cronbach's coeffiecient for each of the items

Question	Average	SD	Cronbach
1a	2.138	1.357	0.932
1b	1.713	1.180	0.931
1c	2.138	1.399	0.934
1d	1.759	1.181	0.932
1e	2.276	1.207	0.933
2a	2.345	1.554	0.932
2b	1.747	1.686	0.932
2c	1.885	1.814	0.932
2d	2.253	1.250	0.930
3a	1.621	1.113	0.931
3b	2.011	1.307	0.930
3c	1.632	1.221	0.930
3d	1.575	1.352	0.931
3e	2.230	1.452	0.931
3f	1.149	0.724	0.937
3g	1.655	1.087	0.930
3h	6.126	1.554	0.938
4a	6.621	0.796	0.937
4b	5.943	1.214	0.936
4c	2.908	1.709	0.930
4d	5.644	1.220	0.934
4e	2.230	1.361	0.930
4f	5.724	1.309	0.931
4g	1.609	1.261	0.933
4h	5.793	1.286	0.935

SD: standard deviation.

research assessment in our particular social context. Although this version is translated and validated for Colombian Spanish, significant language variations in the region are unlikely, and therefore it is a tool that may be useful throughout Latin America.

In addition, it was carried out in a population with a variety of diseases and different educational levels, as well as in both hospitalized and ambulatory patients, ensuring a heterogenous sample and the applicability of the results obtained.

Table 4. Estimation of the level of competence of the participating experts

Expert	Role	Kc	Ka	K	Appraisal
1	Physician	0.90	0.90	0.90	High
2	Physician	0.80	0.80	0.80	High
3	Physician	0.72	0.80	0.76	High
4	Physician	1.00	1.00	1.00	High
5	Physician	1.00	1.00	1.00	High
6	Physician	0.92	1.00	0.96	High
7	Physician	0.71	0.90	0.81	High
8	Nurse	0.86	1.00	0.93	High
9	Physician	0.80	0.90	0.85	High
10	Physician	0.52	1.00	0.76	High

Kc: knowledge coefficient; Ka: argumentation coefficient.

The main limitations of the study include the fact that there was no test/re-test to evaluate if there were changes in the patients' quality-of-life perception over time, nor were subscales or statistical variance, internal and external coherence, or precision tests performed, which are described in other validations[16]. However, the results of the various validations have been so consistent, that they suggest the stability of the original scale's design, beyond the idiosyncrasies of translation. In any case, we believe it would be pertinent to complement these measurements in subsequent studies.

Conclusion

The results of this study suggest that the Colombian Spanish DASS version underwent a language translation and cultural adaptation process that allows it to be considered the conceptual, semantic and technical equivalent of the original version, with adequate psychometric characteristics. Therefore, it may be used in clinical practice and research in our setting to evaluate the quality of life of patients anticoagulated with vitamin K antagonists.

Acknowledgements

To this project's directors at Pontificia Universidad Javeriana.

Funding

This study was funded by Pontificia Universidad Javeriana.

Conflicts of interest

The authors declare no conflicts of interest in this research study.

Ethical disclosures

Human and animal protection. The authors declare that no experiments on humans or animals were performed for this study.

Data confidentiality. The authors declare that they have followed their workplace protocols for publishing patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in this article. The corresponding author is in possession of this document.

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REVIEW ARTICLE

Evidence-based guideline for anticoagulant management of Electrophysiology procedures

Guía basada en la evidencia para el manejo anticoagulante de pacientes sometidos a procedimientos en Electrofisiología

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Abstract

Perioperative management of patients undergoing electrophysiology procedures is challenging, as many of these patients have a high underlying embolic risk and are often on oral anticoagulant therapy. The decision to continue or discontinue oral anticoagulation, or order bridging therapy, is controversial. This article aims to generate evidence-based recommendations for the perioperative management of anticoagulation in patients who, due to their embolic risk, require oral anticoagulation and will undergo cardiac pacing device implantation or arrhythmia ablation. A systematic review has been carried out following the criteria of the PRISMA protocol. The search was performed in the MEDLINE-PubMed, Embase, Cochrane, Google Scholar, NICE, Epistemonikos and LILACS databases. This systematic review included clinical practice guidelines, systematic reviews of the literature, and meta-analyses. The evidence was updated from January 1, 2014, to February 28, 2022. Three clinical practice guidelines (CPGs) and four systematic literature reviews (SLRs) were taken as a body of evidence, which were scored with the AGREE II and AMSTAR II tools, respectively. Evidence-based recommendations, using the GRADE methodology, are generated which highlight that oral anticoagulation with vitamin K antagonists should be ordered continuously for both atrial fibrillation (AF) ablation and device implantation; however, there is not much evidence on direct oral anticoagulation in device implantation.

Keywords: *Cardiac implantable electronic devices. Catheter ablation. Periprocedural anticoagulation.*

Resumen

El manejo perioperatorio de pacientes que requieren procedimientos en electrofisiología es desafiante, pues muchos de ellos tienen alto riesgo embólico de base y, a menudo, están en terapia anticoagulante oral. La desición de continuar, interrumpir la anticoagulación oral o indicar terapia puente es controversial. Este artículo se propone generar recomendaciones basadas en la evidencia sobre el manejo perioperatorio de la anticoagulación de pacientes, quienes, por su riesgo embólico, requieren anticoagulación oral y serán llevados a implante de dispositivos de estimulación cardíaca o ablación de arritmias. Se ha efectuado una revisión sistemática siguiendo los criterios del protocolo PRISMA. La búsqueda se realizó en la base de datos MEDLINE-PubMed, Embase, Cochrane, Google Scholar, NICE, Epistemonikos y LILACS. Esta revisión sistemática incluyó

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Date of reception: 23-06-2022
Date of acceptance: 15-05-2023
DOI: 10.24875/RCCARE.M23000066
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):351-358
www.rccardiologia.com

guías de práctica clínica, revisiones sistemáticas de literatura y metáanalisis. Se actualizó la evidencia desde el 1.º de enero del 2014 hasta el 28 de febrero del 2022. Se tomaron como cuerpo de evidencia 3 guías de práctica clínica y 4 revisiones sistemáticas de literatura las cuales se calificaron con los instrumentos AGREE II y AMSTAR II, respectivamente. Se generan recomendaciones basadas en la evidencia, usando la metodología GRADE, en las que se destaca que la anticoagulación oral con antagonistas de la vitamina K debe indicarse de forma ininterrumpida tanto para ablación de FA, como para implante de dispositivos y ablación de arritmias; no obstante, no hay mayor evidencia de la anticoagulación oral directa en el implante de dispositivos.

Palabras clave: *Dispositivos cardíacos electrónicos. Ablación por catéter. Anticoagulación periprocedimiento.*

Introduction

Electrophysiologists are often faced with the dilemma of balancing the risk of thromboembolic events against hemorrhagic complications in patients undergoing invasive procedures (cardiac electronic device implantation, cardiac arrhythmia ablation). Many of these patients have a high underlying embolic risk and are generally being treated with oral anticoagulants.

Previous guidelines recommended interrupting oral anticoagulation and using periprocedural heparin bridging therapy[1]. This therapy was controversial, as interrupting oral anticoagulation increases the risk of embolic events. Likewise, implanted patients are susceptible to implantation pocket bleeding[2]. This guideline seeks to update the indications for periprocedural anticoagulation in patients undergoing electrophysiology procedures.

Materials and method

This guideline was developed according to the standards provided by the 2017 methodological guideline for the Adoption-Adaption of Evidence-Based Clinical Practice Guidelines produced by the Ministry of Health and Social Protection[3]. A systematic literature review (SLR) was performed in the MEDLINE, Embase, LILACS and Cochrane Library databases. The official websites of clinical practice guideline (CPG) developing groups and repositories were also searched: NICE, Epistemonikos, GuiaSalud, CENETEC and the Ministry of Health of Chile, Ecuador, Peru and Colombia. Google and Google Scholar, as well as topical experts, were used to search for grey literature to track references of interest. The search strategy was constructed using MeSH, Emtree and DeCS keywords, depending on the source consulted.

The search horizon was January 1, 2014, to February 28, 2022, to identify the available updated evidence. It was restricted by type of study to CPGs and SLRs, considering the vast amount of scientific work on the subject. The search was not restricted by language.

Inclusion criteria

- Type of study: secondary CPG and SLR studies.
- Population: patients on chronic oral anticoagulation therapy (with warfarin or direct oral anticoagulants [DOACs] at high and moderate risk of embolic events, who underwent cardiac device implantation (pacemakers or cardioverter-defibrillators) or atrial fibrillation or flutter ablation.
- Intervention: uninterrupted oral anticoagulation with warfarin or DOACs: apixaban, rivaroxaban, edoxaban, dabigatran.
- Comparator: heparin bridging therapy or suspension of oral anticoagulation.
- Outcomes: thromboembolic or hemorrhagic events and pocket hematomas.
- Date of publication: January 1, 2014, through February 28, 2022.

Exclusion criteria

No posters or abstracts were considered, due to the small amount of available information.

Screening, selection and quality of the evidence

The search results were independently screened by title and abstract by two investigators, using the Rayyan® tool. Disagreements were resolved by consensus. Based on the screening, full-text documents were evaluated, and the eligibility criteria were verified independently by two investigators. For CPGs, the quality of the evidence was evaluated with AGREE II[4], while AMSTAR-2[5] was used for SLRs.

Table 1. Selected clinical practice guidelines and summary of the evidence

Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 Implantable Cardioverter Defibrillator Guidelines[6]	
The recommendation is for ICD implantation to be performed with a therapeutic INR in patients on VKAs with an estimated annual risk of embolic events greater than 5%. For patients on VKAs with an estimated annual risk of embolic events less than 5%, the recommendation is to perform ICD implantation with a therapeutic INR or temporary suspension of the VKA (without bridging).	Strong recommendation; High-quality evidence.
The 2020 ESC Guidelines for the diagnosis and treatment of atrial fibrillation, developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)[7]	
For patients undergoing AF catheter ablation who have received therapeutic anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban, the recommendation is to perform the ablation procedure without interrupting the OACs.	Class IA
National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018[8]	
Uninterrupted oral anticoagulation is recommended for patients undergoing atrial fibrillation catheter ablation.	GRADE Level of Evidence: Moderate; Degree of Recommendation: Strong.

Given the large amount of information from SLRs, the most updated and best-quality SLRs were established as the body of evidence for generating the recommendations. One investigator did the extraction and the other the review.

Results

A total of 967 documents were found in the various sources consulted. After eliminating duplicates, a database of 845 documents was established, which were then screened by title and abstract. Altogether, 156 full-text documents were reviewed, 50 of which met the eligibility criteria for the review. Annex 1 shows the PRISMA diagram which summarizes the SLR process.

Of the 50 documents included in the SLR, five were CPGs and 45 were SLRs. The quality of the evidence was evaluated in all of them, finding that, in general, the available evidence is of poor quality. The five CPGs had a score of more than 60% on the AGREE II criterion 3; three guidelines were chosen for their currentness and clarity in presenting the data, with a score of more than 60% on the AGREE II domain 4: the Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 Implantable Cardioverter-Defibrillator Guidelines[6], 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[7], and the Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018[8].

Most of the SLRs (n = 40) had critically low quality of evidence scores and the remaining five SLRs were scored as low certainty on AMSTAR-2. In general, the methodological limitations found were the inability to verify the methodology for developing the CPG, lack of *a priori* protocols, protocol registration, unstructured or non-reproducible evidence searches, not reporting the included primary studies' funding, and the quantitative analysis (meta-analysis) of primary studies, which pooled the different types of studies for the estimator's assessment (clinical trials and observational studies). With these findings, four CPGs and five SLRs were established as the body of evidence.

Selection results

The most relevant recommendations were extracted from the three guidelines selected, with their original degree of recommendation, to be adapted to our current guideline. These recommendations are summarized in table 1.

Evidence updating

Characteristics of the systematic literature reviews

The five SLRs included[9-13] were published between 2018 and 2020. The searches spanned the time from the inception of the sources through March 2020. The details of the included SLRs are presented in table 2.

The interventions described include uninterrupted oral DOACs[9,11,12], minimally interrupted DOACs[12,13]

Table 2. Characteristics of the studies included

SLR	Type of study	Intervention	Comparator	Follow up	Primary studies	Procedures	Patients in meta-analysis
Brunetti	SLR	Uninterrupted DOACs	Uninterrupted oral VKAs	4 years	4 RCTs: 4 AXAFA-AFNET 5, 2018 NCT02227550 ELIMINATE-AF, 2019 NCT02942576 Piccini, 2013 NCT00403767 Tomkins, 2010	Atrial fibrillation catheter ablation	Total: 2,114
Mendoza	SLR	Continuous DOAC	Interrupted DOAC	6 years	5 RCTs: 2 Birnie et al., 2018 NCT: 01675076 Ricciardi et al., 2018 Observational: 3 Black-Maier, 2017 Rowley, 2012 Sheldon, 2018	Electronic cardiac device implantation	Total: 864 RCTs: 763 Observational: 101
VanVugt 2021	SLR	Minimally interrupted DOAC	Continuous DOAC	2 years	8 RCTs: 6 Ando, 2019; Nagao, 2019; Reynolds, 2018; Yamaji, 2019; Yoshimura, 2017; Yu, 2018 Observational: 2 Nakamura, 2019; Vlachos, 2017	Atrial fibrillation catheter ablation	Total: 2,168
Romero 2018	SLR	Uninterrupted DOACs	Uninterrupted oral VKAs	3 years	4 RCTs: 4 AXAFA-AFNET 5, 2018 NCT02227550 Kosiuk, 2014 Piccini, 2013 NCT00403767 Tomkins, 2010	Nonvalvular atrial fibrillation catheter ablation	Total: 1,716
Ottoffy 2020	SLR	Uninterrupted or minimally interrupted DOACs	Uninterrupted VKAs	8 years	42 RCTs: 6 Calkins, 2017 Cappato, 2015 Hohnloser, 2019 Nogami, 2019 Kirchhof, 2018 Kuwahara, 2016	Atrial fibrillation catheter ablation	Total: 22,715 RCTs: 2,575 Observational: 20,140

and continuous DOACs at low and high doses, including rivaroxaban, edoxaban, dabigatran and apixaban[10,13]. In three of the SLRs, the comparator was uninterrupted oral vitamin K antagonists (VKAs), in one SLR it was the interruption of DOACs[10], and in another, minimally interrupted DOACs[13]. The follow-up time of the primary studies ranged from two to eight years.

The quality of the evidence of the primary studies for all SLRs was analyzed using the Cochrane risk-of-bias tool. The Newcastle-Ottawa scale for observational studies was applied to two documents[12,13]. The result of the randomized controlled trials (RCTs) was categorized by the SLR authors as low risk of bias, although none of the studies blinded the participants and staff who applied the intervention. For the observational studies, the risk was classified as high due to selection bias and lack of pairing of exposed and non-exposed patients[10], and in the review by Otoffy et al.[12], the observational studies had a low risk of bias.

Outcomes

The outcome evaluated by all five reviews was thromboembolic events and major bleeding events. Three of the SLRs evaluated non-major bleeding[9,11,13]; postoperative hematomas and all-cause mortality[10], total bleeding[13], postablation silent cerebral infarction[11,13] and the composite outcome of major bleeding and thromboembolic events[12,13].

Catheter ablation

Uninterrupted DOACs vs. uninterrupted VKAs

Thromboembolic events

A comparison of uninterrupted DOACs (rivaroxaban, dabigatran, apixaban or edoxaban) vs. uninterrupted warfarin showed no difference in the incidence of thromboembolic events (RR: 0.40; 95% CI: 0.09-1.76)[9]; the review by Romero et al.[11] reported similar findings.

Major bleeding events

After the quantitative synthesis of RCTs in Bruneti et al.'s[9] SLR, 3% (n = 35) of the patients with uninterrupted DOACs were found to have the outcome vs. 5.36% (n = 51) of those who received uninterrupted warfarin, for a more than 39% reduction in the risk of major bleeding (RR: 0.61; 95% CI: 0.39-0.3); the estimated effect persisted in the sensitivity analysis.

Non-major bleeding

A comparison of uninterrupted DOAC therapy (rivaroxaban, dabigatran, apixaban or edoxaban) vs. uninterrupted warfarin showed no difference in the incidence of non-major bleeding events (RR: 1.14; 95% CI: 0.83-1.57)[9] (RR: 1.11; 95% CI: 0.82-1.52)[11].

Composite of major bleeding and thromboembolic events

Only Ottoffy et al.'s[12] review included this composite outcome of the combination of major bleeding and thromboembolic events, for which they estimated an OR of 0.35 (95% CI: 0.17-0.73) based on RCT, with a finding favoring uninterrupted DOAC therapy compared with uninterrupted VKA.

Minimally interrupted DOACs vs. continuous DOACs

VanVugt's[13] SLR found no significant difference in the combined outcome of major bleeding and thromboembolic events when comparing minimally interrupted DOACs vs. continuous DOACs (OR: 1.2; 95% CI: 0.49-2.92).

Device implantation

Mendoza et al.'s[10] review evaluated the effect of continuous and interrupted DOAC therapy in cardiac device implantation. Based on the combination of two RCTS, no differences were found in the risk of developing postoperative pocket hematomas (RR: 1.15; 95% CI: 0.44-3.05), thromboembolic events (RR: 1.02; 95% CI: 0.06-16.21), clinically significant bleeding (RR: 1.54; 95% CI: 0.45-5.27) and all-cause mortality (RR: 2.04; 95% CI: 0.19-22.35).

GRADE assessment and the generation of recommendations

The certainty of the evidence was also assessed with the GRADE[14] methodology, using the GRADEpro tool. Uninterrupted DOACs vs. uninterrupted VKAs were

Table 3. Summary of recommendations

Recommendations	Level of Evidence (GRADE)	Degree of Recommendation
For patients undergoing AF catheter ablation who have received therapeutic anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban, the recommendation is to perform ablation without interrupting the DOACs.	Moderate	Strong
Uninterrupted DOAC use is recommended for patients undergoing AF catheter ablation, compared to uninterrupted VKA use, to reduce the risk of major bleeding in patients who do not have an indispensable requirement for VKA use.	Moderate	Strong
The recommendation is to give the last DOAC dose without interruption. For agents given twice a day, like dabigatran or apixaban, the last dose is given in the morning on the day of the procedure. For agents given once a day, like rivaroxaban or edoxaban, the last dose is given the night before catheter ablation.	Low	Weakly in favor
The recommendation is for electronic cardiac device implantation to be performed with a therapeutic INR in patients on VKAs with an estimated annual risk of embolic events greater than 5%. For patients on VKAs with an estimated annual risk of embolic events less than 5%, the recommendation is for ICD implantation to be performed with a therapeutic INR or with temporary suspension of the VKA (without bridging).	High	Strong
No difference was found in the use of continuous vs. interrupted DOACs in electronic cardiac device implantation.	Moderate	Weakly in favor

evaluated in atrial fibrillation ablation with regard to the outcomes of thromboembolic or major bleeding events, minor bleeding, silent cerebral infarctions and the composite of major bleeding and thromboembolic events. Minimally interrupted DOACs vs. uninterrupted DOACs were evaluated in the composites of major bleeding or thromboembolic events, total bleeding and minor bleeding. Furthermore, continuous DOACs vs. interrupted DOACs were evaluated in electronic cardiac device implantation in terms of the outcomes of pocket hematomas and thromboembolic events. The findings of the GRADE evaluation are presented in Annex 2. The recommendations were evaluated by experts from different specialties (cardiology, electrophysiology and clinical epidemiology).

Discussion

Recommendations

After reviewing the evidence and sending it for consensus among experts from different specialties (cardiology, electrophysiology and clinical epidemiology), the following recommendations were drafted (Table 3):

Atrical fibrillation ablation

– The recommendation is to perform ablation without interrupting DOACs in patients undergoing atrial fibrillation (AF) catheter ablation who have received therapeutic anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban (GRADE Level of Evidence: Moderate; Degree of Recommendation: Strong).

Justification: this recommendation is taken from the 2020 ESC Guidelines[7] for AF, which received an AGREE II domain III score of 90%.

– The recommendation is to use uninterrupted DOACs in patients undergoing AF catheter ablation instead of uninterrupted VKAs, to reduce the risk of major bleeding in patients who do not have an indispensable requirement for VKA use (GRADE Level of Evidence: Moderate; Degree of Recommendation: Strong).

Justification: This recommendation comes from the systematic literature reviews analyzed[9,11,12], in which uninterrupted DOACs vs. uninterrupted VKAs were found to reduce the risk of major bleeding events by 39%[9] (RR: 0.61; 95% CI: 0.39-0.93). The strength of the recommendation was evaluated using the GRADEpro tool (Annex 2).

– The recommendation is for the last dose of DOAC to be given without interruption. For agents given twice a day, like dabigatran or apixaban, the last dose is given in the morning on the day of the procedure. For agents given once a day, like rivaroxaban or

edoxaban, the last dose is given the night before catheter ablation (GRADE Level of Evidence: Low; Degree of Recommendation: Weakly in favor).

Regarding the minimally interrupted vs. continuous strategy, the systematic review by VanVugt, et al.[13] showed no differences between these interventions in either the composite of major bleeding or thromboembolic events or the composite of total bleeding, minor bleeding or silent cerebral embolism. The GRADE assessment of this systematic review indicates low quality evidence, due to masking bias in the primary studies. For now, imitating the guidelines of the primary studies (AXAFA AFNET 5, RE-CIRCUIT, VENTURE AF, ELIMINATE AF[15-18]) appears to be the most appropriate strategy.

In the primary studies, which compared uninterrupted DOACs vs. uninterrupted VKAs in FA ablation procedures (such as in RE-CIRCUIT for dabigatran), the morning dose was taken on the day of ablation, at the patient's usual time. In the AXAFA AFNET 5 study for apixaban, the DOAC was continued on the morning of ablation, while in the VENTURE AF study, the last dose of rivaroxaban was taken at dinner time, and in the ELIMINATE AF study the last dose of edoxaban was ordered to be taken the night before the procedure.

Electronic cardiac device implantation

– The recommendation is for electronic cardiac device implantation to be performed with a therapeutic INR in patients on VKAs with an estimated annual risk of embolic events greater than 5%. For patients on VKAs with an estimated annual risk of embolic events less than 5%, the recommendation is for implantable cardioverter defibrillator (ICD) implantation to be performed with a therapeutic INR or temporary interruption of a VKA (without bridging) (GRADE Level of Evidence: High; Degree of Recommendation: Strong). *Justification:* this recommendation is taken from the Canadian Cardiovascular Society 2016 Implantable Cardioverter-Defibrillator Guidelines[6], which achieved an AGREE II domain III score of 85%.

No difference was found between the use of continuous DOACs vs. interrupted DOACs in electronic cardiac device implantation (GRADE Level of Evidence: Moderate; Degree of Recommendation: Weakly in favor).

The above recommendation arose from the analyzed systematic literature review[10], which included two RCTs (Ricciardi[19] and BRUISE CONTROL 2[20]). This SLR compared continuous DOACs (not interrupting even the morning dose) vs. interrupted DOACs (stopping them two days before or according to kidney function) and found no differences in the risk of developing postoperative pocket hematomas, thromboembolic events or clinically significant bleeding (the degree of recommendation was evaluated using the GRADEpro tool, Annex 2). Therefore, either of the two strategies, continuous or interrupted DOACs, are equally valid in patients undergoing electronic cardiac device implantation.

Acknowledgments

The authors would like to thank Prof. Dr. Omar Segura, Vice Rector of Research FUCS, and the clinical epidemiologist Kelly Chacón Acevedo for their support and contributions to the design and methodology of the study. We also thank Dr. Sergio Andrés Ovalle, fellow of Cardiology FUCS, for his contribution to the collection of information.

Funding

This guide has not received any funding.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Supplementary data

Supplementary data are available at DOI: 10.24875/RCCARE.M23000066. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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REVIEW ARTICLE

How to perform a transseptal puncture safely and effectively

Cómo realizar una punción transeptal de manera segura y exitosa

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Abstract

Initially described in 1959 as a technique to measure left atrial pressures, and later used during balloon mitral valvuloplasty, transseptal puncture (TSP) is frequently the access route for procedures involving the left heart chambers. Currently, it is mostly used in electrophysiology laboratories for arrhythmia ablation and during left atrial appendage occlusion procedures. However, with the ongoing development of percutaneous mitral valve interventions, it is expected that a greater number of interventional cardiologists will be using this technique in the near future. In this article, we review the technique for performing TSP safely, and we provide recommendations and different strategies to deal with difficult TSPs.

Keywords: *Transseptal puncture. Arrhythmia ablation. Structural cardiology. Complications.*

Resumen

Introducida inicialmente en la década de los cincuenta para la evaluación de las presiones de la aurícula izquierda y posteriormente para la realización de valvuloplastia mitral, la punción transeptal es, con frecuencia, la vía de acceso para efectuar procedimientos que involucren las cavidades izquierdas. En la actualidad, se usa comúnmente en los laboratorios de electrofisiología, tanto para la ablación de arritmias en cavidades izquierdas, como para los procedimientos de cierre percutáneo de orejuela. No obstante, con la llegada de diversas técnicas para el manejo percutáneo de la válvula mitral, se espera un aumento progresivo de su uso por parte de cardiólogos intervencionistas. En este artículo, se revisa la técnica para hacer una punción transeptal segura y se dan recomendaciones y estrategias para el manejo de la punción transeptal difícil.

Palabra clave: *Punción transeptal. Ablación de arritmias. Cardiología estructural. Complicaciones.*

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Date of reception: 24-12-2022
Date of acceptance: 13-06-2023
DOI: 10.24875/RCCARE.M23000070
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):359-368
www.rccardiologia.com

Introduction

Transseptal puncture (TSP) was originally introduced in 1959 for measuring left atrial pressures[1,2], and rapidly evolved as an access route for managing mitral valve disease. However, the development of techniques to indirectly measure left atrial pressure using balloon catheters, together with a decreased prevalence of rheumatic valve disease, led to the technique rapidly disappearing from interventional cardiology laboratories. Toward the end of the 80s, the technique was infrequently used, and interventional cardiology training programs no longer had a large enough volume to provide adequate training for their fellows, significantly increasing the rate of complications[3]. With the advent of atrial fibrillation ablation at the end of the 90s[4], the technique experienced a resurgence: in only five years, the number of TSPs grew 60 times[5] and it is a common procedure in electrophysiology labs today. This experience has been harnessed in atrial appendage occlusion interventions[6] and, more recently, in percutaneous mitral valve interventions[7,8]. However, TSP continues to be a high-risk procedure which must be performed by highly trained personnel. In an analysis of the causes of pericardial effusion during atrial appendage occlusion procedures, up to 9% of the effusions occurred during TSP[9,10], showing the importance of proper technique during this procedure.

This article provides a step-by-step review of the technique for performing TSP safely using different imaging aids, as well as the management of difficult approaches and complications.

Operator training and experience

It is important for training programs to include both theoretical and practical aspects of TSP. A review of anatomy, possible risks and complications, as well as the use of simulators in the company of an experienced operator can help improve the skill of fellows-in-training in performing these procedures. As the operator's experience increases (measured by the number of TSPs performed per year), the rate of complications decreases significantly. It has been determined that an operator must perform at least 50 TSPs to have an "acceptable" level[11], while performing more than 45 TSPs per year is considered a high volume which, in turn, results in a significant reduction in the time required to obtain transseptal access and in the rate of complications[12]. Therefore, it is recommended that procedures involving TSP be performed by high-volume operators.

Before transseptal puncture: the importance of anticoagulation

Although, in the initial years, the use of anticoagulants was considered to be an absolute contraindication for TSP, today it is recommended that procedures involving TSP be performed without interrupting anticoagulation[13]. This also applies for patients treated with direct oral anticoagulants (DOACs), in whom, although the evidence establishes that their uninterrupted use could be just as safe or even safer than uninterrupted warfarin use[14], most electrophysiologists (63%) omit at least one dose before the procedure[13]. Although there is a fear that anticoagulant use prior to the procedure could increase mortality and the length and amount of bleeding if cardiac tamponade should occur, the available evidence indicates the opposite[15].

In addition to a prior anticoagulant, heparin is recommended before performing TSP, as both the guidewires and transseptal sheaths are highly thrombogenic. In our practice, 10,000 units of unfractionated heparin are infused prior to femoral puncture (in order to avoid thrombus formation on the femoral guidewires and introducers), with another 3,000 units after TSP to maintain the ACT > 300 seconds. Administering heparin only after performing TSP does not reduce the risk of bleeding, but does significantly increase the risk of thrombogenesis in the left atrium and should therefore be avoided.

Tools for performing transseptal puncture

There are various transseptal introducers which may be useful, depending on the procedure being performed. For ablations, deflectable introducers (Agilis, Abbot; Vizigo, Biosense Webster) are preferred, as they make it easier to manipulate the catheters in the left atrium. For procedures involving introducer exchange (for example, percutaneous atrial appendage occlusions), SL0 (Abbot) introducers are preferred, as their curvature (50°) facilitates left superior pulmonary vein cannulation and allows a high-support guidewire to be installed at this point. When using different introducers, it is important to consider their varying lengths in order to select an appropriately sized transseptal puncture needle (that is, not using a long needle in a short introducer, as it can easily inadvertently puncture other vascular structures).

There are additional tools which are not currently available in Colombia, like the SafeSept (Pressure Products) and Versacross (Baliss) guidewires. Both reduce the risk of complications and time required to obtain

transseptal access[12] and therefore, if available, could be considered.

Fluoroscopy-guided transseptal puncture

Fluoroscopy is the most basic form of TSP guidance. Although the fossa ovalis (FO) is not directly visible on fluoroscopy, the use of other anatomical landmarks and appropriate placement of reference catheters can help locate it in a simple way. The anatomical landmarks which help locate the FO are:

- The coronary sinus, which can be located by inserting an electrophysiology catheter in it.
- The noncoronary aortic cusp, which can be located with a catheter through a retroaortic artery.
- The left main bronchus, which marks the position of the roof of the left atrium.
- The conduction system, which is easily located with an electrophysiology catheter and is directly related to the position of the aorta (making a catheter in the aorta unnecessary).
- The thoracic vertebrae.

Technique for performing fluoroscopy-guided TSP (Fig. 1)

- Step 1: locate the orientation of the interatrial septum, introducing an electrophysiology catheter toward the right ventricle. The fluoroscopy unit is angulated to the left to allow the catheter located in the bundle of His to be seen straight on; this angulation places the fluoroscopy ray parallel to the interatrial septum. Most of the procedure will be done in the left oblique plane.
- Step 2: advance the transseptal sheath to the superior vena cava, using a guidewire. Then withdraw the guidewire and advance the TSP needle. When inserting the needle, it is important to use the internal guidewire, as this keeps plastic fragments from being dragged along and potentially embolized. Although it is a common practice, we suggest not to manually modify the curvature of the guidewire, as an excessive curvature may make it difficult to advance the needle within the introducer (and even cause perforation). The tip of the needle should be located 1 cm from the tip of the transseptal dilator, aligning the curvature of the sheath and the needle (Fig. 2) and orienting them toward the 4 or 5 o'clock position.
- Step 3: in the left oblique position, slowly pull back the sheath, watching the falls (which are seen as jumps toward the right of the screen). The first fall corresponds to the entry to the right atrium (it is very subtle and not always visible), and it is followed by a larger fall which corresponds to the entry to the FO. While this would seem to be the appropriate site, at this point, the sheath should be pulled back slightly, watching for a third fall. This corresponds to the lower part of the FO.
- Step 4: evaluate the position of the tip of the dilator in the right oblique view. The angulation needed for this is determined by a perpendicular position to the left oblique obtained in the septum evaluation: if the septum was found at 40° from the left oblique, the perpendicular is 50° to the right. This allows the interatrial septum to be viewed perpendicularly in its full extension. In this projection, ensure that the tip of the dilator is not pointing toward the aorta, nor toward the vertebrae.
- Step 5: return to the left oblique and pull the needle back 2 cm. This leaves the tip of the dilator without support. Push the sheath softly with the dilator, watching the behavior of the tip and the curvature: when it is in the FO, the tip tends to remain fixed (in the vertical axis) and the sheath curvature tends to rise up, increasing the curve. If the tip rises and falls freely, it is probably on a smooth wall (for example, toward the torus aorticus or toward the posterior wall) and should be repositioned. Injecting contrast at this point helps detect septal tenting; in some cases, a tattoo even remains (Fig. 3). If there is a catheter in the coronary sinus, the 3 o'clock position in the sinus will correspond approximately to the location of the FO (as long as the catheter has been advanced to the cardiac border).
- Step 6: advance the needle until it is out of the dilator in the left oblique. The interatrial septal puncture will feel like a sudden loss of resistance; if there is too much tenting, the dilator can "jump" to the other side uncontrollably, and therefore it is not advisable to create a lot of tenting on entering. Before advancing the dilator, contrast should be injected to confirm the location of the needle in the left atrium, determine the position of the atrial wall and establish how far the sheath and dilator can be advanced.

However, as much as possible, puncture guided solely by fluoroscopy should be avoided, as it significantly increases the risk of complications compared with TSP performed under echocardiographic guidance[12].

Echocardiography-guided transseptal puncture

In addition to increasing the safety of the procedure, the use of echocardiography (either transesophageal or intracardiac) to guide TSP has several benefits:

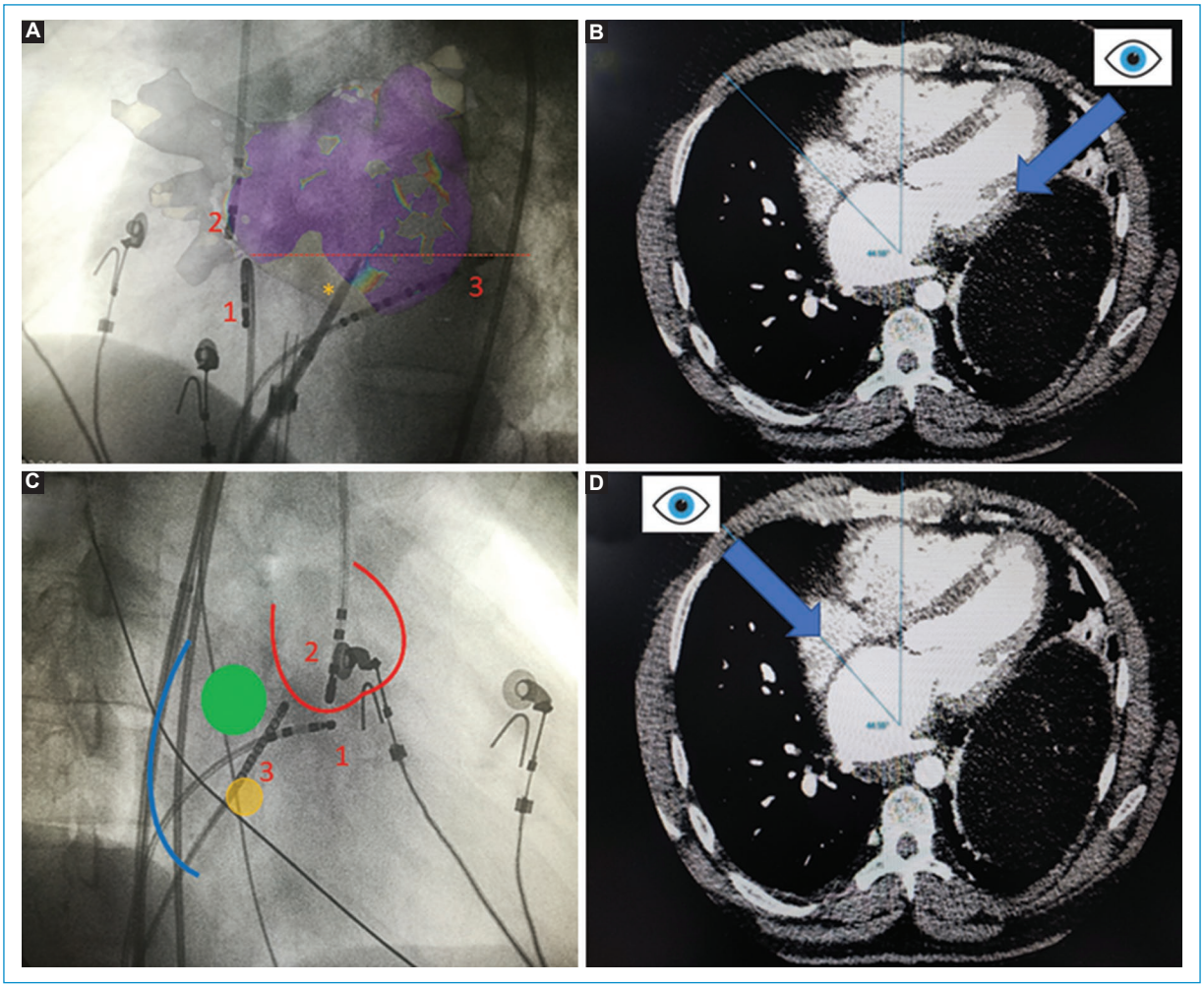

Figure 1. Location of the fluoroscopic anatomical landmarks for TSP. **A:** left anterior oblique image showing the fluoroscopic landmarks and their relationship to the left atrium (superimposed slide). A catheter in the right ventricle (1), a catheter in the aorta (2), a catheter in the coronary sinus (3) and the transseptal introducer can be seen. The relationship between the tip of the coronary sinus catheter and the puncture site (dotted red line) can be seen. **B:** locating the right ventricular catheter pointing directly toward the operator achieves a parallel position to the atrial septum. **C:** right anterior oblique view showing the fluoroscopic landmarks; note the close relationship between the catheter at the bundle of His (1) and the aortic catheter (2); therefore, a catheter does not need to be placed in the aorta (red silhouette) if one can be placed in the bundle of His. The FO (green circle) is located above the coronary sinus ostium (yellow circle), which is marked by a catheter (3). The atrial border (blue border) is in line with the vertebrae. When performing the puncture, the introducer should not be pointing toward the aorta or the vertebrae. **D:** a position at a 90° angle to the left oblique will be perpendicular to the atrial septum, allowing its length to be clearly seen.

– It helps detect anatomical variants of the interatrial septum that modify its fluoroscopic configuration, including marked heart rotation[16,17].
– It helps immediately detect previously formed thrombi or those that may form during the procedure[18].
– It facilitates the manipulation and proper placement of the transseptal introducer in the desired site within the FO.
– It detects cardiac tamponade early, as it allows real-time monitoring of the pericardial space.

Transesophageal vs. intracardiac echocardiography: Which is better?

In general, the choice is based on the operator's experience with one modality or the other, rather than on their availability (both are widely available in the country). Most of the time, electrophysiologists prefer to use intracardiac echocardiography (ICE), while interventional cardiologists prefer transesophageal echocardiography (TEE). For atrial appendage occlusion

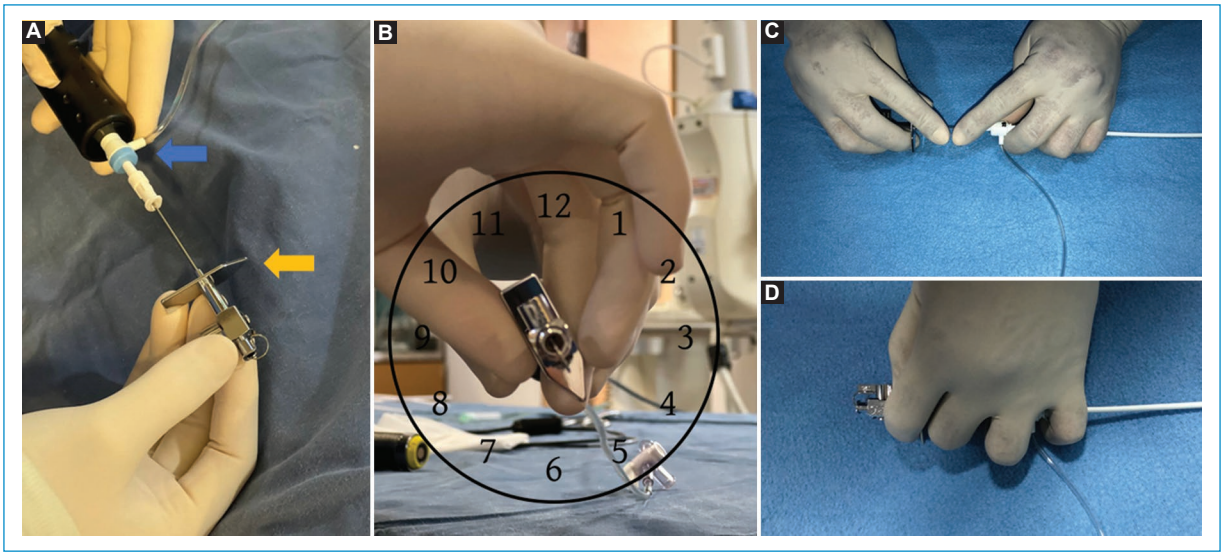

Figure 2. **A:** it is important to align the introducer and needle before starting to drop from the SVC toward the FO. To do this, the sheath irrigation port (blue arrow) should be aligned with the needle tip marker (yellow arrow). **B:** once the sheath and needle are aligned, they are positioned clockwise pointing toward 4 or 5 o'clock. **C:** hand position to ensure needle alignment with the introducer: using both hands, the transseptal sheath irrigation port is aligned with the needle marker. Keeping the index fingers together keeps the needle from accidentally protruding. **D:** when a single operator performs the TSP while handling the ICE probe, the right hand handles the probe while the left hand simultaneously manipulates the sheath (placing the port between the 4th and 5th fingers) and the needle (placing the marker between the 1st and 2nd fingers).

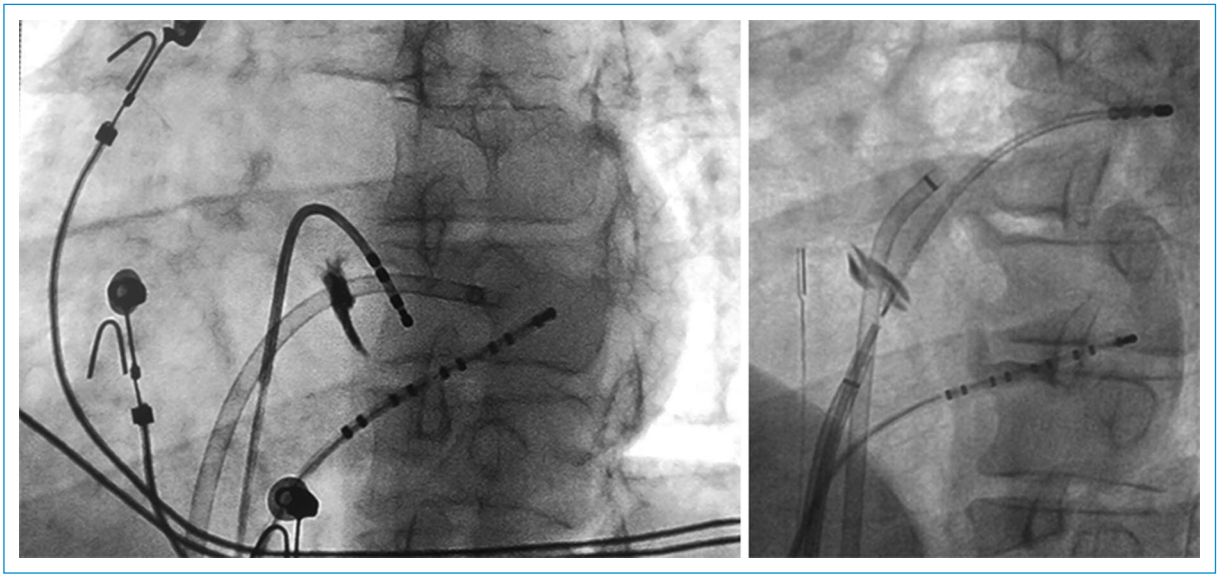

Figure 3. Examples of tattoos made in the FO, marking an appropriate puncture site. Note that, in the image on the left, the right ventricular catheter is not directly aimed at the observer, which indicates that the position is not parallel to the atrial septum. In this case, greater left angulation would be needed to be parallel.

procedures, most (both electrophysiologists as well as interventionists) use TEE, and few groups use ICE exclusively. Although there are reports of transcatheter aortic valve replacement and atrial septal defect closures using ICE[19,20], it is infrequently used worldwide.

For TSP, we believe that ICE is the better option. Compared with TEE, ICE offers images with the same

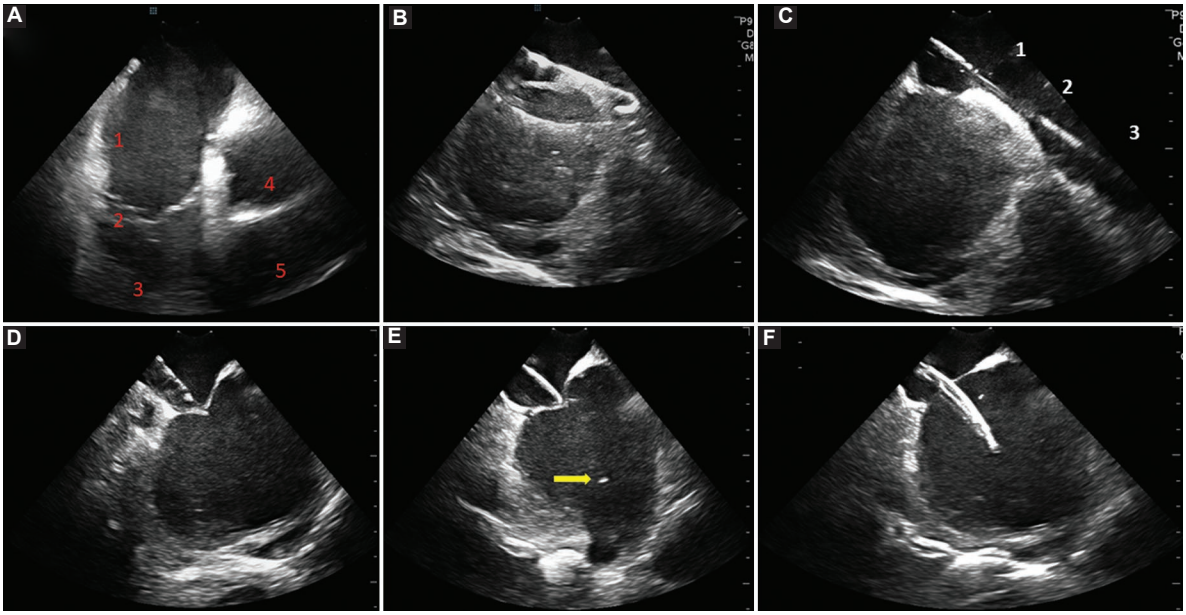

Figure 4. Sequence of images during ICE-guided transseptal puncture. **A:** right home view. The right atrium (1), tricuspid valve (2), right ventricular inflow tract (3), aorta (4) and right ventricular outflow tract (5) can be seen. **B:** image of the SVC with the guidewire inside it. **C:** advancement of the sheath (3) and dilator (2) over the guidewire (1) toward the SVC. **D:** picture of tenting over the interatrial septum. **E:** pasing the needle toward the left atrium, which is visible as a bright white point. **F:** passing the sheath through the septum.

or even better quality[21], does not require general anesthesia (which, in turn, reduces the patient's costs and risks), and decreases the number of people needed in the operating room. This last point is especially important, as its handling by the operator him/herself avoids the need for three or more people (an anesthesiologist, anesthesia assistant and echocardiographer) in the operating room. Having fewer people in the operating room is associated with a lower risk of infection[22] and fewer people exposed to ionizing radiation (which is especially high for the echocardiographer, due to the position he/she must occupy in relation to the source of radiation, and the need to have his/her hands within the radiation field).

Transseptal puncture guided by ICE and without fluoroscopy (Fig. 4)

By 2011, 50% of electrophysiologists were routinely using ICE in atrial fibrillation ablation procedures[23], accumulating extensive experience in handling this equipment over the years. Significantly, all the steps used to guide TSP with ICE can be performed without fluoroscopy[24], which has led to highly experienced laboratories conducting "fluoroless" TSP. However, the steps described below can be combined with reference fluoroscopy to facilitate TSP until enough confidence is gained with the sequence guided exclusively by ICE:

- Step 1: locate the ICE probe in the middle of the right atrium (RA), oriented toward the tricuspid valve. This is known as the "right home view" (to differentiate it from the "left home view," used in atrial appendage occlusion procedures with ICE); from this position, rotate the probe clockwise until the pulmonary veins are within the visual field.
- Step 2: using the probe handle, tilt it posteriorly until the superior vena cava (SVC) is visible. In some cases, it must be tilted a bit to the right to visualize the full length of the SVC. In this position, guidewire and transseptal sheath advancement toward the SVC can be easily seen.
- Step 3: slowly withdraw the sheath, watching how it slides from the VC toward the RA. As it nears the FO, the probe's right and posterior tilting is slowly removed. The anterior or posterior puncture site can be evaluated by rotating the probe clockwise or counterclockwise, respectively. For arrhythmia ablation procedures and atrial appendage occlusions, inferior punctures are preferred, but toward the center (in an anteroposterior direction) of the FO.
- Step 4: once in position, perform the puncture (the needle's position within the left atrium can be verified

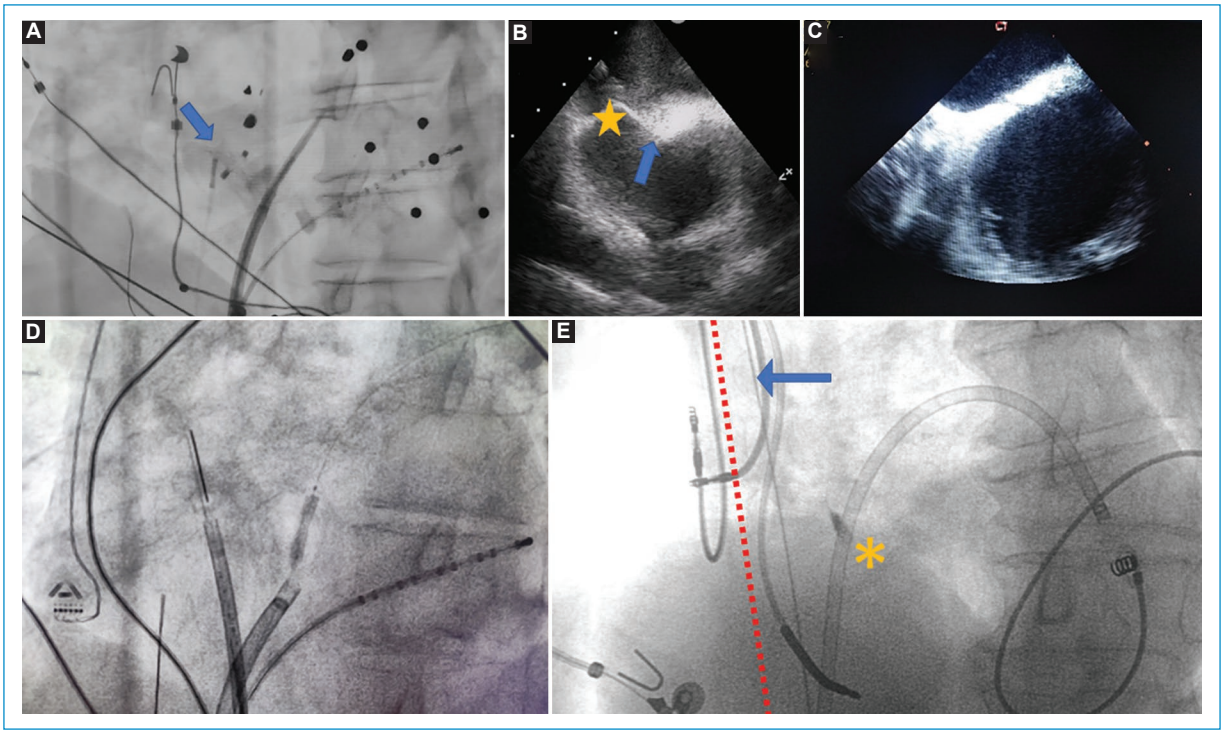

Figure 5. Special situations which entail method changes during TSP. **A:** in patients with atrial septal defect closure devices (blue arrow), a more inferior and posterior TSP is preferred. Although the puncture could also be done through the device, this risks trapping the catheter. **B:** in some patients, the distance between the inferior vena cava and the FO makes it difficult to tent at the desired site (yellow star), as when the sheath is pushed, it slides upward (blue arrow) instead of tenting. **C:** an example of a thickened interatrial septum. These septa may require the use of radiofrequency to facilitate needle passage. **D:** in patients with rigid/thick septa which do not allow the transseptal sheath to be passed, the hole may need to be dilated with (6 mm) peripheral angioplasty balloons; after this, the transseptal sheath is easily advanced. **E:** an example of the proper location of the guidewire in a patient with stimulation cables. The guidewire (blue arrow) should pass between the electrode path (marked in this case by the dotted line) and the interatrial septum, to keep the sheath from dislodging the cable when it falls into the FO. Note the tattoo at the FO from a previous puncture (yellow asterisk).

by injecting saline solution) and advance the entire system as already described.

Difficult scenarios and how to resolve them (Fig. 5)

Superior vena cava thromboses

In patients with SVC thromboses, the traditional technique of dragging the TSP system from the superior cava to where it falls into the FO is not possible. In this situation, it is preferable to use a "down-up" technique: using an electrophysiology catheter as a guide, the TSP sheath is advanced to the desired point in the FO. Once it is situated, the catheter is withdrawn and the dilator and (unexposed) puncture needle are advanced, without losing the sheath position in the FO. Great care must be taken when advancing the dilator outside of the sheath, so as not to lose the position. Once the tip of the dilator is in position over the FO, TSP is performed using the conventional technique.

The presence of atrial septal defect closure devices (Fig. 5A)

In patients with atrial septal defect closure devices there are two options: to puncture through the device or puncture below the device. As much as possible, puncturing through the device should be avoided, as there is a risk of the catheters being trapped[25], and punctures posterior and inferior to the device should be preferred. If the puncture is made through the device, the access should be sufficiently dilated (using balloons) to facilitate the movement of sheaths and catheters.

Difficulty in achieving proper tenting

In patients with severe RA dilation, the distance between the inferior vena cava and the atrial septum increases, making tenting difficult; when pushed, the sheath slides up without exerting enough pressure on the FO (Fig. 5B). In these cases, once the tip of the dilator is successfully positioned in an adequate puncture area, the needle is pushed before tenting. This allows the needle to act as an anchor and keep the sheath from sliding upward. If tenting is still not achieved, a 0.014" guidewire can be advanced by its rigid end to puncture the septum and function as an anchor before pushing the sheath to achieve tenting.

Elastic or rigid/thick septa

Patients with elastic septa have a higher risk of inadvertent atrial perforation, as the septum can move up to the posterior or lateral left atrial wall during tenting. In these cases, it is recommended that the puncture be done pointing toward the left veins (in order to have more room to move the septum) and always with ICE visualization. If the puncture cannot be accomplished with that maneuver, it is suggested that radiofrequency be applied to the needle (using an electrosurgical unit) to facilitate its passage.

In patients with stiff/thick septa, an electrosurgical unit can also be used to facilitate needle passage (Fig. 5C). Alternatively, a 0.014" guidewire can be advanced by its rigid end to facilitate septal puncture. Advancing sheaths in patients with this type of septum (especially deflectable sheaths that have a larger caliber compared with the dilator) may be difficult. In these cases, changing to a nondeflectable sheath may facilitate the transeptal passage. If this is not possible, the operator should be prepared to dilate the entry through the interatrial septum with a 6 mm peripheral angioplasty balloon (Fig. 5D).

The presence of cardiac stimulation device cables

Patients with cardiac stimulation device (CSD) cables, especially those implanted within the last year, have a higher risk of cable dislocation during TSP, as the sheath can become tangled with the cable as it slides down from the cava. This occurs more often with atrial devices, as they generally flow from the SVC toward the right appendage with a loop which is most often located at the FO. In these patients, it is important to ensure that the guidewire passes between the cable loop and the FO (Fig. 5E) to keep it from pulling on the loop and dislocating the cable when it falls toward the FO.

Transseptal puncture complications

Several factors increase the risk of complications during TSP, including the operator's experience (< 45 TSPs per year), older patients, performing TSP without echocardiographic guidance, and failing the first TSP attempt[12]. Transseptal puncture complications can be fatal, and therefore should be detected and treated promptly.

Cardiac tamponade

Cardiac tamponade is the most feared complication during TSP, with a global incidence of 1.6%[12]. However, with echocardiographic guidance, this incidence reduces significantly, to as low as 0.2%[26]. In the event of tamponade, heparin reversal with protamine is recommended, along with percutaneous drainage. This is generally enough to stop most bleeds. If necessary, anticoagulant reversal with four-factor prothrombin complex concentrate (for patients on Xa inhibitors or warfarin; 50 IU/kg dose)[27] or idarucizumab (for patients on dabigatran)[28] can be considered. In most cases, this treatment may be enough to stop the bleeding without the need for surgical treatment[29], especially if the effusion was only caused by the transseptal needle.

Thrombus formation

It is easier to *prevent* thrombus formation than to treat a formed thrombus. When the heparin dose is delayed until after TSP, up to 10% of patients can have visible thrombi on the transseptal guidewires and sheaths[30-32]. Connecting the sheaths to a continuous flow of heparinized saline solution may also be useful, as it prevents thrombi from forming within the sheath lumen. In cases where a thrombus has already formed, vigorous aspiration through the sheath is recommended, attempting to capture the thrombus.

Inadvertent puncture of other structures

Puncture of the posterior right atrial wall is generally not serious as long as the dilator and sheath have not been advanced, as this is a low-pressure chamber. The

procedure can usually be continued without complications, constantly monitoring the pericardial space. If the dilator and sheath have been advanced, they should not be withdrawn until pericardial drainage has been established and everything is ready for an emergency thoracotomy. If the puncture is done too anteriorly, there is a risk of puncturing the aorta. Most of these punctures connect the RA with the noncoronary cusp of the aorta or the sinotubular junction, and rarely with the ascending aorta[33]. The first two cases do not usually carry the risk of tamponade, while puncturing the ascending aorta does (as this implies passing through the pericardial space). If this occurs, whatever has been introduced into the aorta (needle, dilator or sheath) should not be withdrawn. An aortogram should be performed to determine the exact site of aortic penetration, the cardiovascular surgeon should be alerted, and the patient should be prepared for emergency pericardial drainage. Cusp or sinotubular junction punctures tend to heal completely with no intervention during follow up, even if the dilator was advanced. Although some cases have been described in which the defect in the ascending aorta was closed using ductus occlusion devices[34-36], this should only be attempted once the support of a cardiovascular surgeon has been obtained. It is worth noting that, in the largest series of inadvertent aorta puncture cases, echocardiographic guidance was not used for the punctures and the authors recognize that this complication could have been avoided by using it.

Conclusion

Transseptal puncture is a technique which has been increasingly used with the advances in complex arrhythmia ablation and the percutaneous management of cardiac conditions. Despite having considerable risks, these can be significantly reduced by using a proper technique, employing echocardiographic guidance and having an experienced operator. Mastery of intracardiac echocardiography makes this approach much easier and even allows procedures to be performed without fluoroscopy.

Funding

The authors declare that they have received no funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Human and animal protection. The authors declare that no experiments were conducted on humans or animals for this study.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Approach to patients with left ventricular assist device and its complications at the emergency department

Atención del paciente con dispositivos de asistencia ventricular izquierda y sus complicaciones en el servicio de urgencias

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Abstract

Advanced heart failure is becoming more frequent and, in this population, left ventricular assist devices have emerged in the last thirty years as bridge-to-transplant or destination therapy for those with a contraindication for transplant. These devices are continuous flow, contrary to the normal hemodynamic physiology, which leads to associated complications with the interaction between the device and the patient, a phenomenon known as "hemocompatibility." One of its implications is the absence of a central pulse and the need to measure blood pressure through uncommon methods such as Doppler. Various complications are frequently associated with this and can be grouped under the mnemonic $A_2B_2C_2D_2$, in Spanish including those specific and related to the device. Each of these must be recognized for early and prompt diagnosis and treatment, including prompt cardiopulmonary resuscitation, if indicated, to impact the survival of these patients.

Keywords: *Ventricular assist device. Heart failure. Complications. Pump. Cardiopulmonary resuscitation.*

Resumen

La falla cardiaca avanzada es cada vez más frecuente. En esta población, los dispositivos de asistencia ventricular izquierda han emergido en los últimos treinta años como una terapia puente al trasplante o definitiva en aquellos con contraindicación para este. Estos dispositivos son de flujo continuo, contrario a la fisiología hemodinámica normal, fenómeno que conlleva una serie de complicaciones asociadas a la interacción entre el dispositivo y el paciente, la cual se conoce como "hemocompatibilidad". Una de sus implicaciones es la ausencia de pulso central y la necesidad de toma de presión arterial a través de métodos poco frecuentes, como el Doppler. Las diferentes complicaciones asociadas a este son frecuentes y pueden reunirse bajo la mnemotecnia $A_2B_2C_2D_2$, incluyendo aquellas específicas y relacionadas con el dispositivo. Es necesario reconocer cada una de estas para el diagnóstico y tratamiento tempranos y oportunos, incluyendo el inicio precoz de maniobras de reanimación en caso de estar indicado, para impactar la supervivencia de estos pacientes.

Palabras clave: *Dispositivo de asistencia ventricular. Falla cardiaca. Complicaciones. Bomba. Reanimación cardiopulmonar.*

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Date of reception: 20-01-2023
Date of acceptance: 23-05-2023
DOI: 10.24875/RCCARE.M23000067
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):369-379
www.rccardiologia.com

Introduction

The prevalence of advanced heart failure has been growing and accounts for up to 10% of all patients with heart failure[1]. Previously, the only definitive treatment for these patients was heart transplantation but left ventricular assist devices (better known as LVADs) have emerged in the last 30 years as an alternative for patients waiting for transplant, and even as definitive or palliative treatment in patients for whom transplantation is contraindicated[2]. However, this is not an innocuous treatment, and it is estimated that approximately 70% will require hospital readmission within a year of implantation[3]. These devices are a reality in Colombia, and based on the premise of more than 40,000 people having advanced heart failure in the country, the number of possible candidates is not negligible and will continue to grow, as will the frequency of their visits to the emergency room[4]. For all of these reasons, emergency room staff must be trained on these devices and be familiar with the diagnosis and treatment of their main complications. In response to this, we present below a description of LVADs, their complications, handling and treatment in this setting.

The history of left ventricular assist devices

In 1953, John Gibbon began the era of mechanical circulatory support by finishing the first open heart surgery successfully using a cardiopulmonary bypass machine in an 18-year-old woman[5]. In 1963, Michael DeBakey and Domingo Liotta implanted a paracorporeal device for the first time in a patient by the name of George Washington, after aortic valve replacement; however, this patient died four days later[6,7]. The advent of these techniques brought along the challenge of supporting patients who could not be taken off the pump after cardiac surgeries. This is where the idea of providing prolonged ventricular assistance was born, leading to the establishment of a United States National Institutes of Health program in 1964 to create a total artificial heart (TAH)[8]. During this same decade, DeBakey and Liotta were able to successfully implant a paracorporeal device in a patient who could not be taken off the pump after aortic and mitral valve replacement, and after 10 days the device was able to be removed and the patient was discharged, constituting the first successful case of temporary support up to discharge. On the other hand, in 1969, the first version of a TAH was implanted in a 47-year-old man who survived for 64 hours before receiving a heart transplant, but later died from infectious complications[7,8].

In 1972, the LVAD development program was established in the United States, and formal research was begun, as TAH development improved. During the 80s, patients on transplant waiting lists were able to be sustained with a TAH for up to 620 days; however, hemodynamic, infectious and hemorrhagic complications, as well as death, were the common denominator[8]. In 1984, the first LVAD was implanted, and, in this same year, studies showed their usefulness as inpatient bridge-to-transplant therapy. However, the possibility of a patient being discharged with one of these devices was still a utopian dream[8]. It was in 1994, 30 years after their invention, that a patient was able to be discharged with an implanted, portable LVAD. These devices, known as first generation devices, had a pulsatile flow that mimicked the native heart's systolic and diastolic flow[2,8].

In 2001, the REMATCH study demonstrated their benefit in patients with advanced heart failure, even as long-term treatment, reducing the risk of all-cause mortality by 48% and showing a 52% one-year survival rate[9]. Despite this advance, these LVADs had limitations: they did not last long, they were heavy and noisy, and they required valves and multiple components to function[8].

At the beginning of the millennium, research migrated to continuous flow devices with the advent of second generation and axial flow devices like HeartMate II in 2008[2,8]. Two years later, their superiority compared with pulsatile flow LVADs was proven, increasing survival from 24 to 58%[10]. Although promising, they were still very large until the appearance, in the last decade, of centrifugal continuous flow devices. These are smaller, implanted in the apex, and the motor is intrapericardial. The first of these was HeartWare, which was removed from the market in 2021 because it increased the incidence of cerebrovascular accidents (CVAs)[2].

Finally, in the last five years, the first third-generation device appeared with continuous, centrifugal flow, and with a completely magnetic levitation motor, which reduces the risk of thrombosis. This device, HeartMate III, showed a 92 and 58% reduction in the risk of LVAD thromboses and CVAs, respectively[11]. From then on, it was the device of choice.

Basic components of left ventricular assist devices and the impact of continuous flow

The three LVADs used over the last two decades have been HeartWare, HeartMate II and HeartMate III[12].

They all have six components in common: 1) an apically-implanted inflow cannula, 2) a pump that transfers the blood to an outflow graft (3) which takes the blood to where it connects with the ascending aorta. A percutaneous lead (4) projects through the abdominal wall and connects the pump directly to an external controller (5) which monitors the device function parameters and is connected to a power source, which can be a portable or fixed battery (6).[12] (Fig. 1)

They all have four basic parameters reported by the controller: a) the pump speed reported in revolutions per minute, b) the power, measured in Watts, which indicates the current applied to the pump, c) the flow, analogous to cardiac output and expressed in L/min, which is actually an estimate based on the power and speed of the pump and, finally, d) the pulsatility index (PI), an indirect measure of the magnitude of the changes in flow and speed as the native left ventricle contracts[12,13].

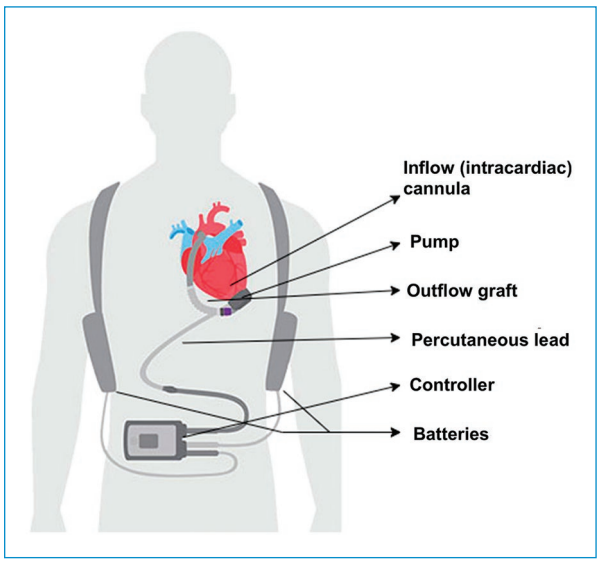

Figure 1. Components of left ventricular assist devices *(adapted from https://www.cardiovascular.abbott/us/en/patients/treatments-therapies/heart-failure/understanding-lvad-therapy.html).*

The physiological impact of continuous flow

The continuous flow of LVADs provides a non-physiological circulation with negative physiological impacts. It is illogical to think that adding a device that functions differently from the heart, a pulsatile pump that has evolved over 750 million years, will have no repercussions on a pulsatile circulation[14]. This close relationship between the LVAD and the heart is responsible for unique complications in this population. This interaction is described under the term "hemocompatibility"[15].

The areas most affected by the continuous flow are precisely those with greater pulsatility. In these sites, pulsatile circulation exerts an antithrombotic effect, as these are areas with greater recirculation and stasis, like the ventricles and aortic arch. This explains the risk of thromboses in these sites in LVAD patients[14].

All of the devices lead to more stress than red blood cells can tolerate, and therefore continuous low-grade hemolysis is common[14]. Other implications include microvascular dysfunction, angiogenic factor release, greater vascular stiffness, sympathetic tone, the risk of aortic regurgitation and proinflammatory cytokine release[15,16]. Von Willebrand factor polymers are also destroyed, leading to acquired von Willebrand syndrome[15].

Initial assessment of patients with left ventricular assist devices

There are unique aspects in the initial assessment of patients with LVADs. When taking the history, it is essential to ask about recent device alarms, heart failure symptoms, changes in urine color suggestive of hemoglobinuria, fever or secretion around the percutaneous lead or other symptoms suggestive of a hemolytic or infectious process.

Since all patients with LVADs should be on anticoagulation with warfarin and platelet antiaggregation with aspirin, tolerance to the medications must be verified as well as the lack of side effects like nosebleeds, melena or hematochezia.

These patients do not have a palpable peripheral pulse, and the different conventional methods for measuring blood pressure are not reliable. Blood pressure measurement will be achieved by palpatory or automatic methods in less than 10 to 50% of cases, respectively. The most reliable method for measuring mean arterial pressure (MAP) in these patients is Doppler[17], which consists of using a regular cuff while the radial artery is insonated. The sound of the radial artery flow is detected with the Doppler, and then the cuff is inflated to 20 mmHg above where this sound disappears. Finally, the cuff is deflated, and the MAP corresponds to the value at which the continuous flow sound reappears[18].

Some useful laboratory tests for assessing these patients include a complete blood count, coagulation times, liver profile and LDH as a hemolytic marker. The electrocardiogram changes after LVAD implantation, with

interference on the tracing; however, it continues to be useful for detecting arrhythmias[19].

All of this helps to suspect one of the various complications associated with LVADs. Thus, the authors propose the mnemonic $A_2B_2C_2D_2$ to remember the potentially fatal or specific complications while caring for these patients (Table 1).

Table 1. LVAD-associated complications

A_2	Arrhythmias
	Cerebrovascular accidents
B_2	Pump thrombosis
	Bleeding
C_2	Altered consciousness and CPR
	Controller alarms
D_2	Right heart failure
	Driveline infection

CPR: cardiopulmonary resuscitation.

Complications associated with left ventricular assist devices

A_2: arrhythmias

At least 30 to 40% of patients will be hospitalized for an arrhythmia within the first two years after implantation[13]. Causes of hospitalization include ventricular scar reentry, the insertion area of the inflow cannula and mechanical irritation around it[12,20,21].

Due to mechanical support, there is a greater tolerance of arrhythmias; there are even reports of cases of recurrent ventricular fibrillation (VF) for days to weeks[13,22]. At least 53% of the patients will be clinically asymptomatic[20]. However, a drop in flow should alert to the possibility of a ventricular arrhythmia, as these can cause flow drops of up to 32% and are not as tolerable as was thought[23].

At least 50% of adults with LVADs have atrial fibrillation (AF) prior to implantation, and some of them improve thanks to lower left atrial pressures[13]. In the event of an AF after implantation, it rarely manifests clinically and will depend on whether right ventricular dysfunction occurs[12,24]. Treatment is similar in patients without LVADs and is guided by the patient's symptoms and stability, but it should be remembered that anticoagulation is indicated in all patients with LVADs[21].

Ventricular arrhythmias are reported in fewer than 20 to 50% of patients and the risk is high mainly in the first weeks after implantation. If the patient had an ICD before, one of the manifestations will be device discharges while awake; otherwise, they will cause few and nonspecific symptoms like dizziness, nausea and fainting[13,20].

The management of these arrhythmias will depend on their clinical presentation. In patients with ICDs, these should be inhibited with a magnet, to prevent further discharges. If the patients are unstable, they should be sedated and cardioverted; if they are stable, the approach will depend on the duration of the arrhythmia. For arrhythmias with a long or unknown duration, right ventricle and aortic valve thrombi should be ruled out. If these are ruled out or the arrhythmia has a short duration, treatment may be started with IV amiodarone, or cardioversion if that fails[12,13,21]. The latter does not interfere with device function, and the LVAD does not need to be turned off or have the batteries disconnected[21].

Finally, if a small, collapsed left ventricle is found on bedside echocardiography, a bolus of IV fluids is indicated, and, if there are findings suggestive of a suction or hypovolemic event, the pump speed should be reduced[13].

A_2: cerebrovascular accident (CVA)

Along with right heart failure, CVAs continue to be the main cause of death in the first six months after implantation and, after this period, they become by far the main cause of death[25]. An estimated 10% of patients will have at least one CVA during follow up, with similar proportions of ischemic and hemorrhagic events[26]. Their main risk factors include female sex, advanced age, arterial hypertension, active infection, time on LVAD support and type of device implanted, among others[26].

HeartMate III is associated with a 58% reduction in the risk of CVAs compared with axial flow devices (HeartMate II); however, despite these advances, the rate of CVAs continues to be at least 9.9% during the first two years[11]. These cases appear to have a J-curve behavior, with the greatest risk during the first three months after implantation and after the first year of follow up[27].

Ischemic CVAs

Ischemic CVAs in patients with LVADs are mostly embolic, due to either passing a thrombus from the left ventricle through the device, or thrombus formation within the system, aortic valve, aortic arch, sinus of Valsalva, etc.

In some cases, they may also be due to a septic embolus within the context of systemic infection or device-related endocarditis[27].

Although LVADs are not an absolute contraindication for systemic thrombolysis, it is clear that most patients will have contraindications to this treatment. Likewise, there is the theoretical consideration that thrombolysis will be less effective since the embolic material in these patients is made up of not only fibrin, but also denatured proteins[28]. It is also unclear if, given their continuous flow, the therapeutic time window is different. Therefore, the current evidence goes back to case reports, and its use is limited to patients without contraindications and suboptimal anticoagulation.

Mechanical thrombectomy has the same indications as in patients without LVADs and is a safe intervention. Despite this, there are certain considerations for its use in this context[27]. Magnetic resonance imaging is prohibited in patients with LVADs, while brain perfusion computed tomography is not available in most of the country's tertiary care centers, and its yield and decision making based on its results are still not clear in patients with continuous flow devices. Thus, mechanical thrombectomy in our setting is relegated to patients in the therapeutic window with computed tomography angiography evidence of a large vessel being affected.

Regarding blood pressure, it has been suggested previously that a MAP of 70 to 130 mmHg be maintained in the first 24 hours[29].

Hemorrhagic CVAs

There are many reasons to believe that intracerebral hemorrhages (ICHs) and subarachnoid hemorrhages (SAHs) are a catastrophe for patients with LVADs. Their onset is a contraindication to heart transplantation. Furthermore, short-term mortality increases significantly and is greater than in patients with ischemic CVAs. According to INTERMACS registry data, survival after a hemorrhagic CVA is 45.3, 34.8 and 30.3% at 1, 6 and 12 months, respectively[26].

Intracerebral hemorrhages and SAHs are multifactorial in patients with LVADs. Anticoagulation is, undoubtedly, one of their main determinants; increased blood vessel fragility has also been described, due to the continuous flow, along with decreased pulse pressure. Finally, the previously described acquired von Willebrand syndrome has been reported due to pump destruction of this factor[28].

Despite understanding their main risk factors and these pathophysiological changes, their onset is still not fully understood. With the latest devices, the risk has diminished, but has not been eliminated. Likewise, evidence of ICHs has been found regardless of the INR level, so the explanation is more than overanticoagulation[28,29]. The most common characteristic in patients with intracerebral bleeding is acquired von Willebrand syndrome[30].

A simple head computed tomography is the diagnostic method of choice and computed tomography angiography is useful for evaluating vascular anatomy and determining the source of the bleeding. There is no contraindication to arteriography but do remember that magnetic resonance imaging is contraindicated.

Treatment for ICHs and SAHs in patients with LVADs is still not clear and, for now, the recommendations for patients without these devices are used for both medical and surgical management. There is a consensus among experts and scientific societies in recommending a MAP between 70 and 90 mmHg in these patients[12,13].

While the suspension of anticoagulation and its reversal with prothrombin complex or fresh frozen plasma is indicated, there is a risk of device-associated thrombotic events[12,28]. Therefore, more conservative management is suggested, reversing anticoagulation only for small ICHs with no major neurological deficit, and even maintaining the INR within the therapeutic range. Meanwhile, in the rest of the cases, anticoagulation may be reversed until an INR less than 1.4 is achieved[30]. Although the outlook is promising, its safety has not been validated.

B_2: bleeding

Non-intracerebral hemorrhages are common in patients with LVADs. They are represented by surgical bleeding immediately after implantation and episodes of gastrointestinal bleeding after three months. An estimated 22 to 32% of patients will have significant bleeding episodes and, together with infection, this is the second most common cause of hospital readmissions and accounts for 2% of deaths in this population[3,28].

The pathophysiology of hemorrhages in this population is multifactorial and includes coumarin anticoagulation and antiplatelet aggregation with aspirin, acquired von Willebrand syndrome, and changes in the vascular wall anatomy, including angiogenesis secondary to continuous flow with the subsequent appearance of arteriovenous malformations, mainly in the gastrointestinal, nasopharyngeal and intracerebral areas[15,28].

Gastrointestinal bleeding has a variable clinical presentation but is usually in the upper tract and rarely

leads to hemodynamic instability. The diagnostic approach is similar to that of patients without LVADs. The choice of endoscopic study depends on the anatomical region in which the source is suspected, in which case upper GI endoscopy is the most used. If the source is not found or there is hemodynamic instability, arteriography could be considered, which could be diagnostic and therapeutic[28].

The initial treatment of gastrointestinal bleeding is similar to that of patients without LVADs, with regard to fluid resuscitation and early endoscopic intervention. Proton pump inhibitors are indicated since the main anatomical bleeding site is the gastric mucosa[28]. If a blood product transfusion is required, irradiated red blood cells should be used for transplant candidates to avoid immunization.

It has been recommended that anticoagulation reversal be limited to patients with major or life-threatening bleeding, understanding the risk of device thrombosis that this entails, especially with the use of prothrombin complex. In the rest of the cases, dual anticoagulant and antiplatelet treatment should only be temporarily suspended or even continued, depending on the severity (if bleeding is minor and not clinically significant)[12].

Successful case series and varied results have been reported with octreotide treatment (a somatostatin analogue that increases vascular resistance, decreases angiogenesis and improves platelet aggregation) as well as studies in which it is applied monthly for prophylaxis[28]. In addition, taking omega 3 has been reported in this scenario; however, the use of either of these depends on each institution's protocol.

B_2: pump thrombosis

Pump or LVAD thrombosis is characterized by the presence of any thrombus within the flow of any of the device's components: the inflow cannula, pump or outflow graft[12]. It is considered a potentially fatal event, setting up a condition similar to left ventricular outflow tract obstruction, and has clinical signs and symptoms ranging from progressive dyspnea to acute heart failure, cardiogenic shock and even death[28]. Its incidence has progressively decreased with the advent of magnetic levitation devices (HeartMate III) that provide a 92% reduction in the risk of pump thrombosis (1.4 vs. 13.9%; $p < 0.001$)[11].

This diagnosis involves two scenarios: a) thrombosis in the internal cannula or inside the pump and b) thrombosis in the outflow graft. The first is characterized by the triad of acute heart failure, hemolysis (LDH more than three times above the upper limit of normal) and rapid flow reduction. Outflow graft thrombosis is not necessarily associated with hemolysis and may be caused by external compression or graft torsion, etc.[12,28]. Table 2 shows the main clinical and imaging differences between the two obstruction sites.

The finding of a rapid change in flow and power, together with elevated LDH, is the classic finding in these cases[12]. Computed tomography angiography is the imaging modality of choice to confirm outflow graft thrombosis[28]. Bedside echocardiography is very useful and can show indirect signs, like left ventricular dilation, aortic valve opening, severe mitral regurgitation and turbulent flow, etc.[31].

There is insufficient evidence to recommend a treatment strategy in patients with device thrombosis. The expert consensus recommends ensuring an INR between 2.5 and 3.5. If, despite this, thrombosis occurs or persists, anticoagulation should be started with unfractionated heparin. In more select cases and as a last resort, the use of systemic thrombolysis with or without glycoprotein IIb/IIIa inhibitors has been described; however, the risk of bleeding is extremely high[11,12,28]. The use of thrombolysis in this scenario is still not clear and has the same considerations presented in the section on ischemic CVAs. Recently, a protocol was described for administering low doses of rt-PA, repeated according to the clinical and paraclinical response, achieving a 69.2% rate of resolution[32]. Nevertheless, other authors have reported lower rates of resolution with high rates of major bleeding using similar dosing schemes, and therefore their use is subject to the institutional protocol[33].

Finally, outflow graft thrombosis could benefit from percutaneous treatment and, if any of the previous treatments fail or the patients are unstable or in cardiogenic shock, extracorporeal support, device replacement or heart transplantation are indicated[12,28,32].

C_2: altered consciousness and CPR

Approximately 13% of patients with LVADs will experience loss of consciousness, corresponding in most cases to orthostatic syncope[12]. The scene is challenging to deal with, since the acceptance of a lack of pulse in these patients may lead to a delay in beginning compressions in the event of a true LVAD failure. There is also controversy regarding the possibility of dislodging the inflow cannula with compressions; however, this has been found to be a rare event and manual compressions are considered to be safe[34].

Table 2. Differences in the array of LVAD thromboses

	Cannula or pump thrombosis	Graft thrombosis
Signs and symptoms	Progressive dyspnea Acute heart failure	Dyspnea Distal embolism
Onset	Short	Progressive
Hemolysis	Yes	No or scant
Device parameter	Low flow and high power	High power
Laboratory findings	Elevated LDH Anemia Tea-colored urine	Absent
Bedside echocardiography	– Dilated LV – Severe mitral regurgitation – Turbulent flow within the internal cannula on Doppler – Visible thrombus within the LV	– Dilated LV – Lack of thrombi in the LV – No turbulent flow within the internal cannula – Turbulence within the graft on Doppler, in a high left parasternal or right parasternal plane
Computed tomography angiography	No obstruction within the graft	Confirms graft obstruction or stenosis and identifies the cause

LDH: lactate dehydrogenase, LV: left ventricle.
Adapted from Ben Gal T et al., *2021*[12].

Outside of the hospital setting, the chain of survival is similar. If untrained people witness a sudden collapse and there is no pulse, chest compressions should be started as soon as possible, and the emergency system should be activated[35]. The latter can instruct the passer-by, by telephone, to begin these maneuvers, if he/she is not trained to identify patients with LVADs. Subsequently, the patient should ideally be transferred to a center with LVAD experience or where the device was implanted[35]. If trained rescuers are available, the two main actions in a patient with altered consciousness are to determine if there are signs of lifelessness or poor perfusion, and confirm if the device is functioning[12].

The absence of signs of life is evaluated by answering the two classic questions: Is the patient unresponsive to stimuli? and Is breathing absent or abnormal? If the answer to both questions is "Yes," the authors recommend beginning compressions, as their benefit outweighs the risk of performing them if there is no cardiac or pump arrest. Also, confirming device functioning can significantly delay beginning resuscitation maneuvers. Other measures for evaluating perfusion include a MAP < 50 mmHg, capnography values falling to less than 20 mmHg and, if available, carotid or femoral arterial Doppler[12,13].

After beginning the maneuvers, LVAD function should be investigated. The controller has a visual signal on its screen indicating its proper functioning. The two main causes of intrinsic device failure are percutaneous lead dysfunction and lack of batteries; therefore, the apex should be auscultated to confirm the device's sound, and each of its components and connections should be verified.

These two assessments will allow an initial conclusion to be reached: in patients with LVADs who are perfused and whose device is functioning properly, it is highly unlikely that their altered consciousness is due to the heart, and thus compressions could be stopped, continuing with ventilatory support and studying other causes like hypoxemia, CVA, hypoglycemia, intoxications, etc.[12].

If the patient has poor perfusion but the device is working, chest compressions should be continued[12,36]. In this scenario, it is important to consider the rapid use of extracorporeal circulation support based on the length of resuscitation, the availability of the resource and the patient's prognosis[35].

During advanced life support, the use of adrenaline, antiarrhythmics and external defibrillation has the same considerations as in patients without LVADs[36]. The limitations of the therapeutic effort and the presence of unequivocal signs of death, like fixed pupils, rigidity or intra-arrest echocardiographic asystole must be kept in mind as elements for considering terminating resuscitation efforts.

If the LVAD is not working, efforts should be made to restart it and change the batteries and the controller, if necessary. If despite checking the entire device and attempting to restart it this is not successful, chest

compressions should continue along with advanced life support measures with the same considerations mentioned above[12]. Echocardiography in critical patients with LVADs is very useful, as this can help evaluate signs of right ventricular dysfunction, look for indirect signs of pump obstruction or volume depletion, confirm if the aortic valve opens during systole, and identify possible causes of cardiac arrest, etc.[31]. Figure 2 presents an algorithm that summarizes the approach to patients with LVADs and altered consciousness, as well as the recommendations for beginning cardiopulmonary resuscitation.

C_2: controller and alarms

Left ventricular assist devices have two alarm levels: warning and critical. The first is yellow, intermittent and requires attention, but not necessarily emergency attention; these alarms include: low battery, low flow, low speed, a disconnected battery cable, etc.[37] The red alarms, on the other hand, are critical, constant and require emergency action; these include: pump arrest, percutaneous lead disconnection, disconnection of both batteries, less than five minutes of battery time, and minimum flow (less than 2.5 L/min)[37].

Pump arrest, although feared, is rare. In these cases, with decreased cardiac output and stasis, ventricular thrombi may form, and therefore care should be taken when deciding to restart the LVAD. If there is hemodynamic instability, the LVAD should be restarted regardless of the time elapsed, as its benefits outweigh the risks; initiating heparin anticoagulation should also be considered[12,37]. If the patient is stable and the LVAD failure only lasts a couple of minutes, it can be restarted; otherwise it should not be restarted, and the patient should be evaluated at his/her LVAD center[12].

The low flow alarm is another important scenario. It has multiple causes including dehydration, right heart failure, cannula obstruction, etc. If the alarm is silenced by assuming the Trendelenburg position, this indicates hypovolemia and, in that case, intravenous fluids would be indicated[13]. Bedside echocardiography can also help narrow down the cause of this alarm[36].

The initial approach to any alarm is to verify each of the controller elements, including the percutaneous lead connection, the two different batteries and their charges, as well as apical auscultation to confirm pump function; management of each alarm will depend on its specific cause. Table 3 shows other possible alarms, their potential causes and their specific approach.

D_2: right heart failure

Right heart failure (RHF) is common and can occur prior to discharge (early RHF) or after discharge (late RHF). According to the INTERMACS registry, its prevalence in the first month after implantation reaches 24%, then declines and remains chronically at approximately 8 to 10%[38]. This has prognostic implications, since its onset is related to lower survival and a higher risk of all the previously described complications[39].

The pathophysiology of post-LVAD RHF is multifactorial. After implantation, there is an abrupt increase in cardiac output and right ventricular preload; this, together with decreased pressure within the left ventricle, leads to septal movement and increases the right ventricular workload. The right ventricle is unable to respond to this increased workload and this causes dysfunction, either *de novo* or worsening of chronic dysfunction[40].

The risk factors associated with its early onset include clinical and echocardiographic characteristics like prior right ventricular dysfunction, as well as hemodynamic characteristics (CVP greater than 15, pulmonary artery pulsatility index less than 1.85), among others[41]. There are also factors that favor the onset of late RHF, like arrhythmias, valve disease, the progression of right ventricular dysfunction and pulmonary hypertension[40].

Ventricular arrhythmias should always be ruled out in these cases. The ultimate management of right heart failure is similar to that of patients without LVADs. Right ventricular preload should be optimized, and therefore diuretics are indicated if there is congestion; if there is low output, inotropes with a pulmonary vasodilatory effect should be started promptly[42]. Echocardiography is useful for evaluating the position of the interventricular septum in patients with RHF and LVADs. If it is significantly deviated to the left, flow reduction through the LVAD should be considered. Finally, the use of right ventricular assistance and mechanical circulatory support would be indicated for patients who remain in shock despite the mentioned treatments[42,43].

D_2: driveline infections

Infections are the “Achilles’ heel” of LVADs. These can be specific to the LVADs (cannula, pump, outflow graft or lead infections) or related to the LVADs (endocarditis, bacteremia, mediastinitis, etc.)[12]. They represent the main cause of hospitalization in the first year after implantation and approximately 20% of patients will have a device infection during follow up[3,12].

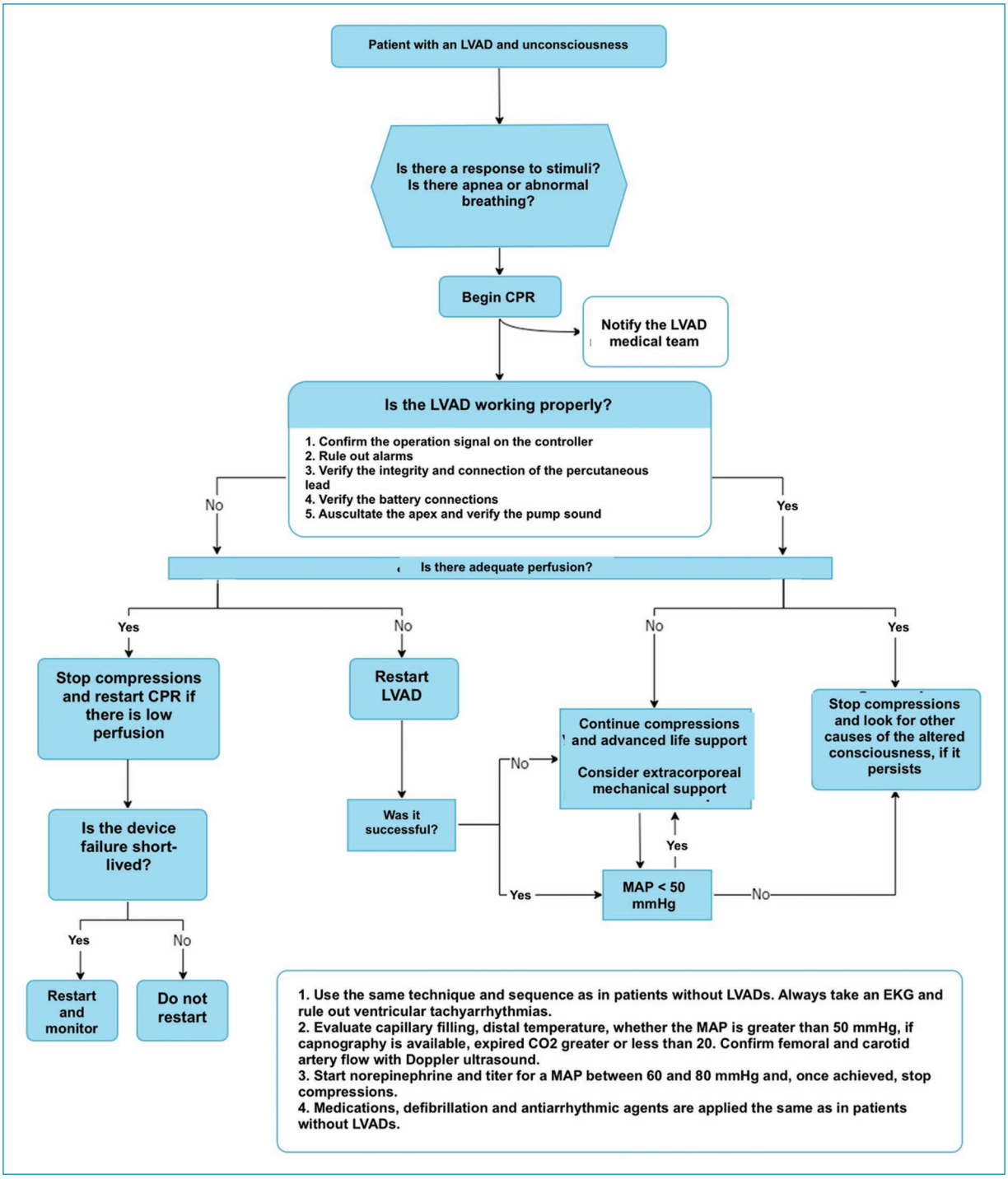

Figure 2. Algorithm of care in patient with LVADs and altered consciousness.

All of the device components are susceptible to infection; the most common infection is of the percutaneous lead (49% of the cases), followed by loco-regional and pump infections with 37 and 14%, respectively[44]. The most frequently isolated germ is *Staphylococcus aureus*, in approximately 56% of cases, but the infection may also be caused by both Gram positive and Gram negative germs[45,46].

It is essential to evaluate the integrity and the exit site of the percutaneous lead in the abdominal wall. When in doubt, a set of blood cultures should be taken, and cultures attempted of the local collections to identify the

Table 3. Complications visible on the controller and their management

Complication	Causes	Considerations	Management
Pump failure	No power source	Check the connections and battery	Emergency cardiology assessment; in the event of shock, restart the pump, give anticoagulation and inotropic support
Low power	– Battery with no charge – Disconnected percutaneous lead		– If it is due to a low charge, connect to a steady power source – In the event of primary failure, establish support measures and consider replacing the device
High power	– Thrombosis – Hypertension – Electrical failure	Bedside echocardiography looking for direct or indirect signs of device thrombosis	– Ensure a MAP of 70-90 mmHg – Actively search for hemolysis, including LDH measurement – Start anticoagulation with UFH in the event of thrombosis – Consider replacing the device in the event of electrical failure
High flow	Infections/sepsis	Evaluate the power; when the power is normal, it is associated with vasodilation and sepsis	Close follow up, consider actively searching for device-specific or associated infections
Low flow	– Suction events – Hypovolemia – Right heart failure – Cannula obstruction – Hypertension – Graft obstruction – Arrhythmias – Very high speed	Bedside echocardiography: – Septal deviation or misalignment of the cannula with the mitral valve in suction events – Turbulent flow or regurgitation on Doppler in the event of cannula obstruction or pump malfunction – Presence of blood clots – Low end-diastolic volume, collapsed vena cava in the event of hypovolemia	– Perform an EKG and echocardiogram – Anticoagulation for thrombosis – Inotropes for shock – Cardioversion for arrhythmias and hemodynamic instability or short-lived VT/VF – Fluid resuscitation for hypovolemia or suction events

EKG: electrocardiogram; VF: ventricular fibrillation; UFH: unfractionated heparin; LDH: lactate dehydrogenase; MAP: mean arterial pressure; VT: ventricular tachycardia. *Adapted from Long B* et al., *2019*[36] *and Cook* et al., *2017*[37].

causal germ. In the event of systemic disease or sepsis, empirical intravenous antibiotics should be started to cover Gram positive cocci and enterobacteria, keeping the local resistance profiles in mind[12].

Conclusions

Left ventricular assist devices are an increasingly common treatment for which emergency staff must be trained. They are the result of more than 50 years of research on mechanical circulatory support and are useful in patients with advanced heart failure as a bridge to transplant or as definitive therapy. They have differential care, including a different method for taking blood pressure. They have frequent complications associated with their functioning, including ischemic and hemorrhagic cerebrovascular accidents, thrombosis, device infections, significant bleeding, RHF and altered consciousness, gathered under the $A_2B_2C_2D_2$ mnemonic. Each has a specific approach, including beginning chest compressions if there is a lack of response to stimuli and absent or abnormal breathing, while the device's function is checked. Finally, each of these interventions should be balanced with the consideration of redirecting the therapeutic efforts, if necessary, in patients whose indication is purely palliative.

Funding

The authors declare that they have received no funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Resilience as a protective factor in a successful aging process

Resiliencia como factor protector dentro del proceso de envejecimiento exitoso

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Abstract

Physiological resilience is acquired according to the individual's capacity to adapt to stress. The aim of this article is to describe the factors that influence resilience in older adults. This is a narrative review based on a database search (PubMed and BVS) with MeSH and DeCS descriptors and keywords such as: resilience, physiological resilience and older adults. Of the 67 initial articles, 23 met the inclusion criteria for analysis and 10 were selected. The individual exposome influences changes in the epigenome, allowing a differential response to the allostatic load and access to active aging that can be modified through early and lasting interventions in older adults to impact on improved quality of life. Modifiable and multidomain contributors to resilience (intrinsic and extrinsic) are the key to its enrichment and contribute to a successful aging process in older adults.

Keywords: *Resilience. Physiological resilience. Older adults. Allostasis.*

Resumen

De acuerdo con la capacidad individual de adaptación al estrés se adquiere la resiliencia fisiológica. El objetivo de este artículo es describir los factores que influyen en la resiliencia de los adultos mayores. Se trata de una revisión narrativa a partir de la búsqueda en bases de datos (PubMed y BVS) con descriptores MeSH y DeCS, y palabras clave como: resiliencia, resiliencia fisiológica y adultos mayores. De los 67 artículos iniciales, 23 cumplieron con los criterios de inclusión para el análisis y 10 fueron elegidos. El exposoma individual influye en cambios del epigenoma, lo cual permite la generación de una respuesta diferencial a la carga alostática y acceder a un envejecimiento activo que puede ser modificado a partir de intervenciones tempranas y perdurables en el adulto mayor para impactar en la mejoría de la calidad de vida. Los contribuyentes modificables y multidominio de la resiliencia (intrínsecos y extrínsecos) son la clave para enriquecerla y contribuir en el proceso de envejecimiento exitoso de los adultos mayores.

Palabras clave: *Resiliencia. Resiliencia fisiológica. Adultos mayores. Alostasis.*

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Date of reception: 31-01-2023
Date of acceptance: 02-05-2023
DOI: 10.24875/RCCARE.M23000060
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):380-384
www.rccardiologia.com

Introduction

Over the last few years, a more positive perspective of aging has emerged under the term "successful aging"[1], which reveals the importance of coming back to concepts like resilience or the ability to respond adaptively to adverse conditions, integrating central and specific body systems[2]. The expression "allostatic load" is also familiar in the medical setting, used to quantify and measure different and successive parameters that the body is forced to modify to adapt to different situations, whether physical, psychosocial, or environmental changes[3].Thus, the exposome is defined as "all environmental exposures to which human beings are subjected from conception onward, and arises as a new strategy to reveal the risk factors for environmental diseases"[4] (translated); this determines the epigenome, which is "made up of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes on or off, controlling the production of proteins in particular cells"[5]. As shown in figure 1, there is a relationship between these variables.

The first scientific review of resilience as an adaptation phenomenon in the context of risk or adversity took place in the 1970s and, since then, different approach strategies have arisen. The first studies physical resilience or the capacity to resist functional decline after exposure to a stressful factor; the second deals with psychological resilience resulting from the ability to adapt in the face of significant sources of psychological stress[6,7].

Internal factors are involved in approaching the different types of resilience, like the intrinsic capacity, biological reserve, and people's psychological resources, as well as external factors like the support network, economic support and cultural context. The balance between these factors is key in responding to the allostatic load and maintaining the body's homeostasis[2-7].

Currently, the potential for recovery in older adults is predicted using static tests of the physiological reserves built throughout life (functional, cognitive and nutritional status, multimorbidity, grip strength, social support network, depressive symptoms). However, understanding that successful aging is not disease-free aging but rather one that incorporates a better response to illness[8], a review of the literature is justified to address the relevance of the dynamic concept of resilience, as an opportunity to transcend the robustness-fragility spectrum to benefit older adults.

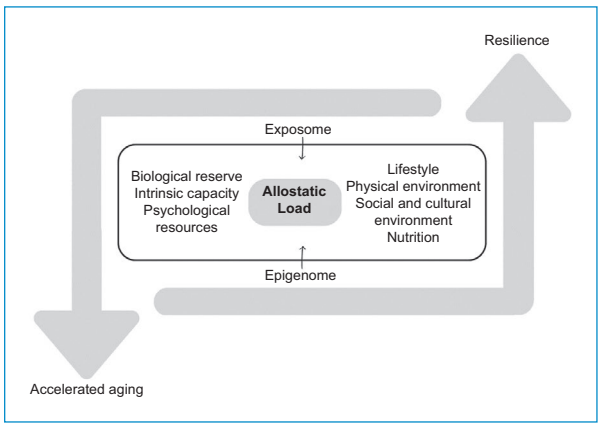

Figure 1. Relationship between the exposome and epigenome which affect aging.

Materials and method

A review of the literature was performed through a bibliographic database search (PubMed and BVS) including a reference document to clarify key concepts. The search criteria were based on the MeSH and DeCS descriptors which were used by combining words: resilience, physiological resilience and older adults; filters were used for the year of publication, limiting the search to the last five years, including only articles in English and Spanish.

The documents were organized by database, and the titles and abstracts were then read to focus the search on data referring to physiological resilience in older adults.

The inclusion criteria were: reviews and systematic reviews with the descriptors (resilience, physiological resilience and older adults) published in the last five years, in English or Spanish. The exclusion criteria were: reviews older than five years, those that were not related to the relevant topics, or reviews focused on resilience in young adults or resilience in the face of a specific disease. Of the 67 initial articles, 23 met the inclusion criteria for analysis and title and abstract reading; 10 of these were chosen for the narrative review.

Results

The 10 articles included approached resilience differently and focused on the following key points: one on the types, one on the trajectory of the associated morbidity, three on neurobiology, three on the modifying exposure factors and two on the clinical approach[9-15].

As a result of the search and corresponding reading of the articles, the relevance of including the study of resilience as a protective factor within the process of successful aging can be affirmed[11,13], considering the individual exposome which, when acted on, can cause modifications in the epigenome, allowing a differential response to the allostatic load[14].

Due to the heterogenous nature of the data included in the selected reviews, a narrative synthesis was used to present the results.

Generalities

Resilience is defined as the ability to respond adaptively to adverse conditions, integrating central and specific body systems. It is divided into physical resilience, or the ability to resist or recover from functional decline after an acute or chronic health stressor, and psychological resilience, defined by the American Psychological Association as the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress[1-6].

Central and peripheral neurobiological stress resilience mechanisms have been described, with the first being: a) decreased hippocampal neurogenesis, b) reduced activation of the dopaminergic neurons projecting to the prefrontal cortex, c) less norepinephrine release in the locus ceruleus, and d) increased activation and postsynaptic transmission of dopaminergic neurons projecting from the ventral tegmental area to the nucleus accumbens[7,11]. Peripherally, changes occur with psychosocial stress, increasing the production of proinflammatory cytokines[12], and environmental stress that incorporates hormonal and signaling changes in the hypothalamic-pituitary-adrenal axis, causing early metabolic imbalance that fosters cardiovascular diseases[8,10].

The path of morbidity in resilience

Resilient centenarians are able to develop anti-inflammatory mechanisms to fight age-related molecular damage. Thus, the “theory of morbidity compression” described by Franceschi et al. in 2018[5], presents three morbidity models based on centenarian patients, in whom the first model believes that the onset of morbidity is constant, and the years of life gained are accompanied by increased morbidity. In a second model, both the onset of morbidity as well as years of life accumulated move toward the right, with no gains or losses in morbidity, and in the third model, the onset of morbidity is delayed and accompanied by accumulated years of life, leading to morbidity compression. This theory was tested in a study in Massachusetts which indicated that the centenarian cohort lived 96% or more of their lives functionally independent and in good health[2,8].

Resilience modifiers have been described throughout the life cycle; the protective factors include a solid social support network, intrinsic behavior traits (optimism) and individual and group active coping strategies that facilitate the adaptive response[2]. Meanwhile, some stress factors refer to passive coping responses (avoidance, impotence), surgeries, hospitalizations, chemotherapy, periods of inactivity, acute pathophysiological processes, and psychosocial and environmental stressors. Chronicity and the isolated or simultaneous occurrence of the factors described are associated with greater or lesser vulnerability[9-15].

Resilience in clinical care

The suggested way of measuring resilience includes evaluating the recovery pathway throughout life, using stimulus-response tests and the evaluation of micro-recoveries after exposure to stress factors. The results of these tests can be presented through two perspectives: a) the recovery phenotype using the Fried model which is measured according to age, comorbidity and functional status prior to the stressor, with the latter being the strongest predictor of recovery; or b) the differential approach of expected vs. observed recovery according to interindividual variability[13,15].

As clinical studies are performed, different biomarkers are defined which interpret the cellular senescence mechanisms: inflammation, mitochondrial dysfunction and muscle deterioration[14] described in table 1.

One example of clinical assessment is the blood pressure system: blood pressure and heart rate changes with position changes which can be used as decreased cardiovascular resilience and increased mortality in evaluating hormonal, vascular and physiological changes. However, there is insufficient evidence, since the tests must be validated, reproducible and safe for routine use. Nevertheless, the loss of resilience anticipates the clinical onset of fragility, especially when evaluated by the body’s subsystems[14].

Comprehensive geriatric assessment

Multidisciplinary assessment in older adults is a static test that allows biological status measurement, which, when conducted longitudinally, favors monitoring of cognitive, physical and psychosocial reserves,

Table 1. Biomarkers of aging

Inflammation	Metabolic and mitochondrial function	Genetic expression
C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor receptor -1 (TNFR-1), monocyte chemoattractant protein -1 (MCP- 1); growth differentiation factor -15 (GDF-15), periostin, tumor necrosis factor receptor type 1 and 2 (TNFR 1,2), soluble vascular cell adhesion molecule -1 (sVCAM-1) and interleukin -6 (IL-6)	Fatty acids, lactate, ketones, acylcarnitines, free amino acids, and insulin-like growth factor-1	Circulating microRNAs (miRNAs)

also helping identify patients with low resilience or at risk of deterioration. Although it is believed that pre-rehabilitation interventions at earlier ages are what lead to positive results in increased resilience[14].

Global and individual resilience in the face of stressors

Currently, most of the clinical predictors of recovery are static tests of physiological reserves in several functional dimensions. Dynamic measurement of resilience must be included to complete clinical intuition based on comprehensive geriatric assessment and, therefore, boost clinical resilience management. To widen the perspective of medicine, which is focused on disease management, it is important to routinely evaluate the recovery potential of older adults within a holistic focus to provide information about the expected rehabilitation time, for early discharge[14].

Likewise, comprehensive geriatric assessment allows an interpretation of the individual's physical, social and cognitive characteristics as well as physical resilience characteristics like mobility, independence in activities of daily living and perception of overall good health; social resilience characteristics like strong family and friendship ties, development in a community, and having a role within his/her setting; and, finally, resilient cognitive and psychological characteristics like adaptive coping styles, satisfaction, optimism and hope in life. Thus, it should be noted that it is complicated to create predictive resilience models, even when classified by stressors or acute stress conditions[13].

Multidomain interventions

Interventions that deal with low physiological resilience are known as senotherapeutic interventions, belonging to "a therapeutic group that contributes to healthy aging and is classified as senolytic, selectively eliminating senescent cells; and senomorphic, modulating senescent cells by blocking the senescence-associated secretory phenotype (SASP); and inflammation and senescent cell clearance by the immune system"[9]. These interventions include nutritional management, this being one of the most studied strategies, ranging from calorie restriction with a moderate food intake (animal protein and fat, low-calorie diet) to Mediterranean-type diets and regular mealtimes. The interventions also include exercise, maintaining the usual circadian rhythms, active lifestyles and coping strategies or cognitive-behavioral therapy[13].

Things that have generated interest in the physiological resilience field include studies seeking to decrease persistent low-grade inflammation, phosphate toxicity, decreased nuclear factor erythroid 2–related factor 2 (Nrf2), diminished metabolic capacity, depressed mitochondrial biogenesis, and the low-diversity gut microbiome found in comorbid older adults. Now, it should be noted that studies based on physical hormone therapies, like brain and muscle stimulation, and nutraceuticals like vitamin D and omega-3, improve immune status, as do mTOR inhibitors and Nrf2 agonists[15].

Conclusions

For geriatricians, whose main goal is to foster active and healthy aging, understanding the relationship between stress and chronic age-related illnesses which significantly affect older adults goes beyond understanding the importance of generating positive adaptive changes to impact geriatric syndromes and decrease the risk of accelerated aging. Thus, teaching and applying resilience in clinical practice, beginning with the training of healthcare professionals, gains interest and relevance as it is constituted as a preventive and comprehensive perspective in approaching older adults.

Technological advances deal with issues related to the molecular mechanisms responsible for mediating the allostatic load and resilience in vulnerable populations, with the ultimate goal of developing effective intervention strategies and implementing leadership programs in the face of challenges and an environment of constant change. As a result of this review, we also

believe it is advisable to implement objective measurement tools to document the acquisition of this skill.

In conclusion, estimating resilience should go beyond neurobiological factors and include an assessment of stressors and environmental modifiers, including behavioral factors, due to their interindividual variability.

Funding

The authors declare that there were no sources of funding for the included evidence sources, nor for the literature review of any of the authors.

Conflicts of interest

The authors declare no potential conflicts of interest.

Ethical disclosures

Human and animal protection. The authors declare that no experiments on humans or animals were conducted for this study.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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REVIEW ARTICLE

Coronary artery anomalies: a review of the literature and proposal for a new classification

Anomalías de las arterias coronarias: una revisión de la literatura y propuesta de una nueva clasificación

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Abstract

Coronary artery anomalies (CAA) are anatomical abnormalities, usually congenital, that affect the origin, course, and termination of one of the three main epicardial coronary arteries. These may lead to adverse outcomes such as myocardial ischemia, heart failure, coronary artery disease and/or sudden death. Since their first descriptions to the present day, and thanks to the development of new technologies, more information and better characterization of these anomalies has been obtained, requiring that the original classifications be revised and updated. The aim of this article is to propose a possible new classification that combines anatomical features and the degree of clinical significance to try to achieve a better understanding, and thus facilitate the clinical choice of treatment. A narrative review was performed and cases from our experience are included.

Keywords: *Coronary arteries. Anomaly. Classification. Tomography.*

Resumen

Las anomalías de las arterias coronarias son alteraciones anatómicas, usualmente congénitas, que afectan el origen, el curso y la terminación de alguna de las arterias coronarias epicárdicas principales. Estas pueden llevar a desenlaces adversos, como isquemia miocárdica, falla cardiaca, enfermedad coronaria o muerte súbita. Desde sus primeras descripciones hasta la actualidad, y gracias al desarrollo de nuevas tecnologías, se ha obtenido más información y mejor caracterización de estas anomalías, lo que hace necesario revisar y actualizar las clasificaciones originales. Este artículo se propone plantear una posible nueva clasificación que combina las características anatómicas y el grado de significado clínico para intentar lograr un mayor entendimiento, y así facilitar la decisión clínica para la elección del tratamiento. Se realizó una revisión narrativa y se incluyen casos de nuestra experiencia.

Palabras clave: *Arterias coronarias. Anomalías. Clasificación. Tomografía.*

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Date of reception: 21-02-2023
Date of acceptance: 16-06-2023
DOI: 10.24875/RCCARE.M23000065
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):385-396
www.rccardiologia.com

Introduction

Coronary artery anomalies (CAAs) are rare anatomical abnormalities which must be appropriately identified and characterized, as they are the second most common cause of sudden cardiac death in young athletes[1], and a cause of chest pain in the general population.

With the growing use and availability of coronary computed tomography angiography as the standard of care for patients with chest pain, coronary artery anomalies and variants are increasingly common[2], most of which have no clinical importance. However, some may cause myocardial ischemia and potentially fatal arrhythmias. It is important to differentiate between clinically relevant anomalies that may require intervention and incidental variants that pose little or no risk for the patient. The purpose of this review is to define these anomalies, discuss the accepted imaging techniques for evaluating them and propose a new classification to better understand them.

Materials and method

A narrative review of the literature on CAAs was performed using the PubMed database and some guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following key words and search strategy were used: coronary [All Fields] AND ("artery"[All Fields] OR "arteries"[All Fields]) AND ("anomaly"[All Fields] OR "anomalies"[All Fields]) AND ("pulmonary origin"[All Fields] OR "APOC"[All Fields] OR "ALCAPA"[All Fields] OR "ARCAPA"[All Fields] OR "opposite sinus"[All Fields] OR "interarterial"[All Fields] OR "subpulmonic"[All Fields] OR "intraseptal"[All Fields] OR "CALM"[All Fields] OR "congenital atresia"[All Fields] OR "bridging"[All Fields] OR "aneurysm"[All Fields] OR "fistula"[All Fields]) AND ("ischemia"[All Fields] OR "ischemic"[All Fields] OR "death"[All Fields] OR "arrhythmias"[All Fields] OR "SCD"[All Fields] OR "angina"[All Fields] OR "chest pain"[All Fields] OR "dyspnea"[All Fields] OR "syncope"[All Fields] OR "malignant"[All Fields]) AND ("nomenclature"[All Fields] OR "classification"[All Fields] OR "incidence"[All Fields] OR "prevalence"[All Fields] OR "outcome"[All Fields] OR "prognosis"[All Fields] OR "mortality"[All Fields] OR "surgery"[All Fields] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "guidelines"[All Fields] OR "imaging"[All Fields] OR "stress"[All Fields] OR "exercise"[All Fields] OR "magnetic resonance"[All Fields] OR "tomography"[All Fields] OR "CCTA"[All Fields] OR "echocardiography"[All Fields]) and the filters "Books and Documents, Meta-Analysis, Review, Systematic Review."

Results

A total of 148 results were included, from which the topical narrative review was performed, and representative cases from our experience are included.

Coronary artery anomalies are anatomical, usually congenital, abnormalities that affect one of the four main coronary arteries. Given the wide spectrum of anatomical variants, coronary anomalies are those which occur in less than 1% of the population[3] and are associated with adverse events[4]. However, cadaver studies and tomographies establish a prevalence between 1 and 7%[3]; but this could be greater if myocardial bridges are included[5]. Several molecular and genetic factors are involved coronary artery embryogenesis during gestational weeks 4-6, including vascular endothelial growth factor, which is responsible for the aortic origin of the coronary arteries; however, the predominant etiology leading to these anomalies is still unclear[5,6].

The usual coronary artery anatomy is divided into four main branches: the right coronary artery (RCA), which originates in the right sinus of Valsalva; and the anterior descending artery (AD) and the circumflex artery (Cx), both originating from a common trunk (LCT) in the left coronary which arises from the left sinus of Valsalva. The posterior (PD) and posterolateral (PL) descending coronary arteries have different variations: originating from the RCA, that is, right dominant, in 70% of cases; arising from the circumflex artery, that is, left dominant, in 10% of cases; and the remainder arising from both arteries, known as codominant arteries, in 20% of cases[7]. However, the differences in dominance are not considered to be coronary artery anomalies.

From an anatomical point of view, CAAs can be divided into origin, course and termination anomalies (Table 1). However, although this classification proposed by Gentile et al.[8] helps understand them from an anatomical and developmental perspective, the classification proposed by Rigatelli et al.[4] (Table 2) includes those that are clinically significant.

Anatomical classification

Origin anomalies

Origin anomalies are defined based on the site from which the anomalous coronary artery arises, which may be the aorta or the pulmonary artery system. Those with an aortic origin are more common and have a lower mortality[8]. Another origin anomaly is the lack of a normal origin,

Table 1. Coronary anomalies

Origin anomalies	Anomalous pulmonary origin of the coronary arteries	Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) Anomalous origin of the right coronary artery from the pulmonary artery (ARCAPA) Anomalous origin of the circumflex artery from the pulmonary artery Total anomalous origin of the coronary arteries from the pulmonary artery (TCAPA)
	Anomalous aortic origin of the coronary arteries	Anomalous origin of the left main coronary artery from the right sinus of Valsalva Anomalous origin of the right coronary artery from the left sinus of Valsalva Anomalous origin of the anterior descending coronary artery from the right sinus of Valsalva Anomalous origin of the anterior descending coronary artery from the right coronary artery Anomalous origin of the circumflex artery from the right sinus of Valsalva Anomalous origin of the circumflex artery from the right coronary artery Single coronary artery Inverted coronary arteries Others
	Congenital atresia of the left main trunk	
Course anomalies	Myocardial (or coronary) bridge Coronary aneurysm	Symptomatic-asymptomatic Congenital or acquired
Termination anomalies	Coronary arteriovenous fistula Coronary stenosis	Congenital or acquired Congenital or acquired

Adapted from Gentile F, et al.,2021[8].

such as an absent left main trunk, which has two possible presentations: an independent source of the Cx and AD, considered to be an anatomical variant with no clinical repercussions (0.67%)[9], or left main trunk atresia, in which this arterial segment is hypoplastic and results in a fibrous tract, with patients subject to myocardial ischemia[10].

Below, we present three coronary origin anomalies, from our practice:

– Left coronary trunk origin from the right sinus of Valsalva: the anomalous origin of the left coronary artery in the right sinus of Valsalva is a rare malformation which represents 0.15% of the cases in Angelini et al.'s series[3]. The anomalous LCT which arises from the right sinus has four subcategories, depending on its trajectory: interarterial, in which the LCT runs between the aorta and the pulmonary artery; intramyocardial, intramural in the ascending aorta and retroaortic[11]. Of these, the LCT with an initial intramural course in the wall of the ascending aorta (Fig. 1) carries the highest risk of sudden cardiac death, followed by the interarterial course, and therefore both are considered to be malignant trajectories[12].

  Several hypotheses have been proposed to explain the coronary ischemia mechanism: the expansion of the aortic and pulmonary roots during systole could compress a common trunk with an anomalous course, or excessive angulation at the origin of an anomalous coronary artery could affect the lumen when the aortic root is dilated during the cardiac ejection phase. The clinical presentation of patients with anomalous origin of the left coronary artery from the right sinus of Valsalva varies and depends largely on the classification of its course. Only 20% of the patients have symptoms, which mainly include exertional angina, dyspnea or syncope[1,13,14]. Unfortunately, sudden cardiac death may be the initial manifestation in some of these cases.

– Single coronary artery: defined as an isolated coronary artery that arises from a single coronary ostium and irrigates the entire myocardium (Fig. 2)[15,16]. It tends to be found incidentally when taking cardiac images for other reasons, and has a prevalance ranging from 0.024 to 0.098% in patients undergoing coronary computed tomography[17-19]. A single coronary artery (SCA) may be isolated or occur with other congenital heart anomalies, including transposition of the great vessels, coronary arteriovenous fistula, tetralogy of Fallot, truncus arteriosus, ventricular septal defect, patent ductus arteriosus, bicuspid aortic valve

Table 2. Classification of coronary artery anomalies

I. Benign coronary artery anomaly	Anomalous origin of the circumflex artery from the right sinus Separate origin of the Cx and the AD Anomalous origin of the Cx from the RCA Type I-IV dual AD Myocardial bridge (score ≤ 5)
II. Relevant: related to myocardial ischemia	Arterial fistula Single coronary artery R-L, I-II-III, A-P Anomalous origin of the LCA from the pulmonary artery (ALCAPA) Atretic coronary artery Hypoplastic coronary artery
III. Severe: potentially related to sudden death	Anomalous origin of the LCA from the right sinus Anomalous origin of the RCA from the left sinus Anomalous origin of the RCA from the pulmonary artery (ARCAPA) Single coronary artery R-L, I-II-III, B Myocardial bridge (score ≥ 5)
IV. Critical: related to sudden death/myocardial ischemia and associated with superimposed CAD	Class II and superimposed coronary disease Class III and superimposed coronary disease

AD: anterior descending; Cx: circumflex; LCA: left coronary artery; RCA: right coronary artery.
Adapted from Rigatelli G, et al., 2005[4].

and patent foramen ovale[20]. There are different SCA classifications in the literature, based on autopsy findings and conventional coronary angiography. In 1979, Lipton et al.[21] suggested a classification system which is divided into two main types: the "R", right type, and "L", left type, to indicate the origin from the right or left coronary sinus, respectively. Single coronary arteries are also divided into three subtypes, according to their anatomical course. Type I, in which there is a single coronary artery arising from the right or left coronary sinus, with the rest of the coronary arteries originating from this one; Type II, in which the single coronary artery arises from the right or left coronary sinus and, in addition, has an anomalous artery emerging from its proximal segment which crosses toward the bottom side of the heart; and Type III, in which the Cx and AD arteries arise separately from the proximal right coronary artery[21].

Depending on the relationship between the SCA and the aorta and main pulmonary artery, Lipton et al.[21] classified SCAs in three categories: Category A, in which the anomalous artery passes in front of the main pulmonary artery; Category B, in which the anomalous artery passes between the ascending aorta and the main pulmonary artery; and Category P, in which the anomalous artery passes behind the aortic root[21,22].

– Anomalous origin of the right coronary artery from the pulmonary artery (ARCAPA): ARCAPA syndrome (Fig. 3) was first described by Brooks, who described a small vessel that originated from the pulmonary artery, traveled across the right ventricular infundibulum and branched[23,24]. This syndrome has an incidence of 0.002%. Two hundred twenty-three cases have been reported in the world, with only eight cases in South America reported by the indexed literature[25]; few cases have been reported in patients over the age of 60. The proposed pathophysiology of ARCAPA begins after birth with deoxygenated blood flow through part of the pulmonary artery toward the RCA; in later phases, there is collateralization and tortuosity of both coronary arteries, with retrograde flow toward the pulmonary artery, and left coronary steal. The shunt produced has been proven to be directly proportional to the diameter of the coronary arteries, and can be up to 25% of the cardiac output, which is also related to a greater Qp: Qs in symptomatic patients[26]. The male sex had a slight predominance (54.5%) with a mean presentation of 14 years; 38% of the patients were asymptomatic at diagnosis and the abnormality was found during studies for a heart murmur[25].
The most common symptoms are angina (22.4%), dyspnea (17%), other symptoms of heart failure (10.8%) and sudden death (6.7%). In symptomatic patients, there was a bimodal presentation around birth and between 40 and 60 years[25]. The most common diagnostic modality is coronary angiography (40.4%), followed by others like echocardiography (26%)[27], in which retrograde coronary flow has been found; coronary computed tomography angiography (15.7%); and magnetic resonance imaging (2%)[28].

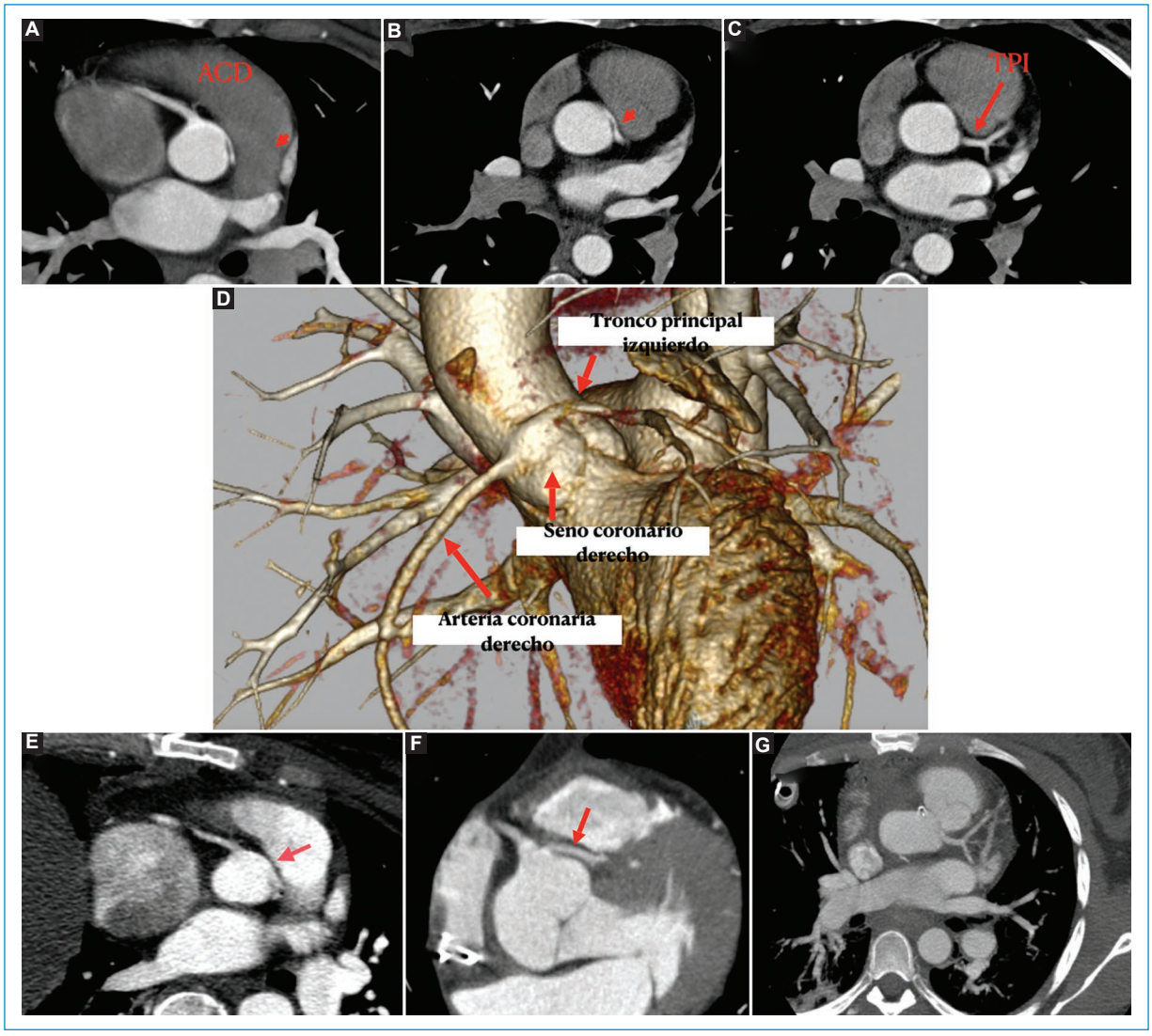

Figure 1. Left main trunk originating from the right (opposite) coronary sinus with an intramural course; the patient had repetitive angina, syncope and chest pain. **A:** coronary tomography showing the left main trunk originating from the right coronary sinus with an intramural course. **B:** malignant intramural and interarterial course of the left coronary artery. **C:** left main trunk (LMT) with its usual distal location and bifurcation into the ADA and Cx. **E, F** and **G:** multiplanar reconstructions immediately after surgery, showing decreased stenosis (arrow) at the origin of the left main trunk due to "unroofing" of the intramural segment of the left main trunk.

Course anomalies

Course anomalies are the most prevalent, as they include myocardial bridges, anomalous courses and the less prevalent coronary aneurysms. The course anomalies include coronary arteries with a retroaortic (Fig. 4), interarterial, subpulmonary (intraconal or intraseptal), prepulmonary or retrocardiac trajectory[8]. The inclusion of myocardial bridges (Fig. 5) as anomalies in the classifications is debated. These are highly prevalent, as 1 in 4 people have a myocardial bridge; however, there are clinically significant bridges which cause adverse cardiovascular outcomes[8].

A myocardial bridge is a congenital coronary defect in which a segment of the epicardial coronary artery passes through part of the heart muscle. The muscle covering the artery is called the myocardial bridge (MB), and the intramyocardial segment is called the tunneled artery[5]. The true prevalence of MBs is not precisely known; however, there are articles which affirm that these MBs are

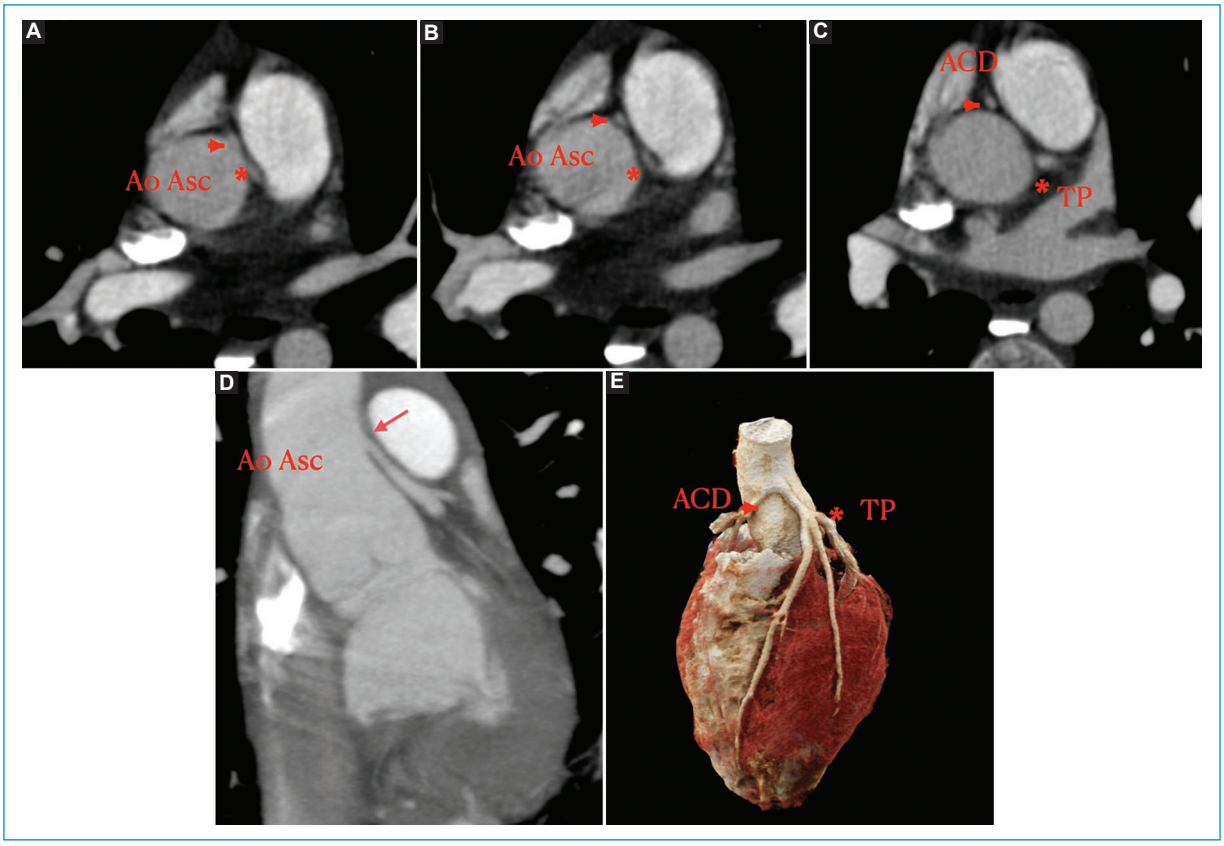

Figure 2. A, B and **C:** axial images showing the origin of the main left trunk (*) and the right coronary artery (arrowhead) from the proximal descending aorta **D:** multiplanar reconstruction showing the origin of the left main trunk 25 mm from the aortic valve plane, above the sinotubular junction. **E:** three-dimensional reconstruction showing the separate origin of both coronary arteries from the proximal ascending aorta.

likely present in approximately 1 out of 3 adults[29]. The rates of MB detection vary significantly, depending on the imaging modality used. The methods most studied to determine the prevalence in the general population include coronary angiography, coronary computed tomography angiography and autopsy studies. The reported prevalence of MBs is 2 to 6% for invasive coronary angiography and 19 to 22% for coronary computed tomography angiography[29]. Autopsy studies are considered the gold standard for identifying MBs, with a prevalence close to 33 and 42% [30]. Regarding anatomical location, 67 to 98% of MBs are located in the ADA, most frequently in its proximal and middle segments. The Cx and RCA are affected less often[31,32]. Keeping in mind the high rate of MBs detected on autopsy, coronary computed tomography angiography is considered to be the most sensitive modality, compared with invasive coronary angiography and intravascular imaging, for general diagnostic purposes. For many years, MBs were considered to be a completely benign phenomenon. This was based on the observation that close to 85% of coronary blood flow occurs during diastole, while MBs are characterized by systolic arterial compression. Therefore, only approximately 15% of the coronary blood flow is at risk of being affected by a significant MB, a seemingly clinically irrelevant fraction. The reality, however, is more complex, and is characterized by the interrelationship of anatomical and physiological factors that affect each other dynamically, not just throughout the cardiac cycle, but also throughout the patient's life[5]. Sternheim et al.[5] commented that both the depth of the tunneled segment as well as its length play an integral role in providing the substrate which ultimately leads to ischemic symptoms in some cases. It is thought that the depth of the tunneled artery (> 2 mm) and the length of the intramyocardial tract (> 25 mm)[33] could be related to a higher degree of systolic compression and potentially be symptomatic. The depth of the MB also has

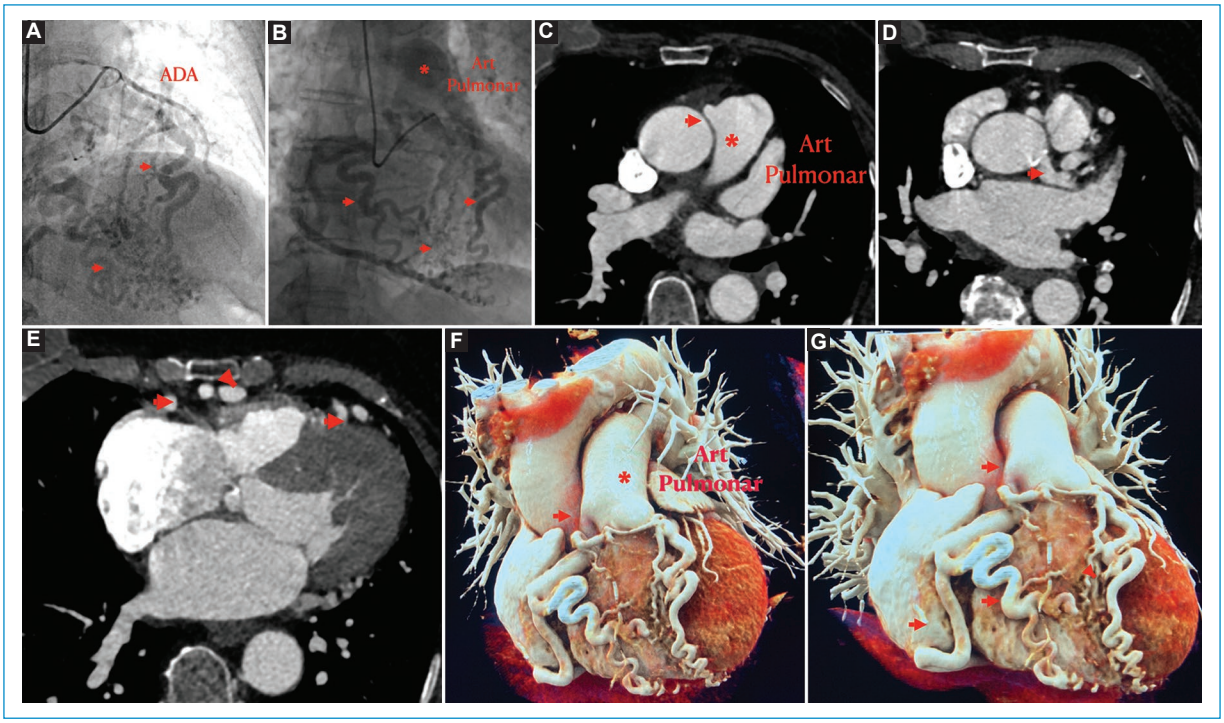

Figure 3. A: selective arteriography images of the left coronary artery showing filling of the anterior descending artery and several collateral circulation branches, with filling of a dominant right coronary artery, in the latest phase. **B:** retrograde filling of the pulmonary artery constituting a left to right shunt. **C, D** and **E:** computed tomography angiography with contrast images showing the origin of the right coronary artery from the proximal aspect of the pulmonary artery (arrowhead in Fig. C). The left coronary and anterior descending arteries are dilated (arrowheads in Fig. D), and there are multiple collateral circulation vessels (arrowheads in Fig. E). **F** and **G:** cinematic rendering three-dimensional reconstruction images showing the origin of the right coronary artery (arrowhead in Fig. F) from the proximal pulmonary artery trunk (*) and siginficant dilation of the coronary arteries, both the anterior descending as well as the ventricular branches of the right coronary artery (arrowheads in Fig. G).

implications for treatment, especially when surgical intervention is considered. The length of the tunneled segment is important not only in relation to the amount of the artery affected, but also to number of branches affected by the MB. This is relevant from a clinical point of view when considering MBs in the ADA which affect the diagonal or septal branches.

Termination anomalies

The termination anomalies are arteriovenous fistulas and coronary stenosis. Coronary artery fistulas are characterized by an abnormal connection between the coronary artery and a heart chamber or toward the coronary sinus, or even toward pulmonary veins or arteries, or the systemic venous system[34]. These are rare malformation which occur in 4% of all congenital heart defects, with an incidence of 0.09% of the adult population undergoing diagnostic angiography[35].

Functional classification

Rigatelli et al.[4] propose dividing the anomalies into benign, relevant, severe and critical, based on their clinical significance. Benign anomalies are anatomical abnormalities which do not lead to myocardial ischemia, such as the separate origin of the Cx and AD from the left coronary sinus and the origin of the Cx from the RCA or with a separate ostium from the right coronary sinus, since they usually have a non-malignant retroaortic trajectory (Fig. 4). Relevant anomalies are those associated with myocardial ischemia; some examples include atretic tracts, hypoplastic tracts, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) and coronary fistulas. Severe anomalies, such as a malignant interarterial course, anomalous origin of the right coronary artery from the pulmonary artery and a single coronary ostium, are associated with sudden death. Finally,

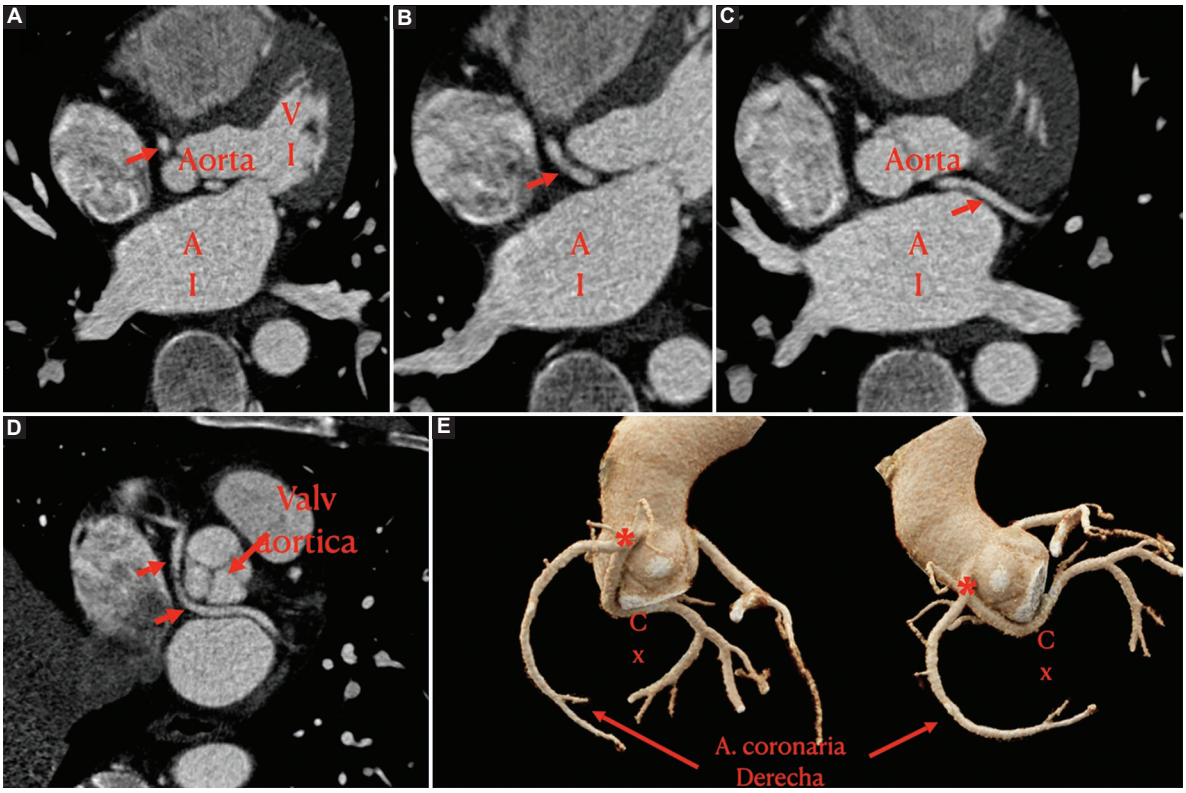

Figure 4. A-D: computed tomography with contrast axial images with cardiac synchronization showing the retroaortic trajectory of the circumflex artery originating from the right coronary sinus (see arrows). Curved muliplanar reconstruction showing the retroaortic pathway of the circumflex artery to its location in the left atrioventricular groove (D). **E:** three-dimensional reconstruction images showing the common ostium (*) in the right sinus of Valsalva for the right coronary artery and the retroaortic circumflex artery. The retroaortic course of the circumflex artery is clearly seen.

critical anomalies are any from Class II and III with associated atherosclerotic coronary disease.

Diagnostic methods

The diverse imaging techniques available for diagnosing coronary artery anomalies include: echocardiography, coronary computed tomography angiography, magnetic resonance imaging and coronary arteriography.

Currently, coronary tomography is the gold standard, above coronary arteriography, due to its anatomical detail of the coronary arteries and extracoronary structures[36-38]. Magnetic resonance imaging, with new technologies, has emerged as an alternative to tomography in selected patients[39].

Echocardiography

Transthoracic echocardiography is an initial assessment method that is mostly used for evaluating pediatric patients, as their acoustic window allows the ostia and, in some cases, the proximal tract, to be evaluated. It is a noninvasive, portable and radiation-free study. It provides functional and valvular information; however, in view of the difficulty in finding an adequate acoustic window in adult patients and lack of evaluation of the coronary pathway, it does not play a prominent role in the approach to adult patients with coronary artery anomalies. A transesophageal echocardiogram has more diagnostic worth for semi-invasive evaluation of the origin of the coronary arteries in adult patients[6,36,40].

Coronary computed tomography angiography

Prior to the standardization of coronary computed tomography angiography, invasive angiography was the gold standard for diagnosing coronary artery anomalies. Modern tomographs, with their high spatial and temporal resolution, have allowed cardiac synchronization with

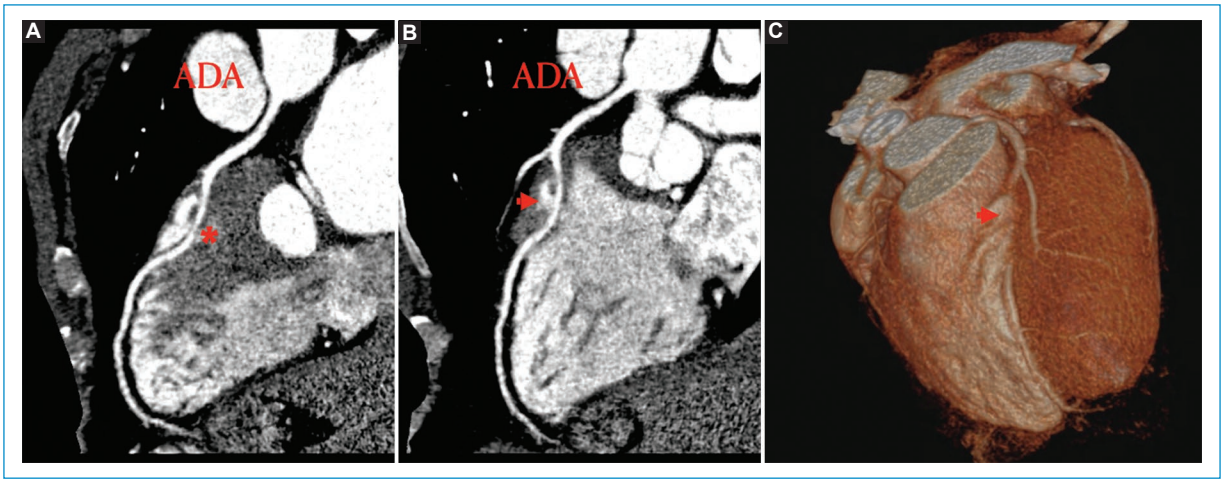

Figure 5. **A** and **B:** multiplanar images showing a deep intramyocardial bridge of the middle third of the anterior descending artery with extrinsic compression (*) due to a "milking" phenomenon. **C:** three-dimensional image showing the partial disappearance of the trajectory (arrowhead) of the middle third within the anterior interventricular sulcus.

increasingly high heart rate thresholds. Many studies have proven their improved sensitivity for detecting coronary artery anomalies, compared with invasive angiography[35]. One of their disadvantages is the dose of radiation. Prospective acquisition, retrospective acquisition with dose modulation, dose modulation according to the patient's habitus and interactive reconstruction are ways of decreasing radiation in tomographs today, with high diagnostic performance[41], reaching very low radiation doses, which is very important in pediatric patients.

Magnetic resonance imaging

This has emerged as an alternative to tomography in pediatric patients[39]. One of the advantages is the evaluation of ventricular and valvular function, as well as the presence of late enhancement due to fibrosis, which suggests the relationship between the anomaly and myocardial ischemia[42]. The disadvantages are the cost, the acquisition time, patient cooperation, the need for anesthesia in some cases, low spatial resolution and the limitations due to artifacts caused by devices. This leads to magnetic resonance being a tool in selected patients and, for now, it will play a secondary role in the evaluation of these diseases.

Coronary angiography

This has been replaced by coronary tomography for the anatomical description of coronary anomalies[43]. Its disadvantages, such as its invasive nature, lack of 3D imaging and spatial resolution, have led to diagnosis by tomography. It has uses like intravascular ultrasound (IVUS) and functional evaluation, such as coronary fractional flow reserve (FFR), which provide anatomical and functional information, respectively.

Discussion

A standardized approach for evaluating coronary artery anomalies, with careful data collection and cooperation between the different specialties is probably the way to improve risk stratification and choose the optimal management of coronary artery anomalies. For this, it is useful to introduce a classification scheme for developing an approach to the complex topic of coronary artery anomalies. While the traditional classifications cover some of the rarer variants, they are not very practical and intuitive.

In our experience, the best way to understand coronary anomalies is to look at their anatomical abnormalities and, from there, differentiate between clinically significant anomalies and those that are probably incidental. We propose an anatomical-functional classification (Table 3) in which coronary artery anomalies are divided into benign and potentially symptomatic anomalies.

Benign coronary anomalies are those with no hemodynamic repercussions and which therefore do not cause symptoms. Patients scheduled for heart or aortic

Table 3. Anatomical-functional classification of coronary artery anomalies

	Origin anomalies	Course anomalies	Termination anomalies	Treatment
Benign	Anomalous origin of the circumflex artery from the right sinus of Valsalva or from the RCA Anomalous origin of the anterior descending artery from the right sinus of Valsalva or from the RCA Anomalous origin of the LCA from the right sinus of Valsalva Anomalous origin of the RCA from the left sinus of Valsalva Separate origin of the Cx and AD Anomalous origin of the RCA and/or LCA from the ascending aorta or sinotubular junction	Superficial and short myocardial bridge Prepulmonary trajectory Transeptal trajectory Retroaortic trajectory Dual AD types I-IV Arterial duplication	Systemic termination	Do not require complementary studies
Potentially symptomatic	Single coronary artery Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) Anomalous origin of the right coronary artery from the pulmonary artery (ARCAPA) Anomalous origin of the Cx from the pulmonary artery Total anomalous origin of the coronary arteries from the pulmonary artery Congenital atresia of the left main trunk Hypoplastic/atretic coronary ostium	Hypoplastic/atretic coronary artery Deep and long myocardial bridge Intramural trajectory Interarterial trajectory Aneurysm	Arterial fistula	Consider complementary functional studies and/or invasive angiography Multidisciplinary management

AD: anterior descending; Cx: circumflex; LCA: left coronary artery; RCA: right coronary artery.

root surgery should be excluded from this classification, as, while the anomaly itself is not relevant, it may lead to complications related to the surgical procedure.

Benign anomalies include coronary artery anomalies with the coronary originating from the opposite sinus, separate origins of the AD and Cx, and the Cx originating from the RCA, which are not clinically significant anomalies if there is no concomitant trajectory anomaly[11,13,14]. Superficial (less than 2 mm depth from the epicardial surface) and short (less than 25 mm length of the tunneled tract) intramyocardial bridges provide less ischemia to cause symptoms in patients, and therefore are also classified as a benign anomaly.

Potentially symptomatic anomalies are those that can be hemodynamically significant and, therefore, present a broad spectrum of clinical signs and symptoms. These are the ones that Rigatelli et al.[4] traditionally classify as relevant and severe, and which may be related to myocardial ischemia and sudden death, respectively, and which, in practical terms, will require complementary functional studies and interdisciplinary management to determine treatment, when detected. Therefore, in our classification, they are gathered under the same concept of potentially symptomatic.

Unlike Rigatelli et al.'s[4] classification, our classification excludes the association between coronary anomalies and atherosclerotic coronary disease, due to its appropriate analysis using the CAD-RADS™ 2.0 reporting system[44] and the E modifier, making this association a separate entity, which includes the study of plaque in coronary disease and nonatherosclerotic stenosis within a single system.

The potentially symptomatic CAAs include origin anomalies in which the coronary artery emerges from the pulmonary artery (ALCAPA, ARCAPA, Cx from the pulmonary artery) [25,26] or in which both coronaries originate from the pulmonary artery (TCAPA), as it has a high incidence of clinical manifestations, including neonatal death[45,46].

The potentially symptomatic course anomalies include deep and long MBs, as they lead to a higher rate of symptoms like unstable angina, acute coronary syndrome and sudden death.

An interarterial course (that is, between the aorta and the pulmonary artery), especially when associated with an intramural segment (that is, the proximal part of an anomalous coronary artery contained within the aortic wall), is the anomaly most associated with sudden cardiac death, and therefore is classified as potentially symptomatic.

The risk of sudden cardiac death is minimal or non-existent for retroaortic and prepulmonary courses. The transeptal course, which has limited treatment options, has rarely been associated with ventricular arrhythmias and death and, likewise, is generally considered benign.

Coronary fistulas, as coronary artery termination anomalies, are classified as potentially symptomatic due to the fact that they have a coronary flow steal phenomenon, reducing the myocardial oxygen supply, which leads to heart failure, unstable angina, papillary muscle dysfunction, valve dysfunction and a high rate of endocarditis[35]. Another coronary artery anomaly is systemic termination, which is also an infrequent finding. This entity must be distinguished from the previously described coronary artery fistulas. Distinguishing between these two entities is important, as the coronary arteries in coronary artery fistulas tend to be enlarged and tortuous. On the other hand, systemic termination of a coronary artery does not tend to produce this pattern, as there is usually not a significant pressure difference between the coronary artery and the systemic artery in which it terminates, and therefore there is no associated coronary steal phenomenon.

A better understanding of these anomalies, together with the standardized approach for evaluation and management, anatomical and functional data collection for risk stratification, and collaboration between different disciplines are essential for optimizing outcomes in this population[47].

Conclusions

Coronary computed tomography angiography with contrast is the gold standard for evaluating coronary artery anomalies. These can cause sudden death, ischemic disease and heart failure. Treatment decisions require multidisciplinary management and depend on the anatomical findings and their hemodynamic repercussions, which are included in a new classification of these anomalies.

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Human and animal protection. The authors declare that no experiments were conducted in humans or animals for this study.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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CLINICAL CASE

Stentless strategy in a non-atherosclerotic acute coronary syndrome: spontaneous coronary dissection

Una estrategia sin stent en síndrome coronario agudo sin aterosclerosis: disección coronaria espontánea

*Mario Buitrago-Gómez[1,2], María Uribe-Forero[1,2], Jessica Neira-Moreno[1,2], Diego Ramírez[1,2], and Carlos Salazar[1,2]**

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Abstract

Although atherosclerosis represents the leading cause of coronary artery disease and, therefore, acute coronary syndrome, several other entities may be also identified. We present the case of a patient with acute myocardial infarction caused by a spontaneous coronary artery dissection.

Keywords: *Acute coronary syndrome. Myocardial infarction. Coronary artery dissection. Ischemic cardiomyopathy.*

Resumen

Aunque la aterosclerosis representa la principal causa de enfermedad coronaria, y en consecuencia, de síndrome coronario agudo, otras entidades pueden identificarse como causantes. Se presenta el caso de un paciente con infarto agudo de miocardio causado por una disección espontánea de la arteria coronaria.

Palabras clave: *Síndrome coronario agudo. Infarto agudo de miocardio. Disección coronaria espontánea.*

Introduction

Ischemic heart disease accounts for half of worldwide cardiovascular deaths. However, several entities may cause myocardial injury, besides atherothrombotic coronary artery disease. Spontaneous coronary artery dissection represents less than 5% of the etiologies of acute coronary syndromes[1]. However, its timely detectionmay impact on patients' quality of life and burden of disease, preventing unnecessary interventions, readmissions and morbidity. We present the case of a patient who presented an acute coronary syndrome which, despite his previous medical history, was not due to atherosclerosis.

Clinical case

A 56-year-old-male with previous arterial hypertension presented to the emergency department with a complaint of a non-ST-segment elevation myocardial infarction (NSTEMI) secondary to emotional stress. Transthoracic echocardiogram (TTE) reported a preserved left ventricle ejection fraction (LVEF) without wall motion abnormalities. He underwent coronary angiography

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Date of reception: 18-03-2023
Date of acceptance: 15-05-2023
DOI: 10.24875/RCCAR.23000021
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):397-399
www.rccardiologia.com

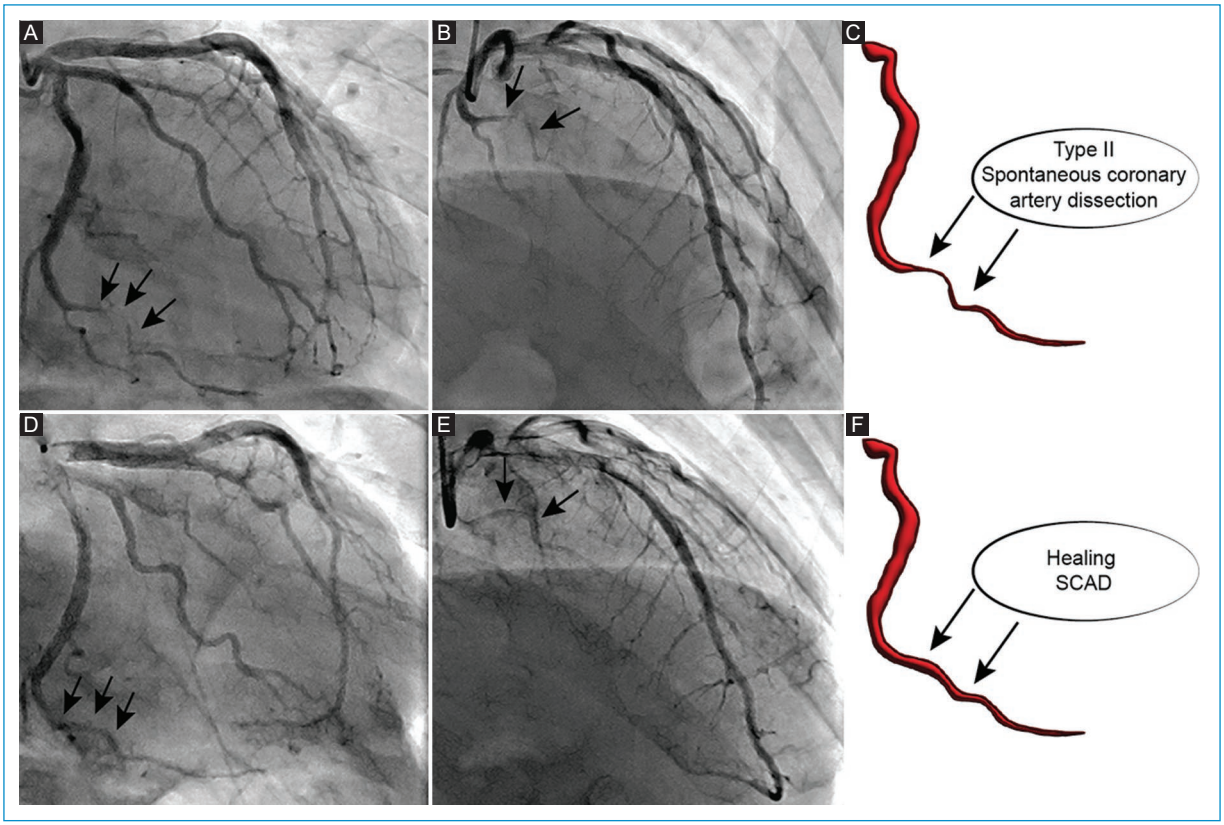

Figure 1. A-B: coronary angiogram showing an abrupt vessel caliber reduction in the third marginal artery. **C:** a diagram of the angiographic finding of the spontaneous coronary artery dissection. **D-E:** coronary angiogram follow-up of the SCAD on the third marginal artery. One month later, the defect had successfully healed, as shown in diagram (**F**), with no need for interventions other than medical surveillance and appropriate treatment.

which reported no atherosclerotic coronary artery disease but a type II spontaneous coronary artery dissection (SCAD) in the third left marginal artery (Fig. 1). Considering the patient's hemodynamic stability, coronary tortuosity, and vessel diameter, conservative management with clinical monitoring was selected rather than percutaneous coronary intervention.

Two months later, the patient was readmitted in the context of an acute coronary syndrome, with no wall motion abnormalities found on TTE. The coronary arteriography documented that the SCAD had healed spontaneously (Fig. 1). He was discharged with significant symptom improvement, and single antiplatelet and beta-blocker therapy was prescribed.

Discussion

Spontaneous coronary artery dissection refers to a separation of the coronary artery wall due to an identifiable emotional or physical stressor (such as emotions or extreme Valsalva maneuvers) and not related to atherosclerotic coronary artery disease, trauma or iatrogenic[2,3]. It causes 4% of acute coronary syndromes. This patient represents an uncommon and higher-risk presentation of SCAD considering that it is significantly more prevalent in women and those with underlying conditions such as arteriopathies, inflammatory and hormonal conditions[4,5].

More than 90% of the patients present with chest pain, even with acute coronary syndrome. Although almost all patients heal spontaneously within 35 days of the event, the prevalence of recurrent myocardial infarction or cardiac readmission is higher than for other non-atherosclerotic causes of acute coronary syndrome such as takotsubo cardiomyopathy[6].

This patient presented a type 2 SCAD which corresponds to the most common pattern of presentation, referring to an intramural hematoma producing an angiographic image of a long , abrupt reduction of the vessel diameter[2]. Coronary angiography is the first diagnostic step for SCAD; intravascular imaging such as optic coherence tomography or intravascular

ultrasound should only be considered whenever percutaneous intervention guidance is required or the angiographic lesions are not clear[7]. In this case, an intravascular image was not taken due to the high tortuosity and risk of associated complications, such as extension of the dissection or occlusion of the vessel.

Conservative management may be a good management strategy in stable patients with no signs of active ischemia, representing a reduction in major cardiovascular outcomes during the first month[5]. Otherwise, PCI may be considered through several approaches ranging from implantation of a long eluting stent to direct stenting without predilatation or balloon angioplasty without stent implantation[4]. Medical management with antiplatelets and statins may be controverted since the mechanism of damage is not attributed to atherosclerosis, and antianginal therapy is related to medical readmission in 20% of cases. However, beta-blockers are associated with a 64% reduction in recurrent SCAD in the following 3.1 years[2].

Conclusion

Spontaneous coronary artery dissection represents a high-morbidity cause of ischemic heart disease. Correct identification and management based on the patient's symptoms and stability reduces recurrence and readmission. The interventional cardiologist must be a leader in the field of the broad spectrum of acute coronary syndrome and coronary artery disease, taking into account non-atherosclerotic entities that require conservative management, when warranted, or be clear about the various percutaneous techniques to solve the problems of facing rare conditions such as SCAD; The treating physician will always play a relevant role in monitoring and identifying triggering factors.

Funding

The authors declare that they have not received funding from any entity.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Data confidentiality. The authors declare that they have followed their workplace protocols for the publication of patient data.

Right to privacy and informed consent. The authors have obtained written informed consent from the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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LETTER TO THE EDITOR

Physical capacity and physiological variables with cardiac failure in a rehabilitation program

Capacidad física y variables fisiológicas con insuficiencia cardíaca en un programa de rehabilitación

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To the editor:

We read with interest the article by Betancourt-Peña[1], titled: "Changes in physical capacity and some physiological variables in patients with heart failure at six and twelve weeks of a cardiac rehabilitation program," published in your journal in October 2021. We would like to highlight the usefulness of the sociodemographic characteristics of patients in Cali, Colombia, during the months of September to December 2017, which showed that the patients were predominantly male, accounting for four out of five individuals. The most common insurance regimen of the participants was the contributive regimen; their average left ventricular ejection fraction (LVEF) was 34.9 ± 1.4. The change in absolute value of the weight and body mass index (BMI) variables was minimal during the 12 weeks of rehabilitation; this change did not show a statistically significant difference ($p > 0.05$). The initial and final systolic blood pressure (SBP) measurements behaved similarly, and at the end of rehabilitation there was a 12.2 mmHg reduction for the initial SBP and a 17.4 mmHg reduction for the final SBP. The initial heart rate reduced 6.2 beats/min at the end of rehabilitation, but the greatest change was recorded during the first six weeks, with a reduction of 6.8 beats/min., which was statistically significant ($p = 0.005$). The oxygen consumption and metabolic equivalent variables showed a progressive increase during rehabilitation of 3.6 ml/kg/min and 1.1 ml/kg/min, respectively; however, we share some observations that we believe would enrich the data analysis, especially aimed at staff working in rehabilitation programs with this group of patients.

The intention is to compare these findings with other published studies related to physiological changes. A quasi-experimental study by Ávila-Valencia et al.[2] from September to December 2016, in patients with heart failure who attended a cardiac rehabilitation (CR) program in a clinic in Cali, Colombia, showed that, at the beginning and end of the predominantly aerobic exercise program, the resting heart rate (HR) variable decreased significantly (73.3 ± 2.7), SBP decreased 13.7 mmHg ± 4.1 and the VO_{2max} and METs statistically significantly increased (5.4 ± 0.9) on the stress test. However, weight (71.3 ± 3.4), BMI (26.1 ± 1.1) and resting diastolic blood pressure (DBP) (70 ± 2.8) at the end of the stress test did not change significantly.

A retrospective, qualitative literature review was performed at Universidad del Gran Rosario in 2020[3], using 10 articles selected through a search of the scientific databases. The analyzed articles include a study by Rhodes et al.[4], which indicates that, during the six months prior to beginning the rehabilitation program, 188 patients 6 to 17 years old performed exercise tests

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Date of reception: 02-05-2023
Date of acceptance: 26-06-2023
DOI: 10.24875/RCCARE.M23000068
Available online: 01-02-2024
Rev Colomb Cardiol. 2023;30(6):400-401
www.rccardiologia.com

with expiratory gas analysis, 71 of whom did not have a sufficiently serious congenital heart defect to be included in the study, and 33 of whom were excluded because they had a VO_{2max} and peak work rate lower than the predicted 80%. They found that the effect of the cardiac rehabilitation program on peak exercise led to a significant increase in VO_{2max} (from 26.4 ± 9.1 to 30.7 ± 9.2 ml/kg/min) and peak work rate (from 93 ± 32 to 106 ± 34 W).

Moreover, in their quasi-experimental study evaluating VO_2p measured by exercise load, tested before and after a receiving a concurrent supervised conventional effort training program, Ku-González et al.[5] determined that 70.6% were males, with an average age of 61.5 ± 8.9 years, and an average left ventricular ejection fraction of 38 ± 4.6%; 96.8% of the HF was ischemic, and 55.9, 29.4 and 5.9% were in New York Heart Association class I, II and III, respectively, with an average volume of 504.34 ± 164 MET-min/week. An analysis of the patients in the risk groups according to maximal effort tolerance through the VO_2p reached on the initial stress test showed that they achieved a VO_2p-load of 5.9 ± 2.1 MET, and 74.4% of the population was in groups C and D, who achieved < 7 MET on the initial stress test. The average training volume awarded was 504.3 MET-min/week ± 164.7, with a Rho = 0.486 (p = 0.008) in the analyzed patients.

Many studies have shown that cardiovascular exercise confers important benefits to patients with heart failure, generating peripheral and central adaptations such as improved skeletal muscle metabolism, endothelial function and cardiac output redistribution; as well as increased vasodilation and hemodynamic changes in heart chamber volumes, ejection fraction and resting and exercise pulmonary pressure. In prescribing exercise for patients with heart failure, the guidelines and protocols usually recommend testing to determine the initial functional capacity and risk stratification and diagnose any other undiagnosed diseases, although these patients are usually already stable and well-studied when they are referred. This testing can be performed on a treadmill or using an arm or leg ergometer[6].

Therapeutic intervention in patients with congenital heart disease is a tool that healthcare professionals around the world should evaluate and use, especially given the pathophysiological differences of patients with these disorders. Therefore, specific forms of the elements to be considered are necessary when establishing treatment goals in the various healthcare fields.

Funding

The authors declare they have received no funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Human and animal protection. The authors declare that no experiments were conducted on humans or animals for this study.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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