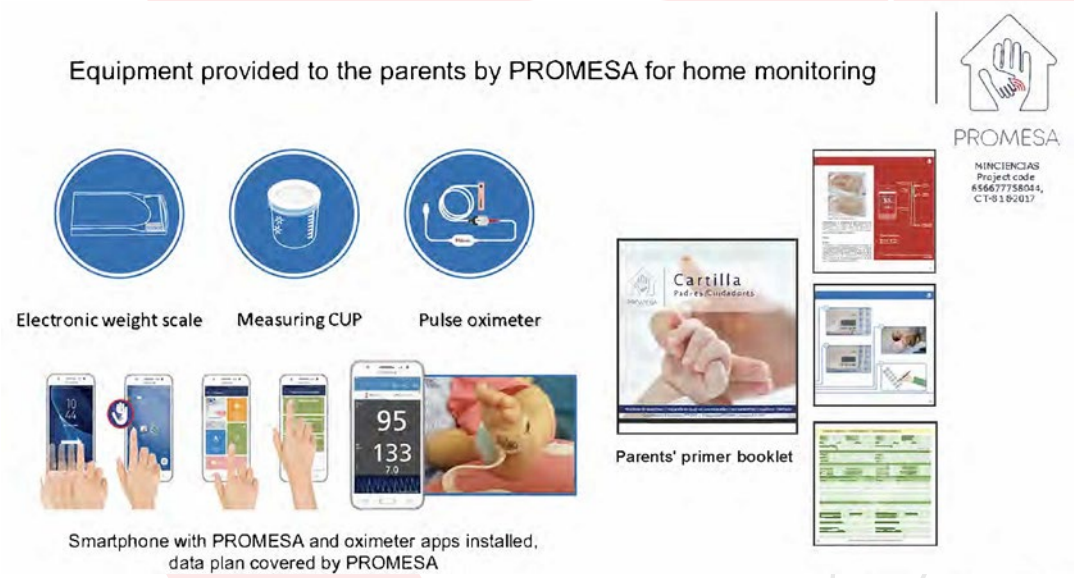
Revista Colombiana de
Cardiología

Volume 32 Number 2 March / April 2025
ISSN: 2938-1525
www.rccardiologia.com
www.revcolcard.org
Indexada en / *Indexed in*: Scopus, DOAJ, EBSCO, EMBASE, MIAR



Equipment provided to the parents by PROMESA for home monitoring. *J. Castro et al.* Innovative first-of-its-kind home monitoring program for children with complex congenital heart diseases.

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EDITORIAL

Cardiac resynchronization therapy: an opportunity for the right moment

Resincronización cardíaca: una oportunidad para el momento oportuno

Julián Aristizábal

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Heart failure has a global prevalence of approximately 3%, thus affecting more than one million people in Colombia[1], and being responsible for close to 300,000 deaths in the United States in 2014[2].

Despite the development of pharmacological therapies that have reduced this disease's morbidity and mortality, there is still a significant residual risk with a notable additional impact on quality of life and healthcare costs. In this regard, cardiac resynchronization therapy (CRT) constitutes an additional tool that has proven to have a favorable complementary impact on reducing mortality and hospitalization for heart failure, improving left ventricular ejection fraction and recovering quality of life[3].

One of the relevant concepts for understanding the impact of CRT is to understand the idea of dyssynchrony: the heart's electrical activation in patients with left bundle branch block (LBBB) causes abnormalities in the heart chambers' contraction sequence, leading to a lack of atrioventricular, interventricular and intraventricular synchrony. There is a significant impact on the left ventricle's mechanical and electrical function, and correcting dyssynchrony is a priority in heart failure. This situation could be associated with the more negative prognosis for patients with heart failure and LBBB vs. other intraventricular conduction disorders[4].

Consequently, to select a candidate for CRT, several criteria must be taken into account: left bundle branch block, QRS duration longer than 150 ms, three months of optimal medical treatment, persistent II-III functional class or ambulatory class IV and no reversible causes. Of course, several elements must be specified:

- In patterns other than LBBB, the QRS duration must be greater than 150 ms. Today we know that even patients with indeterminate morphology, but greater than 150 ms, respond well to resynchronization therapy, unlike patients with right bundle branch block[5].
- In patients with a QRS duration between 120 and 149 ms, the level of recommendation is lower due to the potentially lower beneficial effect of the therapy.
- The presence of atrial fibrillation with rapid ventricular response may attenuate the benefit of CRT, as the percentage of biventricular stimulation may be reduced. In this situation, rhythm control, ideally with pulmonary vein ablation, or ventricular response control with medication or His bundle ablation, will allow adequate resynchronization.

Cardiac resynchronization therapy is traditionally done by inserting an electrode in the coronary sinus, in order to stimulate the basal posterior or posterolateral region of the left ventricle (an area with delayed activation due to the LBBB). Despite correct device implantation,

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Date of reception: 29-12-2024
Date of acceptance: 14-01-2025
DOI: 10.24875/RCCARE.M25000151
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):53-54
www.rccardiologia.com

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multiple factors – anatomical factors, scars, electrode displacement, and diaphragmatic capture, among others – prevent an optimal response in almost a third of patients. How do we resolve this problem? In recent years, alternatives to coronary sinus CRT have been developed, based on a novel principle: physiological pacing. This concept denotes the use of the native electrical system (AV node, left branch or left bundle branch) to transmit the electrical impulse through an electrode in direct contact with these elements, which is inserted in the ventricular septum and advanced until contact is confirmed with the left branch. This bypasses the blockage point in most patients with LBBB[6].

The initial attempts achieved direct AV node pacing but had a high threshold and a significant rate of electrode dislocation. The original report by Huang et al.[7] constituted the starting point of a new method of physiological pacing, left bundle branch pacing (LBBP). Being a new therapy, and having CRT as a reference therapy, many centers began to evaluate the usefulness of LBBP compared to conventional CRT. Díaz et al.[8] published their experience with LBBP as an initial strategy, with promising results. Later, a meta-analysis was published gathering the current evidence, with a predominance of observational studies, which showed that LBBP is associated with a significant reduction in total mortality and hospitalization for heart failure, compared with conventional CRT. Multiple controlled clinical trials are underway, but the guidelines[9] have begun to shift toward considering LBBP as more than a promise. Naturally, these controlled clinical trials must be published to corroborate the current results; time will determine their congruence.

There are still some issues to resolve, perhaps one essential one: to increase the number of patients benefiting from the therapy. In the Colombian Heart Failure Registry (RECOLFACA)[1], less than 5% of patients had CRT. Awareness of treatments other than the already established pharmacological therapies, the emergence and consolidation of heart failure referral centers, and the perfection of therapies like LBBP create new opportunities for patients. Now is the opportune time to take advantage of them.

Conflicts of interest

I have no conflicts of interest in the matter discussed.

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EDITORIAL

Crisis in the health sector: effective challenges and coping strategies

Crisis en el sector salud: desafíos efectivos y estrategias de superación

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The current financial crisis in Colombia's healthcare system represents a significant challenge that impacts not only institutional functionality but also the quality of patient care. This editorial examines the underlying causes of this crisis and its consequences for health care, and proposes urgent measures to mitigate its impact.

A crisis is defined as a sudden, temporary, unplanned state that may be triggered by multiple factors and creates upheaval, disruption or disorganization in different settings. In the organizational setting, especially within the healthcare system, crises occur when the usual methods for handling problems are insufficient. Therefore, it is essential to identify and deal with the factors that cause these situations, as well as implement effective strategies to keep them from worsening.

In the health sector, crises are often associated with financial problems derived, in our case, from the failure of health maintenance organizations (EPS, in Spanish) and the Healthcare System Resources Administrator (ADRES, in Spanish) to pay both public and private hospitals and clinics. This situation has diminished the healthcare institutions' capacity to provide appropriate and timely patient care, as well as meet their financial responsibilities toward their employees and healthcare providers.

One of the most alarming aspects is the lack of payment for services rendered at many of these institutions, which has led to healthcare providers seeking new work opportunities, even outside the country. For example, Spain has authorized more than 8,000 Colombian physicians to practice in its territory, which indicates the high level of training of healthcare professionals in our country.

According to data from *Asociación Colombiana de Clínicas y Hospitales* [Colombian Association of Clinics and Hospitals], the arrears in payments for services has reached 18 trillion pesos, an astronomical figure that, over the last few years, has seriously hindered the acquisition of supplies and technologies needed for proper care. The immediate consequences of this crisis are increased morbidity and mortality and a significant increase in requests, complaints, claims, suggestions and grievances (PQRS, in Spanish). Furthermore, the impact of inflation and a rising exchange rate further complicate the situation, as almost 80% of the supplies and medications are imported.

The accumulation of debts with providers and financial instability have worsened the situation, leaving many public and private hospitals on a tightrope, unable to effectively care for their patients. To deal with this crisis, rapid solutions must be found to improve institutional liquidity, such as seeking new funding sources, obtaining soft loans and issuing securities to provide periodic payment flows. It is also vital for Congress to prioritize approval of the liquidity law currently under discussion in the Seventh Senate Commission.

In conclusion, the current hospital crisis is a significant challenge that affects the essential right to health in Colombia. Strategic measures must be adopted to ensure liquidity and access to healthcare services, which entails a firm government commitment to ensuring prompt payment of healthcare institutions. Only a comprehensive approach will restore the citizens' confidence in the healthcare system and ensure appropriate and timely services for all Colombians.

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Date of reception: 01-02-2025
Date of acceptance: 20-02-2025
DOI: 10.24875/RCCARE.M25000153
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):55
www.rccardiologia.com

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ORIGINAL ARTICLE

Experience of a single center in Colombia: endovascular management of pediatric aortic coarctation

Experiencia de un único centro en Colombia: manejo endovascular de la coartación aórtica pediátrica

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Abstract

Introduction: *surgery, balloon angioplasty, or endovascular stent placement are common approaches for aortic coarctation. Although percutaneous methods have historically proven to be safe, a consensus on their efficacy and complications is lacking. The aim of this study is to describe the experience with both percutaneous techniques in a highly complex center without attempting to establish a direct comparison.* **Objective:** *to describe the experience of both percutaneous techniques in a high-complexity center without intending to establish a direct comparison..* **Method:** *a retrospective study in Colombia (2011-2022) evaluated aortic coarctation patients, analyzing outcomes of balloon angioplasty or stent placement. Data on interventions, complications, and follow-up were analyzed for immediate, short-term, medium-term, and long-term periods.* **Results:** *a total of 61 patients (37 native coarctations, 24 recoarctations) were evaluated, with a mean age of 13 (1-17). Thirty-three patients underwent balloon angioplasty and 28 patients had endovascular stent placement. Success rates were stratified by coarctation type and pre- and post-angioplasty gradient. Balloon angioplasty: 86.7% success (native), 88.8% (recoarctation). Stent placement: 81.8% success (native), 83.3% (recoarctation). The most common complication was hypertension, with a frequency of 37.7%, higher in the stent group.* **Conclusions:** *both techniques proved safe, with balloon angioplasty showing a high success rate. Long-term complications were minimal, but being a single-center study with heterogeneous ages limits generalization, emphasizing the need for larger prospective studies.*

Keywords: *Aortic coarctation. Native coarctation. Recoarctation. Balloon angioplasty. Endovascular stent placement.*

Resumen

Introducción: *la cirugía, la angioplastia con balón o la colocación de endoprótesis endovascular son enfoques comunes para la coartación aórtica. Aunque los métodos percutáneos han demostrado seguridad históricamente, falta consenso sobre su eficacia y complicaciones. El objetivo de este estudio es describir la experiencia de ambas técnicas percutáneas en un centro de alta complejidad sin pretender establecer una comparación directa.* **Objetivo:** *describir la experiencia de ambas técnicas percutáneas en un centro de alta complejidad sin pretender establecer una comparación directa.* **Método:** *un estudio retrospectivo en Colombia (2011-2022) evaluó pacientes con coartación aórtica, analizando resultados de angioplastia con balón o endoprótesis. Datos de intervenciones, complicaciones y seguimiento se analizaron en períodos inmediato, corto, medio y largo plazo.* **Resultados:** *evaluación de*

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Date of reception: 11-01-2024
Date of acceptance: 13-01-2025
DOI: 10.24875/RCCARE.M25000137
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):56-62
www.rccardiologia.com

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61 pacientes (37 nativa, 24 recoartación), edad promedio 13 (1-17). Angioplastia con balón (33 pacientes) y colocación de stent (28 pacientes). Tasas de éxito estratificadas según tipo de coartación, gradiente pre y post-angioplastia. Angioplastia con balón: éxito 86.7% (nativa) y 88.8% (recoartación). Endoprótesis: éxito 81.8% (nativa) y 83.3% (recoartación). Complicación más común: hipertensión, incidencia 37.7%, mayor en endoprótesis. **Conclusiones:** *ambas técnicas mostraron ser seguras, mostrando una tasa de éxito elevada la angioplastia con balón. Son mínimas las complicaciones a largo plazo, pero al ser un estudio dentro de un único centro y la presencia de edades heterogéneas limitan generalización, destacando necesidad de estudios prospectivos más amplios.*

Palabras clave: *Coartación aórtica. Coartación nativa. Recoartación. Angioplastia con balón. Colocación de endoprótesis endovascular.*

Introduction

Aortic coarctation accounts for 5-8% of all congenital heart defects[1,2]. Surgery, transcatheter balloon angioplasty (BAP) or endovascular stent placement (ESP) are the corrective treatment approaches for coarctation[3]. Surgery is historically preferred for native coarctation; nevertheless, it increases operative and early mortality rates in low birthweight neonates, extends hospital stays, and could produce paraplegia when repeated[3-7]. Recoarctation encompasses residual and recurrent coarctation; its incidence varies depending on the age of repair and the patient´s aortic arch anatomy, among other factors[1-8]. The standard treatment for recoarctation is BAP, as it avoids the need for repeat surgery and contributes to a high success rate and a low risk of aneurysms and dissection; however, patients usually require additional reintervention[9,10]. Some institutions and clinicians consider this technique the initial corrective choice in native coarctation with suitable anatomy, in the presence of significant collateral vessels, and when surgery is contraindicated; nevertheless, it has been suggested that it produces a higher rate of recoarctation and aortic wall complications[1,7,9,11].

Later, ESP was introduced. The literature shows higher efficacy and safety, and lower vascular complications than BAP, in older children and adults[12]. The outcomes of ESP in small children are not well established because of the challenge of stents accommodating aortic somatic growth[13,14]. A lack of consensus persists about the effectiveness and complications of each transcatheter approach. Patients require long-term follow-up to treat complications such as hypertension, aneurysms, and recoarctation, despite advances in percutaneous techniques, technology, and patient eligibility[15-17]. The objective of this study is to present our experience at a high-complexity center in managing coarctation of the aorta using two endovascular techniques, with no intention of directly comparing the effectiveness of one technique versus the other.

Method

We retrospectively searched the hemodynamic, echocardiographic, and clinical data of patients with either native coarctation or recoarctation who underwent BAP or ESP between January 2011 and February 2022 in a high complexity center in Colombia. This study includes patients of all ages with aortic coarctation, defined as an upper to lower limb systolic pressure gradient > 20 mmHg or evidence of obstruction on echocardiography or computed axial tomography imaging. We collected data from all patients on weight, age, associated cardiac defects or genetic anomalies, echocardiographic gradient, hemodynamic pre- and post-intervention peak-to-peak gradient, balloon and stent technical specifications, and mortality. Immediate complications were defined as any arterial wall injury or technical complication derived from the catheterization. During ten years of follow-up, we assessed late complications defined as aneurysms, hypertension, or recoarctation. We divided complications into short-term (between one month and less than one year), medium-term (between one year and less than three years), and long-term (from more than three years to 10 years of follow-up)[18].

Trained pediatric cardiologists performed the transcatheter interventions under general anesthesia. In all cases, the Seldinger technique was used to access the femoral vein and artery; administer 100 IU/kg of intravenous heparin; introduce a guidewire from the ascending to the descending aorta; perform an anteroposterior and lateral aortogram; measure the coarctated and diaphragmatic segment, as well as the transverse aortic diameter; and obtain the peak-to-peak gradient pre and post-intervention[19-21]. The balloon size was selected based on the diaphragmatic aortic diameter or the coarctated diameter, assuring a maximum balloon inflation size of three times the stenosis. Children underwent ESP only if the stent could expand further. Hemostasis was achieved through manual pressure.

We defined a successful catheterization as a post-intervention residual peak-to-peak gradient < 20 mmHg or a > 50% reduction if the gradient was < 20 mmHg pre-intervention.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) or mean and standard deviation (SD), depending on their distribution. Categorical variables are presented as percentages and absolute values. Student's t-test was used to compare continuous variables. A $p < 0.05$ was considered statistically significant. The analysis was performed using RStudio® software.

Results

We included 61 patients, 37 with native coarctation and 24 with recoarctation; 33 underwent BAP, and 28 underwent ESP. Twenty of the recoarctated group had had previous surgery, three had had a prior angioplasty, and one had had surgery and percutaneous treatment. Some patients initially scheduled for stenting underwent balloon placement instead, based on the type of coarctation found during the procedure, and at the physician's discretion. However, no patients initially planned for balloon placement required stenting.

Three patients had a genetic association: Di George, Turner, and Goldenhar syndromes. The most common cardiac defects related to aortic coarctation were bicuspid aortic valve (50.82%), persistent ductus arteriosus (18.03%), and ventricular septal defect (16.39%). Eight patients had hypoplastic aortic arch (13.11%).

Patients undergoing ESP were over the age of eight, except for one three-month-old patient with native coarctation. This patient had a ventricular defect and tubular arch hypoplasia; he had undergone two repeat interventions in the short term because of residual coarctation, an unsuccessful first ESP, and a recoarctation two months after the first procedure. The baseline patient characteristics are presented in tables 1 and 2.

The balloon used for stent placement had a median diameter of 12 mm (IQR 12-14 mm) and an inflation pressure of 8 atmospheres (IQR 7-12 mm). Detailed specifications of the stents used in ESP are shown in table 3. Thirty-three patients underwent BAP; 11 patients used TYSHAK balloons, five patients used MINI TYSHAK, seven ANDRA balloons, four POWERFLEX, two MAVERICK, one ULTRA-THIN DIAMOND, one MUSTANG, and one XXL; we excluded one balloon corresponding to a patient who had previously undergone an ESP at another institution.

The ESP's median hemodynamic residual gradient decreased from 35 mmHg (IQR 25-45 mmHg) pre-angioplasty to 2 mmHg (IQR 0-5 mmHg) post-angioplasty. For BAP, the median reduction was from 27.5 mmHg (IQR 20-40 mmHg) to 10 mmHg (IQR 7-19 mmHg). Success rates and pre- and post-angioplasty gradients for ESP and BAP, divided by native coarctation and recoarctation, are presented in table 4. The success rate for all groups was similar (85.2%); BAP had a combined success rate of 87.9% versus 82.1% for ESP.

Thirteen patients experienced recoarctation; three recoarctated patients underwent surgery, and ten underwent a new angioplasty. The observed incidence of recoarctation was 24% in BAP patients versus 17% in ESP patients. Five patients had immediate complications (during the same interventional hospital admission); two BAP patients experienced a cerebrovascular and cerebellar stroke, and three ESP patients experienced subclavian artery flow disruption, iliac artery stenosis, and stent migration. There were two deaths unrelated to the hemodynamic treatments: one patient died in the hospital during a pulmonary banding and another patient died four years after stent implantation during an ascendent aortic replacement. Forty-two patients attended short-term follow-ups, 28 medium-term follow-ups, and 10 long-term follow-ups, six of whom completed 10 years of follow-ups. The frequency of hypertension, taken from the patients' last follow-ups, was 37.7%: 50% in the stent implantation group versus 27.27% in BAP patients. Complications are shown in tables 5 and 6. None of the patients developed aneurysms.

Discussion

We aimed to describe our ten-year experience with percutaneous management, either ESP or BAP, in 61 patients with native coarctation or recoarctation. The order of occurrence of associated cardiac defects is comparable to the ones reported in other studies[22,23]. The majority of patients had native coarctation (60.66%), and most of them underwent ESP (59.5%). We used the established definition of a successful dilatation to evaluate effectiveness[24]. The patients with recoarctation had undergone surgical correction previously and were diagnosed with restenosis evidenced by nuclear magnetic resonance imaging or angiography tomography on follow-up.

Table 1. Baseline patient characteristics

Features	n = 61
Age (years)	13 (1-17)*
Weight (kg)	27 (5.2-49.5)*
Associated genetic syndrome	3 (4.92)
Associated cardiac defect	
Atrial septal defect	5 (8.20)
Ventricular septal defect	10 (16.39)
Patent ductus arteriosus	11 (18.03)
Hypoplastic aortic arch	8 (13.11)
Bicuspid aortic valve	31 (50.82)
Shone syndrome	4 (6.56)

*Median (IQR).

Table 2. Patients' characteristics divided by type of percutaneous treatment

Features	Endovascular stent placement (n = 28)	Balloon angioplasty (n = 33)
Age (years)	16 (13-23.5)*	1 (0-9)*
Weight (kg)	47.25 (36-60)*	6.8 (3.6-23)*
Native coarctation	22 (78.57)	15 (45.45)
Recoarctation	6 (21.43)	18 (54.55)

*Median (IQR).

Table 3. Stent specifications

Type of stent	Length (mm)	n	%
Covered Platinum Cheatham	39	6	21.43
Atrium Advanta	41	8	28.57
Naked Platinum Cheatham	39	1	3.57
Genesis Blue	24	1	3.57
Covered Platinum Cheatham	45	2	7.14
Begraft	39	3	10.71
Andra	35	1	3.57
Andra XL	39	1	3.57
Advanta	36	1	3.57
Covered Platinum Cheatham	28	1	3.57
Advanta	61	2	7.14
Begraft	59	1	3.57
		28	

It must be noted that ESP patients were significantly older than BAP patients due to the stent delivery sheath size being unsuitable for small children or aortic somatic growth, given the stent´s inability to self-expand[9,25]. Although surgery is commonly preferred in the early stages of life, and ESP is selected for patients over the age of six or with a general weight above twenty kilograms, in reality, stent implantation could also be used in younger patients with promising results[26,27]. In our case, most patients who underwent ESP were older than eight, with the exception of a three-month-old patient with native coarctation. This patient was initially considered for surgery but due to hemodynamic instability on hospital admission, other options were considered. After thorough discussion with the pediatric cardiac surgery team, it was determined that surgery was not a viable option and posed significant risks for the patient. As a result, ESP was performed, which proved to be effective in this case. Further studies must be done comparing adult-sized and covered stents in pediatrics[27,28].

Multiple studies have reported higher success rates with ESP than with BAP[12,29,30]. Endovascular stent placement on its own has been reported as a highly effective and safe treatment for patients with aortic coarctation, showing success rates of up to 99% and good short-, medium-, and long-term results in patients with coarctation and recoarctation[31-33]. Our study, however, did not show comparable efficacy, which may be attributed to our level of experience with BAP and the larger number of patients who underwent this procedure in comparison to those who received ESP. Therefore, BAP still proves to be a safe and effective technique to treat coarctation, especially in patients with recoarctation[34,35]. Its effectiveness remains questionable for native coarctation, with a recurrence rate of up to 27% according to the literature, and a success rate of around 94%[10,34,35].

Although both transcatheter techniques have high success rates and efficacy, it should be noted that BAP has a higher rate of aortic wall complications[36]. Balloon angioplasty's higher incidence of vascular complications compared to ESP has been discussed. Theoretically, significant balloon expansion to relieve the stenosis increases the risk of aortic wall complications, such as aneurysms and dissection[37]. In a literature review focused on aortic wall injury outcomes, the incidence of aneurysms and dissection was 0-13% for BAP, 0-5% for bare stent placement, and < 1% for covered stent placement[38]. Our patients undergoing BAP did not present aortic wall complications; this can be explained by the low-profile balloons that required shorter introducing sheaths. Our findings correlate with those of another

Table 4. Hemodynamic data for balloon angioplasty and endovascular stent placement, divided by native coarctation and recoarctation

	Pre-angioplasty gradient	Post-angioplasty residual gradient	p	Success rate
Native coarctation				
Balloon angioplasty (n = 15)	24 (18-41)	10 (7.2-14.8)	0.000	86.7% (13/15)
Endovascular stent placement (n = 22)	36 (25.8-47.5)	2 (0-4.8)	0.000	81.8% (18/22)
Recoarctation				
Balloon angioplasty (n = 18)	28.0 (20.0-37.0)	10 (7-20)	0.001	88.8% (16/18)
Endovascular stent placement (n = 6)	19 (12-26)	5 (2-5)	0.012	83.3% (5/6)

Table 5. Complications

Complications	Endovascular stent placement (n = 28)		Balloon angioplasty (n = 33)	
	Native coarctation (n = 22)	Recoarctation (n = 6)	Native coarctation (n = 15)	Recoarctation (n = 18)
Late complications				
Arterial hypertension	10 (45.5)	4 (66.7)	4 (26.7)	5 (27.8)
Recoarctation	2 (9.1)	3 (50)	3 (20)	5 (27.8)
Immediate complications	1 (4.5)	2 (33.3)	2 (13.3)	0 (0.0)
Death	0 (0.0)	1 (16.7)	1 (6.7)	0 (0.0)

Table 6. Follow-up complications

Follow-up complications	Endovascular stent placement		Balloon angioplasty	
	Native coarctation	Recoarctation	Native coarctation	Recoarctation
Short-term follow-up (from the hemodynamic intervention to < 1 year of follow-up) (n = 42)				
Hypertension	9 (69.2)	4 (66.7)	2 (25.0)	6 (66.7)
Recoarctation	1 (6.7)	0 (0)	2 (20.0)	4 (36.4)
Medium-term follow-up (from 1 year to ≤ 3 years of follow-up) (n = 28)				
Hypertension	0 (0.0)	4 (100.0)	2 (40.0)	6 (66.7)
Recoarctation	1 (16.7)	2 (50.0)	0 (0)	0 (0)
Long-term follow-up (from > 3 years to 10 years of follow-up) (n = 10)				
Hypertension	1 (100.0)	2 (100.0)	0 (0)	1 (14.3)
Recoarctation	0 (0.0)	1 (50.0)	0 (0)	2 (28.6)

study that experienced no aneurysms and minimal vascular complications using TYSHAK balloons[39].

In terms of recoarctation, a few more patients were recorded within the BAP group compared to the ESP group (eight vs. five), both in cases of native coarctation and recoarctation. In the literature, recoarctation patients undergoing BAP had a recurrence incidence of 27.8%; other studies report 15%[40]. Patients with native coarctation who underwent BAP in our study presented a recoarctation incidence of 20%. This is similar to that reported in other studies (21% and 25%)[41], with a higher incidence observed in neonates (83%) and infants (39%) compared to older children (7%)[42]. In another study, the incidence of recoarctation in children under one year of age was 44%[43].

As for hypertension, the incidence in our study was 37.7%, based on the patients' last follow-ups (50% in ESP versus 27.27% in BAP patients). This has also been seen in other studies, where the incidence of hypertension varies according to the age at repair and length of follow-up[44].

Studies have shown an incidence of up to 77% before stent implantation, and a range of 20 to 70% after repair[31,44]. Pediatric patients have been reported to have adequate blood pressure control after long-term follow-up, with hypertension more commonly seen in younger patients[45]. Moreover, as in our study, the sample of patients in long-term follow-up was small, which suggests that no definitive conclusions can be drawn. In contrast, after coarctation or recoarctation repair in adult patients, there was a decrease in hypertensive patients, going from a 74% to a 24% incidence at the latest follow-up[46]. Since this was not within the scope of the objectives for this article, further studies are needed on the effects of ESP and BAP on hypertension in these patients, to assess whether these procedures affect the need to increase or decrease the dosage of antihypertensive medications.

Although investigating associated defects was not one of the study's objectives, it is worth mentioning that it was very interesting to find a high percentage of patients with a bicuspid aortic valve (51%). The correlation of this defect with aortic coarctation has been reported to be as high as 85%, and our study's results were similar, though lower, likely related to the number of patients in the study[47].

Conclusion

In this ten-year retrospective study, we presented our experience with the percutaneous management of aortic coarctation, using both ESP and BAP. Our findings contribute to the evidence on managing aortic coarctation through percutaneous techniques, particularly shedding new light on their effectiveness in pediatric patients. Notably, both ESP and BAP demonstrated high effectiveness in treating coarctation and recoarctation. Contrary to the prevailing literature, our study concluded that BAP appeared to be more effective than ESP. However, this finding may be influenced by the sample size analyzed.

Potential complications from intervention were also examined. Aneurysms, hypertension, and recoarctation were studied, revealing that neither of the techniques exhibited a significant need for further long-term interventions, nor did they lead to aneurysm formation. Likewise, further attention must be given to hypertension in long-term follow-up, considering the small sample size in our study.

Despite these valuable insights, it is important to acknowledge that our study was conducted within a single center, which may restrict the generalizability of our results to a wider population. In the same way, the inclusion of patients spanning various pediatric age groups introduced heterogeneity in the data, limiting our ability to assess the effectiveness and safety of percutaneous techniques across different age categories. Moreover, not all patients were able to attend their scheduled follow-up appointments, with only 42 patients participating in at least one follow-up assessment. This limitation hampers the completeness of long-term data, making it challenging to draw comprehensive conclusions regarding the outcomes of these interventions over time. It is necessary to continue research on a larger scale, with prospective studies, to refine treatment strategies and improve outcomes for patients with aortic coarctation.

Limitations

Due to the retrospective nature of this study, information regarding the decision to switch from ESP to BAP was not consistently documented across all patient records. As a result, we cannot accurately determine the number of patients initially scheduled for stenting who ultimately underwent balloon angioplasty. Prospective studies, with a particular focus on complications, are needed to provide more comprehensive insights into this matter. Additionally, given the low number of patients who continued with medium- and long-term follow-up, the conclusions regarding patient outcomes over time are limited. Future studies with a larger sample size and extended follow-up periods are required to draw more definitive conclusions.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing this manuscript.

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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

Innovative first-of-its-kind home monitoring program for children with complex congenital heart diseases

Programa innovador y pionero de monitoreo domiciliario de niños con cardiopatías congénitas complejas

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Abstract

Introduction: *Complex congenital heart diseases (CHDs), especially hypoplastic left heart syndrome (HLHS), are highly vulnerable during the interstage period, and home monitoring programs are used to prevent morbidity/mortality.* **Objective:** *To describe the creation and execution of an innovative Home Monitoring Program (HMP) adapted for Colombia.* **Method:** *Caregivers were provided with a smartphone with an application, pulse oximeter, scale, training, and education. Follow-up was conducted in person or via virtual audio/video. The control center reviewed the monitoring data, and the HMP provided continuous education reinforcements through every contact with caregivers and via social media/website.* **Results:** *Fifty-eight patients were identified as possible candidates; 4 (7%) died before discharge, and 37 (64%) met the exclusion criteria. Seventeen patients were discharged with home monitoring, and five did not complete monitoring. The program conducted an average of 217 days of monitoring, with 1,381 routine audio follow-up calls, 550 video calls, and 102 in-person follow-up visits. A total of 2,382 timely alerts were detected and addressed, with 94.5% managed via audio calls and 40 instances requiring hospitalization. Seventy percent of patients in the HMP reached the second intervention.* **Conclusions:** *Modern telecommunication enabled the adaptation of a successful HMP to a feasible project that could support patients with complex CHDs during the highly vulnerable interstage period, maximizing the success of surgical interventions and the efficacy of limited resources in our region.*

Keywords: *Interstage. Complex congenital heart defect. Norwood procedure. Hypoplastic left heart syndrome. Mortality.*

Resumen

Introducción: *Las enfermedades cardíacas congénitas complejas (ECC), especialmente el síndrome de corazón izquierdo hipoplásico (SCHIH), son altamente vulnerables durante el período interestadio, y los programas de monitoreo domiciliario se utilizan para prevenir la morbilidad/mortalidad.* **Objetivo:** *Describir la creación y ejecución de un innovador Programa de Monitoreo Domiciliario (PMD) adaptado para Colombia.* **Método:** *Se proporcionó a los cuidadores un teléfono inteligente con*

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Date of reception: 22-02-2024
Date of acceptance: 13-01-2025
DOI: 10.24875/RCCARE.M25000138
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):63-73
www.rccardiologia.com

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una aplicación, oxímetro, báscula, capacitación y educación. El seguimiento se realizó en persona/virtual de audio/video. El centro de control revisó los datos de monitoreo, y el PMD proporcionó refuerzos continuos de educación en cada contacto con los cuidadores y a través de redes sociales/sitio web. **Resultados:** *Se identificaron 58 pacientes como posibles candidatos, 4 (7%) fallecieron antes del alta, 37 (64%) cumplieron con los criterios de exclusión. Diecisiete pacientes fueron dados de alta con monitoreo domiciliario, y cinco no completaron el monitoreo. El programa realizó un promedio de 217 días de monitoreo, con 1,381 llamadas de seguimiento de audio, 550 video llamadas y 102 controles en persona. Se detectaron y abordaron 2,382 alertas oportunamente, el 94.5% se manejaron mediante llamadas de audio y 40 momentos requirieron hospitalización para manejar la alerta. El 70% de los pacientes en el PMD alcanzaron la segunda intervención.* **Conclusiones:** *La moderna telecomunicación permitió adaptar exitosos PMD a un proyecto factible que podría apoyar a pacientes con ECC complejas durante el período interestadio de alta vulnerabilidad, maximizando el éxito de las intervenciones quirúrgicas y la eficacia de los recursos limitados en nuestra región.*

Palabras clave: *Interestadio. Defecto cardíaco congénito complejo. Procedimiento de Norwood. Síndrome de corazón izquierdo hipoplásico. Mortalidad.*

Introduction

In Colombia, congenital malformations are the second leading cause of death among infants under one year old, contributing to 23% of total fatalities from 2005 to 2017[1]. By 2015, nearly 8,000 children had been born with congenital heart disease (CHD) in our country, leading to 2,434 cardiac surgeries annually[2]. Neonates with CHD may require surgical, interventional, or mixed palliative procedures to stabilize their hemodynamic status, and the Norwood procedure, in particular, emerges as the highest-risk category, with a 13.8% mortality rate[3]. The period between discharge after the initial palliation and the second surgery, known as the interstage in hypoplastic left heart syndrome (HLHS), poses a heightened vulnerability, with an up to 22% mortality rate during this phase[4,5].

The interstage period proves critical for these patients, as common viral illnesses increase the risk of dehydration and hypovolemia, potentially leading to hemodynamic decompensation[6,7]. Internationally, several specialized centers have implemented Home Monitoring Programs (HMPs) for HLHS patients during the interstage, significantly reducing mortality from 10% to 2%. These programs serve as practical tools for identifying and preventing complications, allowing for timely adjustments in patient management[4,5,7].

However, in Latin America, more reports are needed on interstage mortality or the existence of HMPs to date. Furthermore, in Colombia, unique challenges such as geographical and socioeconomic obstacles, low parental/caregiver education levels, nutritional deficiencies, and limited access to specialized centers could impede the follow-up care of these children and potentially impact outcomes. These challenges have prompted the development of an HMP tailored to our environmental conditions.

The PROMESA project, an acronym in Spanish for the Home Monitoring and Education Program for Infants with Complex CHDs, was conceived with two core pillars: education and the extensive use of telecommunication tools. These components were strategically employed to overcome limited resources and maximize monitoring reach in areas lacking local pediatric cardiology providers or general pediatric services. This paper provides an insight into the development and initial outcomes of the PROMESA project.

Methods

Colombia is located in the northeast corner of South America. It is a developing country, with deep economic, structural development, and sociocultural inequalities noted within its regions[8-10].

All newborn or infant patients discussed at the cardiovascular surgery conference (CVSC) of the congenital and pediatric cardiology service at the Fundación Cardiovascular de Colombia (FCV) were evaluated, with potential candidates being patients with complex CHDs undergoing the following procedures: a Norwood procedure with Blalock-Taussig shunt (BTS) or Sano connection, a hybrid procedure, systemic-to-pulmonary shunt placement, or pulmonary artery banding (PAB). Once they successfully completed the educational program (ED), they were discharged to the HMP.

Exclusion Criteria: end-of-life palliation, palliative procedures beyond the neonatal/infant age, the inability to conduct patient follow-up (e.g., international patients), no data plan coverage with the available provider, and insurmountable limitations (as determined by the psychology assessment) in family members or caregivers

acquiring the specific skills needed for monitoring, despite multiple educational attempts.

For the five-day ED, educational aids developed by the team included a primer booklet for parents, in both a printed and digital edition, containing general information about CHD, red flags, and equipment handling. It also had a dedicated space for clinical and parental notes, where important dates and appointments were recorded for parents. A printed primary-level caregivers' booklet and digital version were also provided to the parents to share with their most frequent medical or nursing providers. Complementary educational videos and an online educational course were accessible for watching or downloading free of charge through the project website (https://hic.fcv.org/co/inéditos-cardiovascular/servicios/programa-promesa/programa-promesa), YouTube/project promise and the Udemy website.

The educational focus encompassed understanding the diagnosis, the goals of care until the second intervention, recognizing red flags or alarm signs, acquiring the skills to take monitoring measurements, and the use of the equipment provided by the program. Parents/caregivers were supplied with a smartphone (Samsung Galaxy J5, Suwon-si, South Korea) with a calls and internet package, as well as a pre-installed app developed for the project (Google Play/promesa) in which parents entered the monitoring data and could also find educational resources and links to the project website (https://hic.fcv.org/co/instituto-cardiovascular/servicios/programa-promesa/programa-promesa) and social networks on Facebook and Instagram. Another element provided was a pulse oximeter (iSpO2Rx, pulse oximeter, Masimo Corporation, Irvine, CA) installed on the smartphone, which displayed oxygen saturation, heart rate (HR), and pulse index measurements through the app accompanying the sensor, with the capacity to share measurements almost instantly. An electronic scale (SECA 334, Hamburg, Germany) and a measuring cup were also provided (see Fig. 1).

Once the app data and vital signs were received at the hospital control center, the software developed to receive the data automatically classified them as within or outside of pre-established parameters, labeled them as normal or in the alarm range, and presented them on the dashboard. If the parent/caregiver successfully completed the ED but the patient was not discharged, the project psychologist carried out weekly follow-ups in the hospital to reinforce the teaching. Before discharge, the materials and supplies were delivered to the family.

Table 1. Alarm signs

1. Feeding problems Feeding volume < 100 ml per kilogram of weight per day Longer feeding time (unusually prolonged bottle or breastfeeding time or > 20 minutes)
2. Weight issues Weight loss > 30 g/day No weight gain or weight loss < 30 g/day Failure to gain ≤ 20 grams (0.02 kg) of weight for three consecutive days Sudden weight gain ≥ 100 grams/day (0.1 kg)
3. Emesis/Diarrhea
4. Diarrhea
5. Diaphoresis
6. Irritability/inconsolable with or without an unwell appearance
7. Respiratory problems Tachypnea Respiratory distress
8. Oxygen saturation outside the specified target Oxygen saturation > 90% Oxygen saturation < 75%
9. Skin color abnormalities Unusual or increased cyanosis Unusual or increased pallor
10. Fever Axillary measurement over 38 °C

Monitoring activities began after discharge (Fig. 2), including surveillance and red flag reporting (Table 1), along with complying with the outpatient follow-up schedule. Educational content was created based on the questions parents asked the monitoring staff and was made available directly in the team's app and website. Additionally, psychology staff conducted virtual art therapy and motivational activities.

Monitoring ended once the patient entered the institution for the second surgery, either palliative or corrective, or when the patient was no longer considered to be a candidate for the second intervention due to altered care goals or death. Closure activities included returning project materials and supplies and a debriefing session with the families.

Statistical analysis

A descriptive analysis of all the study variables was carried out, reporting percentages for the categorical variables and measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) for the numerical variables. In addition, each

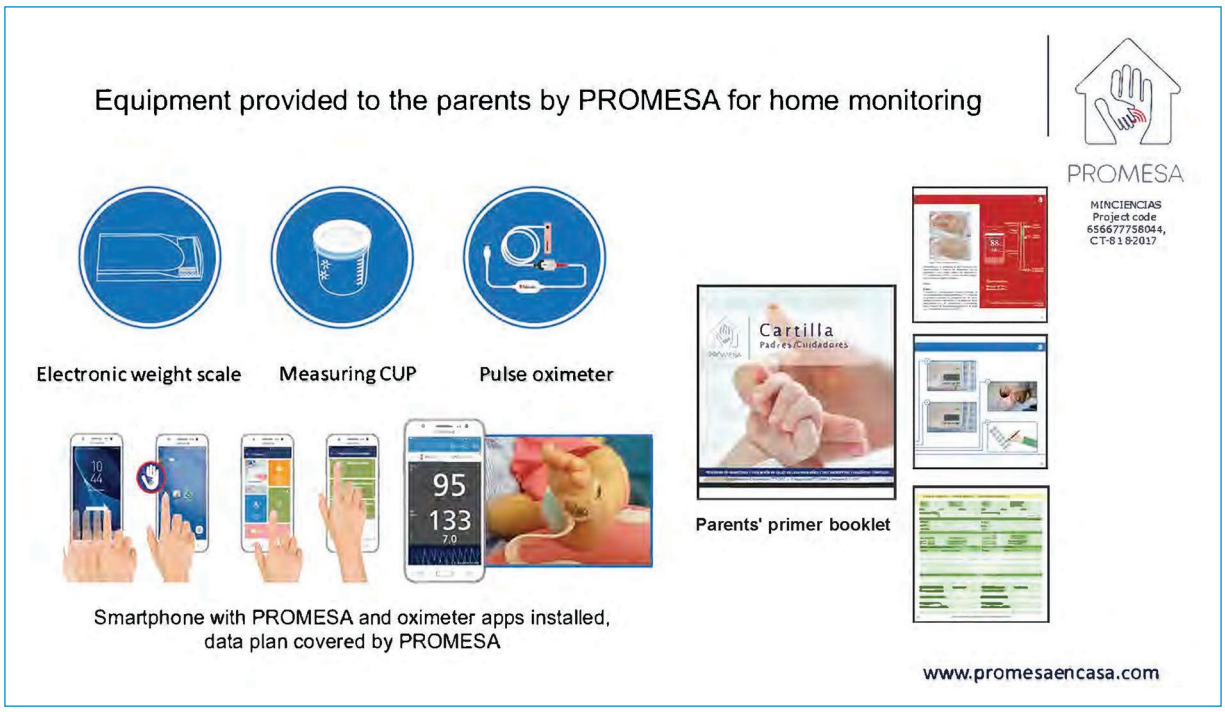

Figure 1. Equipment provided to the parents by PROMESA for home monitoring. The hospital's control center received vital signs from the app, automatically categorizing them as normal or alarming based on pre-established parameters. The project psychologist conducted weekly follow-ups for parents who completed the educational component, and materials were provided to families before patient discharge.

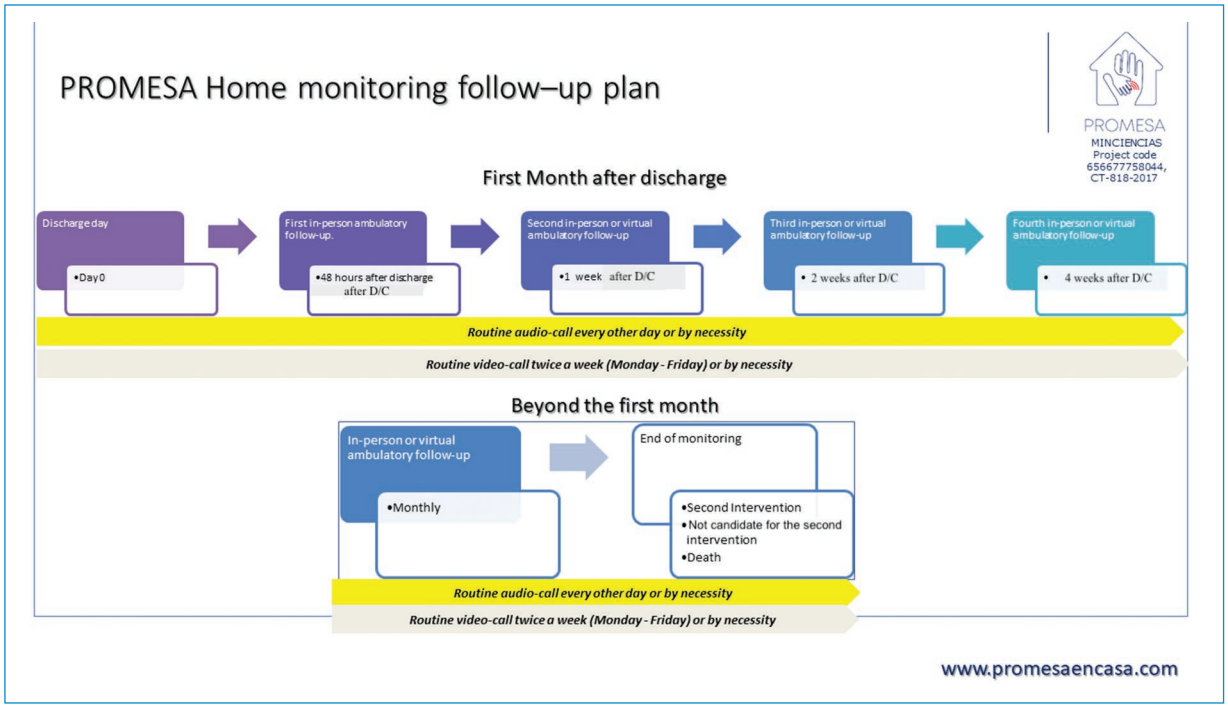

Figure 2. PROMESA home monitoring follow-up plan. The plan included parents performing and reporting oximetry twice a day, daily weight, recording intake volume (ml of milk formula in the last 24 hours or the number of breastfeeding or mixed feeding sessions).

point of contact was defined as the denominator; that is, each patient data point or attempted contact with the patient's parents/caregivers during the follow-up time, regardless of the method used (audio call, video call, in-person visit). The STATA IC®17 statistical package was used.

Ethical considerations

The FCV's Ethics Committee approved the research study, and its planning and execution complied with the Declaration of Helsinki. In addition, informed consent was obtained from all participants for the education phase, and a second consent was obtained for the monitoring phase. The Ministry of Science, Technology, and Innovation partially supported this work (grant 753 of 2016 and grant 818-2017, code 656677758044). Written permission for patients appearing in photographs (even masked) was obtained by the authors from the subjects' parent(s) or guardians.

Results

Initial program phase

Out of 914 patients discussed at the CVSC between February 2019 and September 2020, there were 58 possible candidates; 4 (7%) patients died before discharge, and 37 (64%) met the exclusion criteria (Fig. 3).

Therefore, 17 patients participated in the monitoring (29%), 12 of whom reached the second surgical procedure in the initial phase of this program (Table 2).

Patients who did not complete monitoring

Of the five patients who did not complete monitoring, one was a patient with double outlet right ventricle + atrioventricular canal (DORV + AV) canal with PAB whose parents withdrew their consent after three months in the program, due to perceived stress with the monitoring activities. Two patients were not candidates for a second surgical procedure: one patient with HLHS-BTS who developed a severe aortic root aneurysm with inadequate pressures; and another with pulmonary atresia and intact ventricular septum (PA-IVS), who after a successful percutaneous pulmonary valvotomy, was considered to benefit from medical management without a second intervention. In a fourth patient, adequate monitoring could not be done due to a lack of adherence to all the measurements required.

Finally, the fifth patient had PA-IVS with a BTS, required early postoperative placement of stents in the fistula and left pulmonary branch, was on enoxaparin anticoagulation, and died suddenly during the monitoring period without any alarms detected or reported in the days before the event.

Patient monitoring

The average duration of follow-up per patient was 217 days; on average, each patient recorded 486 oxygen saturations and HRs, 113 weights, and 167 intake records. (Table 3).

A total of 2,382 red flags were found within the clinical data sent by the monitoring devices; the most frequent were those related to weight and nutrition parameters, with the first being failure to gain ≥ 20 grams (0.02 kg) daily for three consecutive days, with 682 red flags (28.63%), followed by feeding volumes < 100 ml per kg of weight per day, with 520 red flags (21.83%). Most of the red flags (94.5 %) were addressed by audio calls (2,251 moments). In 64 moments, red flags were verified as clinically insignificant. In 67 moments, the caregivers were instructed to consult for an in-person assessment. Furthermore, in 40 of these moments, there were varying lengths of hospitalization to handle the alerts such as a feeding volume lower than 100 ml/kg/day (37.5%), weight loss or no weight gain (35%), documented out-of-range oxygen saturation (12.5%), sudden weight gain (10%), and parents' perception of unwellness or risk (5%). For example, one patient had an accidental episode of beta-blocker overdose, which was identified and managed in a timely fashion.

In 1,381 routine follow-up audio calls (with an average of 77 per patient), 984 red flags were identified, prompting 60 moments (audio calls) to recommend an in-person medical assessment. Various reasons for family support are shown in figure 4, similar to reports from high-income countries that use tablet-based devices for similar purposes.

Satisfactory contacts were possible in 80.76% of the total 550 video calls. However, only 58% had good or excellent sound or image quality; nevertheless, a risk symptom was able to be identified in one patient (respiratory distress) and an unwell appearance in another two. Finally, 102 in-person visits were carried out, with four patients discovered to have ongoing red flags.

Monitoring and video calls were temporarily suspended when the patients had programmed (catheterizations) or non-programmed hospitalizations, although

Figure 3. Patient selection process.
*CVSC: cardiovascular surgical conference.

Table 2. General characteristics of the patients included in the Home Monitoring Program

Characteristics	n	%
Total number of patients being monitored	17	100
Total number of patients who reached the second intervention	12	70.59
Time elapsed between the 1st and 2nd surgery (days), median (Q1-Q3)	216.75 (63-521)	
Deaths	1	5.88
Sociodemographic variables		
Gender (female)	9	52.94
Age (days), median (Q1-Q3)	66 (4-558)	
Birth weight (grams), median (Q1-Q3)	3,004 (1,035-3,645)	
Urban dwellers	7	41.18
Socioeconomic stratification*		
1	6	35.29
2	6	35.29
3	4	23.53
4	1	5.88
Type of health insurance		
Subsidized	10	58.82
Contributive	7	41.18
Clinical variables		
Univentricular physiology	11	64.71
Patients by Diagnosis		
Pulmonary atresia	6	35.2
DORV+AVSD (AV canal)	2	11.76
VSD Type 3 (Inlet) (AV canal type)	2	11.76
Single Ventricle	4	23.52
HLHS	2	11.76
TOF pulmonary stenosis	1	5.88
Associated genetic diagnoses		
Down syndrome	3	17.65
DiGeorge syndrome	2	11.76
History of prematurity	1	5.88
Neurological comorbidity	2	11.76
Characteristics at the first stage		
Timing of the first stage intervention		
Urgent	1	5.88
Scheduled intervention	16	94.12
Surgical weight, median (Q1-Q3)	3,682 (2,850-6,840)	
Use of inotropic support	16	94.2
Duration of inotropic support (days), median (Q1-Q3)	24.69 (6-73)	
Length of stay (LOS)		
Global LOS (days), median (Q1-Q3)	77.35 (26-209)	
ICU LOS (days), median (Q1-Q3)	68.88 (18-209)	
Pre-intervention time (days), median (Q1-Q3)	17.94 (0-60)	
Post-intervention time (days), median (Q1-Q3)	59.41 (15-149)	

*Socioeconomic stratification performed by the National Administrative Department of Statistics (DANE, in Spanish).
AV: atrioventricular; AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; LOS: length of stay; TOF: tetralogy of Fallot; VSD: ventricular septal defect.

Table 3. Monitoring activities and red flags

Characteristics	n = 17	%
Monitoring time (days)	217 (63-521)	
Audio calls (total)	1,381	
Calls per patient	77 (11-156)	
Identified red flags		
Low appetite	71	5.13
Weight loss	172	12.44
Tachypnea	59	4.27
Dyspnea	68	4.92
Cyanosis	94	6.80
Diarrhea	73	5.28
Emesis	142	10.27
Diaphoresis	195	14.10
Irritability	110	7.95
Calls that prompted an in-person medical assessment	60	4.34
Video calls (total)	681	
Video calls per patient	43 (6-89)	
Satisfactory	550	80.76
Unsatisfactory or not performed		
Hospitalized	66	9.69
Parents are unavailable due to in-person administrative insurance tasks	31	4.55
Unanswered-no explanation	30	4.41
The monthly data plan ended earlier than expected	2	0.29
The staff cardiologist was not available	2	0.29
Video call quality (good or excellent)		
Video quality	394	57.86
Audio quality	394	57.86
Video calls that prompted an in-person medical assessment	1	0.44
In-person follow-up	102	
Red flags identified (dyspnea and irritability)	4	0.59
Immunization schedule complete	17	100
Palivizumab	8	47.06
Red flags	2,382	
Failure to gain ≥ 20 grams (0.02 kg) for three consecutive days	682	28.63
Feeding volume < 100 ml per kilogram of weight per day	520	21.83
Sudden weight gain ≥ 100 grams/day (0.1 kg)	215	9.03
Oxygen saturation > 90%	170	7.14
Oxygen saturation < 75%	168	7.05
Single-day weight loss > 30 grams (0.03 kg)	101	4.24
Medical alert (child taken to the emergency room by parents)	13	0.55
Heart rate < 90 beats/minute	4	0.17
Decision made regarding red flag		
Addressed by audio call	2,251	94.50
No contact necessary, data confirmed to indicate no risk	64	2.69
An in-person medical evaluation is recommended	67	2.81
Hospitalization required	40	1.68
Parameters recorded by app-platform		
Oxygen saturation	486 (12-1,142)	
Weight	113 (5-272)	
Intake records	167 (3-591)	

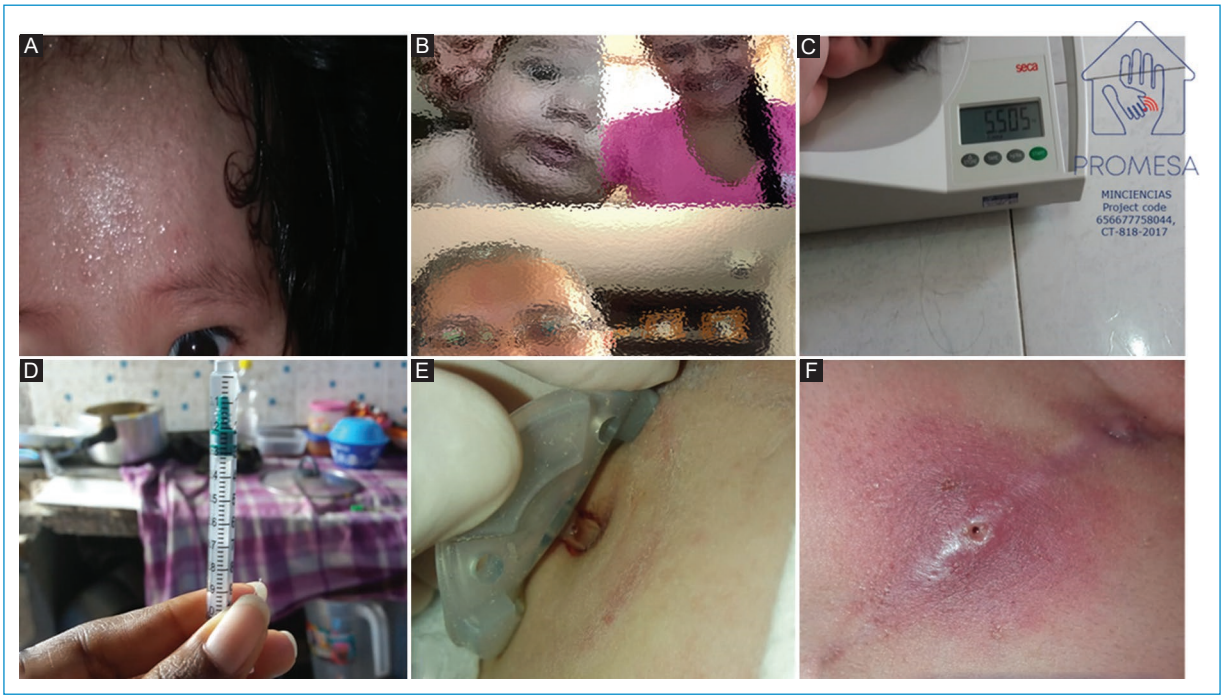

Figure 4. Examples of some virtual activities performed during home monitoring. **A:** image obtained during an evaluation of reported symptoms. **B:** video call image. **C:** weight data verification. **D:** dosage virtual counseling support. **E** and **F**: virtual follow-up of a G-tube ostomy and a surgical wound.

phone-call contact was maintained. Monitoring was restarted once discharge was reported. A summary of the results can be seen in the table 3.

Information on the costs, staff, and resources required to implement the single-patient program and the medium-term projection can be requested from the corresponding author.

Discussion

This is a pioneer study in Latin America and is an innovative solution in the region to support children and their families during the complex phases of CHD treatment; to the author's knowledge, no other similar programs have been reported in the region. The results are difficult to compare since the PROMESA project was designed for Colombia; however, the experience gained could be valuable and worth sharing with other centers.

Surviving the first hospital phase is a challenge for patients with complex CHD, especially HLHS, and their survival to later surgical stages is a quality indicator for specialized pediatric cardiac surgery centers worldwide[6], and the 2012-2016 Society of Thoracic Surgeons' (STS) registry reported a mortality of 15.5% for Norwood surgery, and 18.6% for hybrid procedures in HLHS (stent implantation in the ductus and PAB). It is important to note that other palliations considered to be less complex can also carry significant risks, and the same group reported a mortality of 10.1% for PAB, 7% for systemic to pulmonary fistulas, and 11% for neonatal central fistulas[3]. Together with the previously mentioned difficulties in a developing country, the inclusion of other neonatal palliations within the monitoring coverage was justified, because they are also high risk. This preselected cohort showed a high complexity, suggested by the high number of patients deemed to be inoperable (17 patients, 29.3%) and a 6.8% surgical mortality among the preselected group.

The HMPs were designed mainly for HLHS and achieved significant reductions in mortality in some reports[7]; the program presented in this article, with its adaptations and limitations, including the COVID-19 pandemic, managed to bridge 70% of the patients to the second intervention.

Audio calls allowed quick contact, with high availability and sensitivity to detect potential red flags (984 times) and manage most of them, avoiding unnecessary emergency room consultations. They were also an effective monitoring tool, with the added benefit of lowering the

risk of exposure to the novel infectious disease for both patients and families. The video calls were challenging in terms of image and sound quality due to connectivity limitations (48% rated less than good). Still, they allowed us to visually evaluate the patients' appearance and support the resolution of many of the alerts generated, working as a filter. In addition, the video calls were positively received by parents as they were perceived to be a more personal communication than audio calls. Nonetheless, in-person visits will always be necessary. In some cases, they identified patients with red flags that had not been detected by parents or any other means, such as audio calls or video calls, although this was infrequent in this cohort. The widely available smartphones facilitated automated and timely transmission of clinical data between parents and the HMP, as well as virtual home visits to provide guidance[7].

The HMP enabled the provision of continuous guidance in various aspects, as can be seen in the fact that 100% of the patients completed the basic vaccination schedule. However, only 47% of the patients succeeded in applying the palivizumab schedule prescribed by the program (71.4% of those with subsidized insurance plans and 30% of those with contributive insurance plans p: 0.117); the latter, per se, illustrates the difficulty in overcoming some access barriers, regardless of the type of insurance. In addition, parents experience a psychosocial burden during the interstage[11,12], which was increased by the COVID pandemic; the HMP helped provide emotional support through the various telecommunication resources used.

Regarding the deceased patient, in addition to the described risks, he lived in a hard-to-reach site in the Pacific region of Colombia. The death occurred suddenly during monitoring, when he was in the process of returning to the cardiovascular center for reassessment. He was followed for 410 days, a prolonged time due to non-clinical factors and transportation limitations related to the COVID-19 pandemic. The other two patients, also classified as unsatisfactory outcomes, were related to failure to adhere to the monitoring activities or stress associated with them. While there were no statistically significant differences between specific variables and these outcomes, possibly because of the sample size, the higher percentages (70%) of unsatisfactory results in the lowest socioeconomic strata are noticeable, with presumed inequalities in obtaining medical and legal resources. The literature suggests that socioeconomic and environmental factors may affect the outcome of critical CHDs[13]. There were no differences according to weight at the time of surgery, type of cardiac physiology, gender, or age at the first stage.

In July 2021, the HMP activities restarted with a new cohort of patients as part of the FCV's congenital and pediatric cardiology service, and currently have over 20 patients under surveillance. To finalize, even with our region's difficulties, 70% of patients in the HMP were able to reach the second intervention, and 2,382 red flags in the cohort were detected and addressed in a timely fashion, making this project unique in Latin America. However, more studies will be needed for our region.

Conclusions

A novel project in our region, like PROMESA, takes advantage of the current telecommunication advances to adapt the HMP from first world countries into a feasible tool to support complex CHD patients during the high vulnerability interstage while they achieve the clinical condition for a second palliative procedure or corrective intervention, maximizing outcomes and effectively using our country's limited resources.

Acknowledgments

The authors acknowledge the support of Colciencias (now Ministerio de Ciencia y Tecnología – MinCiencias) in sponsoring the project with code 656677758044, CT-818-2017 of Colciencias (now MinCiencias). We thank Joan Nieves RN, Dr. Chitra Ravishankar, and Dr. Maxime Cannesson for providing valuable advice during the project development, and Dr. Ana Uribe and Universidad Pontificia Bolivariana for their crucial effort during the entire project.

Funding

COLCIENCIAS funded this project through contract number 818-2017, executed by Fundación Cardiovascular de Colombia and Universidad Pontificia Bolivariana.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing this manuscript.

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ORIGINAL ARTICLE

Impact on in-hospital outcomes with the initiation of a sodium-glucose cotransporter-2 inhibitor (SGLT2i) in acute decompensated heart failure

Impacto en los desenlaces intrahospitalarios con el inicio de un inhibidor del cotransportador de sodio-glucosa 2 (iSGLT2) en insuficiencia cardíaca aguda descompensada

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Abstract

Introduction: *sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially used in the management of type 2 diabetes mellitus, have also demonstrated efficacy in symptomatic chronic heart failure (CHF), regardless of left ventricular ejection fraction (LVEF). Their early use in acute heart failure could have an impact on outcomes during the hospital stay.* **Objective:** *to assess the impact on in-hospital outcomes after early initiation of an SGLT2 inhibitor in patients with acute decompensated heart failure with reduced LVEF.* **Materials and method:** *this was a retrospective cohort taken from the MALEOS registry, in which patients with acute decompensated heart failure, with LVEF ≤ 40% and without prior use of an SGLT2i, were selected and retrospectively classified according to whether or not they started an SGLT2i during hospital admission. The final outcome was a composite of death, prolonged hospital stay (> 21 days), or the need for inotropes. A Cox regression analysis was performed, and results were summarized using Kaplan-Meier survival curves.* **Results:** *a total of 173 patients were recruited; 53 were started on an SGLT2i. The use of an SGLT2i reduced the composite outcome in a multivariate adjustment model (5/37), compared to not using it (48/136), HR 0.37 (95% CI 0.12-0.45, p 0.009). The outcome was less frequent in those who also received an angiotensin receptor/neprilysin inhibitor (ARNI) or a beta blocker.* **Conclusions:** *the in-hospital addition of an SGLT2i to treatment, in patients with acute decompensated heart failure with LVEF ≤ 40%, resulted in an improvement in primary outcomes, with a reduction in hospital stay and improved survival to discharge.*

Keywords: *Heart failure. Acute disease. Sodium-glucose transporter 2 inhibitors. Mortality. Length of stay.*

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Date of reception: 20-05-2024
Date of acceptance: 10-01-2025
DOI: 10.24875/RCCARE.M25000149
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):74-84
www.rccardiologia.com

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Resumen

Introducción: *los inhibidores del cotransportador de sodio-glucosa 2 (iSGLT2), inicialmente usados en el manejo de la diabetes mellitus tipo 2, también han demostrado eficacia en insuficiencia cardíaca crónica (ICC) sintomática, independientemente de la fracción de eyección del ventrículo izquierdo (FEVI). Su uso temprano en insuficiencia cardíaca aguda podría impactar los desenlaces durante la estancia hospitalaria.* **Objetivo:** *evaluar el impacto en los desenlaces intrahospitalarios tras el inicio temprano de un iSGLT2 en pacientes con insuficiencia cardíaca aguda descompensada con FEVI reducida.* **Materiales y método:** *estudio de cohorte retrospectiva a partir del registro MALEOS, en el que se seleccionaron pacientes con insuficiencia cardíaca aguda descompensada, con FEVI ≤ 40%, sin uso previo de iSGLT2. Se clasificaron de manera retrospectiva según el inicio o no de iSGLT2 durante el ingreso hospitalario. El resultado final evaluado fue compuesto por: muerte, estancia hospitalaria prolongada (> 21 días) o requerimiento de uso de inotrópicos. Se realizó un análisis por regresión de COX y los resultados se resumieron con el uso de las curvas de supervivencia de Kaplan-Meier.* **Resultados:** *se captaron 173 pacientes en total; a 53 se les inició un iSGLT2. El uso de iSGLT2 redujo en un modelo de ajuste multivariado el resultado combinado (5/37), comparado con quienes no lo recibieron (48/136), HR 0.37 (IC 95%: 0.12-0.45; p = 0.009). El resultado fue menos frecuente en quienes, además, recibían un antagonista del receptor de neprilisina (ARNI) o un betabloqueador.* **Conclusiones:** *la adición intrahospitalaria de un iSGLT2 al tratamiento de pacientes con insuficiencia cardíaca aguda descompensada con FEVI ≤ 40%, mejoró los desenlaces primarios ya que redujo la estancia hospitalaria y mejoró la supervivencia hasta el alta.*

Palabras clave: *Insuficiencia cardíaca. Hispanos. Enfermedad aguda. Inhibidores del cotransportador de sodio-glucosa 2. Mortalidad. Tiempo de internación.*

Introduction

Acute heart failure (AHF) consists of the onset of signs and symptoms of heart failure requiring treatment and, at times, hospitalization[1]. This abnormal heart function may occur in patients with prior heart disease, termed chronic heart failure (CHF)[1], or in patients with no prior heart disease, which is known as *de novo* or new-onset AHF[2].

Heart failure (HF) is a global public health problem affecting more than 23 million people. In the United States, an estimated 5.1 million people are affected, according to the National Health and Nutrition Examination Survey (NHANES)[3]. Unlike other cardiovascular diseases, the prevalence, incidence and mortality of HF is rising[4,5], and more than 1 million hospitalizations attributed to this disease are reported every year, as well as several million hospitalizations that include it as a secondary diagnosis[6-8]. Patients admitted for AHF have an average age of more than 70, and approximately half are males[1].

After the clinical diagnosis of HF, patients are hospitalized, on average, almost once a year[9]. The morbidity and mortality caused by HF have a high economic cost worldwide. In 2012, $30.7 million dollars were spent on HF care in the United States[10]. Up to 60% of patients are hospitalized for a new decompensation within six months. As such, in-hospital HF mortality ranges from 7.1 to 12.9%[11], and stands at 10.7% at 30 days[12]; 18.7% at six months[8]; and 30 to 40% at one year[12].

Pharmacological medical management has changed substantially over the last few years, with new treatment strategies that improve MACE points[13]. Today we have sodium-glucose cotransporter-2 inhibitors (SGLT2i) that significantly lower the risk of cardiovascular death or hospitalization for HF in patients with CHF, regardless of their left ventricular ejection fraction (LVEF)[14-16]. The combined SGLT1/2 inhibitor, sotagliflozin, has also been shown to improve clinical outcomes in patients with diabetes and a recent episode of worsening HF (WHF)[17]. In this study, we seek to evaluate the impact on in-hospital outcomes of starting an SGLT2i for acute decompensated heart failure with reduced LVEF, in a cohort taken from the MALEOS registry[18].

Materials and method

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee at Clínica Versalles (GPC-CEI-0108), following the Colombian rules governing research (Resolution 8430/1993 of the Ministry of Health and Resolution 2378/2008 of the Ministry of Social Protection).

Study design and participants

In this retrospective cohort study, data were taken from the MALEOS registry, compiled at a referral institution in the southwest of Colombia, from January 2020 to December 2022. The selected patients were over the age of 18, with acute decompensated HF, an LVEF ≤ 40% and no prior history of treatment with an SGLT2i.

They were classified retrospectively according to whether an SGLT2i was started during their hospitalization, a decision made at the discretion of the attending physician. Pregnant patients, patients with chronic kidney disease (CKD) with a GFR less than or equal to 15 ml/min, duplicate medical records and those with more than 10% missing data were excluded. A prolonged hospital stay was defined as more than 21 days, based on the results of previous studies in which hospital stays of 22 or more days were associated with mortality[19,20].

Statistical analysis

The information was collected in Microsoft Office Excel® and analyzed using the Stata 17 TM (Stata Corp, College Station, TX, USA) statistical package. The characteristics of the study population were summarized using descriptive statistics. A univariate analysis was done to determine the distribution of the quantitative variables. The assumption of normality was examined using the Kolmogorov-Smirnov test, rejecting the null hypothesis of normality and assuming that the variables had a non-normal distribution when p was less than 0.05.

For variables with a normal or parametric distribution, the data were summarized using mean and standard deviation (SD), while median and interquartile range (IQR) were used for those with a non-normal distribution. Qualitative variables were summarized as percentages in a frequency table.

Grouping the sample into patients with or without SGLT2i use, a bivariate analysis was used to evaluate the comparative variables between the groups using the emergency room admission data for each outcome. The groups were compared, taking a $p < 0.05$ as significant. Fisher's test or Chi^2 were used for qualitative variables and Student's *t* or Mann-Whitney U tests for continuous variables, with a significant $p < 0.05$ (OR: gross odds ratio; 95% confidence interval [CI]).

To control for the potential biases detected (information and confounding), data were analyzed using descriptive statistics with subsequent bivariate and multivariate analyses. Significant variables were included in a logistic regression to determine a probable association. The initial or saturated model was constructed with variables that reported *p* values equal to or less than 0.25 on the bivariate analysis and, using the backward method, the most parsimonious model was selected according to the statistical likelihood test. Variables were considered significant with a $p < 0.05$ (OR: adjusted odds ratio; 95% CI). To determine the performance of the most parsimonious model, ROC curve analyses were done. For the model presented, the area under the curve was 0.78, with $p < 0.001$, which means that the selected variables account for the reported outcome.

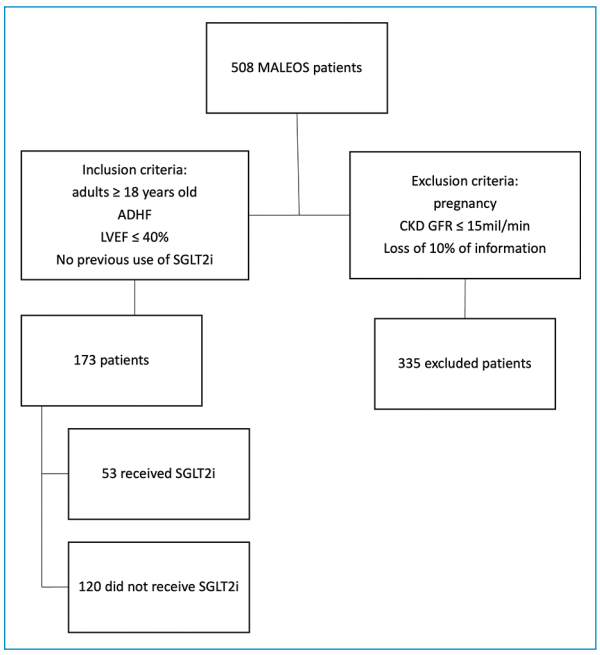

Figure 1. Data gathering process.

The final outcome evaluated was the composite of death, prolonged hospital stay (> 21 days), or the need for inotropes. A Cox regression analysis was done, and the results were summarized using Kaplan-Meier survival curves.

Results

Out of 508 patients, a total of 173 who were admitted for AHF care in the emergency room were captured; 53 were treated with an SGLT2i and 120 were not (Fig. 1). Table 1 lists the initial characteristics of the patients included in the study. The mean age was 67.8 years (SD: 15.5 years), 39.3% were females and 89.6% were Latino (mestizo); the main HF etiology was ischemia, with 54.9%, the main associated comorbidities were hypertension (67%) and diabetes mellitus (31.2%). Table 1 describes other patient characteristics and their medications at the beginning of the study.

Out of the 173 registered patients, 53 were started on an SGLT2i. Table 2 differentiates the characteristics of the patients who were started on an SGLT2i

Table 1. Clinical-demographic characteristics of the evaluated population

Characteristics	Description	Summary measure	
		(n = 173)	%
Age/years	Mean	67.8 15.5 SD	
Sex	Male	105	60.7
	Female	68	39.3
Ethnicity	Latino (mestizo)	155	89.6
	Afro american	18	10.4
Weight/kg	Mean	69.4	16.3 SD
BMI/kg/m^2	Mean	25.9	5.4 SD
Diabetes mellitus	Yes	54	31.2
	No	119	68.8
Dyslipidemia	Yes	·32	18.5
	No	141	81.5
Hypertension	Yes	116	67
	No	57	33
Hypothyroidism	Yes	29	16.8
	No	144	83.2
Atrial fibrillation	Yes	46	26.6
	No	127	73.4
Chronic kidney disease	Yes	44	25.4
	No	129	74.6
Chronic obstructive pulmonary disease	Yes	25	14.5
	No	58	85.5
Cancer	Yes	3	1.7
	No	170	98.3
Cirrhosis	Yes	6	3.5
	No	167	96.5
Heart failure etiology	Ischemic	95	54.9
	Hypertensive	36	20.8
	Arrhythmic	16	9.2
	Valvular	11	6.4
	Dilated	6	3.5
	Other	1	0.6
	Not determined	8	4.6
ACE inhibitor/ARB	Yes	76	43.9
	No	97	56.1
MRA	Yes	36	20.8
	No	137	79.2
ARNI	Yes	19	11
	No	154	89
BB	Yes	69	39.9
	No	104	60.1
Loop diuretics	Yes	51	29.5
	No	79	70.5
Prior use of inotropes	Yes	2	1.2
	No	118	98.8
Iron	Yes	2	1.2
	No	118	98.8
Duration of the disease/days	Median	526	IQR (379-764)
Hospitalizations for heart failure in the last year	Median	1	IQR (1-2)

(*Continues*)

Table 1. Clinical-demographic characteristics of the evaluated population *(continued)*

BMI: body mass index; ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor/neprilysin inhibitor; BB: beta blocker; IQR: interquartile range.

compared to the group without this treatment; no statistically significant differences were found between the two groups prior to emergency room admission.

The patients' main signs and symptoms of decompensation on admission were orthopnea in 167 patients and lower extremity edema in 109 patients. Paroxysmal nocturnal dyspnea and bendopnea were less frequent in those started on an SGLT2i (HR: 0.46; CI: 0.22-0.96; p = 0.026 and HR: 0.16; CI: 0.02-0.54; p = 0.001, respectively); in addition, patients with NYHA II-III and Stevenson B classifications were the most frequent in both groups, with a higher frequency of NYHA IV and Stevenson C in the SGLT2i group, the main cause of decompensation was acute coronary syndrome. The remaining variables were similar (Table 3).

Table 4 shows the bivariate analysis of the clinical outcomes in response to the patients' in-hospital treatment, according to SGLT2i initiation. Patients with an SGLT2i received more MRAs and ARNIs and fewer ACE inhibitors/ARBs; the most frequently used

Table 2. Characteristics prior to emergency room admission, by SGLT2i treatment

Characteristics at the beginning of follow-up	Description	Total	SGLT2i treatment		HR	95% CI	p
			Yes (n = 53)	No (n = 120)			
Age/years	Median	67.8 (15.5 SD)	68.8 (14.9 SD)	67.37 (15.7 SD)	01.01	0.98-1.03	0.569
Sex	Male	105	29	76	0.69	0.34-1.42	0.284
	Female	68	24	44			
Ethnicity	Latino (mestizo)	155	50	105	2.3	0.62-13.35	0.174
	Afro american	18	3	15			
BMI/kg/m^2	Mean	25.9 (5.4 SD)	25.28 (4.7 SD)	26.3 (5.7 SD)	0.96	0.91-1.03	0.259
Diabetes mellitus	Yes	54	22	32	1.95	0.93-4.05	0.052
	No	119	31	88			
Dyslipidemia	Yes	·32	8	24	0.71	0.26-1.80	0.444
	No	141	45	96			
Hypertension	Yes	116	37	80	1.16	0.55-2.50	0.684
	No	57	16	40			
Hypothyroidism	Yes	29	9	20	01.02	0.38-2.58	0.956
	No	144	44	100			
Atrial fibrillation	Yes	46	16	30	1.29	0.59-2.81	0.476
	No	127	37	90			
Chronic kidney disease	Yes	44	11	33	0.69	0.29-1.61	0.347
	No	129	42	87			
Chronic obstructive pulmonary disease	Yes	25	6	19	0.68	0.21-1.92	0.436
	No	148	47	101			
Cancer	Yes	3	2	1	4.66	0.23-27.7	0.996
	No	170	51	119			
Cirrhosis	Yes	6	1	5	0.44	0.00-4-11	0.450
	No	167	52	115			
Heart failure etiology	Ischemic	95	29	66	0.14	0.17-1.16	0.175
	Hypertensive	36	9	27			
	Arrhythmic	16	7	9			
	Valvular	11	4	7			
	Dilated	6	3	3			
	Other	1	0	1			
	Not determined	8	1	7			
ACE inhibitor/ARB	Yes	76	25	51	1.21	0.59-2.43	0.568
	No	97	28	69			

(*Continues*)

Table 2. Characteristics prior to emergency room admission, by SGLT2i treatment *(continued)*

Characteristics at the beginning of follow-up	Description	Total	SGLT2i treatment		HR	95% CI	p
			Yes (n = 53)	No (n = 120)			
MRA	Yes	36	9	27	0.70	0.27-1.71	0.409
	No	137	44	93			
ARNI	Yes	19	8	11	1.76	0.57-5.15	0.250
	No	154	45	109			
BB	Yes	69	22	47	1.10	0.53-2.23	0.771
	No	104	31	73			
Loop diuretic	Yes	51	16	35	01.05	0.48-2.23	0.891
	No	122	37	85			
Prior use of inotropes	Yes	2	1	1	2.28	0.02-18.1	0.550
	No	118	52	119			
Iron	Yes	2	1	1	2.28	0.02-18.1	0.550
	No	118	52	119			
Duration of the disease/days	Median	526 IQR (379-764)	432 IQR (353-611)	586 IQR (421-790)	0.99	0.99-1.00	0.206
Hospitalizations for heart failure in the last year	Median	1 IQR (1-2)	1 IQR (1-2)	1 IQR (1-2)	1.28	0.89-1.83	0.180

BMI: body mass index; ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor/neprilysin inhibitor; BB: beta blocker; IQR: interquartile range.

Table 3. Clinical characteristics on emergency room admission, by SGLT2i treatment

Characteristics at the beginning of follow-up	Description	Total	SGLT2i treatment		HR	95% CI	p
			Yes (n = 53)	No (n = 120)			
Orthopnea	Yes	167	29	78	0.65	0.32-1.33	0.199
	No	66	24	42			
Paroxysmal nocturnal dyspnea	Yes	74	16	58	0.46	0.22-0.96	0.026
	No	99	37	62			
Bendopnea	Yes	36	3	33	0.16	0.02-0.54	0.001
	No	137	50	87			
Rales	Yes	45	11	34	0.66	0.27-1.51	0.294
	No	128	42	86			
Lower extremity edema	Yes	109	37	72	1.54	0.74-3.31	0.217
	No	64	16	48			
Ascites	Yes	13	3	10	0.66	0.11-2.72	0.538
	No	160	50	110			

(*Continues*)

Table 3. Clinical characteristics on emergency room admission, by SGLT2i treatment *(continued)*

Characteristics at the beginning of follow-up	Description	Total	SGLT2i treatment		HR	95% CI	p
			Yes (n = 53)	No (n = 120)			
Hepatomegaly	Yes	5	1	4	0.56	0.01-5.83	0.600
	No	168	52	116			
Jugular distension	Yes	19	8	11	1.76	0.57-5.15	0.250
	No	154	45	109			
NYHA classification	I	20	5	15	1.53	0.17-1.83	0.066
	II	54	15	39			
	III	68	20	48			
	IV	31	13	18			
Stevenson classification	A	22	6	16	2.89	0.24	0.152
	B	125	36	89			
	L	7	1	6			
	C	19	10	9			
LVEF/%	Median	28 IQR (20-33)	28 IQR (21-34)	26 IQR (20-32)	0.98	0.94-1.02	0.439
Probable cause of decompensation	ACS	51	19	32	0.12	0.06-0.17	0.000
	Hypertensive crisis	10	2	8			
	Arrhythmia	21	7	14			
	Mechanical	8	4	4			
	PE	4	1	3			
	Infections	16	2	14			
	Overload	28	11	17			
	Non-adherence	7	1	6			
	Other	10	3	7			
	Not determined	18	3	15			
Creatinine	Median	1.10 IQR (0.9-1.5)	1.10 IQR (0.9-1.4)	1.1 IQR (0.9-1.5)	0.44	0.31-0.61	0.000
Urea nitrogen	Median	23 IQR (17.5-31)	21 IQR (17-28)	24 IQR (18-36)	0.96	0.94-0.99	0.015
Sodium	Median	·138 IQR (136-140)	138 IQR (135-140)	138 IQR (136-140)	01.01	0.93-1.11	0.663
Potassium	Median	4 IQR (3.8-4.0)	4.2 IQR (3.8-4.0)	4.0 IQR (3.7-4.0)	0.28	0.19-0.38	0.496
Hemoglobin	Median	12.9 IQR (11-14.3)	13 IQR (11.6-14.9)	12.8 IQR (10.6-14.2)	0.01	0.10-0.48	0.194

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; ACS: acute coronary syndrome; PE: pulmonary embolism; IQR: interquartile range.

concomitant medications were BBs, with 90.5%, followed by ARNIs with 86.8%. Treatment with an SGLT2i reduced the combined outcome, which occurred in 9.4% of the patients on an SGLT2i vs. 26.6% of the group without this medication (HR: 0.28; CI: 0.08-0.81; p = 0.011). The evaluation of the aggregated combined

Table 4. Inpatient heart failure treatment, by SGLT2i treatment

Characteristics at the beginning of follow-up	Description	Total	SGLT2i treatment		HR	95% CI	p
			Yes (n = 53)	No (n = 120)			
ACE inhibitor/ARB	Yes	36	4	32	0.22	0.05-0.69	0.004
	No	137	49	88			
MRA	Yes	105	45	60	5.6	2.34-14.86	0.000
	No	68	8	60			
ARNI	Yes	84	46	38	14.1	5.58-40	0.000
	No	89	7	82			
BB	Yes	144	48	96	2.4	0.82-8.5	0.086
	No	29	5	24			
Loop diuretic	Yes	127	40	87	1.16	0.52-2.68	0.683
	No	46	13	33			
Combined outcome*	Yes	37	5	32	0.28	0.08-0.81	0.011
	No	136	48	88			
Death	Yes	7	3	13	0.46	0.08-1.80	0.239
	No	166	53	107			
Need for inotropes	Yes	12	3	9	0.74	0.12-3.13	0.661
	No	161	50	111			
Prolonged stay	Yes	16	1	15	0.13	0.00-0.92	0.026
	No	157	52	105			
Stay/days	Median	7 IQR (4-12)	7 IQR (4-13)	7 IQR (4-11)	0.97	0.93-1.01	0.202
Iron treatment	Yes	7	1	6	0.36	0.00-3.14	0.338
	No	166	52	114			

*Combination of death, need for inotropes or prolonged hospitalization.
ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker;
MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor/neprilysin inhibitor; BB: beta blocker; IQR: interquartile range.

outcome shows a trend in favor of fewer prolonged hospital stays in the group with an SGLT2i (HR 0.13; IC 0.00-0.92).

The reduction in the composite outcome remained significant after a regression model to adjust for multiple variables with the use of SGLT2i (aHR 0.37; CI: 0.12-0.45; p = 0.009). The additional variables that consistently explained the reduction in the combined outcome were the use of ARNIs (aHR 0.45; CI: 0.19-0.26; p = 0.014), BBs (aHR: 0.33; CI: 0.13-0.54; p = 0.022) and an NYHA III-IV classification (aHR: 1.84; CI: 1.16-2.92; p = 0.008) (Table 5).

Moreover, SGLT2i initiation in patients with AHF showed an increased survival on in-hospital follow-up (HR: 0.68; CI: 0.55-0.72; p = 0.004) (Fig. 2), compared with not using an SGLT2i in the emergency room.

Discussion

Starting an SGLT2i in patients hospitalized for decompensated HF with reduced LVEF proved beneficial due to a significant reduction in the combined outcome of death, prolonged hospital stay (> 21 days) and the need for inotropes, with a clinically relevant impact. The main contributor within the composite outcome was the smaller number of patients with a prolonged hospital stay, which has an effect in positive outcomes for the patients and lower costs for the public health sector.

The results obtained show that starting an SGLT2i for HF not only benefits ambulatory patients, but also in-hospital treatment[14,16,17,21-23]. Studies with empagliflozin in patients with CHF with reduced ejection

Table 5. Multivariate analysis according to treatment with combined outcome

Characteristics	Description	Total	Combined outcome*		HRc* 95% CI	HRa** 95% CI	P
			Yes (n = 37)	No (n = 136)			
SGLT2i	Yes	53	5	48	0.28 (0.08-0.81)	0.37 (0.12-0.45)	0.009
	No	120	32	88			
ARNI	Yes	84	11	73	0.36 (0.15-0.84)	0.45 (0.19-0.26)	0.014
	No	89	26	63			
Beta blockers	Yes	144	25	119	0.29 (0.11-0.78)	0.33 (0.13-0.54)	0.022
	No	29	12	17			
NYHA classification	I-II	74	9	65	2.6 (1.92-7.84)	1.84 (1.16-2.92)	0.008
	III-IV	99	28	71			

Combined death, inotropic requirement or prolonged hospitalization.
*Crude analysis.
**Multivariate analysis adjusted for confounders.
SGLT2i: SGLT2 inhibitor; ARNI: neprilysin receptor antagonist; NYHA: New York Heart Association.

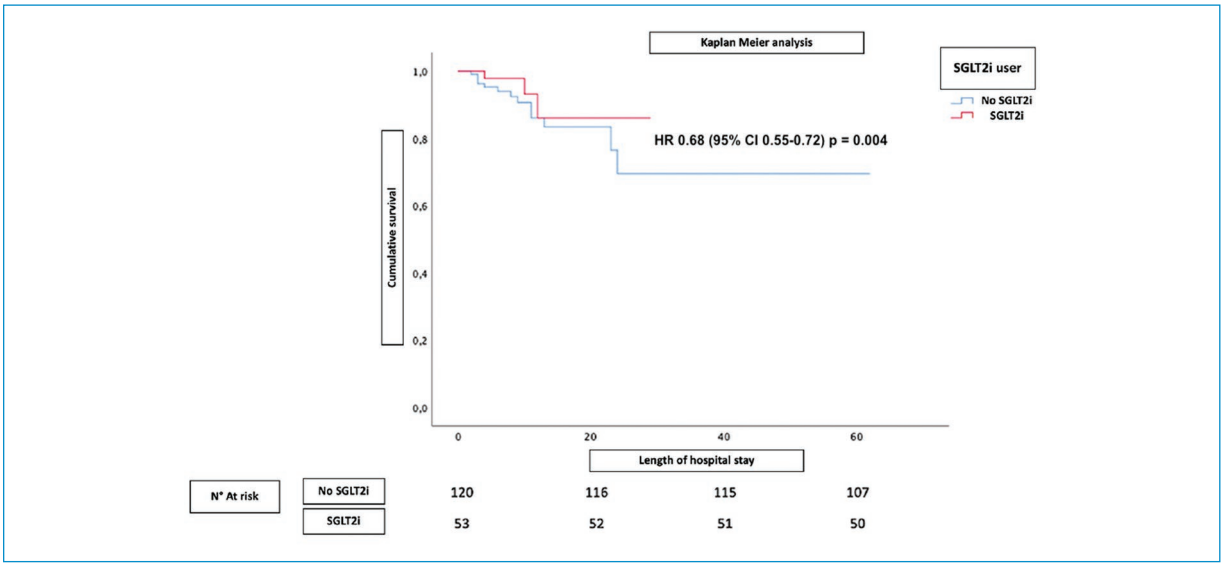

Figure 2. Hazard ratio (HR) and 95% confidence interval (CI) for inpatient survival with SGTLT2i vs. not starting the medication. Cox regression analysis.

fraction (EMPEROR-Reduced)[16] and preserved ejection fraction (EMPEROR-Preserved)[15] showed that empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in ambulatory patients with CHD, regardless of diabetes and ejection fraction, but these studies excluded hospitalized patients. Some large-scale pharmacological trials in patients hospitalized for AHF have not been able to show convincing beneficial effects. By contrast, we now have the EMPULSE trial, a large-scale clinical trial that evaluated the effect of empagliflozin on hospitalized patients and showed improvement in the markers of decongestion. A sub-analysis of congestion also showed greater weight loss and a reduction in NT-proBNP levels, indicating effective and sustained decongestion[5,9,14,24].

Once a reduced LVEF was confirmed, an SGLT2i (empagliflozin or dapagliflozin, depending on availability) was started within 36 hours of admission. The patients for whom an SGLT2i was prescribed had fewer

dyspnea symptoms, but lower extremity edema as their cardinal symptom, with a worse Stevenson classification as well as more patients in NYHA III, and the main cause of decompensation was still ischemic heart disease. Comparing results, we found that 13.6% of those in the EMPULSE study received combination therapy with an ARNI, unlike our study, with 86.8%, achieving better adherence to the international guidelines for HF management, as we had studies available on the importance of adding an ARNI to treatment[25-27]. This study included patients both with and without diabetes mellitus, unlike the SOLOIST-WHF study, whose population was made up solely of diabetic patients. Our data support the idea that adding empagliflozin or dapagliflozin to the standard pharmacological treatment for HF with reduced ejection fraction, regardless of diabetes, was well tolerated and produced a clinical benefit in the primary outcomes. Therefore, an SGLT2i should be considered in the effective pharmacological treatment of patients hospitalized for decompensated AHF, even for Hispanics, regardless of whether they have diabetes mellitus, an aspect which also has biological plausibility based on the optimization of cardiac energy metabolism provided by these drugs through relative hypoglycemia and a neurohormonal impact, and apparently no diuretic effect per se[24,28-30].

Our combined outcome contributes to the main studies evaluating the use of an SGLT2i in decompensated AHF, highlighting the importance of beginning the pharmacological strategy early, with positive results in hospital stay, thus reducing the number of days of hospitalization, as this is the most important risk factor for adverse events and worse health outcomes[24,31]. The use of an SGLT2i, alone or in combination, as a standardized strategy for managing HF with reduced LVEF in patients with severely decompensated HF within the Hispanic population, could improve hard outcomes during hospitalization.

Strengths

This study contributes positive data to the evidence on SGLT2i initiation in patients with acutely decompensated HF and reduced ejection fraction. The study data provides real-world evidence in the Hispanic population.

Limitations

Patients were only evaluated up to hospital discharge; there was no safety data on the use of an SGLT2i in the outpatient setting.

Our N is much lower than that of other international studies using an SGLT2i.

This is a single-center descriptive, observational analytical study.

Potential clinical implications and future studies

A positive impact on the inpatient treatment of patients with acutely decompensated HF with low ejection fraction, including the Hispanic population. Data for this study was taken from the MALEOS registry, which continues to enter patients into its database every six months, which could adjust the N for future studies.

Conclusions

Starting an SGLT2i to treat patients with decompensated AHF with LVEF ≤ 40% resulted in fewer adverse events in this population during their hospital stay.

The combined use of an SGLT2i in the standard care of patients with HF with low ejection fraction showed improvement in inpatient mortality and length of hospital stay.

The main cause of HF decompensation continues to be ischemic heart disease, and it is important to add new pharmacological tools to HF treatment to positively affect healthcare systems.

Acknowledgements

We would like to thank Clínica Versalles for approving data handling, supporting this study, and providing the setting for obtaining the information, protecting data confidentiality and handling.

We also thank Revista Colombiana de Cardiología for fostering spaces for disseminating registries and knowledge of national statistics and epidemiology, within the field of cardiology.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent and ethical approval. The authors have obtained approval from the Ethics Committee for analyzing routinely obtained anonymized clinical data, and therefore informed consent was not required. The pertinent guidelines have been followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in drafting this manuscript.

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ORIGINAL ARTICLE

Use of strain and left ventricular myocardial work intraoperatively and risk of postoperative cardiovascular complications in coronary patients

Uso de deformación y trabajo miocárdico del ventrículo izquierdo en el intraoperatorio y riesgo de complicaciones cardiovasculares posoperatorias en pacientes coronarios

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Abstract

Introduction: *Myocardial revascularization surgery is one of the cornerstones in the management of patients with ischemic heart disease. Intraoperative echocardiographic evaluation plays a crucial role in the management of these patients. However, the utility of Global Longitudinal Strain (GLS) has not been fully defined in revascularization surgery.* **Objective:** *To explore the value of global longitudinal strain and myocardial work efficiency in predicting major cardiovascular complications in patients undergoing myocardial revascularization.* **Materials and method:** *This was a retrospective cohort study. Patients with coronary artery disease and an ejection fraction greater than 30% who underwent myocardial revascularization surgery and intraoperative echocardiography from September 2023 to April 2024 were included. They were followed from the time of surgery to the seventh postoperative day or to discharge, to detect cardiovascular complications.* **Results:** *A total of 35 patients were included, with a median age of 68 years. Thirty-four patients underwent elective surgery. Twenty-nine patients were weaned easily off the pump, with a median cardiopulmonary bypass time of 67 minutes. The median ICU stay was three days. No deaths or extubation failures were reported. The median left ventricular GLS was -12.5% and the median MW was 75%. Patients with lower strain were found to have a higher likelihood of developing low cardiac output or shock, cardiogenic edema, and/or difficult weaning off the pump. Regarding the MW, no statistically significant correlation or difference was found with the complications in the bivariate analysis.* **Conclusion:** *Global longitudinal strain may help predict cardiovascular complications in coronary patients undergoing myocardial revascularization surgery.*

Keywords: *Strain. Echocardiography. Cardiovascular complications. Coronary disease.*

Resumen

Introducción: *La cirugía de revascularización miocárdica es una de las piedras angulares en el manejo de los pacientes con cardiopatía isquémica. La evaluación ecocardiográfica intraoperatoria es una parte sustancial en el manejo de estos pacientes. No obstante, la utilidad de GLS no se ha definido completamente en cirugia de revascularizacion.* **Objetivo:** *Explorar el valor de la deformación longitudinal global y la eficiencia de trabajo miocárdico en la predicción de complicaciones cardiovasculares mayores en pacientes llevados a revascularización miocárdica.* **Materiales y método:** *Estudio de cohorte ambispectiva, en el que se incluyeron pacientes con enfermedad coronaria y FEVI > 30%*

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Date of reception: 07-06-2024
Date of acceptance: 10-01-2025
DOI: 10.24875/RCCARE.M25000150
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):85-91
www.rccardiologia.com

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llevados a cirugía de revascularización miocárdica y a quienes se les realizó ecocardiografía intraoperatoria desde septiembre de 2023 hasta abril de 2024. Fueron seguidos desde el momento de la cirugía hasta siete días posoperatorios o el alta para detectar las complicaciones cardiovasculares. **Resultados:** *Se incluyeron 35 pacientes, con mediana de la edad de 68 años; 34 de ellos fueron sometidos a cirugía electiva y 29 presentaron fácil salida de bomba, con una mediana del tiempo de CEC de 67 minutos. La mediana de tiempo en UCI fue tres días. No se presentaron eventos de muerte y falla de extubación. La mediana del GLS de ventrículo izquierdo fue de -12.5% y la del MW fue de 75%. Se observó que aquellos con menor deformación tenían mayor posibilidad de presentar bajo gasto cardiaco o choque, edema cardiogénico o difícil salida de bomba, o ambos. Respecto al MW, no se encontró ninguna correlación o diferencia significativa a nivel estadístico en el análisis bivariado con las complicaciones.* **Conclusión:** *El GLS puede ayudar a predecir complicaciones cardiovasculares en el paciente coronario llevado a cirugía de revascularización miocárdica.*

Palabras clave: *Deformación. Ecocardiografía. Complicaciones cardiovasculares. Enfermedad coronaria.*

Introduction

Coronary artery bypass grafting (CABG) is one of the cornerstones of treatment for patients with ischemic heart disease[1-4]. Approximately 371,000 procedures are performed annually in the United States[5]; these patients have a high risk of adverse events and greater morbidity and mortality due to their cardiovascular risk profile, multiple comorbidities, and perioperative complications[1,5-8]. Currently, the mortality rate is 1.5 to 2% in experienced centers[9,10], with a high rate of complications, which may occur in up to 40% of patients[11,12]. Major cardiovascular complications are very important due to their high impact on patients' morbidity, mortality and prognosis. Therefore, it is essential to identify this population's risk factors or predictors for experiencing these events postoperatively.

Intraoperative echocardiographic evaluation is a substantial part of modern cardiac anesthesiology[13,14]. Among the echocardiographic parameters evaluated, left ventricular ejection fraction (LVEF) is essential in coronary patients, as it has prognostic value and helps predict survival[1-3,15-17]. However, it only evaluates radial systolic function[13,14,17,18] and has several technical limitations including subjective measurements based on the operator's experience, dependency on geometric assumptions and ventricular load conditions, and low sensitivity for detecting subclinical systolic function abnormalities[1,13-15,17,18]. Over the last few years, echocardiographic techniques have been created to measure myocardial systolic function that could overcome these limitations[13,14]. One of these is myocardial deformation analysis, "strain," through 2D speckle tracking, which is less load dependent, has less inter-observer variability and is not based on geometric assumptions[13,19]. This evaluation can provide a more accurate and reproducible measure of regional and global left ventricular contractility[3,15,20], as well as have greater sensitivity for detecting subclinical left ventricular dysfunction when the LVEF is preserved (>50%)[15,20].

Global longitudinal strain (GLS) is the most validated and frequently used parameter for evaluating left ventricular function[13,19,20]. Most of the data on left ventricular deformation has been obtained from awake patients with spontaneous breathing and evaluated with transthoracic echocardiography[13,19,21-24]. As far as patients with ischemic heart disease, the usefulness of GLS has not been completely established in patients undergoing CABG surgery[1,13,24]. However, some studies suggest that GLS could be an independent predictor of long-term outcomes after CABG, especially in patients with preserved LVEF[1,15,25-31]. In addition, the literature proposes another novel parameter to consider, derived from GLS, which consists in non-invasive measurement of myocardial work, including both deformation as well as load in its analysis throughout the cardiac cycle[14]. It also helps explore myocardial performance by calculating the efficiency of myocardial work in the face of hemodynamic changes[14]. However, there is limited data for this method in the surgical setting[14,32-35], especially regarding its use in patients undergoing CABG[14].

The objective of this study was to explore the value of GLS and myocardial work (MW) efficiency for predicting major cardiovascular complications in patients undergoing surgical myocardial revascularization with preserved LVEF.

Materials and method

This was an observational, analytical cohort study with ambispective data collection, which included all patients with coronary disease who underwent CABG at Clínica Medellín de Occidente between September 2023 and April 2024, with an LVEF greater than 30%

(the echocardiographic classification was used to determine the cut-off of severely affected LVEF, since it has already been described as a predictive factor for a higher risk of perioperative complications), and intraoperative transesophageal echocardiography measuring GLS and MW. Those who underwent mixed surgery, emergency surgery or reintervention were excluded.

The echocardiograms were done after anesthesia induction and prior to beginning the surgical incision, and were performed by cardiovascular anesthesiologists with training in intraoperative transesophageal echocardiography. A VIVID S70N ultrasound machine was used. Three 2D views were used: mid-esophageal four-chamber, mid-esophageal two-chamber, and mid-esophageal long axis.

Image processing to measure GLS and MW was done with ECHOPAC software based on the recording available on the machine, after surgery. The evaluator who took the measurements was trained and standardized on the GLS and MW measurement protocol.

Patients were followed from surgery up to the seventh postoperative day or to discharge, whichever came first. Clinical (age, sex, body mass index, comorbidities, EUROSCORE II scores, preoperative LVEF, and number of diseased vessels), intraoperative (type of surgery, clamp time, extracorporeal circulation time, use of vasoactive medications, GLS and MV), postoperative (final lactate, at 12 and 24 hours, and ICU stay) and cardiovascular complication (arrhythmias, cardiogenic shock, myocardial infarction, cardiogenic edema, hypertensive crisis and death) variables were collected.

The protocol was approved by the Human Research Ethics Committee at Universidad CES and the research committee at Clínica Medellín.

Statistical analysis

Descriptive statistics were used to describe the populations' characteristics: absolute and relative frequencies for qualitative variables and median and interquartile range for quantitative variables. The rank sum test (Mann-Whitney U) was used to compare the GLS and MW values between the groups with or without complications.

Results

The median age of the 35 patients (8 females and 27 males) was 68 years, and the median body mass index was 24.5 kg/m^2. The most frequent comorbidities, in descending order, were hypertension, smoking, dyslipidemia, diabetes mellitus, recent acute myocardial infarction and hypothyroidism. All had some degree of angina classified as CCS 2-4 (74.29% were class 2) and most had functional class deterioration according to the NYHA classification (97.15% were classified as NYHA 2-3) (Table 1).

Table 1. Patients' clinical and preoperative characteristics

Characteristics	n	%
Sex		
Male	27	77.14
Age Me (IQR)	68	(64-68)
BMI Me (IQR)	24.5	(23-27.6)
LVEF % Me (IQR)	58	(42-65)
EuroSCORE II Me (IQR)	1.37	(1.12-2.22)
Comorbidities		
HTN	28	80
Smoking	20	57.14
Dyslipidemia	18	51.43
Diabetes	15	42.86
Recent AMI	14	40
Hypothyroidism	6	17.14
COPD	2	5.71
Peripheral artery disease	2	5.71
Medications		
ACE inhibitors/ARBs	26	74.29
Statins	23	65.71
Beta blockers	11	31.43
Contractility disorders		
Yes	17	48.57
No	18	51.43
Diseased vessels		
1	1	2.86
2	3	8.57
3	31	88.57

Me: median; IQR: interquartile range; BMI: body mass index; LVEF: left ventricular ejection fraction; HTN: hypertension; AMI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease; ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Out of the 35 patients, 34 underwent elective CABG and most (31 patients) had triple (or more) vessel coronary disease. Regarding extracorporeal circulation (ECC) weaning, 29 of 35 patients were easily disconnected from the pump, the median ECC time was 67 minutes, and the median clamp time was 56 minutes. Milrinone and norepinephrine were used as vasoactive medications for all patients; the median final lactate was 2.26, and the median ICU time was three days.

Table 2. Surgical characteristics (intraoperative variables)

Type of Surgery	n	%
Elective	34	97.14
Emergency	1	2.86
ECC Time Me (IQR)	67	(60-91)
Clamp time Me (IQR)	56	(52-77)
Vasoactives		
Norepinephrine (doses)	0.11	(0.1-0.15)
Milrinone (doses)	0.375	(0.3-0.375)
GLS (%) Me (IQR)	–12.5	(–8.6 to –15.3)
MV (%) Me (IQR)	75	(67-82)

Table 3. Postoperative cardiovascular complications

Weaning off the pump	n	%
Easy	29	82.86
Difficult	6	17.14
AF/SVT	7	20
VT	1	2.86
LCO/CS	6	17.14
AMI	1	2.86
Cardiogenic edema	7	20
HTN crisis	4	11.43

AF: atrial fibrillation; SVT: supraventricular tachycardia; VT: ventricular tachycardia; LCO: low cardiac output; CS: cardiogenic shock; AMI: acute myocardial infarction; HTN: hypertension.

Table 4. Comparison of GLS values according to postoperative complications

GLS		p
AF/SVT		
YES	NO	
–13 (–8.4 to –14.3)	–11.5 (–8.75 to –15.45)	0.9671
VT		
YES	NO	
–5.9 (–5.9 to –5.9)	–12.7 (to8.9 to –15.3)	0.1375
LCO/CS		
YES	NO	
–7.5 (–5.7 to –13.75)	–12.9 (–9 to –13.3)	0.0919
AMI		
YES	NO	
–5.9 (–5.9 to –5.9)	–12.7 (–8.9 to –15.3)	0.1375
Cardiogenic edema		
YES	NO	
–8.6 (–7 to –13.7)	–12.95 (–9.05 to –15.75)	0.0578
HTN Crisis		
YES	NO	
–16.5 (–15.5 to –18.9)	–11 (–8.4 to –14.3)	0.0111
Weaning off the pump		
Difficult	Easy	
–8.25 (–7.8 to –13.7)	–12.9 (–9.1 to –15.6)	0.1101

There were no deaths or failed extubations during patient follow up (Tables 2 and 3).

As far as intraoperative echocardiographic evaluation, the median left ventricular GLS was -12.5% and the median MW was 75%. The bivariate analysis showed that patients with less deformation, described in table 4, were more likely to develop low cardiac output or shock, cardiogenic edema and/or difficulty in weaning off the pump (Tables 4 and 5).

Discussion

Intraoperative echocardiographic evaluation is essential in cardiac surgery[13,14]. Among the current echocardiographic parameters, left ventricular GLS measurement has provided a more accurate measure of regional and global contractility[3,15,20], as well as greater sensitivity for detecting subclinical dysfunction that could affect morbidity and mortality, even with preserved LVEF[15,20]. As far as patients with ischemic heart disease who require surgery, several studies have been done implementing the use of GLS; however, its prognostic value for morbidity, mortality and postoperative complications has not been completely established[1,3,8,13,15,24,27].

Some studies suggest that left ventricular GLS may be an independent predictor of long-term outcomes following CABG, especially in patients with preserved LVEF[1,3,15,27]. One of these was published by Olsen et al. in 2012, in which they attempted to determine the prognostic value of GLS after CABG, finding an average left ventricular GLS of –13% in their patients, which was similar to the average (–12.24%) and median (–12.5%) GLS values in our study[1]. However, so far, the reviewed articles show no clearly described specific

Table 5. Comparison of MW values according to postoperative complications

MW		p
AF/SVT		
Yes	No	
84 (80-90)	72 (67-80)	0.231
VT		
Yes	No	
53 (53-53)	76.5 (67-82)	0.0998
LCO/CS		
Yes	No	
70 (67-80)	76.5 (67-82)	0.61
AMI		
Yes	No	
53 (53-53)	76.5 (67-82)	0.0998
Cardiogenic edema		
Yes	No	
80 (65-80)	73.5 (67-83)	0.8528
HTN crisis		
Yes	No	
	75 (67-82)	
Weaning off the pump		
Difficult	Easy	
67 (65-80)	76.5 (70-83)	0.3076

reference value for abnormality in coronary patients, and the value of –20% ± 2, indicated in the current guidelines, is maintained as the cut-off point[28-31]. They also showed that a reduced GLS in patients with preserved LVEF is an independent predictor of major adverse cardiovascular events (MACE)[1].

The study by Gozdzik et al. evaluated ventricular function changes and their correlation with the prediction of poor early and late outcomes, finding that GLS was a predictor for intubation time, the use of inotropes and length of ICU stay[3]. Moreover, Kang et al. published a retrospective study evaluating the prognostic value of GLS compared to LVEF following CABG, which showed that GLS could help differentiate the prognosis in patients with preserved LVEF[15]. Furthermore, in 2022, Wakefield et al. published their study on perioperative left ventricular GLS as a predictive factor for complications and found that the GLS measurement after extracorporeal circulation had greater prognostic value for predicting postoperative outcomes[27]. In contrast, our study showed that patients who developed low cardiac output or cardiogenic shock had less negative GLS values than those who did not have these complications (–7.5 vs. –12.9), with a similar behavior for cardiogenic pulmonary edema (GLS of –8.6 vs. –12.95). In addition, patients who were difficult to wean from extracorporeal support were found to have a low GLS (less negative than –8.25%). On the other hand, patients with hypertensive crises had more negative GLS values (–15.5: –18.9%) than the study median, and close to the normal value described in the literature.

As far as MW, the results show small differences in values between those who experience complications and those who do not. Therefore, no claims can be inferred as to the prediction of postoperative cardiovascular complications nor correlations made with difficulties in weaning from extracorporeal circulation. We can only indicate that most of the study patients had lower MW efficiency than normal (≥ 95%)[33].

One of the study's limitations is its small sample size, which occurred due to the recent increase in comorbidities and systolic function impairment in patients requiring revascularization surgery, which makes it difficult to obtain a large number of patients with preserved LVEF. This has implications regarding its power to detect differences, and therefore the *p* values may not strictly reflect the presence or absence of significant differences between the groups; despite this, the differences in GLS values can be considered clinically relevant. Furthermore, echocardiographic measurement is an observer-dependent tool; however, the evaluators had sufficient prior training, which was intensified before beginning the study, in order to provide more expertise in the use of transesophageal echocardiography.

Finally, in the literature review, the authors found no previous studies evaluating left ventricular GLS and MW for predicting the risk of cardiovascular complications in patients undergoing CABG. Therefore, this study contributes relevant information that can serve as a basis for new studies with larger sample sizes, to be contrasted with these results. Studies are needed to evaluate the predictive performance of GLS and MW in postoperative outcomes, to provide highly applicable information for cardiovascular anesthesiology practice, in order to optimize perioperative outcomes.

Conclusions

Left ventricular GLS can help predict postoperative cardiovascular complications like low cardiac output, cardiogenic edema and difficult weaning off the pump, in coronary patients undergoing CABG. The usefulness of MW in coronary patients undergoing cardiac surgery is unclear, as it is a newly used parameter and requires more research and studies on its clinical implementation.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent and ethical approval. The authors obtained approval from the Ethics Committee to analyze routinely obtained and anonymized clinical data, and therefore informed consent was not required. The pertinent guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing this article.

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Factors associated with infective endocarditis: case and control study

Factores asociados a la endocarditis infecciosa: estudio de casos y controles

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Abstract

Introduction: *Infective endocarditis (IE) is a multisystem disease resulting from infection, usually bacterial, of the endocardial surface of the heart.* **Objective:** *To determine the factors associated with infective endocarditis in patients treated at Hospital Universitario San Rafael de Tunja.* **Materials and method:** *Design: Case-control study. Setting: Hospital. Participants: People with infective endocarditis who were treated at Hospital San Rafael de Tunja between 2009 and 2019. Variables: The dependent variable was the presence of infective endocarditis, diagnosed using the Duke criteria. The independent variables corresponded to the participants' sociodemographic, clinical and background information.* **Results:** *87 cases and 175 controls were included, finding that chronic kidney disease (OR: 145), dental implants (OR: 77), autoimmune disease (OR: 61), male sex (OR: 15), urinary tract infection in the last month (OR: 15), arrhythmias (OR: 13), valvular heart disease (OR: 6), pharyngotonsillitis (OR: 5) and the use of proton pump inhibitors (OR: 2) are risk factors, while the use of aspirin (OR: 0.029) decreases the likelihood of developing endocarditis.* **Conclusions:** *The factors associated with endocarditis in the emergency room at Hospital Universitario San Rafael de Tunja between 2009 and 2019 are, in order of importance: chronic kidney disease, dental implants, autoimmune disease, male sex, urinary tract infection in the last month, arrhythmias, valvular heart disease, pharyngotonsillitis, and the use of proton pump inhibitors; while aspirin use is a protective factor.*

Keywords: *Endocarditis. Infection. Risk factors. Bacteremia.*

Resumen

Introducción: *La endocarditis infecciosa (EI) es una enfermedad multisistémica que resulta de una infección, generalmente bacteriana, de la superficie endocárdica del corazón.* **Objetivo:** *Determinar los factores asociados a la endocarditis infecciosa en pacientes atendidos en el Hospital Universitario San Rafael de Tunja.* **Materiales y método:** *Diseño: estudio de casos y controles. Ámbito: hospitalario. Participantes: personas con endocarditis infecciosa que fueron atendidos en el Hospital San Rafael de Tunja entre 2009 y 2019. Variables: la variable dependiente fue la presencia de endocarditis infecciosa diagnosticada mediante los criterios de Duke; se incluyeron variables independientes que correspondían a información sociodemográfica, clínica y antecedentes de los participantes.* **Resultados:** *Se incluyeron 87 casos y 175 controles; se encontró que las variables enfermedad renal crónica (OR: 145), implantes dentales (OR: 77), enfermedad autoinmune (OR: 61), sexo masculino (OR: 15), infección urinaria en el último mes (OR: 15), arritmias (OR: 13), valvulopatías (OR: 6), faringoamigdali-*

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Date of reception: 02-08-2024
Date of acceptance: 10-01-2025
DOI: 10.24875/RCCARE.M25000156
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):92-98
www.rccardiologia.com

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tis (OR: 5) y uso de inhibidores de la bomba de protones (OR: 2) son factores de riesgo, mientras que el uso de aspirina (OR: 0.029) disminuye la probabilidad de presentar endocarditis. **Conclusiones:** *Los factores que se asociaron a la endocarditis en el servicio de urgencias del Hospital Universitario San Rafael de Tunja entre los años 2009 y 2019 son, en orden de importancia: enfermedad renal crónica, implantes dentales, enfermedad autoinmune, sexo masculino, infección urinaria en el último mes, arritmias, valvulopatías, faringoamigdalitis y uso de inhibidores de la bomba de protones (IBP), mientras que el uso de aspirina es un factor protector.*

Palabras clave: *Endocarditis. Infección. Factores de riesgo. Bacteriemia.*

Introduction

Infective endocarditis (IE) is a multisystemic disease caused by an infection of the endocardium, which is usually bacterial[1]. It has an incidence of 3 to 9 cases per 100,000 people with risk factors[2,3].

As far as its pathophysiology, we now know that, in order for this disease to develop, several independent factors must occur simultaneously, including a septic process (bacteremia) and an altered heart valve surface to produce an adequate site for bacterial insertion and colonization, which ultimately leads to the creation of an infected mass or "vegetation," by burying the proliferating organism within a protective matrix of serum molecules, for example, fibrin and platelets[1,3]. In humans, an injury equivalent to the valve surface may be due to a variety of factors, including turbulent blood flow related to primary valve damage due to systemic diseases, mechanical lesions or repetitive lesions. This endothelial damage triggers the formation of fibrin-platelet deposits on the interstitial edema, a pathophysiological condition first known as "non-bacterial thrombotic endocarditis"[4,5].

This causes characteristic pathological changes in multiple target organs. Pieces of the platelet and fibrin matrix in the vegetation may break off from the infected heart valve and travel with the arterial blood, ultimately lodging in the vascular bed. These septic emboli can involve almost any organ system and may manifest clinically in various ways. Thus, it is important to carry out studies on the possible risk factors for endocarditis, in order to avoid it and, in turn, reduce its potential morbidity and mortality[6,7].

The goal of this paper is to identify the factors associated with infective endocarditis in patients treated at Hospital Universitario San Rafael de Tunja.

Materials and method

Type of study, population and sample

This was a case-control study enrolling patients seen in the emergency room at Hospital Universitario San Rafael de Tunja between 2009 and 2019, who were identified using the international classification of disease codes.

Epi Info version 7.2 was used to calculate the sample size. The following parameters were used to calculate the sample size, based on the study by Lockhart et al.[8]: proportion of exposed cases: 20.2%, proportion of exposed controls: 42.1%, odds ratio to be detected: 3.5, controls per case: 2, confidence level: 95%, and power: 95%, which yielded a sample size of 87 cases and 175 controls. These were selected using simple random sampling.

Criteria for selecting cases

People between the ages of 20 and 60, with a diagnosis of infective endocarditis according to the Duke criteria, seen by the internal medicine and cardiology service at Hospital Universitario San Rafael de Tunja between January 1, 2009, and August 31, 2019. Cases were selected using the following International Classification of Diseases (ICD-10) codes: I33.0, I33.9, I38.0 and I39.0. Those with incomplete medical charts were excluded (one missing variable was cause for exclusion).

Criteria for selecting controls

People between the ages of 20 and 60, seen in the emergency room between January 1, 2009, and August 31, 2019. The controls were selected using simple random sampling of people between 20 and 60 years of age who were seen at the hospital and did not have case-related codes or systemic infectious diseases, excluding those with incomplete medical charts (one missing variable was cause for exclusion).

Variables

Different variables were included; the dependent variable was the presence of infective endocarditis,

identified using the Duke criteria. Some independent (qualitative dichotomous) variables were considered, including sex, age, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease (COPD), urinary tract infection or pneumonia in the previous 30 days, arrythmias, pharyngotonsillitis, autoimmune disease, psychiatric illnesses, dental implants, valvular heart disease, and the use of medications like corticosteroids, metformin, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, omeprazole and anticonvulsants.

Statistical analysis

The database was constructed using Excel version 2013 and was analyzed with the SPSS (version 22) statistical package. The univariate analysis was done using descriptive statistics for each group (cases and controls), establishing absolute and relative frequencies for the categorical variables. Measures of central tendency (mean, median) and measures of dispersion (standard deviation and interquartile range) were calculated for quantitative variables, according to each variable's distribution. To determine the possible associations between categorical variables in the bivariate analysis, tetrachoric tables were constructed using Pearson's Chi-square and the odds ratio, with their respective 95% CIs (< 1: a protective factor, > 1: a risk factor, and 1: no association). The difference in means of the quantitative variables was also determined for the case and control groups. Finally, a binary logistic regression model using the forward introduction method was used in the multivariate analysis, which included the study factors that showed association on the bivariate analysis and those with theoretical value.

Bias

In this study design, the potential biases to be controlled include, first, misclassification; that is, a case being selected as a control or vice versa. To avoid this type of bias, clear inclusion and exclusion criteria were developed to distinguish the groups. The second potential bias is measurement bias, in which the investigators conduct a more detailed search for information in one of the two groups. To correct this, a data collection form is applied by two investigators. The third bias is selection bias, which occurs when the inclusion of cases or controls depends, to a certain extent, on the exposure of interest. To avoid this, controls were selected through simple random sampling. The fourth bias is confounding bias, which was controlled for in the data analysis through binary logistic regression. Finally, we have the missing data bias, in which data are obtained from medical charts, with the potential for incomplete data collection.

Ethical considerations

Based on Resolution 8430 of 1993, which establishes healthcare norms, this is considered a negligible risk study, as it is based on a clinical chart review. In addition, permission was requested from the ethics and research committee at Hospital Universitario San Rafael de Tunja, which was responsible for the custody and handling of patient data.

Results

Participant selection

From January 1, 2009, to August 31, 2019, 15,308 people were admitted to the emergency room at Hospital Universitario San Rafael de Tunja, according to the institution's database, from which patients between the ages of 20 and 60 were selected, amounting to 4,896 people. Of these, a total of 105 cases of endocarditis were identified using the ICD-10 codes, as well as 4,791 patients without this diagnosis.

Simple random sampling was used to select the participants (cases and controls), with 7 cases eliminated (3 with negative imaging studies for endocarditis and 4 with incomplete data) as well as 14 controls (8 were seen in the outpatient department, 7 had incomplete medical charts). Therefore, a new random selection was done to choose the lacking participants (7 cases and 15 controls), thus achieving the sample size with no losses.

Univariate analysis

In the case group, the mean age was 38.74 years, with a standard deviation (SD) of 13.32 years; while in the control group, the average age was 37.19 years, with an SD of 13.46 years. The other characteristics are shown in table 1.

Bivariate analysis

The bivariate analysis determined that male sex, rural dwelling, autoimmune diseases, psychiatric illnesses,

dental implants, chronic kidney disease, arrhythmias, diabetes mellitus, COPD, the use of psychoactive drugs, valvular heart diseases, pharyngotonsillitis, recent pneumonia or urinary tract infections in the month prior to the episode and the use of proton pump inhibitors (PPIs) are risk factors, while the use of aspirin is a protective factor (Table 2).

Multivariate analysis

The multivariate analysis identified the following variables as factors that increase the likelihood of endocarditis (in descending order): chronic kidney disease, dental implants, autoimmune disease, male sex, urinary tract infections within the last month, arrhythmias, valvular heart disease, pharyngotonsillitis and the use of PPIs; while the use of aspirin is a factor that decreases the likelihood of developing endocarditis (Table 3).

Discussion

As reported by Chaudry et al.[9], patients with chronic kidney disease are considered to have a higher risk of endocarditis, which is associated with the use of therapeutic tools like hemodialysis (5.46; 95% CI: 3.28 - 9.10), which entails the use of invasive techniques such as catheter placement and fistula creation. However, our study shows a high odds ratio.

Various investigators have reported that dental procedures generate a risk of endocarditis[10,11]. However, this differs from Strom's findings[12], who reported no association between these variables (aOR 0.3 [95% CI 0.008-11.3]). Despite this assertion, our study found an association between the use of dental implants and the onset of IE.

Similar to Lin et al.'s[13] findings, autoimmune diseases are a risk factor that facilitate endocarditis (11.64; 95% CI: 2.75 - 49.32). This may be related to different causes, like the use of steroids (39.59; 95% CI: 16.59-93.53)[14]; nevertheless, our study did not show this association.

The results regarding the association of sex as a risk factor are different from those reported by Filliatre[15], who determined that there is no association between gender and the onset of endocarditis (1.21 [0.55-2.67]). However, these figures are similar to those of Lin et al.[14], who reported a figure of 2.76, with confidence intervals between 1.45 and 5.27, comparable to the findings of our study.

According to Gagneux et al.[16], valvular heart diseases and prosthetic valves increase the risk of infective endocarditis. Their study showed a risk of 5.49 (95% CI: 1.92-17.9), similar to what we found in our study.

As reported by Krčméry[17], bacterial pharyngotonsillitis has been found to foster the onset of infective endocarditis. Therefore, it is important to adequately manage and monitor this pathological condition.

Arrhythmias are another risk-generating factor according to the results, as they facilitate endothelial injury and create greater turbulence, causing bacterial adhesion to the endocardium. They are also a poor prognostic indicator, since they facilitate septic emboli and hamper patient's potential treatment processes[18].

We found that PPIs can increase the risk of infective endocarditis; however, to date, there are no studies mentioning this relationship, although different studies have related this group of drugs to other systemic diseases like pneumonia[19-21] and gastrointestinal diseases[22,23]. Therefore, it is important to conduct higher order (cohort or clinical trial) studies to prove this association.

An important finding was the association of aspirin as a protective factor. Veloso et al[24] reported that the use of dual aspirin/ticlopidine therapy prevented the formation of vegetations. However, neither of these drugs had a significant effect on its own. The positive effects of antiplatelet drugs are probably due to their control of platelets as an initial pathogenic element in endocarditis, as they inhibit bacterial adhesion and reduce the formation of extracellular thrombi, thus preventing the formation of vegetations[25].

These data have adequate internal and external validity; however, the age and endocarditis diagnosis criteria must be met in order for them to be generalized. Furthermore, it would be prudent to mention that despite controlling all possible biases in the study, the study design, retrospective data collection and unrecorded data may affect the results. Therefore, based on these results, we suggest performing higher order studies to establish this probable association and broaden our therapeutic arsenal against an infectious disease that has a very low prevalence but can be associated with many comorbidities and incur high costs. One limitation of this study is its wide confidence intervals, which may have been affected by the sample size and length of the study.

Table 1. Univariate analysis

Variables	Cases (n = 87)	Controls (n = 175)	p (Chi^2)
Age Years	38.74 ± 13.32	37.19 ± 13.46	0.051
Sex Male	63 (72.4%)	84 (48%)	0.000
Residence Rural	55 (63.2%)	66 (37.7%)	0.000
Diabetes mellitus Presence	28 (32.1%)	18 (10.2%)	0.000
COPD Presence	47 (54%)	46 (26.2%)	0.626
HTN Presence	16 (18.3%)	28 (16%)	0.026
Psychoactive substance use Presence	8 (9.1%)	5 (2.8%)	0.026
Congenital heart disease Presence	8 (9.1%)	16 (9.1%)	0.989
Valve disease Presence	34 (39%)	14 (8%)	0.000
Urinary tract infection Presence	21 (24.1%)	7 (4%)	0.000
Pneumonia Presence	21 (24.1%)	8 (45.7%)	0.000
Heart surgery Presence	4 (4.5%)	7 (4%)	0.820
Dental implants Presence	21 (24.1%)	4 (2.2%)	0.000
Autoimmune disease Presence	22 (25.2%)	6 (3.4%)	0.000
Mental illness Presence	11 (12.6%)	8 (45%)	0.018
Chronic kidney disease Presence	21 (24.1%)	15 (8.5%)	0.000
Arrhythmias Presence	32 (36.7%)	21 (12%)	0.000
Pharyngotonsillitis Presence	40 (45.9%)	20 (11.4%)	0.000
Corticosteroids Presence	6 (6.8%)	23 (13.1%)	0.129
Metformin Presence	17 (19.5%)	21 (12%)	0.103
Aspirin Presence	8 (9.1%)	60 (34.2%)	0.000
Opioids Presence	4 (4.5%)	20 (11.4%)	0.071
PPIs Presence	33 (21.8%)	22 (39.4%)	0.005
Diuretics Presence	19 (21.8%)	29 (16.5%)	0.299
ACE inhibitors Presence	25 (28.7%)	29 (16.5%)	0.022
ARBs Presence	23 (26.4%)	30 (17.1%)	0.078
Anticonvulsants Presence	11 (12.6%)	15 (8.5%)	0.299

COPD: chronic obstructive pulmonary disease; HTN: hypertension; PPI: proton pump inhibitor; ACE inhibitors: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 2. Bivariate analysis

Variables	OR	95% CI	
Male sex	2.844	1.631	4.958
Rural residence	2.839	1.667	4.834
Diabetes mellitus	4.139	2.132	8.037
COPD	3.295	1.921	5.652
HTN	1.183	0.602	2.327
Psychoactive substance use	3.443	1.092	10.861
Congenital heart disease	1.006	0.413	2.452
Valve disease	7.377	3.680	14.789
Urinary tract infection	7.636	3.100	18.811
Pneumonia	6.642	2.803	15.739
Heart surgery	1.157	0.329	4.063
Dental implants	13.602	4.499	41.123
Autoimmune disease	9.533	3.698	24.575
Mental illness	3.021	1.168	7.814
Chronic kidney disease	3.394	1.649	6.986
Arrhythmias	4.267	2.271	8.017
Pharyngotonsillitis	6.596	3.519	12.362
Corticosteroids	0.490	0.192	1.251
Metformin	1.781	0.885	3.583
Aspirin	0.194	0.088	0.428
Opioids	0.373	0.124	1.129
PPIs	4.25	2.281	7.918
Diuretics	1.407	0.737	2.684
ACE inhibitors	2.030	1.101	3.743
ARBs	1.737	0.937	3.222
Anticonvulsants	1.544	0.677	3.521

COPD: chronic obstructive pulmonary disease; HTN: hypertension; PPI: proton pump inhibitor; ACE inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; OR: odds ratio; 95% CI: confidence interval.

Table 3. Multivariate analysis with binary logistic regression

Variables	aOR	95% CI		p
Chronic kidney disease	145.047	11.904	1,767.282	0.000
Dental implants	77.819	3.136	1,930.888	0.008
Autoimmune disease	61.426	6.053	623.370	0.000
Male sex	15.490	3.666	65.446	0.000
Urinary tract infection	15.031	1.153	195.986	0.039
Arrhythmias	13.119	1.959	87.861	0.008
Valve disease	6.767	1.904	24.054	0.003
Pharyngotonsillitis	5.517	1.446	21.049	0.012
PPIs	2.53	1.671	6.189	0.000
Aspirin	.029	0.003	0.276	0.002
Rural residence	2.327	0.921	5.880	0.074
Diabetes mellitus	1.181	0.178	7.834	0.863
Pneumonia in the last month	1.160	0.137	9.782	0.892
ACE inhibitors	1.414	0.287	6.953	0.670
COPD	1.037	0.004	2.315	0.303
Mental illness	0.257	0.011	6.247	0.404
Psychoactive substance use	0.002	0.000	1.135	0.404

Conclusions

The factors associated with endocarditis in the emergency room at Hospital Universitario San Rafael de Tunja from 2009 to 2019 were, in order of importance: chronic kidney disease, dental implants, autoimmune disease, male sex, urinary tract infections in the previous month, arrhythmias, valvular heart disease, pharyngitis, and the use of PPIs; while the use of aspirin was a protective factor.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics

Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing this manuscript.

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ORIGINAL ARTICLE

Relevance of epicardial adipose tissue in heart disease

Relevancia de la grasa epicárdica en la enfermedad cardíaca

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Abstract

Introduction: *Obesity is one of the main public health problems in the world. It is considered a trigger for multiple cardiometabolic diseases, such as acute myocardial infarction, high blood pressure, type 2 diabetes mellitus and ischemic stroke. This increase in fat infiltrates the heart, increasing epicardial adipose tissue (EAT), which ends up generating more inflammation and cardiac abnormalities.* **Objective:** *To study the role of EAT in the development of heart diseases and the best method for diagnosing this adipose tissue.* **Materials and method:** *This was a topical review derived from a critical review of the available literature on EAT, its functions and main diagnostic methods.* **Conclusions:** *There was a clear relationship between EAT and inflammatory processes that cause abnormal cardiac function and lead to atrial fibrillation and atheromatous coronary disease. Today, we have several ways to measure it: magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography. The most accessible method is echocardiography, which is an appropriate and low-cost method; although the gold standards would be CT and MRI, their high cost makes them unaffordable.*

Keywords: *Adipose tissue. Atrial fibrillation. Body composition densitometry. Echocardiography.*

Resumen

Introducción: *La obesidad es uno de los principales problemas de salud pública en el mundo. Se considera detonante de múltiples enfermedades cardionefrometabólicas como el infarto agudo de miocardio, la hipertensión arterial, la diabetes mellitus tipo 2 y el accidente isquémico cerebral. Este aumento de grasa corporal infiltra el corazón y hace que aumente la grasa epicárdica, que termina por generar más inflamación y alteraciones cardíacas.* **Objetivo:** *Estudiar el papel de la grasa epicárdica en el desarrollo de enfermedades cardíacas y encontrar el mejor método de diagnóstico para detectarla.* **Materiales y método:** *Se hizo una revisión de tema, resultado de la revisión crítica de la literatura disponible sobre la grasa epicárdica, sus funciones y principales métodos diagnósticos.* **Conclusiones:** *Se encontró una clara relación entre la grasa epicárdica y los procesos inflamatorios que generan alteración en la función cardíaca y que conducen al desarrollo de fibrilación auricular y enfermedad coronaria ateromatosa. En la actualidad hay varias formas de medirla; la resonancia nuclear magnética, la tomografía y la ecocardiografía; esta última es el método más accesible por ser adecuado y de bajo costo. Pese a que los estándares de oro serían la tomografía y la resonancia, su alto costo las hace poco asequibles.*

Palabras clave: *Tejido adiposo epicárdico. Fibrilación atrial. Densitometría de composición corporal. Ecocardiografía.*

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Date of reception: 23-11-2023
Date of acceptance: 13-01-2025
DOI: 10.24875/RCCARE.M25000157
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;31(2):99-104
www.rccardiologia.com

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Introduction

Epicardial adipose tissue (EAT) was once considered a storage compartment, like other sites within the body, but is now known for its extensive metabolic and endocrine functions[1,2]. Adipose tissue is classified according to its morphology, physiology and embryonic origin. It is divided into two groups: white adipose tissue (WAT) and brown adipose tissue (BAT)[3]. White adipose tissue is derived from mesenchymal stem cells[4] and is considered responsible for energy storage and deposits. It is distributed as both visceral (VAT) and subcutaneous (SAT) adipose tissue[5]. Brown adipose tissue arises from the dermomyotome, consisting of precursor cells[6] resembling musculoskeletal tissue cells, which are genetically derived from similar pathways. Brown adipose tissue (unlike WAT) is stored in small amounts and is highly vascularized and innervated, which gives it a distinctive character and its brown color. Likewise, it has a high metabolic rate, generates heat and contributes to overall metabolism[7].

Epicardial adipose tissue is part of WAT storage, covering 80% of the heart's surface and representing 20% of its total weight[8]. Therefore, EAT is considered part of the VAT. This fat deposit is an important source of local cytokine and hormone production and has autocrine functions[9]. It also regulates heart and blood vessels physiologically through "vasocrine" mechanisms. This cytokine production plays an important autocrine role, with a paracrine effect locally, and an endocrine effect remotely[9]. Epicardial adipose tissue is well known for acting as an energy reservoir for cardiomyocytes, which depend on fatty acid oxidation for energy[10,11]. Although this is an essential source of energy for heart muscle function, over the last few decades, epicardial fat thickening has been found to greatly elevate the risk of developing cardiovascular disease (CVD) and metabolic syndrome (MetS)[12].

The inflammation generated in EAT can have a paracrine effect on the structure and function of surrounding tissues[13,14]. Furthermore, proinflammatory adipokines released in the epicardium (and others in visceral fat) that reach the general circulation can contribute to systemic inflammation which, in turn, promotes the accumulation of EAT and produces positive feedback.

To date, there is no instrument to translate this localized effect. The name "epicardial adipose tissue" is used to differentiate it from paracardial adipose tissue. Epicardial fat is located within the external heart layer (epicardium), and paracardial fat is located in the space between the heart and its surrounding vessels (the paracardial space). It is important to highlight its close anatomic relationship with the underlying cardiac muscle. This location allows EAT to intervene in its local and systemic functions, with different effects on the cardiac tissue[15].

Imaging technology advances allowed visceral fat in different locations (such as intrahepatic, peripelvic and epicardial) to be quantified and analyzed. For several decades, researchers asked themselves the same questions: "What role do these adipose tissues play in specific organs and systems? Is it an unfavorable or protective role, or both? What are their main activation triggers?" After several studies, some of these questions can be answered.

Under normal conditions, EAT acts as a vascular flow regulator through "vasocrine" mechanisms, is a myocardial and coronary protector against inflammatory cells, is a source of fatty acids for the myocardium, provides a barrier against mechanical stress, and supplies multipotent stem cells[16]. By releasing adiponectin, EAT benefits the cardiovascular system by reducing vascular tone, preventing remodeling and counteracting proinflammatory mediators. However, in a dysfunctional state, recent evidence suggests that EAT acts as a local mediator of systemic inflammation. The triggers and mechanisms involved in activating structural and functional changes in EAT during proinflammatory processes have yet to be elucidated. Conditions like obesity, insulin resistance, diabetes and low-grade chronic inflammatory diseases cause a change in EAT toward a proinflammatory phenotype, characterized by the secretion of various cytokines and chemokines that lead to inflammatory cell infiltration and fibrosis[15,16].

Thus, over the last few years, a relationship has been shown between EAT and heart diseases like coronary artery disease, heart failure with preserved ejection fraction and atrial fibrillation[17,18]. Obesity increases unbalanced adipogenesis, producing an abnormal increase in EAT which, in turn, heightens the secretion of proinflammatory cytokines. Other conditions that alter EAT include diabetes mellitus, menopause[19,20], MetS, hypertension, and atherogenic dyslipidemia.

The accumulation of VAT associated with MetS triggers non-alcoholic fatty liver disease (NAFLD) and altered EAT; this has been implicated as a cardio-metabolic risk factor[21-23]. Computed tomography (CT) and magnetic resonance imaging (MRI) allow non-invasive adipose tissue deposit measurements, including pericardial fat[24,25].

However, pericardial adipose tissue deposits are rarely measured outside of research settings. In fact,

according to the literature, while CT is the most validated and reproducible technique for measuring fat (due to its greater spatial resolution compared to MRI[26]), it allows manual segmentation and quantification of epicardial fat and is therefore the method of choice today[26]. Nevertheless, this approach requires laborious, step-by-step manual segmentation of the anatomical structures, making it operator-dependent and time consuming and, therefore, not appropriate for routine clinical practice[26]. Consequently, the development of computer-assisted systems in this setting, with artificial intelligence (AI) solutions including automated and deep learning, has been recently proposed as a solution for rapidly and automatically obtaining reliable measurements of abdominal adipose tissue on CT and MRI[27,28].

Epicardial fat: white, brown or beige

From an embryological perspective, BAT is derived from myogenic progenitors that express Myf5 (which codes for myogenic factor 5) and Pax7[29], while "beige" adipose tissue arises from the transdifferentiation of mature cells, as well as Myf5 precursors and, recently, MYH11+. This variety of origins is a topic for animal model studies[30]. It is well known that BAT generates heat in response to cold temperatures and activates the autonomic nervous system, due to a large number of mitochondria, as well as being involved in the production of uncoupling proteins[31,32]. Despite being phenotypically similar to WAT, EAT highly expresses uncoupling protein 1 (UCP-1, OMIM 113730) in all its membranes, which suggests that it could function similarly to BAT (that is, producing heat). These functional changes have justified the use of a new name for these transdifferentiated adipose cells: "beige" adipocytes[33,34], which are being associated with prolonged exposure to cold climates and the -adrenergic agonist, and have been described over the last decade. Following this train of thought, UCP-1 functions as a proton translocator in the inner mitochondrial membrane, producing a proton flow toward the mitochondrial matrix, decreased ATP, and energy dissipation in the form of heat[36]. Furthermore, EAT expresses peroxisome proliferator-activated receptor-γ coactivator 1α (PPARγC1α, OMIM 604517), which is one of the most important proteins in adipocyte differentiation[6]. In hypothermia, chronic exposure to cold promotes PPARγC1α activation, which means that epicardial fat can protect the myocardium through white tissue stimulation, since it transforms beige adipocytes, prevents the development of ventricular arrhythmias and, thus, plays a cardioprotective role[37]. Therefore, based on this information, EAT acts as a source of local energy in high cardiovascular demand situations, such as ischemic conditions[38].

Epicardial fat: how to measure it?

Increased VAT is associated with a higher cardiovascular and metabolic syndrome risk, just as increased EAT can be considered a marker for heart disease. Therefore, EAT measurement could be used as a potential therapeutic target[39-41]. Previous studies have shown an interest in the relationship between EAT and increased ventricular mass, noting compensatory left ventricular (LV) hypertrophy in response to pressure or volume overload combined with hormonal effects.

Hypertrophy is proportional to the increase in epicardial fat, which has been determined by transthoracic echocardiographic measurements[42,43]. A clinical study by Kim et al.[44] using this technique evaluated 27 people before and after a hypocaloric diet (with a 26.8% reduction in daily caloric intake) and a 12-week aerobic exercise program, and reported a 17.2% reduction in EAT volume at the end of the study. Moreover, Salami et al.[45] evaluated whether there was a difference in EAT thickness between white and black men who were admitted for angina symptoms. The team performed transthoracic echocardiography on 150 patients and reported that right ventricular EAT was significantly greater in white men than black men, concluding that it could be considered an important variable in analyzing the relationship between fat storage and cardiovascular risk. According to the studies mentioned, the main method for measuring epicardial fat is two-dimensional (2D) transthoracic echocardiography, which is a safe, easily reproducible, non-invasive and routine method for patients with suspected cardiovascular disease or a risk of metabolic syndrome[46]. To evaluate epicardial fat using this method, the 2D parasternal long- and short-axis views are analyzed and used to obtain a more precise measurement of the fat thickness in the right ventricle (RV). The thickness is measured perpendicular to the free wall of the RV at the end of systole, in three cardiac cycles, since the epicardial fat is compressed during diastole and yields inaccurate measurements[47].

Echocardiography has many advantages for EAT measurement[47], although other imaging methods used for the quantification of epicardial fat are multislice tomography (MSCT) and MRI, which are considered the gold standards for assessing EAT between the

myocardium and visceral pericardium[48]. With MSCT it is possible to measure volume (3D), as well as to obtain information on coronary artery calcification and stenosis. It has major disadvantages, such as exposure to ionizing radiation and its high cost[49]. On the other hand, MRI has better spatial resolution and volumetric evaluation of adipose tissue, but, unlike MCT, it does not expose the patient to radiation. However, it is also very expensive and time-consuming, which gives it a significant disadvantage[50]. When evaluating costs and irradiation of MCT and MRI, the predictive capacity of transthoracic echocardiography has been evaluated to predict high-risk plaques, confirmed by angioCT, and to assess epicardial fat thickness, the latter considered a good noninvasive predictor. Therefore, echocardiography is the most cost-effective method at present, especially in regions where high-cost imaging is scarce.

In addition, recent studies have investigated the causal link between atrial fibrillation (AF) and EAT. The evidence suggests that a higher EAT volume (measured using cardiac CT or MRI) or fat thickness (evaluated with transthoracic echocardiography – TTE) is not only associated with established AF, but also predicts new-onset AF. Even more importantly, the relationship between EAT and an elevated risk of AF continues to be significant after adjusting for the latter's risk factors, like advanced age, hypertension, heart failure and obesity. A systemic proinflammatory state was already known to elevate the risk of AF, but could EAT really be the local mediator of this process? Serum concentrations of systemic proinflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), increase in patients with AF. Interestingly, these biomarkers are found in abundance in EAT samples from patients with AF. Furthermore, EAT's inflammatory activity, shown by greater uptake of 18-fluorodeoxyglucose detected with positron-emission tomography, was significantly greater in patients with AF, compared to the control group[49]. The EAT in the vicinity of the left atrium (LA) is the most active site, according to the current pathogenesis of AF. The volume of EAT is also associated with adipocyte infiltration in the adjacent myocardium. Histopathological studies showed significant adipocyte infiltration in the posterior wall of the LA, which correlates with a larger EAT volume, particularly in persistent AF. These findings concur with the electrical heterogeneity in this group of patients, as shown by bipolar low voltage areas and fractionated potentials on electroanatomical mapping of the posterior LA[50].

Table 1. Normal epicardial fat measurements with different equipment[46-48]

Equipment	Normal value (mm)
Echocardiography	1-3 mm
Computed tomography	1.5-4 mm
Magnetic resonance imaging	1-4 mm
Ultrasound	1-3 mm

Table 2. Normal epicardial fat values by sex and age[46-48]

Age	Males	Females
20-39 years	1.5-3.5 mm	1-3 mm
40-59 years	2-4 mm	1.5-3.5 mm
60-79 years	2.5-5 mm	2-4 mm
≥ 80 years	3-6 mm	2.5-5 mm

Usefulness of epicardial fat in clinical practice

The relationship between elevated EAT and cardiovascular disease is a matter of debate, especially related to coronary syndromes and atheromatous plaque weakening[40]. Ito et al.[45] studied 117 patients whose epicardial fat volume was measured with multisection CT. The arterial lumens were evaluated with optical coherence tomography to detect thin-cap fibroatheromas. They found that increased EAT volume was associated with atheromatous plaque thinning, which made it more susceptible to rupture. Okada et al.[50] analyzed the relationship between EAT volume and the severity of coronary artery disease in nonobese patients, as well as the potential effect of epicardial fat volume influencing coronary plaque morphology. The results of the above studies lead to the question of normal EAT values on echocardiography, and several studies show these values on both echocardiography and CT (Table 1); we also found EAT values by gender and age (Table 2). Similar to the previous study, Okada et al.[50] found that individuals with higher EAT volume presented greater severity in coronary plaques, which were not necessarily calcified, indicating that the thickness of epicardial fat storage plays a key role in the progression of atherosclerotic coronary artery disease[50].

Conclusions

The abnormal increase in epicardial fat has multiple metabolic alterations, such as increased risk of coronary heart disease and atrial fibrillation, among others, this increase is closely related to the increase in visceral fat and ectopic fat at the hepatic level (fatty liver), so its measurement is essential, so far the gold standard are MRI and MCT, but because of costs it is not viable, then appears an easy and economical method that has large studies and is echocardiography, With this review we wanted to study how reliable and viable this study is in its measurement and it leaves us very good information that its use brings us closer to the diagnosis of EAT and its intervention before it causes cardiac alterations, we must continue in the search for inexpensive and good quality methods for the evaluation of EAT to diagnose and manage this ectopic fat that can trigger so many pathologies.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent and ethical approval. The study does not involve personal patient information, nor does it require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any generative artificial intelligence in writing this paper.

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Revista Colombiana de Cardiología
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REVIEW ARTICLE

Treatment of coronary artery disease with drug-eluting balloons

Tratamiento de la enfermedad arterial coronaria con balones liberadores de fármacos

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Abstract

Drug-eluting balloons have emerged as a promising treatment option for various coronary artery disease presentations due to their ability to deliver antiproliferative drugs directly to the vessel wall without permanent implants. This rapid and homogeneous drug delivery effectively reduces restenosis risk and facilitates vessel healing, while minimizing the likelihood of late thrombotic events. Clinical studies have consistently demonstrated the efficacy and safety of drug-eluting balloons in treating a wide range of coronary artery disease conditions, including de novo lesions, in-stent restenosis, small vessel lesions, and bifurcation lesions. Compared to conventional stents, drug-eluting balloons have consistently shown lower restenosis rates in the medium and long term without increasing the risk of thrombotic complications, making them an attractive alternative for patients with coronary artery disease, particularly those at higher risk of restenosis or stent thrombosis.

Keywords: *Drug-eluting balloon. Drug-eluting stent. Coronary artery disease. Coronary restenosis.*

Resumen

Los balones liberadores de fármacos son hoy una prometedora estrategia para determinadas condiciones anatómicas. La transferencia rápida y homogénea de fármacos antiproliferativos sobre la pared del vaso sin el uso de implantes permanentes, previene el riesgo de eventos trombóticos tardíos y facilita la curación del vaso enfermo. La investigación clínica ha demostrado la eficacia y seguridad de los balones liberadores de fármacos en el tratamiento de diversas presentaciones de la enfermedad arterial coronaria, incluyendo lesiones de novo, reestenosis intrastent, lesiones en vasos pequeños y lesiones de bifurcación. En comparación con los stents convencionales, han demostrado tasas más bajas de reestenosis a mediano y largo plazo, sin aumentar el riesgo de complicaciones trombóticas.

Palabras clave: *Balón liberador de fármacos. Stent liberador de fármaco. Enfermedad arterial coronaria. Reestenosis coronaria.*

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Date of reception: 15-07-2024
Date of acceptance: 10-01-2025
DOI: 10.24875/RCCARE.M25000152

Available online: 30-06-2025
Rev Colomb Cardiol. 2025;31(2):105-113
www.rccardiologia.com

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Introduction

Cardiovascular diseases (CVDs) are the main cause of death and disability-adjusted life years (DALYs) worldwide[1]. According to the World Health Organization's report, in 2019, approximately 17.9 million people died from this cause, accounting for 32% of deaths worldwide[2]. However, a large part of this burden falls on low and middle-income countries; 2 million deaths and 40.8 million DALYs per year were in the Americas[3].

Percutaneous coronary intervention (PCI), which was introduced in 1977, has revolutionized the treatment of coronary artery disease (CAD) and is now the treatment of choice for acute ST-elevation acute coronary syndrome (STE-ACS)[4]. However, balancing the reduction in target lesion revascularization, stent thrombosis and the risk of bleeding continues to be a significant challenge. Although drug-eluting stents (DESs) are the treatment of choice for CAD, drug-eluting balloons (DEBs) are currently a promising strategy for certain anatomical conditions[5].

Clinical research has proven the efficacy and safety of DEBs for treating in-stent restenosis (ISR), as well as other CAD scenarios like de novo, small vessel and bifurcation lesions[6]. Compared with conventional stents, DEBs have proven to have lower mid- and long-term restenosis rates, without increasing the risk of thrombotic complications[6,7]. These devices also offer particular advantages in certain groups of patients, like those with a high risk of bleeding or contraindications for stent placement[6].

Today, there are insufficient studies describing the mechanisms and advantages of DEBs in CAD treatment, as well as their efficacy and safety. Despite their encouraging results, these devices are not systematically used in hemodynamics services. This review intends to describe the main advantages of DEBs over other devices, like DESs, as well as evaluate their efficacy and safety in patients with CAD.

Materials and method

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[8]. The same search strategy was employed in each of the sources consulted.

Source of information

Indexed journal articles were used as the source of information. The following bibliographic databases were secondary sources of information: PubMed, Scopus, Cochrane library, Dimension, Embase, LILACs, and SciELO, restricted to randomized clinical trials or meta-analyses of randomized clinical trials, with no restriction as to year of publication or language.

Search strategy

The following descriptive health sciences terms (DeCS/MeSH) were used, with the Google operator AND: «drug eluting ballon AND drug coated ballon AND paclitaxel coated ballon AND sirolimus coated ballon, coronary artery disease"», as well as the following filters: MH: ("Systematic Review as Topic" OR "Meta-Analysis as Topic") PT: ("systematic review" OR "meta-analysis") OR TI: ("systematic review" OR "revisión sistemática") OR AB: ("this systematic review" OR "esta revisión sistemática" OR "this meta-analysis" OR "este meta análisis") OR TA: "Cochrane Database Syst Rev»).

In the first phase, two investigators independently searched for abstracts in June 2024, with no time limit, and the search was updated monthly up to July 2024. The result of these searches was exported to a bibliographic reference manager (EndNote X.4) to eliminate duplicates and facilitate document management.

Study selection

Two of the review authors (LMTF and RAC) evaluated the studies independently to determine their eligibility, considering the inclusion and exclusion criteria. Discrepancies were resolved through discussion. When an agreement was not reached, a third author was asked to evaluate the study for inclusion.

Only reviews and trials meeting all the following criteria were analyzed: a) systematic or bibliographic reviews, b) randomized controlled trials and meta-analyses, c) study subjects with coronary artery disease, and d) a study intervention involving DEBs. Articles with one or more of the following characteristics were excluded from the analysis: a) not systematic or bibliographic reviews, not randomized clinical trials, like observational or retrospective studies; b) incomplete or statistically different baseline data; and c) full text not available.

Data extraction and analysis

Data extraction and analysis were done following the guidelines in the Cochrane Handbook for Systematic

Reviews of Interventions, and the certainty of evidence was evaluated using the GRADE method[7]. Data related to the study design, sample size, length of follow-up, main endpoints, number of patients, outcomes of the intervention, occurrence of major adverse cardiovascular events (MACE), overall and cardiac mortality, as well as other related clinical outcomes, were extracted from the selected studies. The Criteria for Evaluating the Quality of RCT Documents, recommended by the Cochrane Handbook[7], were used to evaluate the quality of the studies included, according to the following points: sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessments, incomplete outcome data, selective outcome reporting and "other problems." The analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for healthcare interventions[8].

Drug-eluting balloons

A DEB is a balloon catheter without metallic implants, made up of three main components: the active ingredient, the excipient, and the balloon. The first paclitaxel-eluting balloon for treating and preventing coronary restenosis was implanted in 2004[9]. The combined action of these three components ensures the achievement of clinical principles like constant delivery of a therapeutic drug dose, long-term maintenance of the drug concentration in the vessel walls, and low toxicity[10]. Not having a foreign body permanently lodged in the coronary wall facilitates vessel healing, lowers the risk of late-onset thrombotic events, and allows the potential benefit of remodeling based on an uncaged arterial wall.

Drug-eluting balloon angioplasty is a relatively new procedure using semi-compliant balloons coated with a cytotoxic chemotherapeutic drug. It allows the drug to be more evenly disseminated to the endothelial lining, compared with DESs[11]. Although a wide variety of DEBs are available, paclitaxel continues to be one of the preferred coating drugs; however, sirolimus balloon treatment has attracted growing attention. The outcomes of sirolimus-eluting balloon treatment in stent restenosis show comparable rates of target lesion revascularization, target vessel revascularization, myocardial infarction, death from any cause and MACE at two years, compared with DES treatment[12]. The same holds true for comparisons of the outcomes between different coating drugs. A recent multicenter study showed non-inferiority of sirolimus-eluting balloons compared to paclitaxel-eluting balloons for small vessel treatment, as far as angiographic net lumen gain at six months[13]. This was very similar to the outcome of the TRANSFORM I study[14] that evaluated the efficacy of both coating drugs in the same clinical setting.

Mechanism of action of DEBs

The balloon surface is coated with the excipient and a single layer of an antiproliferative drug. The excipients act as drug transporters, enabling greater adherence to the endothelium and the mucus layer during balloon dilation. They also ensure stability prior to the gradual, controlled release, allowing long-term treatment. The most frequently used excipients in clinical practice include urea, iopromide, acetyl tributyl citrate and polyester-based polymers. Once the balloon is inflated, these antiproliferative drugs are evenly distributed to the blood vessel surface and then rapidly infiltrate the wall, where they inhibit smooth muscle cell proliferation and migration, with the distinctive feature of ensuring that the artery's original anatomy remains intact[15].

There is a wide variety of antiproliferative drugs today, like paclitaxel, sirolimus or zotarolimus. The one most frequently used is paclitaxel; its lipophilic properties allow it to pass freely through the cell membranes and then promote the assembly of microtubules, thus halting the cell cycle during the G2/M phase, ultimately leading to apoptosis[16]. Current studies indicate that transluminal angioplasty with DEBs may reduce the activity of inflammatory proteases and delay disease progression[17]. However, paclitaxel's antiproliferative effect is affected by its toxicity. The vessel wall's efficiency in absorbing this drug is inversely related to its lipid content. Thus, diseases like atherosclerosis, which elevate the lipid content of the vessel wall, affect drug absorption[10].

On the other hand, sirolimus, known as rapamycin, crosses cell membranes and binds to its intracellular receptor, thus regulating cell proliferation by controlling the levels of cyclin and cyclin-dependent kinase inhibitors that are needed to transition from stage G1 to stage S in the cell cycle[17]. In his study, Wim Martinet showed that sirolimus lessens atherosclerotic formation by inhibiting macrophage proliferation, lipid accumulation and plaque formation during angiogenesis[18]. Compared to paclitaxel, sirolimus is more lipophilic; however, it is less absorbed by the vessel wall. Meanwhile, recent studies have shown that zotarolimus-coated balloons (a sirolimus analog), inhibit arterial inflammation and neointimal proliferation[19].

DEBs vs. DESs

Endovascular devices are frequently implanted in our hemodynamics laboratories to treat CAD. Ever since Sigwart introduced the first metallic stents in 1980, there have been impressive technological advances in the field of stent therapy. However, the risk of late thrombosis and persistent restenosis in subgroups with complex lesions remains[16]. Other procedure-related complications (stent fractures or malpositioning), as well as delayed vascular endothelial healing and drug hypersensitivity reactions, have also been reported after DES implantation[20].

Despite the development of new DES generations, they have not been able to provide a comprehensive treatment capable of preventing restenosis and at the same time preserving vascular endothelial function. A competent endothelium (both intact and functional) regulates vascular tone and suppresses neointimal hyperplasia, inflammation, and thrombus production. Drug-eluting stent placement alters its structure, and nonselective cytostatic or cytotoxic drug elution drastically reduces the quality of vessel healing and of the regenerating endothelium[16]. Vascular endothelial cells protect against thromboses, lipid uptake and inflammation, while proliferating vascular smooth muscle cells and inflammatory cells have a proliferative and prothrombotic effect. None of the drugs used to date (paclitaxel or sirolimus or its analogs everolimus, zotarolimus and biolimus) have the ability to selectively inhibit any group of vascular endothelial cells[16].

The possibility of an implant-free interventional treatment is one of the main advantages of DEBs, thus reducing the risk of restenosis and late stent thrombosis[10]. Performing angioplasty with a DEB simplifies the procedure and preserves the coronary anatomy, facilitating healing of the diseased vessel and reducing the length of dual antiplatelet therapy[10]. However, the efficacy of DEBs is currently limited to certain anatomic scenarios, awaiting new scientific evidence.

A recent meta-analysis comparing PCI with DEBs vs. devices without DEBs (like conventional balloon angioplasty, bare metal stents or drug-eluting stents) for treating coronary restenosis and de novo lesions showed no significant differences in all-cause mortality, despite lower rates following DEB treatment[21]. After three years of follow-up, all-cause mortality in the DEB group was significantly lower than in the control group (RR: 0.73; 95% CI: 0.53 to 1.00; p = 0.047)[21]. Another meta-analysis evaluating the occurrence of MACE found no differences, either, between groups receiving DEBs vs. DESs (RR: 1.19; 95% CI: 0.87-1.63; p = 0.27)[22]. However, the DAEDALUS patient meta-analysis reported a slightly higher target lesion revascularization rate with DEB treatment for stent restenosis revascularization, compared to DESs[23].

DEBs for in-stent restenosis

In-stent restenosis (ISR) is defined as the onset of a new (greater than 50%) angiographic stenosis within the stent; these stenoses have been classified as focal or diffuse, according to the length of restenosis (focal < 10 mm and diffuse ≥ 10 mm)[11]. The underlying mechanism involves the long-term presence of the metallic stent as a foreign body within the arterial vasculature[10]. Histologically, ISR differs from elastic recoil, which occurs in the first few hours after the revascularization procedure. In ISR, the degree of neointimal hyperplasia increases shortly after stent implantation, with late neoatherosclerotic changes[11]; its incidence ranges from 30 to 40% of patients treated with PCI[20].

In repeat endovascular treatment cases, DEBs are preferable to implanting another permanent metallic layer. Using DEBs instead of DES reimplantation is attractive in patients with multiple prior stent layers and in those who, for clinical reasons, could benefit from a shorter dual antiplatelet therapy regimen[24]. The interventional strategy using DEBs significantly reduces positive vascular remodeling and the inflammatory response, compared to balloon angioplasty alone or stent implantation.

Studies on the use of DEBs for treating ISRs are encouraging; several clinical studies have shown the efficiency and safety of these devices. A French study of 206 elderly patients with ISR showed a low incidence of MACE in the group treated with paclitaxel-eluting balloons[25]. In the PEPCAD China ISR study (a multicenter, randomized, prospective trial of paclitaxel-coated balloons vs. paclitaxel-eluting stents for treating drug-eluting stent ISR), angioplasty with DEBs was not inferior to paclitaxel-eluting stent implantation[26]. The same results were seen in the studies by Alfonso et al.[27] and Hamm et al.[28] evaluating patients treated with DEBs, with a follow-up of three years and six months, respectively (Table 1).

According to the results of a recent meta-analysis with three-year follow-up evaluating angioplasty with DEBs vs. DES reimplantation for treating coronary ISR, both groups were found to be similarly effective and safe for treating ISR with previous metal stent revascularization[29]. However, when treating restenosis with prior DES

revascularization, angioplasty with DEBs was significantly less effective than DES reimplantation[29]. Likewise, in another meta-analysis including 1,586 patients with DES restenosis, DES reimplantation and paclitaxel-eluting balloons were equally valid alternatives. However, paclitaxel-eluting balloons were more angiographically effective for treating DES restenosis[30].

DEBs in small vessel lesions

Currently, 30 to 67% of percutaneous interventions in patients with significant CAD are performed on small vessels[31]. The lack of consensus on the definition of small vessel CAD has contributed to a high degree of heterogeneity in the reference values. However, the most recent studies have identified an angiographic reference vessel diameter of < 2.5 mm as the most appropriate cut-off point[32]. Although DESs are effective in both small and large vessels, late lumen loss occupies a higher percentage of the respective vessel diameter, leading to higher ISR and clinical event rates. Today, DEBs are an attractive alternative for these cases, as they ensure easy access to the lesion, effective dilation of the stenotic vessels, no irritation from metalc stents and shorter dual antiplatelet treatment time[10].

One of the pioneer works evaluating the efficacy and safety of paclitaxel-iopromide-coated balloons in these vessels was PEPCAD I[33]. This study analyzed MACE rates at 12 and 36 months, which were lower in patients who only received DEBs[33]. However, the first randomized clinical trial evaluating PCI outcomes in small vessels treated with paclitaxel-eluting DEBs vs. paclitaxel-eluting DESs (PICCOLETO)[34] was stopped prematurely due to the superiority of the outcomes in the DES group. This study's failure is speculated to have been due to a lower concentration of paclitaxel released in this first-generation balloon, subsequently demonstrated in *in vitro* and animal studies.

Employing the same design, the PICCOLETO II[35] study was performed with a second generation paclitaxel-eluting balloon. Its results showed that paclitaxel-eluting balloons were more effective than everolimus-eluting stents with regard to late lumen loss, the incidence of myocardial infarction and thrombosis. The BELLO study by Labit et al.[36] had a similar outcome. Late lumen loss, and the rates of restenosis and MACE were significantly lower in the percutaneous DEB treatment group. During its three-year follow-up, paclitaxel-eluting balloon treatment was associated with fewer late angiographic losses and similar rates of restenosis and revascularization compared to the DES group[37]. Other more recent studies have shown noninferiority of DEBs compared to DESs, with regard to angiographic results (RESTORE SVD China Randomized Trial)[38] and clinical results (BASKET-SMALL 2)[39]. (Table 2).

DEBs in bifurcation lesions

Coronary bifurcation lesions are found in 20% of percutaneous interventions; unlike other lesions, bifurcation lesions involve both the main as well as side branches[40]. The European Bifurcation Club defines a bifurcation lesion as "a coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant side branch." This side branch is considered significant when the occlusion is accompanied by clinically relevant consequences for the patient (symptoms, an extensive area of ischemia, loss of viability of the irrigated myocardium, effects on left ventricular function) and a greater than 50% stenosis[41].

These anatomic characteristics constitute the biggest technical challenges during PCI procedures and the long-term outcome. One of the main complications is atheromatous plaque displacement during stent implantation in the main branch, with side branch occlusion. There are currently two DEB strategies for treating bifurcation lesions: a) a DEB in the side branch and a DES in the main branch, and b) a DEB in both branches (main and side).

Previous studies analyzing the combination of a conventional metal stent in the main branch with a DEB in the side branch showed a low rate of late lumen loss in the branch treated solely with a DEB[42]. Likewise, recent observational studies focused mainly on the strategy of a DEB in the side branch together with a DES in the main branch have also shown good results in the side branch[43]. A similar result was found in the German PEPCAD-BIF study of 128 patients over the age of 65, which confirmed the efficacy of DEBs for bifurcation disease[44]. Another recent study by Liu et al.[45] evaluated the results of DEBs in the main left artery, with no significant differences as far as the onset of MACE and angiographic results. The minimal diameter of the target vessel lumen before and immediately after PCI increased significantly in both groups.

While DEBs do have advantages in alleviating restenosis and simplifying procedures, there is no definitive consensus for treating these lesions. The results of studies in this field are promising, but larger trials are needed to confirm the long-term efficacy and safety of these devices.

Table 1. Randomized controlled trials on DEBs in ISR

Study	n	Intervention	Follow-up	Angiographic results	p	MACE	p	TLR	p
DEB revascularization in MS ISR									
PEPCAD II	131	DEB (paclitaxel) vs. DES (paclitaxel) revascularization for treating MS in-stent restenosis	6 months (angiographic) 12 months (clinical)	VLL 0.17 ± 0.42 mm vs. 0.38 ± 0.61 mm	0.03	9 vs. 22	0.08	6 vs. 25	0.09
TIS	136	DEB (paclitaxel) vs. DES (paclitaxel) revascularization for treating MS in-stent restenosis	12 months	VLL 0.02 mm vs.0.19 mm	< 0.001	10.3 vs. 19.1	0.213	7.4 vs. 16.2 (TVR)	0.110
DEB revascularization for DES ISR									
PEPCAD DES	110	BLF (paclitaxel) vs. bare balloon revascularization for treating DES ISR	6 months (angiographic and clinical)	VLL 0.43 ± 0.61 mm vs. 1.03 ± 0.77 mm Restenosis 17.2% vs. 58.1%	< 0.001 0.001	16.7 vs. 50.0	< 0.001	15.3 vs. 36.8	0.005
PEPCAD CHINA ISR	220	DEB (paclitaxel) vs. DES (paclitaxel) revascularization for treating DES ISR	9 months (angiographic) 12 months (clinical) 2 years (clinical)	VLL 0.46 ± 0.51 mm vs. 0.55 ± 0.61 mm	< 0.001	16.5 vs. 16 (TLF)	0.92	15.6 vs. 12.3	0.48
ISAR DESIRE III	402	DEB (paclitaxel) vs. DES (paclitaxel) revascularization or bare balloon angioplasty for treating limus-based DES ISR	6-8 months (angiographic) 12 months (clinical) 3 years (clinical)	Stenosis diameter 38 vs. 37.4%	0.007	23.5 vs. 19.3 vs. 46.2 38.0 vs. 37.7 vs. 55.7	0.5 PEB vs. PES 0.91 (PEB vs. PES)	22.1 vs. 13.5 vs. 43.5 33.3 vs. 24.2 vs. 50.8	0.09 (PEB vs. PES) 0.11 (PEB vs. PES)
ISAR DESIRE IV	252	DEB (paclitaxel) vs. DES (paclitaxel) revascularization with prior balloon dilation in patients with limus-based DES ISR	6-8 months (angiographic) 12 months (clinical)	VLL 0.31 ± 59 mm vs. 0.41 ± 0.74 mm	0.27	18.4 vs. 23.3	0.35	16.2 vs. 21.8	0.26
RIBS IV	309	DEB (paclitaxel) vs. DES (everolimus) revascularization for treating DES ISR	6-9 months (angiographic) 12 months (clinical)	Binary restenosis 19% vs. 11%	0.06	18 vs. 10	0.04	16 vs. 8	0.035
RESTORE ISR	172	DEB (paclitaxel) revascularization vs. sequential angioplasty with DEB (paclitaxel) for treating DES ISR	9 months (angiographic) 12 months (clinical)	VLL 0.15 ± 0.49 mm vs. 0.19 ± 0.41 mm	0.54	7.0 vs. 4.7	0.51	5.8 vs. 1.2	0.10
AGENT ISR	125	Comparison of two types of paclitaxel-coated balloons for treating ISR	6 months (angiographic)	VLL 0.397 ± 0.393 mm	0.046	N/S	0.89	7.7% vs. 10.0%	0.89

MS: metallic stent; ISR: in-stent restenosis; MACE: major adverse cardiovascular event; TLR: target lesion revascularization; VLL: vessel lumen loss; DES: drug-eluting stent; TVR: target vessel revascularization; TLF: target lesion failure; PEB: paclitaxel-eluting balloon; PES: paclitaxel-eluting stent.

Table 2. Randomized controlled trials of DEBs in small vessel lesions

Study	n	Intervention	Follow-up	Angiograpic results	p
PICCOLETO I	57	DEB (paclitaxel) vs. DES (paclitaxel) angioplasty in patients with stable or unstable angina and small vessel disease (≤ 2.75 mm)	6 months (angiographic) 9 months (clinical)	MLD 1.11 ± 0.65 mm vs. 1.94 ± 0.72 mm	< 0.001
PICCOLETO II	232	DEB vs. DES angioplasty in patients with small vessel lesions	6 months (angiographic) 12 months (clinical)	VLL 0.04 vs. 0.17 mm	< 0.001
BELLO	182	DEB (paclitaxel) and provisional metal stent vs. DES (paclitaxel) angioplasty in patients with small vessel lesions (reference diameter ≤ 2.8 mm)	6 months (angiographic) 12 months (clinical) 3 years (clinical)	VLL 0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm	0.001
RESTORE SVD	230	DEB (paclitaxel) and provisional metal stent vs. DES (zotarolimus) angioplasty for treating small vessel disease	9-12 months (angiographic) 12 months clinical	VLL 0.26 ± 0.42 mm vs. 0.30 ± 0.35 mm, Stenosis diameter 29.6 ± 2.0% vs. 24.1 ± 2.0%	0.41. < 0.001
BASKET-SMALL 2	758	DES vs. second generation DES angioplasty in patients with de novo lesions (less than 3 mm diameter)	6 months (angiographic) 12 months (clinical)	VLL 0.13 mm (- 0.14 to 0.57 mm) vs. 0.10 mm (- 0.16 to 0.34 mm)	0.72

MLD: minimal lumen diameter.

Other indications for DEBs

Studies have also shown the efficacy of DEBs in other clinical scenarios like acute myocardial infarction. Recently, the PEPCAD NSTEMI[46] study showed that a strategy based solely on DEBs was not inferior to stent treatment in patients with acute myocardial infarction without ST segment elevation. The REVELACION trial[47] had similar results, this time in the context of STE-ACS, in which the DEB strategy was not inferior to DESs in terms of fractional flow reserve.

Several large-scale clinical registries support DEB treatment in patients with diabetes mellitus and chronic coronary disease. The three-year follow-up cohort analysis of patients with diabetes mellitus in the BASKET-SMALL 2 study[48] showed similar MACE rates for DEBs and DESs in de novo coronary lesions. Furthermore, the need for target vessel revascularization was significantly lower in the group of diabetic patients treated with DEBs vs. DESs. Likewise, recent studies evaluate the safety and efficacy of DEBs in chronic total occlusions[49,50].

Conclusions

Today, DEBs are an encouraging strategy for treating CAD in different anatomic contexts like ISR, small vessel lesions and bifurcation lesions. There is also growing evidence that other clinical situations, like large vessel PCIs or even complex coronary procedures, could benefit from an approach based solely on DEBs. Treatment with DEBs avoids the risks associated with stent implantation, maintains vascular permeability and reduces the rate of restenosis. However, the current studies are characterized by small sample sizes and short follow-ups. Long-term evaluations are needed to evaluate the efficacy and safety of these devices.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that the procedures followed were in line with the

ethical norms of the responsible human research committee and in accord with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the institutional ethics committee.

Confidentiality, informed consent and ethical approval. The authors obtained approval from the ethics committee for the analysis of routinely obtained anonymized data, and therefore informed consent was not required. The pertinent guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing this article.

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REVIEW ARTICLE

Diagnosis and treatment of vasovagal syncope: what to do and what not to do?

Diagnóstico y tratamiento del syncope vasovagal: ¿qué hacer y qué no hacer?

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Abstract

Syncope is a condition characterized by a sudden and temporary loss of consciousness, caused by decreased blood flow to the brain. It has a rapid onset and short duration (from a few seconds to a minute) and complete spontaneous recovery, with a cumulative lifetime incidence of approximately 35%. Syncope accounts for 0.6-3% of all emergency department visits worldwide. Approximately 50% of these patients are admitted. Among the various types of syncope, vasovagal syncope, also known as neurocardiogenic syncope, is the most frequent and is a common reason for emergency department visits, resulting in significant distress and negatively impacting patients' quality of life, with costly testing and hospital admissions. Improved guidelines and innovative diagnostic approaches, potentially complemented by technology, may offer avenues for more cost-effective and efficient care. A standardized approach to syncope assessment reduces hospital admissions and medical costs and increases diagnostic accuracy. The initial assessment of all patients presenting with syncope includes a detailed history, physical examination and electrocardiogram, which can diagnose up to 50% of patients and allows prompt treatment and risk stratification. Laboratory tests and neuroimaging have a low diagnostic yield and should be ordered only if clinically indicated. Low-risk patients with a single syncopal episode can often be reassured, with no need for further studies. High-risk patients with cardiovascular disease, a history of arrhythmia, abnormal electrocardiographic findings or severe comorbidities should be admitted to the hospital for further assessment.

Keywords: *Syncope. Tilt table. Arrhythmia.*

Resumen

El síncope es una afección caracterizada por una pérdida repentina y temporal del conocimiento, causada por una disminución del flujo sanguíneo al cerebro, de inicio rápido y breve duración (desde unos pocos segundos hasta un minuto) y recuperación completa espontánea, con una incidencia acumulada a lo largo de la vida cercana al 35%. Representa entre el 0.6 y el 3% de todas las visitas a los servicios de urgencias en el mundo. Aproximadamente, el 50% de ellos son admitidos; entre los diversos tipos de síncope, el vasovagal, también conocido como neurocardiogénico, es la causa más frecuente y es un motivo común de visitas al servicio de urgencias, lo que produce una angustia significativa y afecta de manera negativa la calidad de vida de los pacientes, con pruebas costosas y admisiones hospitalarias. Las directrices mejoradas y los enfoques diagnósticos innovadores, complementados con tecnología, pueden ofrecer vías para una atención más rentable y eficiente.

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Date of reception: 30-10-2024
Date of acceptance: 11-11-2024
DOI: 10.24875/RCCARE.M24000154
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;31(2):114-117
www.rccardiologia.com

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El enfoque estandarizado para la evaluación del síncope reduce las admisiones hospitalarias y los costos médicos, y aumenta la precisión del diagnóstico. La evaluación inicial de todos los pacientes que presentan síncope incluye una historia clínica detallada, un examen físico y un electrocardiograma. Con esto se puede diagnosticar hasta el 50% de los casos y permite hacer un tratamiento inmediato y estratificar el riesgo. Las pruebas de laboratorio y las neuroimágenes tienen un rendimiento diagnóstico bajo y deben solicitarse solo si están clínicamente indicados. Los pacientes de bajo riesgo, con un solo episodio de síncope, a menudo pueden ser tranquilizados y sin necesidad de realizar más investigaciones. Los pacientes de alto riesgo con enfermedad cardiovascular, antecedentes de arritmia, hallazgos electrocardiográficos anormales o comorbilidades graves deben ser ingresados en el hospital para una evaluación más completa.

Palabras Clave: *Síncope. Mesa basculante. Arritmia.*

Overview

Syncope is not a diagnosis in itself, but rather a syndrome with multiple etiologies. It is a common condition, with a cumulative lifetime incidence of approximately 25-35%, in addition to a high rate of recurrence after the initial presentation, which can significantly affect patients' quality of life. Twenty to forty percent of syncopes are vasovagal. This type of syncope affects women 1.5 times more often than men, and the likelihood of vasovagal reactions decreases with age. Most cases begin in adolescence and may reappear after age 50. Only the human species faints, which suggests a possible genetic predisposition; recently, three genes associated with vasovagal syncope (VVS) have been identified[1].

It is essential to diagnose the etiology, since cardiac syncope has a high mortality rate, unlike VVS. Therefore, the first challenge for the physician is to make an accurate diagnosis, as the type of syncope determines its prognosis and treatment.

Diagnosis

The most important aspect in diagnosing is to take a good history. The patient generally provides the key to the diagnosis, since syncope is just the tip of the iceberg. This syndrome may be accompanied by many symptoms that may begin in childhood. Before reaching syncope, patients have multiple symptoms, including fatigue, frequent headaches, feeling cold, orthostatic hypotension, palpitations, chest tightness, dizziness, tinnitus, exercise intolerance, and gastrointestinal and genitourinary symptoms, among others. The autonomic nervous system coordinates all involuntary bodily functions. Symptoms are generally triggered by significant stress (which is not necessarily psychological), as occurs in women of reproductive age during their period (hormonal stress) or after physical stress (for example, in a sauna or jacuzzi or after strenuous exercise).

Vasovagal syncope is diagnosed clinically, and the diagnostic tests ordered by different specialties due to the variety of symptoms are often superfluous.

The tilt test is controversial. In clinical practice, it is not only useful for confirming the clinician's diagnosis, but also for classifying the subtype and, even more importantly, confirming and reassuring the patients that their symptoms are explained by this condition.

It is important to emphasize that this test should be performed by trained staff, with continuous blood pressure and heart rate monitoring. It should preferably include continuous physiological parameters, as autonomic changes occur within seconds and cannot be detected using methods like sphygmomanometers or dynamometers[2].

Treatment

Treatment is divided into three categories: a) nonpharmacological treatment, b) pharmacological treatment, and c) invasive procedures. The goal of treatment is to improve the quality of life, as this condition is not, in itself, fatal (except for the secondary effects of falls, such as brain trauma and fractures, among others).

Nonpharmacological treatment

After making an accurate diagnosis, patients should be reassured as to the benign nature of the syncope, and behavioral measures should be encouraged to eliminate or reduce triggers. These measures include explaining the disease to the patients and avoiding diuretics or vasodilators that can aggravate the symptoms. Among the antihypertensive drugs, alpha blockers, nitrates, beta blockers and calcium channel blockers generate a higher risk and should be discontinued whenever possible. If antihypertensive medication is needed, drugs with protective effects or a low risk of hypotension should be preferred, such as angiotensin converting enzyme inhibitors or angiotensin

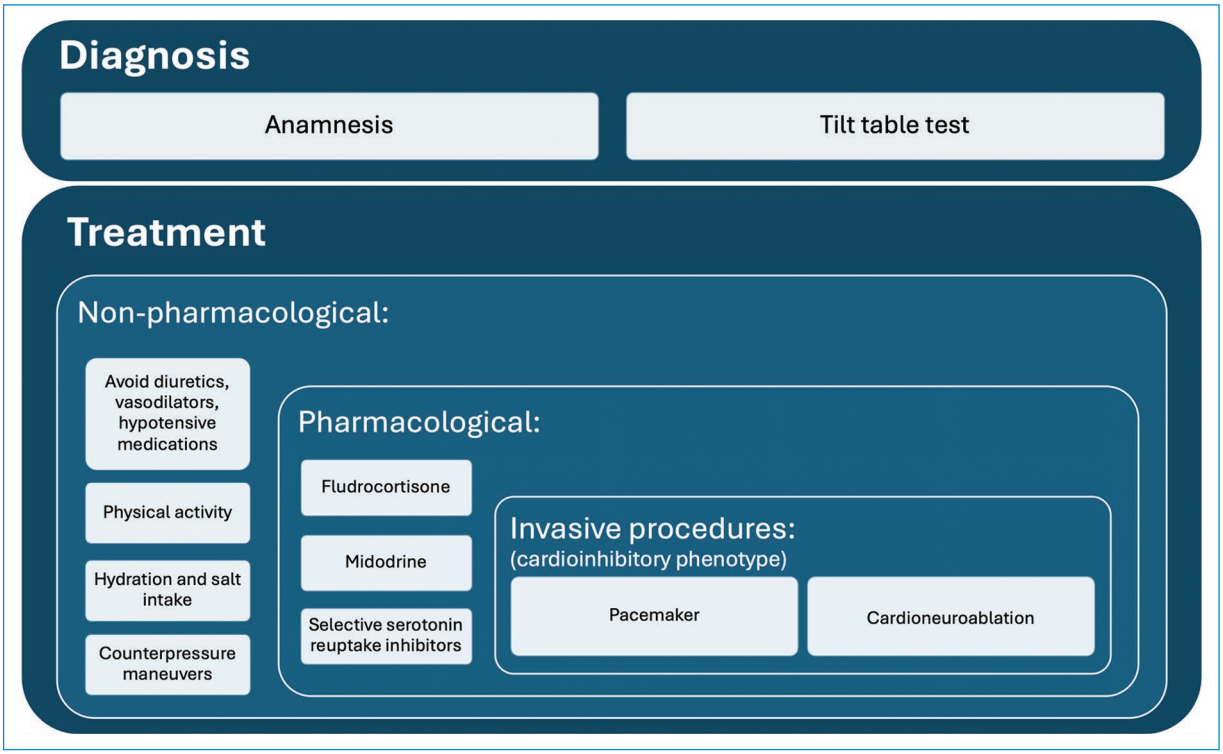

Figure 1. Diagnostic and therapeutic scheme (non-pharmacological and pharmacological) of vasovagal syncope.

receptor blockers, preferably taken before bedtime. Most psychoactive medications, including levodopa, antipsychotics, tricyclic antidepressants, benzodiazepines, trazodone and opioids can cause hypotension and worsen symptoms[3].

The recommendations include avoiding prolonged standing, rapid position changes, and overheated or crowded environments. It is essential for patients to exercise moderately, stay hydrated and eat salty foods, as this will significantly improve symptoms and syncope in patients with VVS. Patients must be aware of the prodromes and assume safe positions when they occur, along with physical counterpressure maneuvers which can themselves significantly reduce syncope recurrence. Physical counterpressure maneuvers like leg crossing, hand gripping and isometric abdominal and arm contractions have proven to be useful for preventing syncope in patients with a significantly long prodrome. Wearing compression stockings is another important measure, especially for patients who must stand for long periods of time. Periods of progressive orthostatic training have proven to be effective, as has yoga, which has beneficial effects on these patients[4].

Pharmacological treatment

If symptoms persist despite nonpharmacological treatment, pharmacological measures should be considered. Fludrocortisone increases renal sodium reabsorption and counteracts the physiological cascade that triggers syncope. It is used mainly in patients with consistently low blood pressure, at a dose of 0.1 to 0.3 mg/day. A recent meta-analysis showed that midodrine, an alpha agonist that acts as a vasoconstrictor, reduces syncope recurrence and can be taken in 2.5 to 10 mg doses, three or four times a day. The consensus guidelines offer weak recommendations for using beta blockers, fludrocortisone and midodrine. There are also recommendations for using selective serotonin reuptake inhibitors (SSRIs), based on recent studies indicating improved quality of life. Selective serotonin reuptake inhibitors can prevent VVS by modulating central nervous system detection of visceral input. Moderate, but consistent, evidence has been found indicating that SSRIs reduce the likelihood of vasovagal syncope and presyncope [RR 0.34 (95% CI: 0.20 to 0.60), p = 0.01][5,6]. A recent meta-analysis highlights the efficacy of midodrine and SSRIs in reducing

the recurrence of spontaneous syncope. Midodrine showed a relative risk (RR) reduction of 0.55, while fluoxetine, especially in patients with concomitant anxiety, had an RR of 0.36. Midodrine is a reasonable choice in patients with recurrent VVS with no history of hypertension, heart failure or urinary retention. While beta blockers have often been used, they are not supported by studies for either improving quality of life or for VVS. Droxidopa, a central and peripheral alpha and beta agonist, has recently been approved by the FDA with good initial results, but requires more studies to validate it[7,8].

Invasive procedures

For recurrent or debilitating cases of syncope which are refractory to the previously described treatments, the treatment strategies depend on age. Several studies have been done on pacemaker implantation in patients over the age of 40, specifically in those with a cardioinhibitory response and recurrent syncope refractory to pharmacological and nonpharmacological treatment. These patients are candidates for dual chamber pacing, especially with closed loop stimulation (CLS), which can reduce syncopal episodes by up to four times and improve the quality of life[9].

When syncope recurs despite implementing the previous strategies in young patients, cardioneuroablation (CNA) should be considered. This type of treatment has emerged as a promising therapy for patients with refractory VVS. A recent meta-analysis suggests a high syncope-free rate following CNA, although more controlled clinical trials are needed to confirm these findings and determine their progression over time. In Colombia, several services already perform this procedure, with up to two years of follow up, showing success and very few complications (Fig. 1)[10].

Conclusion

Patients are the most important source from which clinicians can learn about VVS. Therefore, an accurate history must be taken, listening carefully in order to work together to impact their quality of life. Despite the important advances, much remains to be studied and understood.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing this manuscript.

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CASE PRESENTATION

Aortic valve involvement with Libman-Sacks endocarditis as the onset of secondary antiphospholipid syndrome

Afectación de válvula aórtica con endocarditis de Libman-Sacks como debut de síndrome antifosfolipídico secundario

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disorder that has an incidence of 5 cases per 100,000 people per year. The diagnosis is based on the presence of a clinical event and positive antibodies. The manifestations are systemic, with an 80% prevalence of cardiac valve involvement, including Libman-Sacks endocarditis, valve thickening and thrombosis (predominantly mitral and aortic), mostly when secondary to conditions like systemic lupus erythematosus (SLE). Treatment consists of anticoagulation and primary treatment of collagenopathy. We present the case of a woman with heart failure and severe aortic stenosis as the clinical debut of APS valvular involvement secondary to SLE and Libman-Sacks endocarditis. Positive antibody results confirmed a triple positive APS involving the aortic valve and requiring anticoagulation, which was a secondary etiology as it met the diagnostic criteria for SLE, presenting as Libman-Sacks endocarditis. Anticoagulation is the treatment of choice in most cases that do not require surgery, along with the main collagenopathy treatment.

Keywords: *Thrombosis. Antiphospholipid. Lupus. Aortic valve. Libman-Sacks.*

Resumen

El síndrome antifosfolipídico (SAF) es un trastorno autoinmune que tiene una incidencia de 5 casos por 100 000 personas por año. Su diagnóstico se basa en la presencia de un evento clínico y anticuerpos positivos. Las manifestaciones son sistémicas, con una prevalencia del 80% de compromiso valvular cardíaco, en cuyo caso la endocarditis de Libman-Sacks, el engrosamiento y la trombosis valvular son algunas de dichas formas, con predominio mitral y aórtico principalmente cuando son la manifestación secundaria de entidades como el lupus eritematoso sistémico (LES). El tratamiento consiste en anticoagulación y el manejo primario de la colagenopatía. Se presenta el caso de una mujer con insuficiencia cardíaca, estenosis aórtica grave como debut clínico de afectación valvular por SAF secundario a LES y endocarditis de Libman-Sacks. Con el resultado de los anticuerpos positivos se confirmó SAF triple positivo con compromiso valvular aórtico y requerimiento de anticoagulación, siendo de etiología secundaria al cumplir criterios diagnósticos para LES, presentándose como endocarditis de Libman-Sacks. La anticoagulación es el tratamiento de elección en la mayoría de los casos sin requerimiento quirúrgico, asociado al tratamiento principal de la colagenopatía.

Palabras clave: *Trombosis. Antifosfolipídico. Lupus. Válvula aórtica. Libman-Sacks.*

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Date of reception: 21-12-2023
Date of acceptance: 17-01-2025
DOI: 10.24875/RCCARE.M25000155
Available online: 30-06-2025
Rev Colomb Cardiol. 2025;32(2):118-121
www.rccardiologia.com

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Clinical case

A 52-year-old woman consulted with a complaint of 12 hours of epigastric pain radiated to both upper quadrants, associated with dyspnea and NYHA functional class II-III over the previous two weeks. On admission, her blood pressure was normal, and she was tachycardic (107 bpm) and afebrile, with bilateral rales in the lungs and a systolic murmur over the aorta (grade 2), radiating to the neck. There were no signs of irritation on abdominal palpation. She had a history of hypertension, psoriasis, an upper respiratory infection two weeks prior, and she was a marathon runner (previous heart studies had shown a bicuspid aortic valve without stenosis). She had no history of obstetric problems. Her laboratory tests showed the following: hematocrit 20%, hemoglobin 5.1 g/dl, MCV 60 fL, MCH 15.1 pg, platelets 122,500/mm^3, creatinine 1.4 mg/dl, urea 54 mg/dl, serum glutamic pyruvic transaminase 15 IU/L, serum glutamic oxaloacetic transaminase 14 IU/L, alkaline phosphatase 65 mg/dl, lactate dehydrogenase 350 IU/L, prothrombin time 54%, serum iron 12 mcg/dl, ferritin 31 ng/dl, transferrin saturation 12%, and negative haptoglobin. She had sinus tachycardia on the electrocardiogram, as well as bilateral pleural effusion on abdominal and pelvic computed tomography, with ground glass opacity in the bases. She received a red blood cell transfusion and 24 hours later developed acute pulmonary edema. New laboratory tests were done showing hematocrit 28%, hemoglobin 8.1 g/dl, leukocytes 16,810/mm^3, platelets 79,170/mm^3, creatinine 1.2 mg/dl, urea 57 mg/dl, TSH 2.9 μIU/ml, free T4 1.1 ng/dl, and BNP 1,343 pg/ml. A color Doppler echocardiogram revealed an LVEF of 33%, global hypokinesia, severe aortic stenosis with marked valvular thickening, and severe pulmonary congestion. This was interpreted as decompensated heart failure with reduced left ventricular ejection fraction, and decongestive treatment was started. With multiple differential diagnoses, infective endocarditis with aortic valve involvement was suspected, and therefore blood cultures were done, which were negative. In view of possible myocarditis, cardiac magnetic resonance imaging was done (Fig. 1) showing late transmural gadolinium enhancement in the basal and medial inferoseptal and inferior segments, with signs of microvascular obstruction. A transesophageal echocardiogram (Fig. 2) showed an LVEF of 23%, severe global hypokinesia, a bicuspid aortic valve with marked thickening (10 mm) all the way up to the commissural apex, with fusion of the left coronary and noncoronary leaflets, and severe stenosis (area: 0.4 cm^2, peak velocity: 3.41 m/seg, peak gradient: 46 mmHg).

Gastrointestinal endoscopies were done as part of the anemia work-up, with no pathological findings, along with a peripheral blood smear showing no pathological morphologies, and a negative celiac test. Regarding the kidney failure, a 24-hour urine protein test and renal ultrasound were both normal. A total body PET-CT was done, which reported no tracer uptake in the aortic valve and splenic infarction.

Given the bicytopenia, kidney failure, heart failure with acute aortic valve involvement, microvascular abnormalities on cardiac magnetic resonance imaging and splenic infarction on PET, immunology and serology tests were done for suspected associated rheumatological or hematological diseases, with a positive result reported for lupus anticoagulant and a C4 complement level of 11.1 mg/dl. The etiology of the signs and symptoms was taken to be antiphospholipid syndrome (APS) with aortic valve thickening/thrombosis and, consequently, acute heart failure. Anticoagulation with low-molecular-weight heparin was therefore started, with clinical and paraclinical improvement. She was discharged on acenocoumarol, acetylsalicylic acid and corticosteroids, with the following findings on ambulatory follow-up: 1/320 speckled antinuclear antibodies (ANAs), elevated IgG beta-2-glycoprotein (> 100 U/ml), and anticardiolipin IgG 45 GPL U/ml, thus, confirming the triple positive APS diagnosis. In addition, when the systemic lupus erythematosus (SLE) criteria were reviewed, she had clinical criteria: severe thrombocytopenia (platelet count < 100,000) (4 points); pleural effusion (5 points); immune criteria: positive ANA ≥ 1:80, anticardiolipin antibodies, anti-beta-2 glycoprotein 1 antibodies, lupus anticoagulant (2 points); and low C4 (3 points). Since the patient's score was greater than 10 points and she met the clinical criteria, the disease was classified as SLE with secondary APS and aortic valve involvement with Libman-Sacks endocarditis.

Discussion

Antiphospholipid syndrome is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies (aPLs) and mainly arterial and/or venous thrombosis and/or miscarriage. It has an estimated incidence of 5 cases per 100,000 people per year and a prevalence of 40 to 50 cases per 100,000 people per year[1]. Antiphospholipid syndrome can be classified as primary (when there is no other

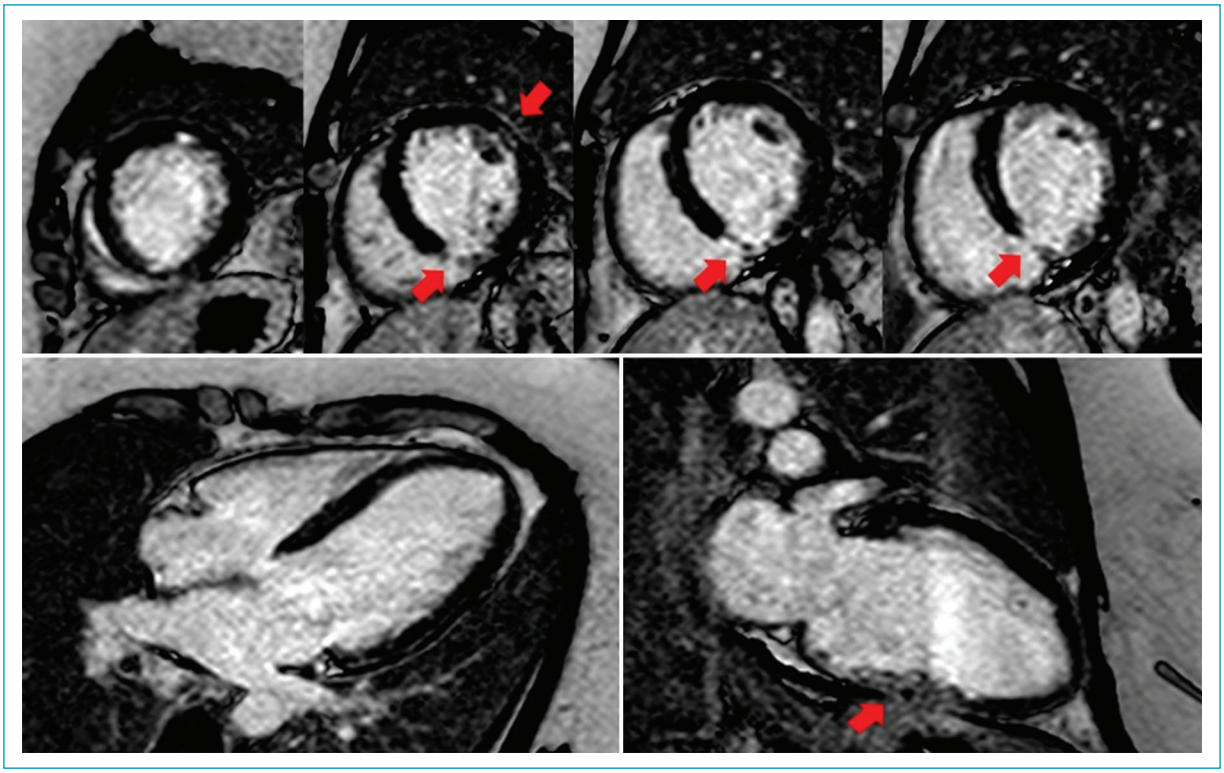

Figure 1. Cardiac magnetic resonance imaging with late transmural gadolinium enhancement in the basal and medial inferoseptal and inferior segments, with signs of microvascular obstruction.

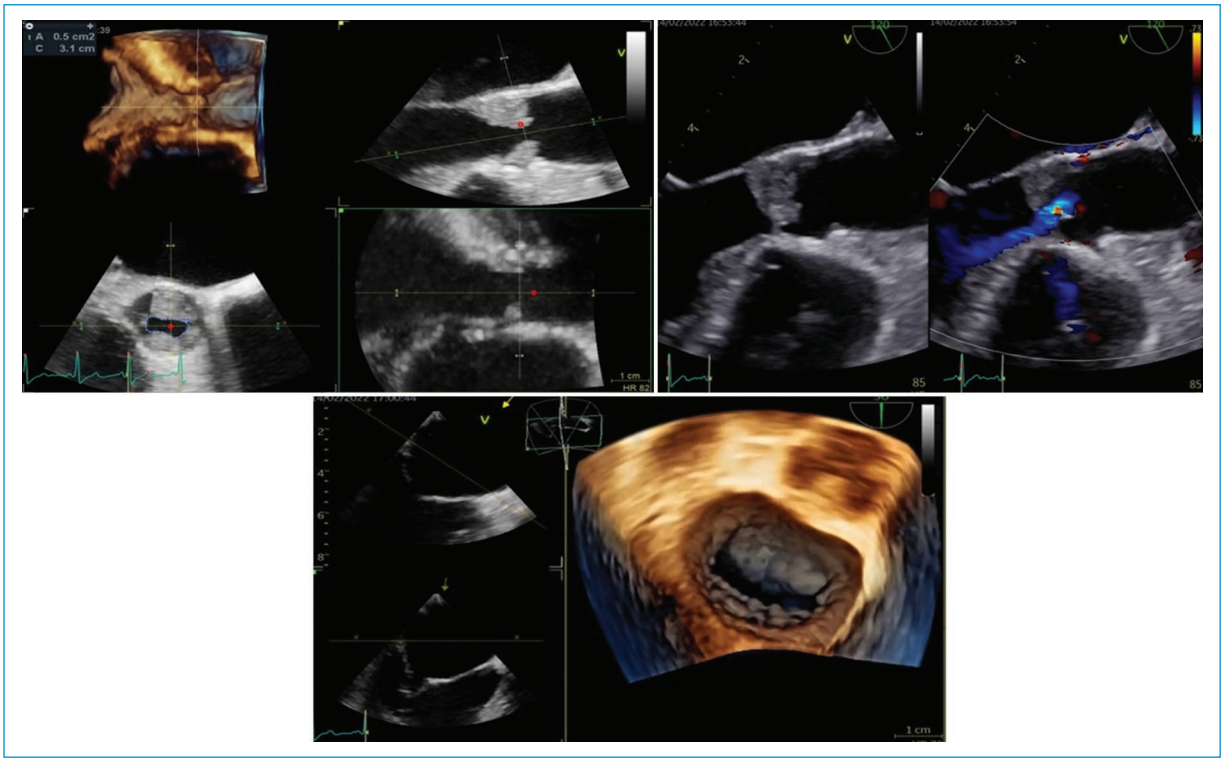

Figure 2. Transesophageal echocardiogram showing severe global hypokinesia, a markedly thickened (1 cm) bicuspid aortic valve and severe stenosis.

autoimmune disease) or secondary (when there is an underlying disorder, most commonly SLE). The APS diagnosis is based on the presence of at least one clinical event and the presence of aPLs –anticardiolipin (aCL), lupus anticoagulant (LA), or anti-β2 glycoprotein-1 (anti-β2GP1)– on two or more occasions, at least 12 weeks apart[1]. The signs and symptoms are vascular thrombosis, nephropathy, *livedo reticularis*, and thrombocytopenia. Brain involvement is prominent in primary APS, in which case strokes (19.8%) and transient ischemic attacks (TIAs) (11.1%) are the most common. Cardiac manifestations of APS include heart valve disease (thickened valves, vegetations and valve dysfunction), coronary thromboses, ventricular dysfunction, intracardiac thrombi and pulmonary hypertension.

Systemic lupus erythematosus and APS may be related; when APS is associated with SLE, it is known as secondary APS, and valve involvement tends to occur as Libman-Sacks endocarditis, affecting 15% of patients with this disease. Sterile valve vegetations are found in this condition. The differential diagnosis includes rheumatic valve disease, infective endocarditis and non-bacterial (marantic) thrombotic endocarditis. The valve thickening in SLE is diffuse and predominantly basal and medial; in rheumatic disease, it occurs at the cusp tips; and in infective endocarditis as well as non-bacterial thrombotic endocarditis, the thickening/vegetation is on the valve coaptation line[2]. The mitral valve is most often involved, followed by the aortic valve[3,4]; regurgitation is the most common abnormality. Homogenous, immobile thickening, and the appearance of "kissing lesions," are typical of APS valve thrombosis. These findings, along with positive aPLs, are consistent with severe aortic stenosis secondary to thrombosis related to a congenital bicuspid aortic valve[5] (BAV). The latter is the most common congenital heart defect, affecting 1 to 2% of the population, with a higher (2:1) male prevalence, and related to aortic stenosis. Aortic valve thrombosis in the context of BAV is a rare complication and has only been reported in a few cases[1]. When BAV is present, valve dysfunction is associated with abnormal blood flow, which can cause endothelial injury and trigger thrombus formation. Furthermore, APS coagulopathy can induce thromboses.

There is no consensus on the definitive treatment of valve thromboses in APS. The regimens used include warfarin, antiplatelet drugs and low-molecular-weight heparin. The efficacy of anticoagulant treatment is a matter of debate[1]. Long-term systemic anticoagulation is the cornerstone of treatment for APS with thrombosis. If it is secondary to SLE with a Libman-Sacks-compatible presentation, corticosteroid treatment of the underlying immune disease is indicated. A minority of patients with APS (4-6%) may require valve surgery. However, surgical patients have a higher rate of complications[1].

Conclusion

Autoimmune diseases have systemic involvement, especially APS, with specific heart valve involvement, as occurred in the case described. Anticoagulant treatment is usually sufficient if there are no comorbidities complicating the clinical picture; in primary conditions like SLE, immunosuppression with corticosteroids is also required.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent and ethical approval. The authors obtained approval from the ethics committee for the analysis of routinely obtained and anonymized data, and therefore informed consent was not required. The pertinent guidelines were followed.

Statement on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing this article.

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