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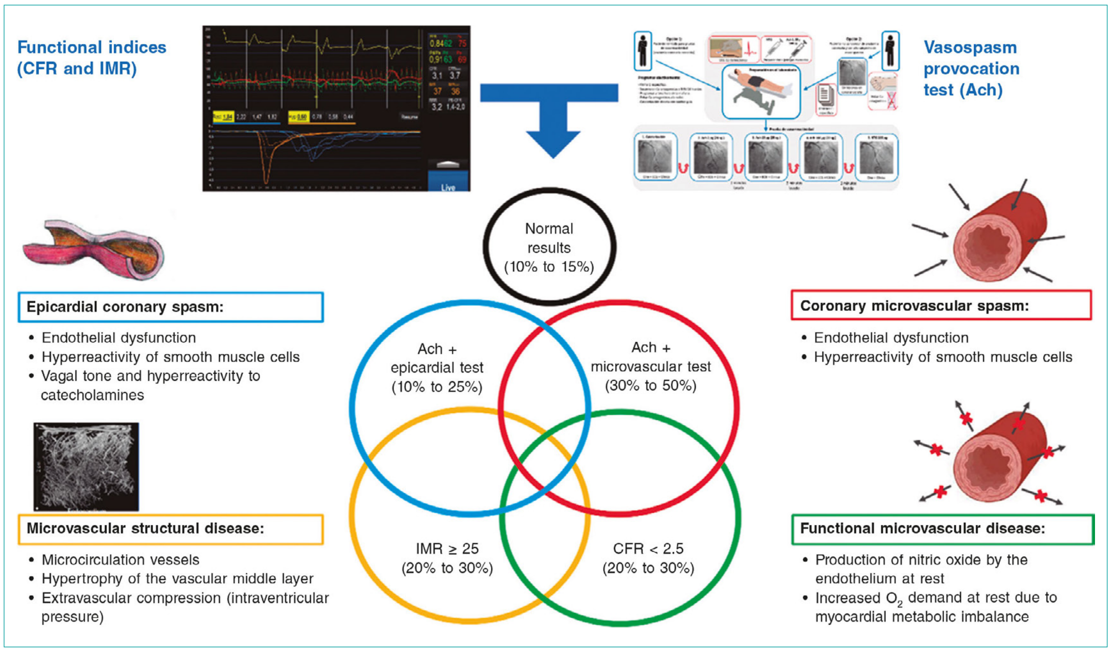

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Editorial

Implementing an ANOCA clinic

Implementando la vía clínica ANOCA

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Simply stated, the goal of diagnostic coronary angiography is to distinguish the cause of a patient's chest pain from 1 of 4 endotypes: *a)* epicardial stenosis; *b)* coronary spasm; *c)* coronary microvascular disease (CMD); and *d)* —equally important—noncoronary chest pain. Crucially, the latter is a diagnosis of exclusion and consequently cannot be confirmed without formal assessment of the other mechanisms (figure 1). Despite this truism, the interpretation of most coronary angiograms is limited to simple "eyeballing" of an epicardial "shadowgram". This approach has a low diagnostic yield with 40% of patients found to have no significant epicardial stenoses—an entity known as angina with no obstructive coronary arteries (ANOCA).[1] Despite the presence of typical angina or evidence of ischemia during noninvasive testing, these patients, are frequently nonchalantly dismissed without a formal diagnosis.

This very large group of patients is heterogeneous, and establishing the underlying cause of ANOCA requires a thorough coronary function testing (CFT) protocol that includes diagnostic angiography, provocation testing for microvascular or epicardial vasospasm, and assessment of CMD.[2] In many centers, however, diagnostic angiography is rarely complemented with CFT. Among those that do, testing is often incomplete, with the result that patients often do not receive a diagnosis of the underlying cause of their ANOCA or benefit from potential endotype-specific treatments. Possible explanations for this behavior include a lack of familiarity with the causes of ANOCA, a lack of knowledge of available testing modalities, concerns about the accuracy of tests, and a belief that the underlying diseases are untreatable.

In a recent article published in *REC: Interventional Cardiology*, Rinaldi et al.[3] describe their single-center experience of the implementation of a specific ANOCA diagnostic and therapeutic protocol at Hospital Clínic in Barcelona, Spain. In this program, all patients with ANOCA underwent systematic CFT including bolus thermodilution for the calculation of coronary flow reserve and the index of microvascular resistance, as well as intracoronary provocation testing to assess epicardial or microvascular spasm. Based on the

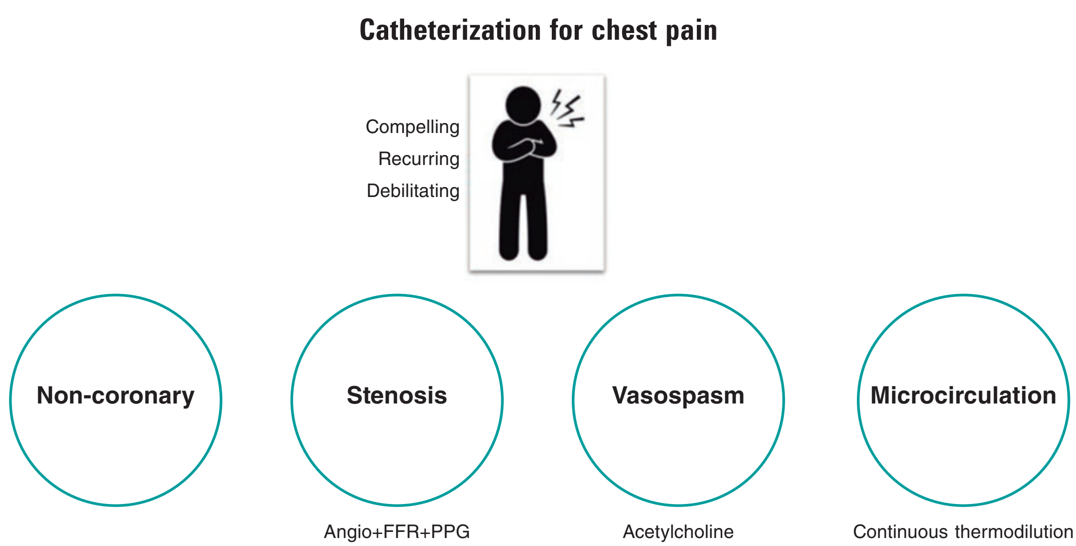

Figure 1. Patients with compelling, recurring, and debilitating chest pain should undergo catheterization with coronary angiography and—when needed—coronary function testing to unravel the mechanism of their pain. Noncoronary chest pain is a diagnosis of exclusion and consequently can only be confirmed if the 3 other mechanisms have been assessed. FFR, fractional flow reserve; PPG, pullback pressure gradient.

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results of these tests, patients were classified into 4 endotypes: *a)* microvascular angina (MVA) (CMD or microvascular spasm); *b)* vasospastic angina (epicardial spasm); *c)* both MVA and vasospastic angina; and *d)* noncoronary chest pain.

The authors demonstrated that, as a result of the identification of specific ANOCA endotypes, there were significant increases in targeted medical prescriptions such as beta-blockers, nondihydropyridine calcium channel blockers, and long-acting nitrates. While this did not translate into a statistically significant improvement in quality of life between baseline and 3 months, angina significantly improved in terms of physical limitation, angina stability, and disease perception. Importantly, the protocol was shown to be safe, with only 3 minor adverse events being reported, all occurring during acetylcholine administration (transient bradycardia, paroxysmal atrial fibrillation with spontaneous cardioversion).

This work has significant strengths that should be highlighted. The CorMicA trial provided the first evidence from a randomized controlled trial of the benefits of systematic CFT with targeted medical therapy.[4] However, to date, scarce real-world data have been available on the implementation of such protocols in routine clinical practice. As such, this small, real-world, observational study is strongly welcomed. More than the clinical results obtained in a relatively small number of patients, the work by Rinaldi et al.[3] is particularly worthwhile for several methodological aspects, 3 of which are discussed below.

(i) Which patients should enter such a program and how? Patients were screened at a specific outpatient clinic and their inclusion was based on well-standardized criteria. Ideally, only patients with compelling, recurrent and invalidating symptoms should undergo CFT. The usefulness of such a program is significantly reduced by the referral of patients with unconvincing symptoms, or those with a high pretest probability of epicardial disease. Notably, the increasing role of coronary computed tomography angiography for the screening of epicardial disease in patients with angina currently allows diagnosis of ANOCA without the use of invasive diagnostic angiography and patients can thus be referred directly for CFT.

(ii) How should CFT be performed? As described by the authors, both microvascular function and coronary vasomotion should be investigated in a strictly standardized manner, preferably in the left anterior descending artery. However, the order of these tests is debatable. In our opinion, it does not make sense to investigate endothelial function and coronary vasomotion with a guidewire in the coronary artery or when the patient has already received vasoactive medications such as nitrates and calcium channel blockers. Consequently, we believe that acetylcholine testing should come first, with epicardial vasodilation being induced with nitrates at the end of acetylcholine testing. The latter also represents an important step (and good clinical practice) before commencing wire-based measurements of microcirculatory function. As for the choice of testing modality, bolus thermodilution should be replaced by continuous thermodilution as it enables the calculation of coronary flow reserve, absolute microvascular resistance (R_μ) and microvascular resistance reserve from absolute volumetric flow rather than from surrogates of flow.[5] Future studies are expected to clarify the clinically relevant cutoff values for the indices derived from continuous thermodilution. These values should allow a more robust definition of CMD, which is currently an unmet need.

(iii) How should these patients be followed up? Patients should be followed up by the same physicians in a dedicated outpatient clinic, and be asked about their symptoms in a structured and systematic way. In this regard, the authors should be commended for the use of structured questionnaires to assess angina and quality of life. The classic Canadian Cardiovascular Society grading system for angina is not appropriate for ANOCA patients as their symptoms often differ from those reported by patients with epicardial disease. Moreover, objective signs of ischemia are often lacking. In the future, it is likely that patients will be given an app on their smartphone to closely monitor their symptoms.[6]

Overall, as with any new program, it is important to recognise that there is a learning phase. However, with a well-structured and standardized program, such as that proposed by Rinaldi et al.,[3] this learning phase is likely to be short. There is now a need for future work addressing the implications of such a protocol on both time and cost in routine clinical practice. For example, in the setting of a busy, real-world catheterization laboratory, how much time, on average, does such a protocol add to the length of the procedure? Furthermore, what are the cost implications, and are they sufficiently counterbalanced by an increase in quality of life and/or symptom control?

To conclude, there are now strong clinical grounds for the systematic implementation of CFT in ANOCA patients. Furthermore, as demonstrated by Rinaldi et al., a standardized and robust testing program can be effectively implemented in real-world practice.[3] Validation of clear diagnostic criteria for CMD is now needed for the results of CFT to be easily interpreted and acted upon. Patients and their referring clinicians deserve nothing less.

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Editorial

Percutaneous pulmonary valve implantation in native outflow tracts: has the time come?

Implante valvular pulmonar percutáneo en tracto de salida nativo: ¿ha llegado el momento?

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INTRODUCTION

Right ventricular outflow tract (RVOT) disease is a common finding in children and adults with congenital heart disease and often occurs as a sequel of previous surgery. Over the past 2 decades, percutaneous pulmonary valve implantation has become more widely used and is recommended by current clinical practice guidelines[1] as the preferred option for patients with previous conduits or bioprostheses.

However, many patients have native or patched tracts (hereafter referred to as native RVOTs) with pulmonary regurgitation as the predominant lesion. In these patients, percutaneous valve placement is more complex due to the RVOT anatomy, its dynamic behavior, larger pulmonary annulus size, and lack of a proper landing zone for the valve. Because of the differences in underlying heart diseases, previous surgical repairs, and various pulmonary artery configurations, RVOT morphology varies widely but can be categorized into 5 subtypes[2] (figure 1).

Repaired tetralogy of Fallot serves as the paradigm, and in these cases, surgery remains the standard of care. However, the development of percutaneous procedures has enabled a larger number of patients with these substrates to be eligible for percutaneous treatment (figure 2).

Two different models of balloon-expandable valves have been authorized to treat dysfunctional bioprostheses and conduits: the Melody (Medtronic, United States) and the SAPIEN valves (XT model, Edwards Lifesciences, United States). Although they have not yet been authorized for implantation in native RVOTs, both (along with the SAPIEN S3) have been used off-label in this setting.

To address the specific characteristics of native RVOTs, several models of self-expanding valves have been developed, such as the Venus-P (Venus MedTech, China, with CE marking for use in Europe since 2022), PULSTA (TaeWoong Medical, South Korea), and Harmony valves (Medtronic, United States, with prior FDA approval). The Alterra valve (Edwards Lifesciences) has also been used. This valve serves as a self-expanding prestent onto which a SAPIEN valve is later implanted.

The characteristics of each of these devices have already been described in detail in a previous issue of *REC: Interventional Cardiology*.[3]

RESULTS OF PERCUTANEOUS VALVES IN THE NATIVE RIGHT VENTRICULAR OUTFLOW TRACT

More information has gradually become available on the favorable results and durability of percutaneous valves. The largest multicenter registry to date,[4] with 2476 patients (82% implanted with the Melody valve and 18% with the SAPIEN device, including 16% with native RVOTs), reported an 8-year survival rate of 91.1% after implantation, and a reintervention rate of 25.1%, which is similar to the rates reported in some surgical series.[5] Nonrandomized comparative studies[6] and a recent meta-analysis[7] also found similar reintervention rates. Some series report higher rates in patients implanted with the Melody compared with the SAPIEN valve,[8,9] although the 2 groups were not directly comparable, with reintervention-free survival rates in patients with SAPIEN being similar to those reported in patients with surgical valves.[8]

The SAPIEN device can be implanted with or without prestenting, depending on the patient's characteristics, with good outcomes. The largest trial published to date included 774 patients implanted with the XT and S3 models[10], 51% of whom had native RVOTs (table 1).

In a study of patients with native RVOTs that included 229 candidates for the Melody valve, the device was finally implanted in 132 patients (58%).[11] The most common reason for avoiding implantation was a prohibitively large RVOT, followed by coronary or aortic root compression. The immediate outcomes of patients with successful implantation were good. However, the low implantation rate demonstrates the limitation of treating native RVOTs with these valves.

Self-expanding valves fill this gap by allowing treatment of larger RVOTs, as they adapt to the anatomy of the RVOT and provide more stable attachment. The series published to date indicate a very high implantation success rate—close to 100%—with good short- and mid-term outcomes and few complications.[12-16] (table 1 illustrates a selection of series representative of patients with native RVOTs).

Drawing comparisons between the results of surgical and percutaneous pulmonary valves is challenging because the types of patients and the anatomies treated are very different. Overall, patients undergoing percutaneous valve implantation are at higher risk and often have bioprostheses or small conduits that require smaller percutaneous valves, which is associated with a higher residual

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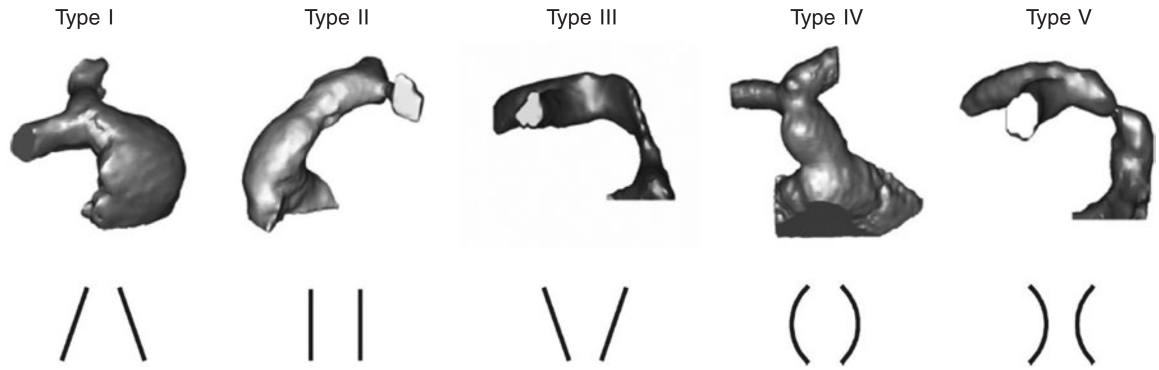

Figure 1. Five types of native RVOT anatomy: I - pyramidal; II - cylindrical or tubular; III - inverted pyramidal; IV - central enlargement; V - central narrowing. (Reproduced from Schievano et al.[2] with permission from the author.)

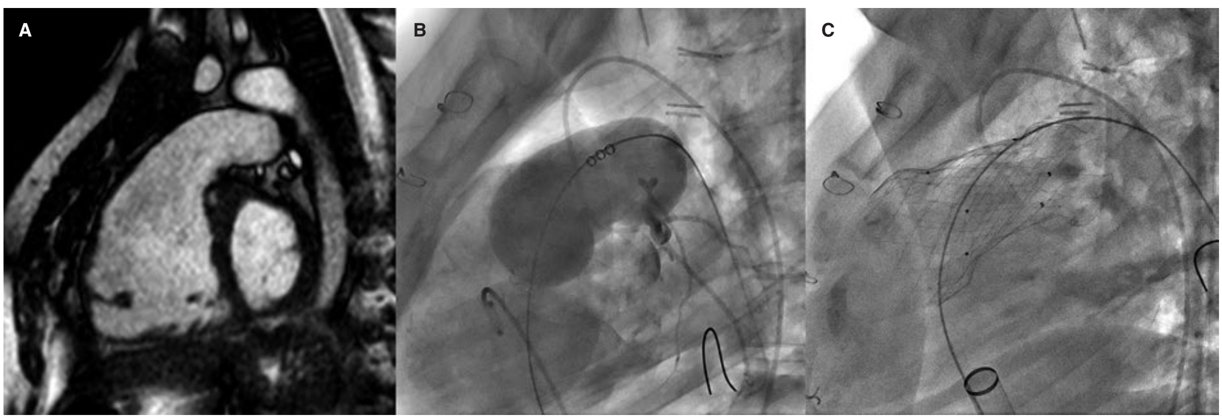

Figure 2. Self-expanding pulmonary valve implantation in an aneurysmal right ventricular outflow tract (RVOT). **A:** severely dilated RVOT on magnetic resonance imaging, with interventricular septal flattening. **B:** balloon sizing test in the RVOT with simultaneous injection into the left main coronary artery. **C:** successful venus-P valve (MedTech, China) implantation in the RVOT.

gradient, leading to a greater need for reintervention,[4,8,9] and a higher rate of endocarditis. This aspect has traditionally led to less favorable results with the Melody series (with a maximum diameter of 22 mm), with durability being one of the issues initially identified, although more recent series have shown positive results. Only indirect comparisons can be drawn with valve procedures in the native RVOT.

PROCEDURAL PLANNING

Multimodal imaging modalities, especially magnetic resonance imaging and computed tomography, are crucial for patient selection and procedural planning. Key aspects include measurement of the RVOT and the pulmonary annulus, and assessment of both the RVOT and the coronary anatomy. Recently, computed tomography guidelines for RVOT assessment[17] have been published with detailed information on the measurements that should be taken, and the cardiac cycle phase.

POTENTIAL PROBLEMS

Valve or stent migration or embolization is a potential complication in patients with large RVOTs due to the lack of an adequate landing zone, with incidence rates between 0% and 4.5%,[11,10,18] and consequently proper valve sizing is of paramount importance.

Stent fractures can lead to loss of integrity and contribute to prosthetic valve dysfunction. Nonetheless, the implications of the occasional finding of an isolated strut fracture remain unclear.

Tricuspid valve injury has been reported in 3% to 6% of patients.[10] However, this rate has dropped significantly with the use of DrySeal introducer sheaths (W.L. Gore & Associates, United States).[10]

Coronary compression is a rare complication nowadays, because coronary angiography is simultaneous and systematically performed during RVOT balloon inflation testing. However, it can be a reason for not performing percutaneous implantation in nearly 3% of patients.[11]

A higher incidence of infective endocarditis has been reported, especially after Melody valve implantation,[6,8,9] with a higher risk when smaller valves are implanted and there is a greater residual gradient. The risk involved with other types of device such as the SAPIEN—whether because of its different composition (bovine jugular vein graft in the Melody compared with bovine pericardium in the SAPIEN) or because of its larger size—is much lower[9] and seems comparable to that of surgical series.

Self-expanding valves are larger, and the proximal end often remains inside the RVOT, which could increase the risk of ventricular arrhythmias. The incidence of nonsustained ventricular tachycardia varies widely (between 0.6% and 40%[11,19,20]), although it is usually a transient phenomenon during the early postimplantation

Table 1. Summary of some of the main trials of patients with native right ventricular outflow tract

Author and year	Patients with native RVOT/Total patients	Valve type	Follow-up	Implant success	Other results	Complications
Malekzadeh-Milani et al.[23], 2014	34/34	Melody	2.6 years	100%	Paravalvular leak in 2 patients during follow-up	3 acute complications (9%): 1 hemoptysis, 1 RVOT obstruction, 1 stent embolization
Meadows et al.[18], 2014	31/31	Melody	15 months (1 month-3.8 years)	100%	No mortality or valve regurgitation	Stent fractures (32%) associated with a higher rate of stenosis. 3 cases of endocarditis. Reintervention in 3 patients
Garay et al.[13], 2017	10/10	Venus P	12 months (4 to 21)	100%	Normally functioning valve, no stent fractures, right ventricular remodeling, and NYHA functional class improvement	None
Martin et al.[11], 2018	132/132	Melody	No follow-up		Complete cohort of 229 patients, but only 58% implanted. Good immediate hemodynamic outcomes	Complication rate of 4% (mostly due to stent migration)
Morgan et al.[24], 2019	41/57	SAPIEN (S3, XT)	5.3 months (1 to 26)	100%	No prestenting. Normally functioning valve at follow-up. No mortality	1 aortic compression, 2 tricuspid valve injury, 1 valve regurgitation
Shahanavaz et al.[10], 2020	397/774	SAPIEN S3 (78%) XT (22%)	12 months (n = 349)	97.4%	Normally functioning valve: 91.5%	Adverse events: 10%. Emergency surgery: 14 patients (1.8%). Tricuspid injury: 3%
Goldstein et al.[19], 2020	143/530	Melody (88%) SAPIEN (22%)	1 year	98%	Normally functioning valve: 98%	1 death. Reintervention rate of 13.3% (mostly unrelated to the valve)
Lee et al.[12], 2021	25/25	PULSTA	33 (± 14) months	100%	Zero cases of valve dysfunction	No significant adverse events
Gillespie et al.[16], 2021	21/21	Harmony	5 years	100%	Implantation in all but 1 patient due to pulmonary hypertension. Normally functioning valve in nonreoperated patients	Valve explantation in 2 patients, 1 death 3 years after implantation, 2 reinterventions (valve-in-valve)
Morgan et al.[25], 2021	38/38	Venus	27 months	97.4%	Normally functioning valve at follow-up	Migration: 2 cases (surgery in 1)
Houeijeh et al.[9], 2023	99/214	SAPIEN XT/ S3 (85%) Melody (15%)	2.8 years (3 months-11.4 years)	Only cases with successful implantation included	Reintervention-free survival at 5 to 10 years: 78.1% to 50.4% (Melody) and 94.3% to 82.2% (SAPIEN)	Severe complications: 2.3%, 1 valve-related death. Endocarditis 5.5/100 patient-years (Melody) and 0.2/100 patient-years (SAPIEN)
Álvarez et al.[14], 2023	8/8	Venus	No follow-up	100%	Normally functioning valve in all	No significant adverse events
Lin et al.[15], 2023	53/53	Venus (28%), PULSTA (72%)	27.5 months	98.1%	No valve regurgitation at 12 months	1 embolization, 1 endocarditis

NYHA, New York Heart Association; RVOT, right ventricular outflow tract.
In studies that are not specific to native RVOT, the results and complications refer to the overall cohort, as the results of native, or non-native RVOTs are often not detailed independently.
Some centers participated in > 1 study, which allowed the same patient to be included in multiple publications.
The most recent series with larger numbers of patients have been prioritized.

phase, and its long-term implications remain unclear. Of note, when comparing surgical with percutaneous pulmonary valve replacement, the early incidence of arrhythmias was lower in the latter.[21] A potential caveat is that catheter access to the arrhythmic substrate can be limited after valve implantation.

The presence of the valve metal mesh with or without previous stents inside the RVOT can pose additional challenges for the surgeon if surgical valve replacement is subsequently required. This is a relative problem, because surgical pulmonary valve replacement also increases the risk of future reinterventions related to resternotomy.

BENEFITS OF PERCUTANEOUS VALVE IMPLANTATION

The possibility of performing percutaneous pulmonary valve implantation offers clear advantages: the procedure is much less invasive, length of stay is shorter,[8] recovery is faster, the mortality rate is very low (from 0.2% to 0.8%),[19] and the cost-effectiveness ratio is more favorable.[22] In patients at high surgical risk, it might be the only available treatment option. The path followed by its "left-sided relatives"—transcatheter heart valves in the aortic position—illustrates that the threshold for the use of percutaneous techniques is decreasing as more experience is gained and technology becomes further refined. In cases of intermediate or low risk, percutaneous valve implantation may delay or avoid the need for surgery in patients who often require multiple interventions during their lifetime. This concept of avoiding sternotomies is relevant due to the added risk of further surgeries and for patients who are candidates for heart transplants. The decision on the best approach to valve implantation in each patient should be made by a multidisciplinary heart team, including health professionals experienced in these types of heart disease.

CONCLUSIONS

Percutaneous pulmonary valve implantation is particularly challenging in patients with native RVOTs. Nonetheless, it is a feasible option that is being used with a high success rate and few complications. However, appropriate candidate selection is essential. Several models of self-expanding valves have been specifically developed for this purpose, with good short- and mid-term results, allowing the treatment of patients with large RVOTs that were previously not amenable to balloon-expandable devices. The latest information suggests that the durability of percutaneous valves may be comparable to that of surgical bioprostheses, although long-term data are lacking, especially with the latest models. Although more studies and follow-up are necessary, percutaneous techniques are already an option for many patients and will likely become an alternative to surgical treatment in the near future.

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CONFLICTS OF INTEREST

None declared.

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Original article

Angina or ischemia with no obstructed coronary arteries: a specific diagnostic and therapeutic protocol

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ABSTRACT

Introduction and objectives*:* A systematic approach to patients with angina with no obstructed coronary arteries (ANOCA) or ischemia with no obstructed coronary arteries (INOCA) patients is not routinely implemented.
Methods: All consecutive patients diagnosed with ANOCA/INOCA were referred to a designated outpatient clinic for a screening visit to assess their eligibility for a NOCA program. If eligible, patients underwent scheduled coronary angiograms with coronary function testing and intracoronary acetylcholine provocation testing. Medical therapy was optimized accordingly. All patients were then followed up at 1, 3, 6, and 12 months. Baseline and 3-month follow-up assessments included the Seattle Angina Questionnaire (SAQ) and EuroQol-5D questionnaire.
Results: Of 77 patients screened, 23 (29.9%) were excluded and 54 (70.1%) were included (29 [53.7%] with INOCA and 25 [46.3%] with ANOCA). Microvascular angina was diagnosed in 19 (35.2%) patients, vasospastic angina in 12 (22.2%), both microvascular angina and vasospastic angina in 18 (33.3%), and noncoronary chest pain in 5 (9.3%). There was a notable increase in the use of beta-blockers, calcium channel blockers and nitrates. Complications occurred in 3 (5.5%) patients. Compared with baseline, there was no difference in the mean EQ-5D score at the 3-month follow-up, but there was a significant improvement in the SAQ score related to physical limitations, angina stability, and disease perception, with no differences in angina frequency or treatment satisfaction. No events were recorded at the 1-year follow-up.
Conclusions: A specific diagnostic and therapeutic protocol can be easily and safely implemented in routine clinical practice, leading to improvement in patients' quality of life.

Keywords: INOCA. ANOCA. Diagnosis. Therapy. Protocol.

Angina o isquemia con arterias coronarias no obstruidas: un protocolo diagnóstico y terapéutico específico

RESUMEN

Introducción y objetivos: El abordaje sistemático en pacientes con angina con arterias coronarias no obstruidas (ANOCA) o con isquemia con arterias coronarias no obstruidas (INOCA) no está bien protocolizado.
Métodos: Todos los pacientes con diagnóstico de INOCA o ANOCA se trasladaron a una clínica ambulatoria específica para evaluar su elegibilidad para el programa NOCA. Si eran elegibles, se sometían a una angiografía coronaria programada con pruebas de función coronaria y provocación intracoronaria con acetilcolina. La terapia médica se optimizó en consecuencia. Todos los pacientes tuvieron un seguimiento a 1, 3, 6 y 12 meses. Al inicio y a los 3 meses se aplicaron los cuestionarios SAQ y EuroQol-5D.

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Resultados: De 77 pacientes se excluyeron 23 (29,9%) y se incluyeron 54 (70,1%) (29 [53,7%] con INOCA y 25 [46,3%] con ANOCA). Se diagnosticó angina microvascular a 19 (35,2 %) pacientes, angina vasoespástica a 12 (22,2 %), angina microvascular y angina vasoespástica a 18 (33,3 %), y dolor torácico no coronario a 5 (9,3 %). Hubo un aumento significativo en el uso de bloqueadores beta, bloqueadores del calcio y nitratos. Se presentaron complicaciones en 3 (5,5%) pacientes. No hubo diferencias en la puntuación media del EQ-5D a los 3 meses y se observó una mejora significativa en la puntuación SAQ respecto a la limitación física, la estabilidad de la angina y la percepción de enfermedad, sin diferencias en la frecuencia de angina y la satisfacción con el tratamiento. No se registraron eventos al año.
Conclusiones: Un protocolo diagnóstico y terapéutico específico podría implementarse de manera fácil y segura en la práctica clínica diaria, y con ello mejoraría la calidad de vida de los pacientes.

Palabras clave: INOCA. ANOCA. Diagnóstico. Terapia. Protocolo.

Abbreviations

ANOCA: angina with no obstructed coronary arteries. **INOCA:** ischemia with no obstructed coronary arteries.

INTRODUCTION

Ischemic heart disease is the leading cause of disability and mortality worldwide and is commonly characterized by the presence of obstructive coronary artery disease (CAD) (defined as any coronary artery stenosis ≥ 50% in diameter).[1] However, up to 60% to 70% of patients with angina and/or documented myocardial ischemia do not have angiographic evidence of CAD.[2] This condition is defined as angina with no obstructed coronary arteries (ANOCA) or ischemia with no obstructed coronary arteries (INOCA) when associated with evidence of myocardial ischemia.[3] Of note, despite the absence of CAD, these patients are at an increased risk of future cardiovascular events such as acute coronary syndrome, heart failure hospitalization, stroke, and repeat cardiovascular procedures compared with healthy individuals.[4,5] Therefore, appropriate management in terms of diagnosis and treatment is of the utmost importance to improve patients' prognosis and outcomes.[6] The Coronary Microvascular Angina (CorMicA) trial demonstrated that a strategy of adjunctive invasive testing for disorders of coronary function together with stratified medical therapy can improve outcomes (ie, reduction in angina severity and enhanced quality of life).[7,8] However, there are still concerns about the implementation in real-world practice of a systematic diagnostic and therapeutic approach in INOCA and ANOCA patients, potentially impacting outcomes and quality of life.

We report our single-center experience of the implementation in clinical practice of a specific diagnostic and therapeutic protocol (no obstructed coronary arteries [NOCA] program) in INOCA and ANOCA patients.

METHODS

Eligibility criteria for the NOCA program

All consecutive patients diagnosed either at our hospital or at our referral centers with angina or ischemia with nonobstructive CAD on coronary angiography were referred to a specific outpatient clinic (the NOCA clinic at Hospital Clínic, Barcelona, Spain) for a screening visit. Nonobstructive CAD was defined as angiographic evidence of normal coronary arteries or diffuse atherosclerosis with stenosis < 50% and/or fractional flow reserve (FFR) > 0.80 if there was stenosis between 50% and 70%. During the screening visit, a team of expert cardiologists confirmed patients' eligibility for the NOCA program based on the following criteria: *a)* diagnosis of ANOCA, defined as stable, chronic typical angina symptoms (eg, chest pain precipitated by physical exertion or emotional stress and relieved by rest or nitroglycerine); *b)* diagnosis of INOCA, defined as the demonstration of myocardial ischemia identified by a noninvasive test with pharmacologic or exercise stress tests such as cardiac single photon emission computed tomography, cardiac magnetic resonance, stress electrocardiography, or echocardiography.[3] The exclusion criteria were: *a)* atypical angina symptoms, and *b)* clearly identifiable noncoronary causes of chest pain (figure 1). The study protocol adhered to the Declaration of Helsinki and the study was approved by our institutional review committee. All patients provided written informed consent to be included in this program and study. The clinical ethics committee gave their approval for a retrospective analysis of the collected data.

NOCA program: diagnostic approach

After patient inclusion in the NOCA program, specialized counseling was provided by expert cardiologists and nurses. All patients were thoroughly informed about their disease, the importance of reaching a specific diagnosis, and the importance implementing tailored therapy. During the counseling sessions, the predicted benefits and low associated risks of an invasive procedure to specifically study coronary microcirculation and vasospasm were explained in detail. All patients provided written informed consent to undergo coronary angiography and intracoronary provocation testing with acetylcholine (ACh).

Subsequently, all patients underwent a scheduled coronary angiogram with a comprehensive diagnostic work-up consisting of the following: *a)* coronary function testing to assess coronary flow reserve (CFR) and the index of microvascular resistance (IMR); *b)* intracoronary ACh provocation testing to assess the presence of coronary vasomotion disorders (eg, epicardial or microvascular spasm).

Coronary function testing was performed using a pressure-temperature sensor guidewire (PressureWire X Guidewire and Coroventis CoroFlow Cardiovascular System, Abbott Vascular, United States) placed in the left anterior descending artery (LAD) as the prespecified target vessel, reflecting its subtended myocardial mass and coronary dominance. Steady-state hyperemia was induced using intravenous adenosine (140 µg/kg/min). If there was severe tortuosity of the LAD or evidence of myocardial ischemia in a region

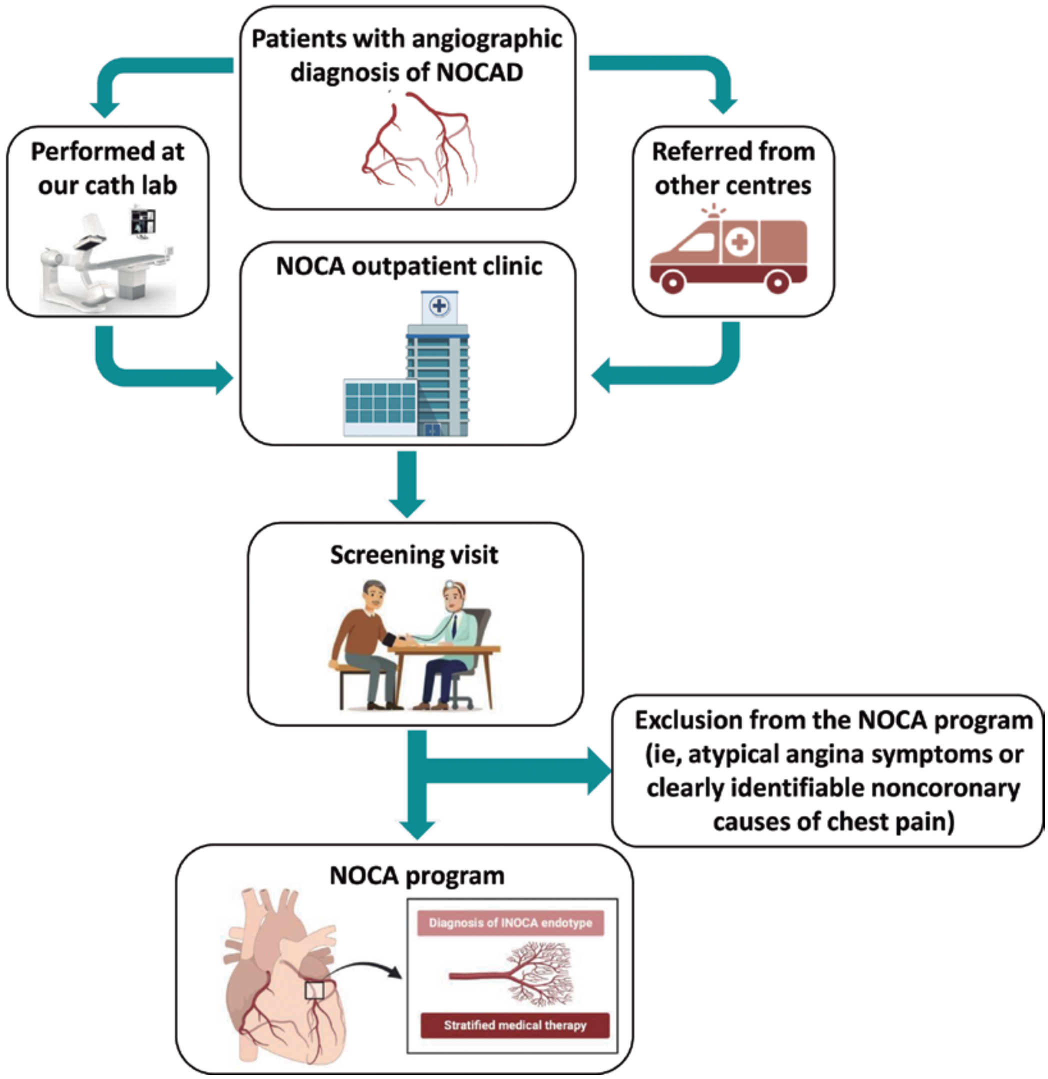

Figure 1. Central illustration. Flowchart for the inclusion of patients in the NOCA program. Cath lab, catheterization laboratory; INOCA: ischemia with no obstructed coronary arteries; NOCA, no obstructed coronary arteries; NOCAD, nonobstructive coronary artery disease.

other than the territory of the LAD, the wire was placed in the right coronary artery or the left circumflex, as per the operator's decision. CFR was calculated using thermodilution, defined as resting mean transit time divided by hyperemic mean transit time (abnormal CFR was defined as ≤ 2.5). IMR was calculated as the product of distal coronary pressure at maximal hyperemia multiplied by the hyperemic mean transit time (normal value < 25).[6,9]

Intracoronary ACh provocation testing was performed with a standardized protocol involving serial ACh infusions for 20 seconds at increasing concentrations (2-20-100 µg in the left coronary artery with an interval of 2-3 minutes between each injection) with concomitant assessment of the patient's symptoms, electrocardiogram documentation, and angiographic scans. Patients taking vasoactive drugs (eg, calcium channel blockers and nitrates) underwent a wash-out period of at least 48 hours before the provocative test.[10,11,12] Epicardial coronary spasm was defined as the reproduction of chest pain and ischemic electrocardiogram changes in association with a reduction in coronary diameter ≥ 90% from baseline in any epicardial coronary artery segment.[13] Microvascular spasm was diagnosed when typical ischemic ST-segment changes (deviation ≥ 1 mm) and angina developed in the absence of epicardial coronary constriction (< 90% diameter reduction).[14]

Subsequently, patients were stratified into 4 endotypes: *a)* microvascular angina (MVA) (evidence of coronary microvascular dysfunction [CMD] defined as any abnormal CFR [< 2.5], IMR [≥ 25], or microvascular spasm); *b)* vasospastic angina (VSA) (CFR ≥ 2.5, IMR < 25 and epicardial spasm); *c)* both MVA and VSA (evidence of CMD and epicardial spasm); and *d)* noncoronary chest pain (CFR ≥ 2.5 and IMR < 25, with neither microvascular nor epicardial spasm).[6]

Any complications occurring during the invasive diagnostic workup were documented, including bradyarrhythmias, atrial fibrillation, ventricular tachycardia or fibrillation, coronary perforations, death from any cause, and any other complications.

NOCA program: pharmacological and psychological therapeutic approach

Once the endotype was identified, medical treatment for each patient was optimized accordingly (table 1). In patients with MVA, treatment with beta-blockers and calcium channel blockers (CCBs) was started or up-titrated. Ranolazine was added if angina symptoms were not fully controlled by beta-blockers and CCBs. In

Table 1. Medical therapy according to the specific endotype of ANOCA/INOCA

Pathogenic mechanism of MINOCA	Therapeutic implications
MVA	Beta-blockers (Nebivolol 2.5–10 mg daily)
	CCBs (amlodipine 10 mg daily, or verapamil 240 mg daily, or diltiazem 90 mg twice daily)
	Ranolazine (375-750 mg twice daily)
VSA	Nondihydropyridine CCBs (verapamil 240 mg, or ciltiazem 90 mg twice daily)
	Long-acting nitrates (isosorbide mononitrate 30 mg)
MVA and VSA	CCBs (verapamil or diltiazem) or beta-blockers
Noncoronary chest pain	Beta-blockers or dihydropyridine CCBs if clinically indicated (eg, hypertension)
	ACEi or ARB if clinically indicated
	Statins if clinically indicated

ACEi, angiotensin-converting enzyme inhibitors; ANOCA, angina with no obstructed coronary arteries; ARB, angiotensin receptor blockers; CCBs, calcium channel blockers; INOCA, ischemia with no obstructed coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary artery disease; MVA, microvascular angina; VSA, vasospastic angina.

patients with VSA, treatment with nondihydropyridine CCBs and long-acting nitrates was started or up-titrated. In patients with both MVA and VSA, treatment with nondihydropyridine CCBs or beta-blockers was started or up-titrated. In patients with noncoronary chest pain, vasoactive drugs were discontinued unless clinically indicated for other reasons. Additionally, treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins was started or up-titrated in all patients. If a patient showed intolerance or had contraindications to a specific medication (eg, asthma for beta-blockers, perimalleolar edema for CCBs, severe bradycardia for both beta-blockers and CCBs), the treatment was tailored and modified accordingly.

Because stress is an important trigger factor for angina symptoms, all patients were also referred to a team of expert psychologists for psychological support.[15]

NOCA program: clinical outcome and quality of life evaluation

All patients were followed up at 1, 3, 6, and 12-months for treatment titration and assessment of clinical outcomes. At the time of coronary angiography (ie, baseline) and at the 3-month follow-up, all patients were administered the Seattle Angina Questionnaire (SAQ) and quality of life questionnaire (EuroQol-5D [EQ-5D]). The SAQ is a validated 19-item self-administered questionnaire that measures 5 dimensions of CAD: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception.[16] The EQ-5D is a standardized, nondisease-specific questionnaire used to describe and evaluate patients' health status and was intended to complement other quality-of life measures.[17] Figure 2 provides a visual representation of all the steps involved for patients included in the NOCA program.

Statistical analysis

Data distribution was assessed according to the Kolgormonov-Smirnov test. Continuous variables were compared using the unpaired Student *t*-test or the Mann–Whitney *U* test, as appropriate. The data are expressed as mean ± standard deviation (SD) or as median and interquartile range [IQR]. Categorical data are expressed as numbers and percentages and were evaluated using the chi-square test or Fisher exact test, as appropriate. A 2-sided P value $< .05$ was considered significant. All analyses were performed using SPSS version 21 (SPSS, United States).

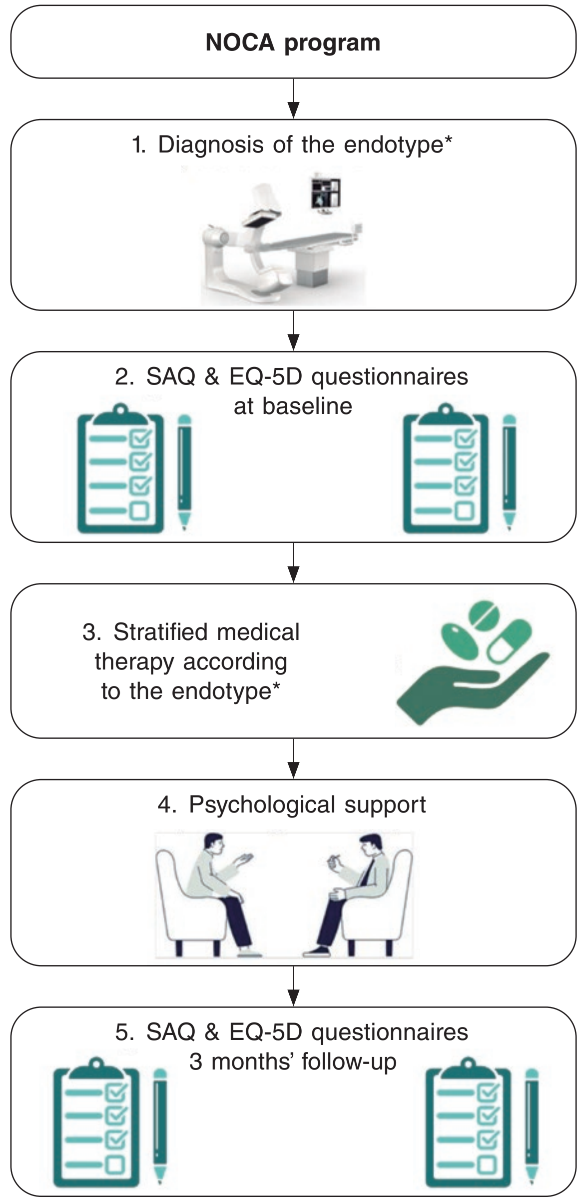

Figure 2. Visual representation of the NOCA program. EQ-5D, EuroQol-5D; NOCA, no obstructed coronary arteries; SAQ, Seattle Angina Questionnaire. * See text for more details.

RESULTS

Baseline characteristics of the study population

From January 2021 to December 2021, a total of 77 patients were screened at the NOCA clinic for inclusion in the NOCA program. Following the screening visit, 23 (29.9%) patients were excluded from the NOCA program: 12 due to atypical angina symptoms and

Table 2. Clinical and angiographic characteristics of patients included in the NOCA program

Characteristics	Study population (n = 54)
Clinical characteristics	
Age	64.4 ± 9.4
Female sex	39 (72.2)
Clinical presentation	
ANOCA	25 (46.3)
INOCA	29 (53.7)
Diabetes mellitus	12 (22.2)
Hypertension	35 (64.8)
Dyslipidaemia	28 (51.9)
Former smokers	3 (5.7)
Current smoker	14 (25.9)
Familiar history of CV disease	5 (9.3)
Previous CV history	
Prior MI	7 (13.0)
Prior PCI	8 (14.8)
Prior CABG	0 (0.0)
COPD	1 (1.9)
CKD (eGFR < 60 mL/min/m²)	4 (7.4)
Depression	15 (27.8)
Anxiety	19 (35.2)
Invasive functional evaluation	
Vessel explored	
LDA	48 (88.9)
LCx	3 (5.6)
RCA	3 (5.6)
IMR	21.2 ± 10.6
Increased IMR (≥ 25)	18 (33.3)
CFR	2.3 ± 1.4
Reduced CFR (< 2.5)	33 (61.1)
Increased IMR (≥ 25) and reduced CFR (< 2.5)	13 (24.1)
Diagnosis (endotype)	
MVA	19 (35.2)
VSA	12 (22.2)
MVA and VSA	18 (33.3)
Noncoronary chest pain	5 (9.3)

ANOCA, angina with no obstructed coronary arteries; CABG, coronary artery bypass graft surgery; CFR, coronary flow reserve; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IMR, index of microcirculatory resistance; INOCA, ischemia with no obstructed coronary arteries; MI, myocardial infarction; MVA, microvascular angina; LAD, left anterior descending; LCx, left circumflex; PCI, percutaneous coronary intervention; RCA, right coronary artery; VSA, vasospastic angina.
Values are expressed as No. (%), mean ± standard deviation or median [interquartile range].

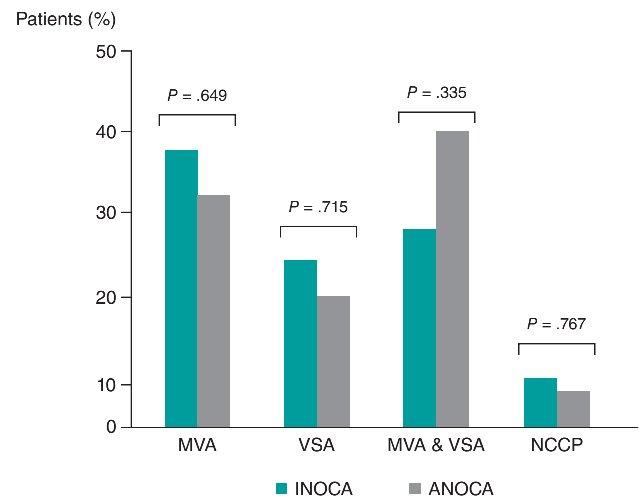

Figure 3. Prevalence of the different endotypes among INOCA and ANOCA patients. ANOCA, angina with no obstructed coronary arteries; INOCA, ischemia with no obstructed coronary arteries; MVA, microvascular angina; NCCP, noncoronary chest pain; VSA, vasospastic angina.

11 due to a clearly identifiable noncoronary cause. Consequently, 54 patients were included in the NOCA program (mean age 64.4 ± 9.4 years, 39 [63.9%] women). A total of 29 (53.7%) patients had INOCA and 25 (46.3%) had ANOCA. All clinical and angiographic characteristics of the study population are shown in table 1.

NOCA program: diagnosis of the specific endotype and complications

The results of the invasive functional assessment are presented in table 2. The mean IMR and CFR values were 21.2 ± 10.6 and 2.3 ± 1.4, respectively. MVA was diagnosed in 19 (35.2%) patients, VSA in 12 (22.2%), and both MVA and VSA in 18 (33.3%). Finally, 5 (9.3%) patients were diagnosed with noncoronary chest pain.

Among INOCA patients, MVA was diagnosed in 11 (37.9%) patients, VSA in 7 (24.1%), both MVA and VSA in 8 (27.6%), and noncoronary chest pain in 3 (10.3%). Among ANOCA patients, MVA was diagnosed in 8 (32.0%) patients, VSA in 5 (20.0%), both MVA and VSA in 10 (40.0%), and noncoronary chest pain in 2 (8.0%). There were no statistically significant differences in the prevalence of any endotype between INOCA and ANOCA patients (all $P > .05$, figure 3).

Complications occurred in 3 (5.5%) patients during intracoronary ACh provocation testing: 2 (3.7%) patients had transient bradyarrhythmias and 1 (1.8%) patient had paroxysmal atrial fibrillation that spontaneously reverted to sinus rhythm.

NOCA program: treatment optimization according to the specific endotype

Inclusion in the NOCA program led to statistically significant changes in medications after diagnosis of the specific endotype. There was a significant increase in the use of beta-blockers (33.3% before vs 57.4% after, $P = .008$), nondihydropyridine CCBs (9.3% before vs 37.0% after, $P < .001$), and long-acting nitrates (46.3% before vs 63.0% after, $P = .012$). There were no statistically significant differences in any other medications before and after the

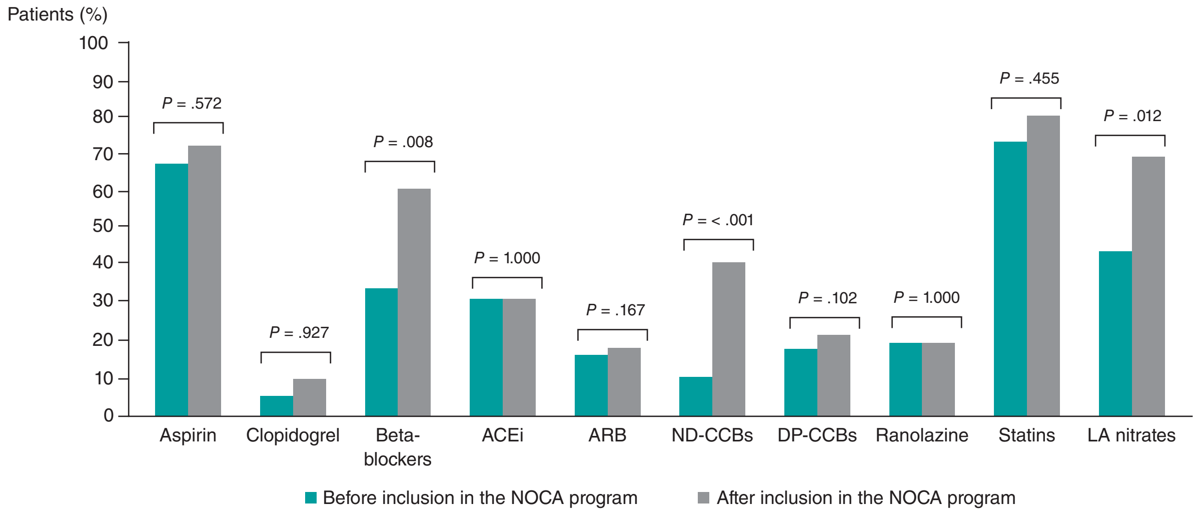

Figure 4. Differences in medical treatment before and after patient inclusion in the NOCA program. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DP-CCBs, dihydropyridine calcium channel blockers; LA, long-acting; ND-CCBs, nondihydropyridine calcium channel blockers.

invasive assessment (all $P > .05$, figure 4). All changes in medications according to the specific endotype of ANOCA/INOCA are shown in figure 5.

NOCA program: clinical outcome evaluation

At 3 months of follow-up, there was no statistically significant difference in the mean EQ-5D score compared with baseline (64.8 ± 18.1 at baseline vs 66.1 ± 17.1 at 3 months of follow-up, $P = .302$) (figure 6). However, there was a statistically significant improvement in the SAQ score in terms of physical limitations (59.7 ± 19.3 at baseline vs 66.2 ± 16.9 at 3 months of follow-up, $P = .037$), angina stability (57.1 ± 28.1 at baseline vs 75.8 ± 22.3 at 3 months of follow-up, $P = .010$), and disease perception (42.5 ± 13.9 at baseline vs 50.8 ± 16.3 at 3 months follow-up, $P = .015$). No statistically significant difference was found in angina frequency (74.3 ± 20.4 at baseline *vs* 80.7 ± 19.8 at 3 months of follow-up, $P = .193$) or treatment satisfaction (68.1 ± 12.6 at baseline *vs* 70.5 ± 12.5 at 3 months of follow-up, $P = .950$) (figure 7). No events were recorded at the 1-year follow-up.

DISCUSSION

The main results of our experience can be summarized as follows: *a)* the implementation of a specific diagnostic and therapeutic protocol (NOCA program) in patients with diagnosed with nonobstructive CAD is feasible and allowed a parsimonious use of medical resources; *b)* a comprehensive diagnostic work-up in INOCA and ANOCA patients is safe, with a low rate of mild and transient complications (5.5%); *c)* the inclusion of patients in the NOCA program led to significant changes in medications and a significant improvement in their angina symptoms at the 3-month follow-up with no adverse events at 1 year.

Although accumulating evidence has demonstrated that an approach consisting of a comprehensive diagnostic assessment and stratified medical therapy in INOCA and ANOCA is crucial to improve patients' prognosis, such an approach is far from routinely implemented in clinical practice.[7,8] There are still concerns mainly related to the cost-benefit ratio, the associated prolonged procedural time, increased costs, and the risk of possible associated complications. Furthermore, in the most recent European Society of Cardiology guidelines, invasive coronary function testing is assigned a class IIa ("should be considered") recommendation, while ACh provocation testing is supported by a class IIb recommendation ("may be considered") to assess microvascular spasm and class IIa in patients under consideration for VSA.[3] As a result, the management of these patients is commonly left to physicians' discretion or relies on the experience of each center. Consequently, diagnosis of a specific NOCA endotype is frequently missed, and medical therapy is not optimized. This, in turn, has a significant negative impact on patients' quality of life and clinical outcomes, as well as on health care costs, due to the need for repeat hospitalization or invasive procedures.[18]

In reporting our experience, we demonstrate that a specific diagnostic and therapeutic protocol (ie, the NOCA program) in patients with a previous diagnosis of nonobstructive CAD can be easily implemented in clinical practice. A key innovation of our study, compared with prior publications, is the creation and implementation of a specific protocol for the INOCA/ANOCA population. Additionally, our approach involves a screening visit with assessment by a team of expert cardiologists for patients with a suspected diagnosis of INOCA/ANOCA. This approach improves identification of such patients, and, in our experience, led to the exclusion of almost one third of patients (29.9%) due to atypical angina symptoms or no clearly identifiable coronary causes of chest pain. This is another novelty of our study that could be extremely relevant in the management of these patients. Indeed, the selection of patients to be included in the program may allow clinical resources to be directed to patients who are most likely to benefit, while avoiding repeat invasive procedures and related risks in patients with unclear indications. Additionally, the specialized counseling provided by cardiologists and nurses during the screening visit, together with psychological support, are likely to be vital components of the management of INOCA/ANOCA patients. Indeed, recent studies have demonstrated how psychological factors, such as chronic stress, anxiety, depression, and social stressors are involved in the pathogenesis of MVA and VSA.[19-23] Mental stress has been demonstrated to determine CMD mainly through endothelium-dependent mechanisms and endothelial dysfunction.[24] Similarly, by activating brain areas involved in regulation of neuroendocrine and autonomic nervous systems, mental stress can lead to hyperreactivity of vascular smooth muscle cells, autonomic nervous system dysfunction, oxidative stress, vascular inflammation, and endothelial dysfunction, resulting in an increased propensity to coronary vasospasm.[25-27]

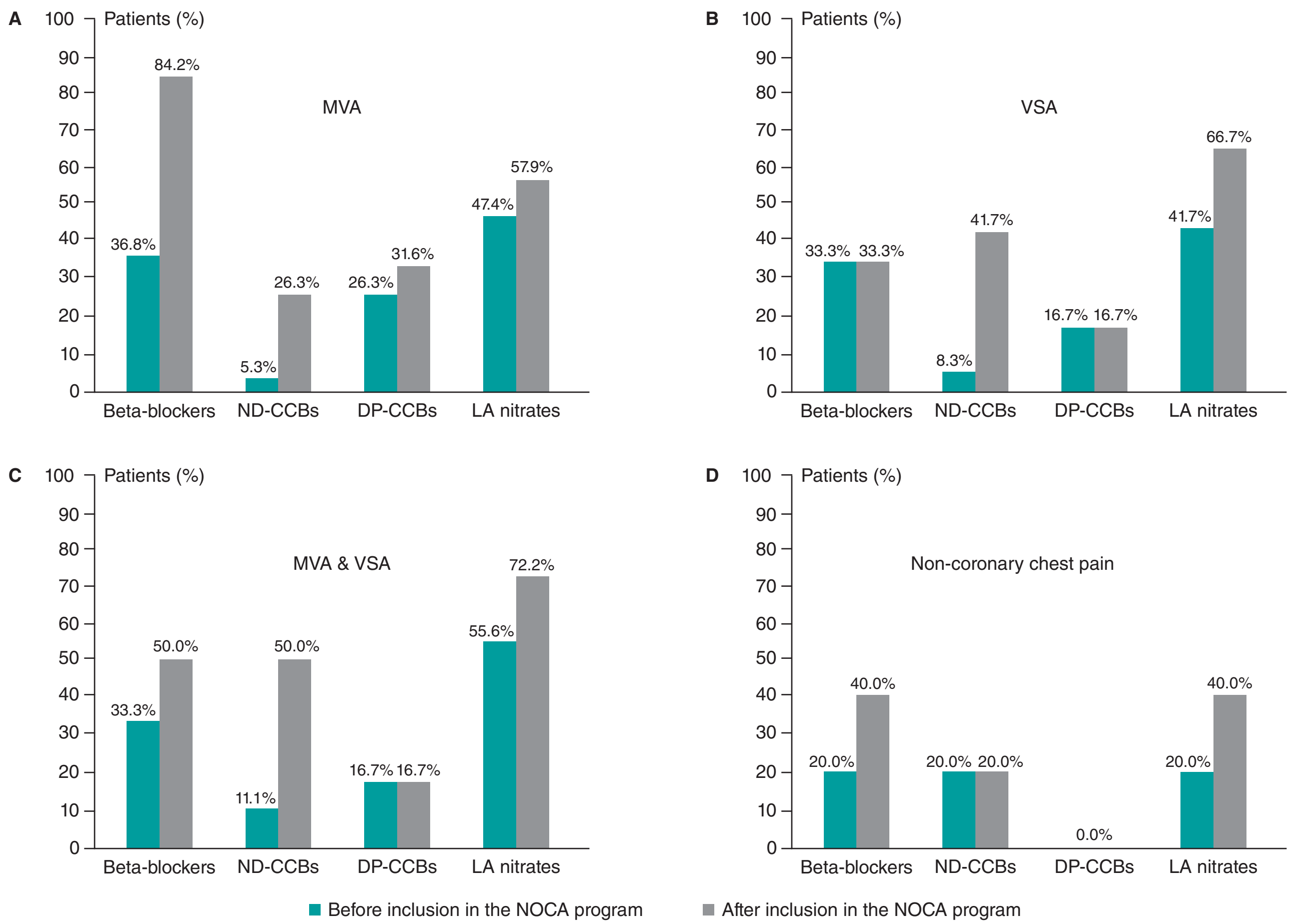

Figure 5. Changes in medications according to the specific endotype of ANOCA/INOCA. A: patients with MVA. B: patients with VSA. C: Patients with MVA and VSA. D: patients with noncoronary chest pain. DP-CCBs, dihydropyridine calcium channel blockers; LA, long-acting; MVA, microvascular angina; ND-CCBs, nondihydropyridine calcium channel blockers; VSA, vasospastic angina.

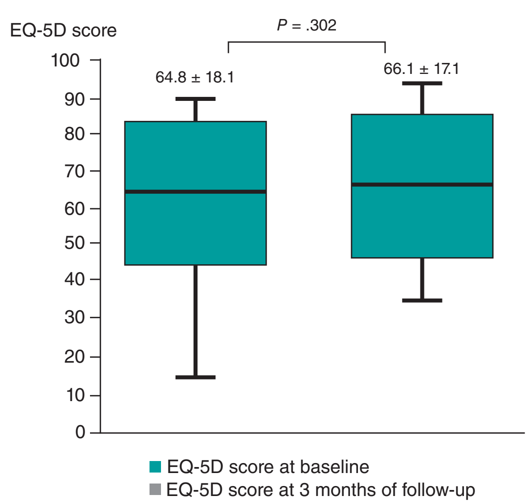

Figure 6. Differences in EuroQol-5D (EQ-5D) score at baseline and at 3 months of follow-up.

Furthermore, in line with previous studies,[28-30] our experience demonstrates that performing a comprehensive invasive diagnostic assessment for the diagnosis of the specific endotype in INOCA and ANOCA patients is safe and is associated with a low rate of mild and transient complications. For all these reasons, patients and clinicians should be reassured about the lack of serious complications and cardiologists should be strongly encouraged to implement a specific diagnostic and therapeutic program in these patients. Indeed, the availability of such a program for INOCA and ANOCA patients may have significant clinical and therapeutic implications, as, in our experience, it resulted in substantial changes in medications and a marked improvement at the 3-month follow-up of the SAQ questionnaire regarding physical limitations, angina frequency, and disease perception. The lower and nonsignificant improvement in the other parameters (eg, angina frequency and treatment satisfaction) could be attributed to the already high baseline values (74.5 ± 19.9 and 69.6 ± 11.9, respectively). Similarly, the absence of a significant improvement in the EQ-5D questionnaire at 3 months might be due to the short follow-up period or the fact that it is a nondisease-specific questionnaire designed to describe and assess patients' health status and is intended to complement other quality-of-life measures.[31]

Study limitations

Some limitations of this study should be acknowledged. First, this is a single-center study with a relatively small sample size and short follow-up. Second, we did not perform a cost-analysis and therefore we cannot speculate on the impact of the NOCA program on health care-related costs. Further studies in larger ANOCA and INOCA populations are warranted. Finally, the absence of a control group precluded a thorough assessment of the improvement in the quality of life among these patients.

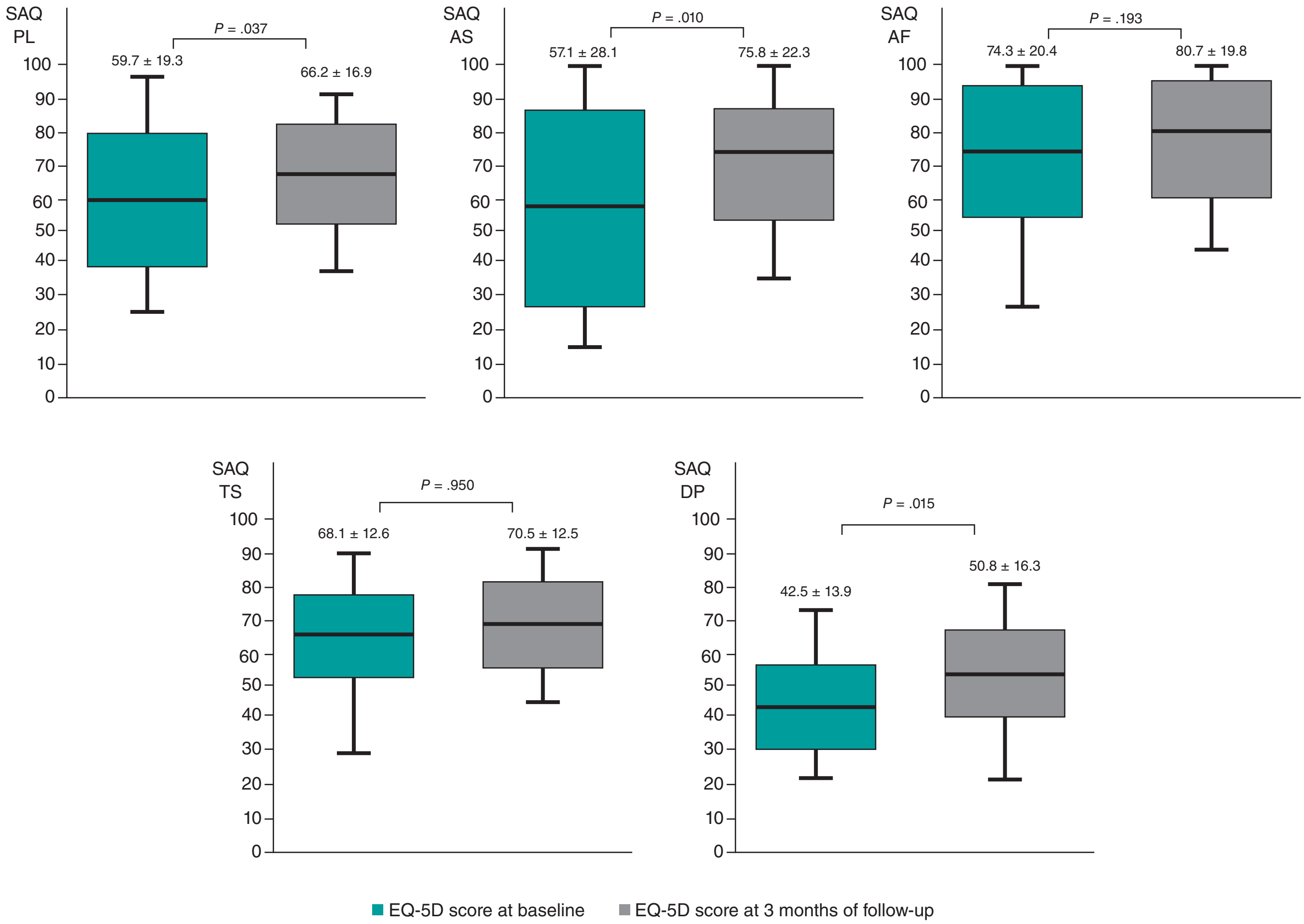

Figure 7. Differences in SAQ score at baseline and at 3 months of follow-up. AF, angina frequency; AS, angina stability; DP, disease perception; EQ-5D, EuroQol-5D; PL, physical limitations; SAQ, Seattle Angina Questionnaire; TS, treatment satisfaction.

CONCLUSIONS

Our experience demonstrates that a specific diagnostic and therapeutic protocol (NOCA program) can be easily and safely implemented in routine clinical practice. Such a protocol could ensure the best care for INOCA and ANOCA patients, as well as improve their quality of life and avoid inappropriate treatments and incomplete investigations. Future evidence from randomized clinical trials or recommendations from international clinical guidelines supporting the implementation of a specific protocol in these patients are strongly warranted.

FUNDING

This study received no funding.

ETHICAL CONSIDERATIONS

The study protocol complied with the Declaration of Helsinki and the study was approved by our Institutional Review Committee. All patients gave written informed consent to be included in this program and study. The clinical ethics committee gave their approval for a retrospective analysis of the data collected. In this work, the possible variables of sex and gender have been taken into account.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used during the preparation of this work.

AUTHORS' CONTRIBUTIONS

R. Rinaldi, F. Spione, F.M. Verardi: data extraction and analysis and manuscript drafting; R. Rinaldi, F. Spione, S. Brugaletta: design and manuscript revision; P. Vidal Calés, V. Arévalos, R. Gabani, D. Cánovas, M. Gutiérrez, M. Pardo, R. Domínguez, L. Pintor, X. Torres, X. Freixa, A. Regueiro, O. Abdul-Jawad Altisent, M. Sabaté: manuscript revision. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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WHAT IS KNOWN ABOUT THE TOPIC?

– Up to 60% to 70% of patients with angina and/or documented myocardial ischemia do not have angiographic evidence of obstructive coronary artery disease. This condition is defined as angina with no obstructed coronary arteries (ANOCA) or ischemia with no obstructed coronary arteries (INOCA) when associated with evidence of myocardial ischaemia. There are still concerns about the implementation in real practice of a systematic diagnostic and therapeutic approach in INOCA and ANOCA patients, potentially impacting outcomes and quality of life.

WHAT DOES THIS STUDY ADD?

– The implementation of a specific protocol (NOCA program) in patients with a diagnosis of nonobstructive CAD is feasible and allowed parsimonious use of medical resources. A comprehensive invasive diagnostic assessment in INOCA or ANOCA patients is safe and is associated with a low rate of mild and transient complications. The availability of a specific diagnostic and therapeutic program for INOCA and ANOCA patients may have important clinical and therapeutic implications, as, in our experience, it led to significant changes in medications and a notable improvement at 3 months of follow-up in the SAQ questionnaire regarding physical limitations, angina frequency, and perception of the disease.

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Original article

On- vs off-hours primary percutaneous coronary intervention: a single-center 5-year experience

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ABSTRACT

Introduction and objectives: In patients with ST-segment elevation myocardial infarction (STEMI) treatment delay significantly affects outcomes. The effect of admission time in STEMI patients is unknown when percutaneous coronary intervention (PCI) is the preferred reperfusion strategy. This study aimed to determine the association between STEMI outcomes and the timing of admission in a PCI center in south-western Europe.
Methods: This retrospective cohort study analyzed the local electronic data from 1222 consecutive STEMI patients treated with PCI. On-hours were defined as admission from Monday to Friday between 8:00 AM and 6:00 PM on non-national holidays.
Results: A total of 439 patients (36%) were admitted on-hours and 783 patients (64%) were admitted off-hours. Baseline characteristics were well-balanced between the 2 groups, including the percentage of patients admitted in cardiogenic shock (on-hours 5% vs off-hours 4%; *P* = .62). The median time from first medical contact to reperfusion did not differ between the 2 groups (on-hours 120 minutes vs off-hours 123 minutes, *P* = .54) and no association was observed between admission time and in-hospital mortality (on-hours 5% vs off-hours 5%, *P* = .90) or 1-year mortality (on-hours 10% vs off-hours 10%, *P* = .97). Survival analysis showed no differences in on-hours PCI vs off-hours PCI (HR, 1.1; 95%CI, 0.74-1.64; *P* = .64).
Conclusions: In a contemporary emergency network, the timing of STEMI patients' admission to the PCI center was not associated with reperfusion delays or increased mortality.

Keywords: ST-segment elevation myocardial infarction. Admisison time. Percutaneous coronary intervention. Emergency medical services. Mortality.

Intervención coronaria percutánea primaria dentro y fuera de horario laboral: experiencia de 5 años de un centro

RESUMEN

Introducción y objetivos: En pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST), el retraso en el tratamiento afecta de manera importante los resultados. El efecto del horario de atención en los pacientes con IAMCEST es dudoso cuando la intervención coronaria percutánea (ICP) es la estrategia de reperfusión preferida. Este estudio tuvo como objetivo determinar la asociación entre los resultados del IAMCEST y el momento de la admisión en un centro con ICP del suroeste de Europa.
Métodos: Estudio de cohorte retrospectivo en el que se analizaron los datos electrónicos locales de 1.222 pacientes consecutivos con IAMCEST tratados con ICP. El horario de atención laboral se definió como la admisión de lunes a viernes de 8 a 18 horas, en días no festivos.
Resultados: Un total de 439 pacientes (36%) ingresaron en horario laboral y 783 (64%) se admitieron fuera del horario. Las características iniciales estaban bien equilibradas entre los grupos, incluyendo el porcentaje de pacientes ingresados en *shock* cardiogénico (en horario laboral el 5% y fuera del horario laboral el 4%; p = 0,62). La mediana de tiempo desde el primer contacto médico hasta la reperfusión no fue diferente entre los 2 grupos (dentro del horario laboral 120 min y fuera del horario laboral 123 min; p = 0,54). No se observó asociación entre el tiempo de admisión y la mortalidad hospitalaria (dentro del horario laboral el 5% y fuera del horario laboral el 5%; p = 0,90) ni la mortalidad a 1 año (en horario laboral el 10% y fuera del horario el 10%; p = 0,97). El análisis de supervivencia no mostró diferencias entre la admisión dentro del horario laboral y la admisión fuera del horario laboral (HR = 1,1; IC95%, 0,74-1,64; p = 0,64).
Conclusiones: En una red de código infarto contemporáneo, el horario de admisión de pacientes con IAMCEST no se asoció con retrasos en la reperfusión ni con un aumento de la mortalidad.

Palabras clave: Infarto agudo de miocardio con elevación del segmento ST. Horario de ingreso. Intervención coronaria percutánea. Emergencia médica. Mortalidad.

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Abbreviations

PCI: percutaneous coronary intervention. **STEMI:** ST-segment elevation myocardial infarction.

INTRODUCTION

Ischemic heart disease is the leading cause of death worldwide. In Europe, despite the decline in incidence and mortality between 1990 and 2009, these trends have slowed in recent years. Moreover, Mediterranean countries showed lower rate of decline during this period.[1]

ST-segment elevation myocardial infarction (STEMI) is a particularly important presentation, associated with high mortality in young individuals.[2,3] Primary percutaneous coronary intervention (PCI) is recommended as the first-line therapy to lower mortality and morbidity in STEMI patients.[4-6] The timing of treatment is crucial for positive outcomes, and minimization of the time from symptom onset to revascularization is essencial.[7,8] While several factors affect treatment timing, emergency system delays play a crucial role as they can be more easily altered by organizational measures and are often used as a quality measurement in STEMI networks.[4,9-13]

To ensure timely treatment, primary PCI centers included in STEMI networks are recommended to have a 24/7 service.[4] However, the impact of admission time (on- vs off-hours) on treatment delay and patient outcomes remains a matter of debate. Some studies and a large meta-analysis have shown that off-hours admission is associated with worse outcomes, partially explained by longer system delays, less guideline-directed management, and less revascularization.[14-16] Conversely, studies in high-volume PCI centers integrated in STEMI networks, demonstrated no differences in outcomes according to admission time.[17-20] Overall, these results are heterogeneous and include populations from different health care systems.

In Europe, efforts have been made to improve STEMI care through public awareness, emergency medical system operations, and the implementation of a full national coverage 24/7 PCI network.[21]

The aim of this study was to determine the association between timing of admission in a PCI center and STEMI patients' outcomes, within a STEMI network in south-western Europe.

METHODS

Study design and population

This retrospective observational cohort study identified 1369 consecutive patients treated with primary PCI at the catheterization laboratory of the Hospital de Braga (Portugal) between June 2011 and May 2016, through the local database that systematically includes all patients undergoing invasive coronary procedures. After an initial analysis, 115 patients were found to have evolved STEMI (> 12 hours since symptom onset) and were therefore excluded. To avoid duplication of results, we excluded 12 records of a repeat episode of STEMI in a patient previously identified in the selected time frame. Lastly, clinical follow-up data were not available for 20 patients, resulting in a final sample of 1222 patients (figure 1). These patients were divided into 2 groups according to admission time (on-hours and off-hours admission), and the main outcome measures evaluated were time delays, in-hospital mortality, and 1-year mortality.

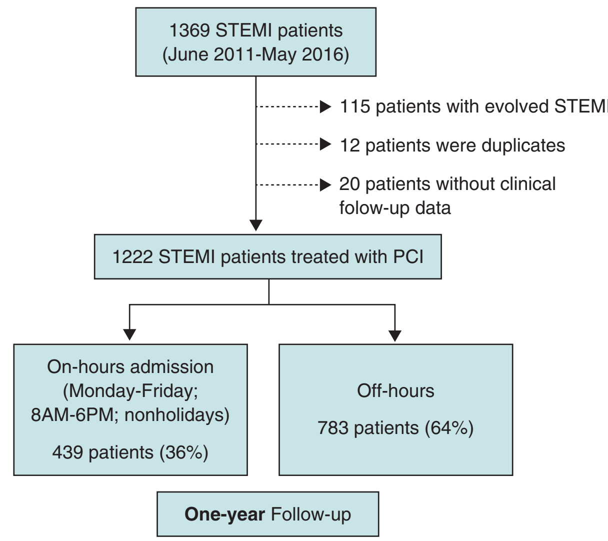

Figure 1. Study flow-chart. PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Definitions

STEMI was defined as the presence of symptoms of myocardial ischemia, associated with electrocardiographic criteria for ST-segment elevation.[4]

Admission time was based on arrival at the catheterization laboratory. On-hours were defined as admission from Monday to Friday between 8:00 AM and 6:00 PM on non-national holidays.

The first medical contact was defined as the first contact with a health service (hospital or primary care clinic). In patients primarily attended by the emergency medical system, the moment when the emergency vehicle carrying a trained physician arrived at the location of the patient was recorded. The reperfusion time was considered as the moment when the angioplasty guidewire crossed the culprit lesion. Time delays from symptom onset to first medical contact (patient-dependent time), from first medical contact to reperfusion (system-dependent time) and from symptom onset to reperfusion (total ischemic time) were characterized.

Patient stratification according to the Killip classification was based on physical examination and the development of heart failure. A Killip class IV classification was assigned to patients in cardiogenic shock.[22]

STEMI network organization

Hospital de Braga has a 24/7 catheterization laboratory service for primary PCI, performed by senior interventional cardiologists (on-call during off-hours). The hospital is the only primary PCI-capable hospital in the Minho region in the north of Portugal and serves approximately 1.1 million people (figure 2). First medical contact can be made by the emergency medical system or in

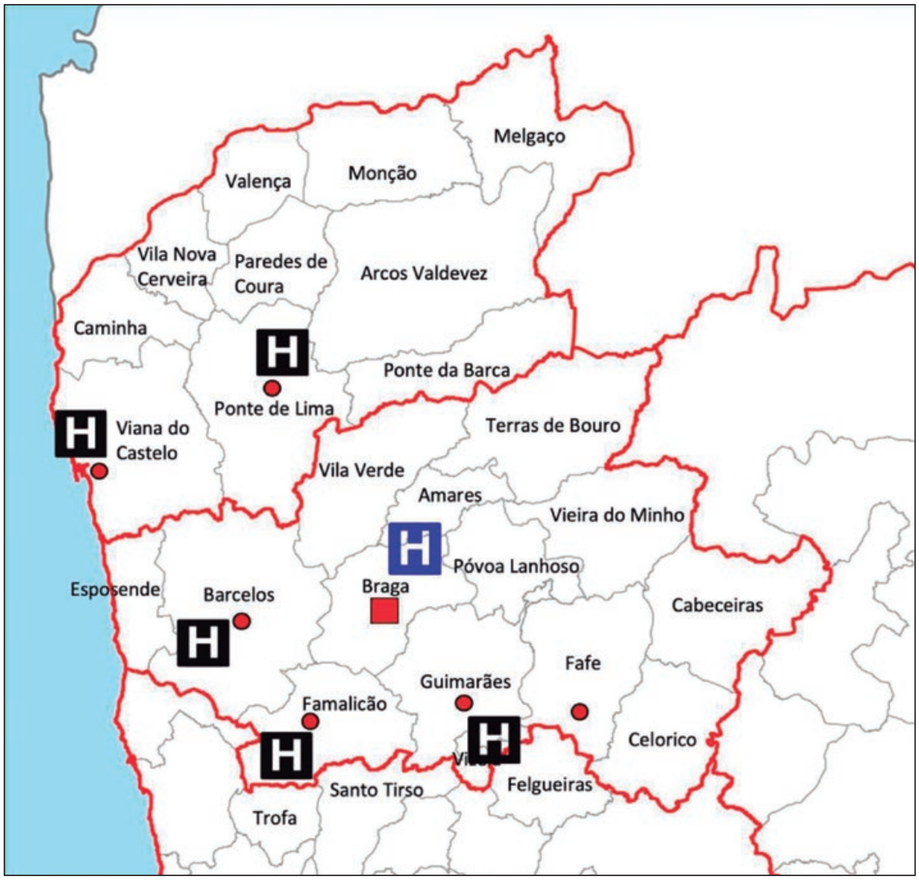

Figure 2. Referral network of the catheterization laboratory of Hospital de Braga.

non-PCI-capable hospitals and clinics, which decide whether to transfer the patient to the PCI-center after consulting the on-call clinical cardiologist. First medical contact can also be made in Hospital de Braga, with rapid triage to primary PCI.

Data collection and statistical analysis

The data for the present study were obtained from the local database of the patient undergoing PCI, the patient's clinical record, and the electronic health registry of Portugal. Clinical and demographic variables were collected.

The IBM Statistical Package for the Social Sciences (IBM SPSS) version 28.0 was used for data treatment. The variables studied to characterize the patients were divided into continuous variables and categorical variables. For the analysis of continuous variables, the distribution was first evaluated. If the variables showed symmetrical normal distribution, the results are presented as mean ± standard deviation, while for variables without normal distribution, the results are reported as median [interquartile range]. To compare continuous variables between the 2 groups of patients, parametric tests were applied for variables with normal distribution and nonparametric tests for the remainder. The Student *t* test for independent samples was used as the parametric test, after evaluation of the homogeneity of variances using the Levene test. The Mann-Whitney *U* test was the nonparametric test applied. For the description of categorical variables, absolute (No.) and relative (%) frequencies were calculated. The comparison of proportions between the study groups was made using the chi-square test or Fisher exact test when the percentage of cells in the table with an expected frequency less than 5 was greater than 20%. The 1-year survival analysis was performed using the Kaplan-Meier method, comparing the groups using the log-rank test. A multivariate analysis with Cox regression was performed, and was adjusted for confounding variables that were statistically significant in the univariate analysis (age, sex, smoking, diabetes mellitus, hypertension, cardiogenic shock, and total ischemia time), to determine if the timing of patient admission was an independent predictor of 1-year mortality. The adjusted hazard ratio (HR) and 95% confidence interval (95%CI) were analyzed to determine the significance of the predictor. In all analyses, results with probability values of $P < .05$ were considered statistically significant.

Confidentiality and ethical considerations

Informed consent for the procedure was obtained in all patients. The confidentiality and anonymity of all collected data were ensured during all phases of the study. This study was approved by the local ethics committee and complies with the provisions of the Helsinki Declaration. Informed consent for the present analysis was waived by the ethics committee due to the retrospective nature of the study.

RESULTS

Baseline characteristics

Between June 2011 and May 2016, of 1222 consecutive patients with confirmed STEMI, a total of 439 (36%) were admitted on-hours

Table 1. Baseline characteristics

	Total (N = 1222)	On-hours (N = 439)	Off-hours (N = 783)	P
Clinical characteristics				
Age, y	61 ± 13	62 ± 13	61 ± 14	.40
Female	269 (22)	102 (23)	167 (21)	.44
Smoking (active or previous)	625 (54)	218 (51)	407 (55)	.18
Dyslipidemia	553 (46)	201 (46)	352 (45)	.72
Diabetes	250 (22)	104 (25)	146 (20)	.04
Hypertension	622 (51)	224 (52)	398 (51)	.89
Previous history				
ACS	84 (7)	28 (6)	56 (7)	.63
PCI	62 (5)	43 (4)	19 (6)	.38
CABG	11 (1)	5 (1)	6 (1)	.50
Presentation				
Direct admission	452 (36)	159 (37)	293 (37)	.68
Anterior MI	642 (53)	229 (52)	413 (53)	.85
Cardiogenic shock	51 (4)	20 (5)	31 (4)	.62
Angiography				
Multivessel disease	583 (48)	215 (49)	368 (47)	.51
Echocardiography				
LVEF	44 ± 10	45 ± 10	44 ± 10	.41

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. Data are expressed as No. (%) or mean ± standard deviation.

and 783 (64%) were admitted off-hours. Baseline characteristics were well-balanced between groups, including the percentage of patients admitted in cardiogenic shock (on-hours 5% vs off-hours 4%; $P = .62$) (table 1).

Comparison of treatment delays

The statistical analysis revealed no significant differences between groups for system-related, patient-related, and total ischemia time (table 2). Similarly, when examining patients directly admitted to the PCI-center, no significant differences were observed in terms of system-related, patient-related, and total ischemia time (table 2).

Association between admission time and outcomes

A 1-year follow-up was completed for all patients included in the analysis. There was no association between on- and off-hours admission time and in-hospital (5% vs 5%; $P = .90$) or 1-year mortality (10% vs 10%; $P = .97$). Equally, in patients admitted on- and off-hours directly to the PCI center, in-hospital (4% vs 7%; $P = .30$) and 1-year mortality (9% vs 13%; $P = .27$) was similar.

Patients who experienced cardiogenic shock had significantly higher rates of both in-hospital (55% vs 3%; $P < .01$) and 1-year mortality (71% vs 7%; $P < .01$) compared with stable patients. However, the time of admission to the hospital did not show a significant impact on the in-hospital (on-hours 50% vs off-hours 58%; $P = .57$) or 1-year mortality (on-hours 65% vs off-hours 74%; $P = .48$) for those with cardiogenic shock.

Hospital admissions for heart failure did not differ in patients admitted on- and off-hours (3% vs 3%; $P = .60$).

Kaplan-Meier curves showed no differences between timings in survival terms (log-rank $P = .95$) (figure 3). The timing of admission was not a predictor of 1-year mortality after adjustment (HR, 1.1; 95%CI, 0.74-1.64; $P = .64$). Independent predictors of mortality at 1-year are depicted in table 3, with cardiogenic shock emerging as the only strong predictor of 1-year mortality.

DISCUSSION

This study suggests that there is no association between the timing of admission in the PCI center and adverse outcomes, in a structured STEMI network that offers PCI as the standard of care 24/7. Patients admitted off-hours had the same characteristics and were offered the same quality of care as those admitted on-hours, reflected by the similarity in treatment delays. Previous studies, in networks that provided the same quality of care whatever the admission time, reported no differences in outcomes.[17-20]

On the other hand, studies that report worst outcomes in patients admitted off-hours, mainly reflect differences in care during this period, with increased delay before revascularization, lower delivery of primary PCI, different procedural characteristics, and fewer available staff during off-hours.[16,23-25] Additionally, several studies found that patients tended to have worse clinical status on admission during off-hours, which adversely impacted outcomes.[16,26] A finding that supports the outmost importance of presentation status is the fact that cardiogenic shock at admission was found to be an independent predictor of 1-year mortality in this study. However, we did not find significant differences in presentation status according to admission time.

This analysis emphasizes that good organization of STEMI networks, with fast-track 24/7 primary PCI, is key to improve patient outcomes and to obviate the adverse impact of off-hours. However, time delays can still be optimized. Public awareness is key to reduce patient-dependent delays, and efforts should be made to improve recognition of symptoms and activation of emergency medical systems. System delays are quality of care indexes, and in this study, they are in the upper margin for benefit of PCI over fibrinolysis (120 minutes).[4,27] This group previously analyzed the impact of interhospital transfer in time from first medical contact to reperfusion, and suggested improvements in chest pain work-up in emergency rooms and prompt transfer protocols after STEMI detection.[28]

Mortality rates in STEMI differ widely among analyses according to the geographical area, time frame analyzed, patient inclusion criteria, and patient management protocols.[29,30] Nonetheless, in this analysis, mortality rates (5% in-hospital and 10% 1-year mortality) were in line with those reported in contemporary registries.[2,31]

To the best of our knowledge, this is the first study in a STEMI network in south-western Europe ensuring the feasibility and safety of on-call off-hours primary PCI in a contemporary STEMI network. This provides substantial reassurance to the usual organization of cath labs with on-call professionals, essential for workload management and organization of the laboratory workforce.

Table 2. Treatment delays

Irrespective of place of FMC	Total (N = 1222)	On-hours (N = 439)	Off-hours (N = 783)	P
Patient-related SO-FMC, min	87 [45-165]	82 [45-160]	89 [48-166]	.30
Emergency system-related FMC-reperfusion, min	123 [92-172]	120 [91-169]	123 [92-173]	.54
Total ischemic time SO-reperfusion	225 [164-354]	220 [159-343]	228 [165-360]	.39
Admitted directly to the PCI-center	**Subtotal (N_1 = 452)**	**On-hours (N_1 = 159)**	**Off-hours (N_1 = 293)**	***P***
Patient-related SO-FMC, min	77 [40-150]	75 [45-155]	78 [40-150]	.96
Emergency system-related FMC-reperfusion, min	88 [68-115]	87 [68-115]	88 [70-115]	.54
Total ischemic time SO-revascularization, min	177 [125-265]	175 [127-254]	177 [124-267]	.92

FMC, first medical contact; PCI, percutaneous coronary intervention; SO, symptom onset.
Values are expressed as median [interquartile range].

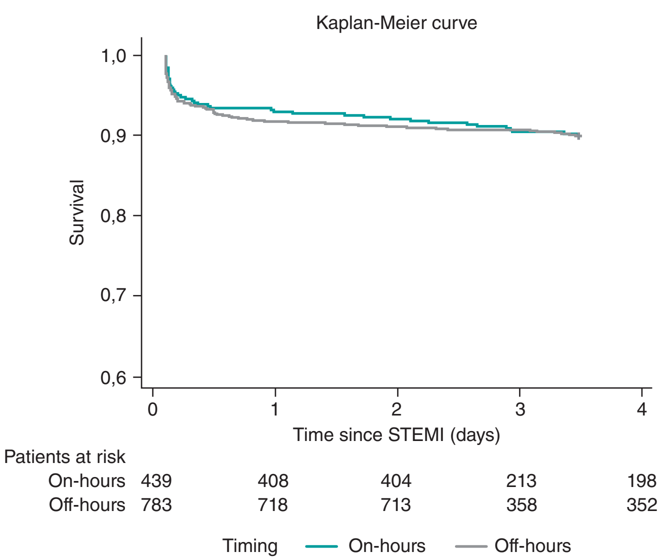

Figure 3. Kaplan-Meier curves for 1-year survival. STEMI, ST-segment elevation myocardial infarction.

Table 3. Predictive factors of 1-year mortality

	Adjusted HR*	95%CI	P
Age	1.08	1.06-1.10	< .01
Cardiogenic shock	12.64	7.60-19.47	< .01
Diabetes mellitus	1.49	0.98-2.26	.06
Hypertension	1.11	0.72-1.73	.63
Sex	1.29	0.78-1.88	.43
Smoking	1.06	0.65-1.74	.81
Total ischemic time	1.00	1.00-1.01	.06

95%CI, 95% confidence interval; HR, hazard ratio.
* Multivariate analysis with Cox regression adjusted for confounding variables that were statistically significant in the univariate analysis (age, cardiogenic shock, diabetes mellitus, hypertension, sex, smoking, and total ischemia time). Admission time was not associated with 1-year mortality in univariate analysis (P = .95).

Study limitations

First, this is a single-center study and may not reflect regional differences in STEMI network organization. Moreover, the results of this study reflect those of a high-volume PC center with a long-standing 24/7 primary PCI program, which may differ from others due to diverse organizational features and available resources. This could be tackled by a future study analyzing national registry data.

Second, the retrospective nature of this study has the limitations inherent to this type of design.

Third, the definition of off-hours admission time is heterogeneous across the literature. In this study, it was defined according to the organizational features of the cath lab, which may not reflect off-hours in other centers/networks.

Additionally, overall mortality in this study may be underestimated, as the group of patients diagnosed in hospitals other than the PCI center and who died before or during transfer were not included in this analysis.

Another limitation of this study is the focus on the management of the patient exclusively until the performance of the primary PCI. Other factors that affect outcomes in these patients, most importantly the delivery of guideline directed medical therapies immediately after revascularization, were not analyzed.

Our findings, based on procedures conducted between 2011 and 2016, may not fully reflect the most current health care trends, given the continuous development of clinical guidelines and treatment approaches. For instance, the reduced use of thrombus aspiration, in line with updated guidelines, highlights the imperative for ongoing research to capture the latest developments in the field.

CONCLUSIONS

In a contemporary emergency network, STEMI patients' admission time in the PCI-center was not associated with reperfusion delays or increased in-hospital and 1-year mortality. Mortality in efficient STEMI networks is primarily affected by the severity of clinical presentation.

FUNDING

None.

ETHICAL CONSIDERATIONS

Informed consent for the procedure was obtained in all cases. The confidentiality and anonymity of all collected data were ensured during all phases of the study. This study was approved by the local ethics committee and complied with the provisions of the Helsinki Declaration. Informed consent for the present analysis was waived by the ethics committee due to the retrospective nature of the study.

Possible sex/gender biases were taken into account and avoided.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The authors did not use artificial intelligence tools during the preparation of this study.

AUTHORS' CONTRIBUTIONS

All the authors contributed to the study design, performed a critical review of the manuscript, gave their final approval, and are fully responsible for all aspects of the study guaranteeing both its integrity and accuracy.

CONFLICTS OF INTEREST

None.

WHAT IS KNOWN ABOUT THE TOPIC?

- The impact of admission time (on- vs off-hours) on treatment delay and patient outcomes remains a matter of debate. Some studies have shown that off-hours admission is associated with worse outcomes, while others disprove these findings.
- Previous analyses are heterogeneous and include populations from different health care systems.

WHAT DOES THIS STUDY ADD?

- Real-world clinical evidence that STEMI patients' admission time to the PCI-center is not associated with reperfusion delays or increased in-hospital and 1-year mortality.
- Mortality in a STEMI network is primarily affected by the severity of clinical presentation.

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Original article

Plaque modification and impact on the microcirculation territory after drug-coated balloon angioplasty. The PLAMI study design

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ABSTRACT

Introduction and objectives: Although drug-eluting stents are the main treatment in percutaneous coronary interventions (PCI), drug-coated balloons (DCB) represent an appealing alternative as they eliminate the risk of stent thrombosis and avoid leaving any metal structure in the vessel wall. However, limited evidence has been published to date on the vessel wall healing processes, plaque remodeling, plaque composition, and the impact on the coronary microcirculation after percutaneous coronary intervention with DCB (DCB-PCI).
Methods: This is investigator-initiated, single-center, single-arm, open-label, pilot study of 30 patients with native vessel disease undergoing DCB-PCI. Intravascular ultrasound and angiography-derived index of microvascular resistance (IMRangio) will be performed before and immediately after PCI, and at 3 months of follow-up.
Conclusions: The study aims to provide new evidence on the modification of atherosclerotic plaque in patients with de novo lesions undergoing PCI with DCB. This will be assessed by examining the change in the percentage of atheroma volume and late lumen enlargement using intravascular ultrasound and by evaluating changes in the microcirculation using IMRangio.
Registered at Clinicaltrials.gov (NCT06080919).

Keywords: Drug-coated balloon. Intravascular ultrasound. Angiography-derived index of microvascular resistance.

Modificación de la placa e impacto en la microcirculación tras la angioplastia con balón farmacoactivo. Diseño del estudio PLAMI

RESUMEN

Introducción y objetivos: Pese a que los *stents* farmacoactivos son el tratamiento principal en las angioplastias coronarias, los balones farmacoactivos representan una alternativa interesante dado que eliminan el riesgo de trombosis del *stent* sin dejar ningún tipo de estructura metálica en la pared del vaso. No obstante, la evidencia en cuanto a los procesos de cicatrización de la pared del vaso, el remodelado, los cambios en la composición de la placa ateroesclerótica y el impacto en la microcirculación coronaria tras el intervencionismo coronario percutáneo (ICP) con balón farmacoactivo aún no se ha esclarecido.
Métodos: Estudio piloto abierto, de un solo grupo, iniciado por el investigador, de 30 pacientes con enfermedad de vaso nativo sometidos a ICP con balón farmacoactivo. Se realizará ecografía intravascular y se determinará el índice de resistencia microvascular derivado de la angiografía (angio-IRM) antes, inmediatamente después y a los 3 meses de seguimiento de la angioplastia.
Conclusiones: Se aportará nueva evidencia sobre la modificación de la placa en pacientes con enfermedad de vaso nativo tratados con balón farmacoactivo, evaluando el cambio en el porcentaje del volumen de ateroma y el aumento luminal tardío, así como los cambios en la microcirculación mediante angio-IRM.
Registrado en Clinicaltrials.gov (NCT06080919).

Palabras clave: Balón farmacoactivo. Ecografía intravascular. Índice de resistencia microvascular derivado de la angiografía.

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Abbreviations

DCB: drug-coated balloon. **EEM:** external elastic membrane. **IMRangio:** angiography-derived index of microcirculatory resistance. **IVUS:** intravascular ultrasound. **PCI:** Percutaneous coronary intervention.

INTRODUCTION

Coronary artery disease is the leading single cause of mortality worldwide, accounting for more than 7 million deaths annually[1] and its prevalence has been increasing in the last 20 years.[2] Percutaneous coronary intervention (PCI) has been crucial in the treatment of coronary artery disease.[3,4] The advent of drug-eluting stents (DES) has substantially reduced restenosis rates through the deposition of antiproliferative drugs in the vessel wall. DES have evolved over the years and have become the gold standard in PCI.[5] Drug-coated balloons (DCB) represent an alternative in the setting of PCI. DCB consist of a balloon coated with antiproliferative agents encapsulated in a polymer matrix.[6] Upon inflation, the balloon brings the antiproliferative drug into contact with the vessel wall. The main goal of DCB is to eliminate the risk of stent thrombosis and achieve lower restenosis rates by not leaving any type of metal structure in the treated segment.[6]

The safety and efficacy of DCB have been extensively studied in de novo coronary artery disease.[6] In small vessel disease, DCB have demonstrated noninferiority to DES in several randomized clinical trials.[7] A recent meta-analysis has shown that the use of DCB, compared with that of DES, is associated with a lower risk of vessel thrombosis and a trend toward a lower risk of acute myocardial infarction.[8] In large vessel de novo lesions, current data do not support the widespread use of DCB over DES, although DCB appear to be safe and effective.[9,10] Nevertheless, there is a need to elucidate the elution on the vessel wall, healing processes, plaque remodeling, plaque composition and the impact on the coronary microcirculation following PCI with DCB.

The present report describes the design and rationale for a study of plaque modification and impact on the microcirculation after PCI with DCB (the PLAMI study).

METHODS

The study will be an investigator-initiated, single-center, single-arm, open-label, pilot study in patients undergoing PCI with DCB for de novo lesions. The study has been approved by the hospital ethics committee on research involving medical products. The study has been registered in ClinicalTrials.gov (NCT06080919).

Procedure

Eligible patients will be informed about the study and will be required to provide signed informed consent prior to inclusion. Patients will undergo DCB-PCI under intravascular ultrasound (IVUS) guidance. Angiography-derived coronary physiology will be assessed after the procedure using Angio Plus software (Pulse Medical Imaging Technology, China). The angiography images will be used to obtain the angiography-derived index of microcirculatory resistance (IMRangio) values, before and after DCB-PCI. All procedures will be performed according to current European guidelines[5]: the target lesion will be predilated with semicompliant balloons or noncompliant balloons, with a diameter equal to the reference vessel diameter and with an appropriate length. Multiple predilations will be accepted. The DCB will be the paclitaxel-coated balloon Pantera Lux (BIOTRONIK AG, Switzerland).

The lesion will then be treated with a DCB with a reference vessel diameter/balloon diameter ratio of 1:1. DCB length will be equal to lesion length + 5 mm. DCB inflation time will be set at 45 to 60 seconds to guarantee correct and complete drug elution. The prespecified reasons for DES implantation after DCB-PCI will be residual stenosis > 30%, dissections > type B and TIMI flow < 3.[6] Angiographic follow-up with IVUS and IMRangio evaluation will be performed 3 months after the index procedure. The study timeline is summarized in figure 1.

IVUS images will be taken before the DCB-PCI, immediately after, and at 3 months of follow-up using the Opticross HD 60 MHz (Boston Scientific Corp, United States) system. All IVUS studies will be performed after intracoronary administration of 200 µg of nitroglycerin. The IVUS images will be acquired at 30 frames per second with an automatic transducer pull back (at 0.5 mm/second) to the proximal reference vessel lesion. As there will be no stents to take as a reference, the proximal and distal side branches adjacent to the treated lesion will serve as references, matching the coronary angiographic images (figure 2). All IVUS images will be analyzed by an independent core lab.

Angiography-derived assessment of coronary physiology will be performed with Angio Plus software (Pulse Medical Imaging Technology, China). For the evaluation of each lesion, at least 2 projections with a difference of > 25° will be selected. The operator will manually mark the points proximal and distal to the lesion, and the system automatically outlines the contours of the detected vessel. If the traced vessel trajectory deviates from the normal lumen, the necessary manual modifications will be performed. The artificial intelligence-assisted software combines the intravascular imaging information with the estimated vessel flow to obtain the IMRangio. All the angiography images will be analyzed by an independent core lab to obtain the IMRangio.

Study population and enrolment criteria

Patients will be screened to ensure they meet the inclusion criteria and none of the exclusion criteria prior to study enrolment. Inclusion criteria consist of an indication to undergo PCI for a de novo lesion according to current guidelines (with no restrictions regarding vessel size).[5] Inclusion and exclusion criteria are summarized in table 1.

Sample size

Because of the exploratory nature of this study, no formal sample size calculation is required. Based on previous pilot studies with similar designs,[12] a sample of 30 lesions is planned to evaluate the impact of DCB on coronary healing and the microcirculatory territory.

Study endpoints

The primary endpoint is the change in percentage atheroma volume evaluated by IVUS from baseline to 3 months of follow-up. Secondary endpoints will include *a)* lumen change from baseline to 3 months of follow-up (minimum, maximum, average areas), *b)* the percentage of progressors and percentage of regressors, *c)* external

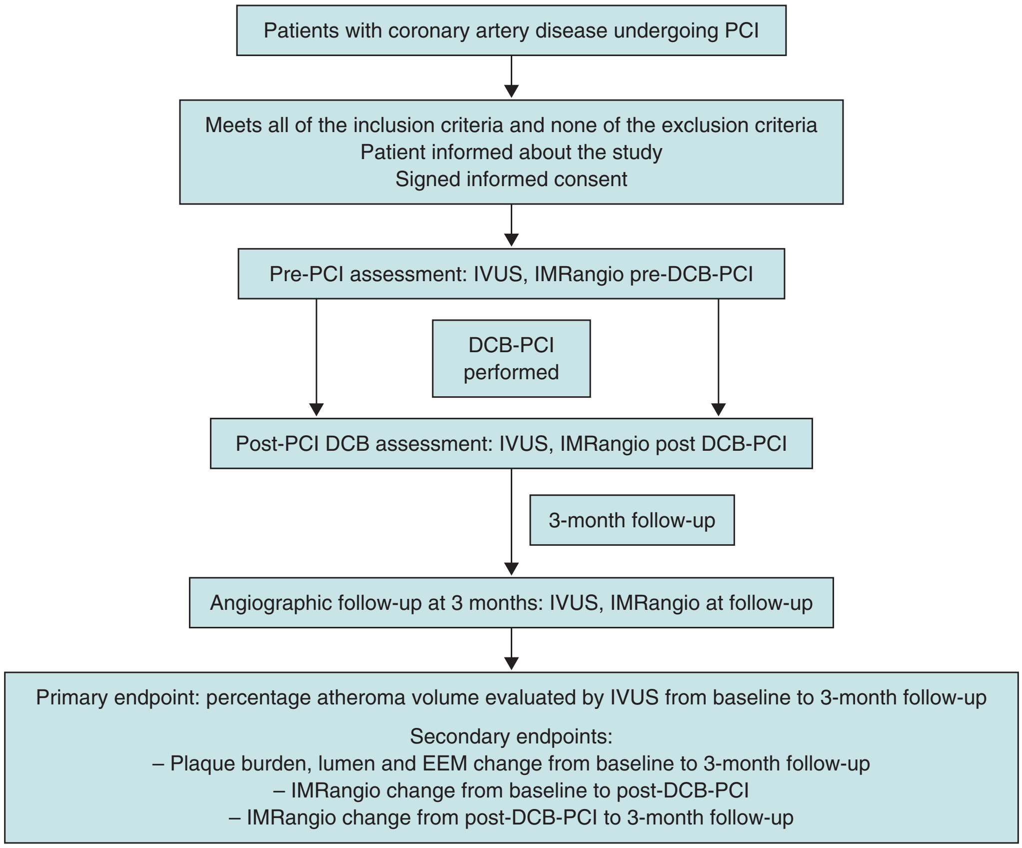

Figure 1. Timeline of the PLAMI study. DCB, drug-coated balloon; IMRangio, angiography-based index of microcirculatory resistance; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

elastic membrane (EEM) change from baseline to post DCB-PCI (average), *d)* EEM change post-DCB-PCI to the 3-month follow-up (average), *e)* the percentage of remodeling types (neutral, negative, and positive), *f)* IMRangio change from baseline to post- DCB-PCI, *g)* IMRangio change from post-DCB-PCI to the 3-month follow-up.

An independent clinical event committee, consisting of cardiologists not participating in the trial, will review and adjudicate all major adverse cardiac events according to the study protocol.

Considering the luminal area as the area delimited by the luminal border, the minimal luminal area is defined as the smallest lumen area within the length of the treated lesion.[13,14] The atheroma or plaque burden is defined as the ratio of atheroma area to the vessel EEM and is calculated by dividing the sum of plaque and media cross-sectional area (CSA) by the EEM CSA.[13,14] As the atheroma area can be calculated in each frame, the total atheroma volume is obtained by taking the sum of the differences between the EEM CSA area and the luminal CSA for all available images.[15] The percent of the volume of the EEM occupied by atheroma is called the percentage atheroma volume.[15,16]

Serial arterial remodeling types will be classified as usual: neutral if there is no change in EEM, negative if there is a decrease in the EEM and positive if vice versa.

Statistical considerations

Continuous variables will be described as mean ± standard deviation or median [interquartile range]. Categorical variables will be described as percentages. The paired *t*-test will be used to compare continuous variables measured before and after treatment in the same patient, and differences in proportions will be tested with the chi-square or Fisher exact test. A *P* value less than .05 (typically ≤ .05) will be considered statistically significant. Statistical analyses will be performed using Stata software version 13.1 (StataCorp LP, United States).

DISCUSSION

Although the use of DES remains predominant in the performance of PCI, complications such as stent thrombosis and in-stent restenosis led to the development of DCB. DCB have the theoretical benefit of not leaving metallic material in the vascular lumen, thereby reducing the possibility of mechanical complications such as malapposition, stent fracture, and stent thrombosis. This could potentially reduce neointimal proliferation and shorten the duration of dual antiplatelet therapy.[6] Current guidelines assign a level IA recommendation to the treatment of in-stent restenosis.[5] While the use of DCB in de novo lesions seems promising, it is not yet widespread. In addition, PCI is not without risks, as it involves a certain degree of injury to the artery wall from balloon inflations and stent struts.[17,19] The vascular response to endothelial cell and smooth muscle cell injury represents a complex network of biochemical responses that involve the immune system. All these factors regulate the processes of neointimal hyperplasia, vascular remodeling, and normal reendothelialization of the arterial wall.[17]

The pathophysiology of restenosis and lumen loss after angioplasty is a complex process involving various factors and is not limited to neointimal hyperplasia.[19] Acutely, plain old balloon angioplasty

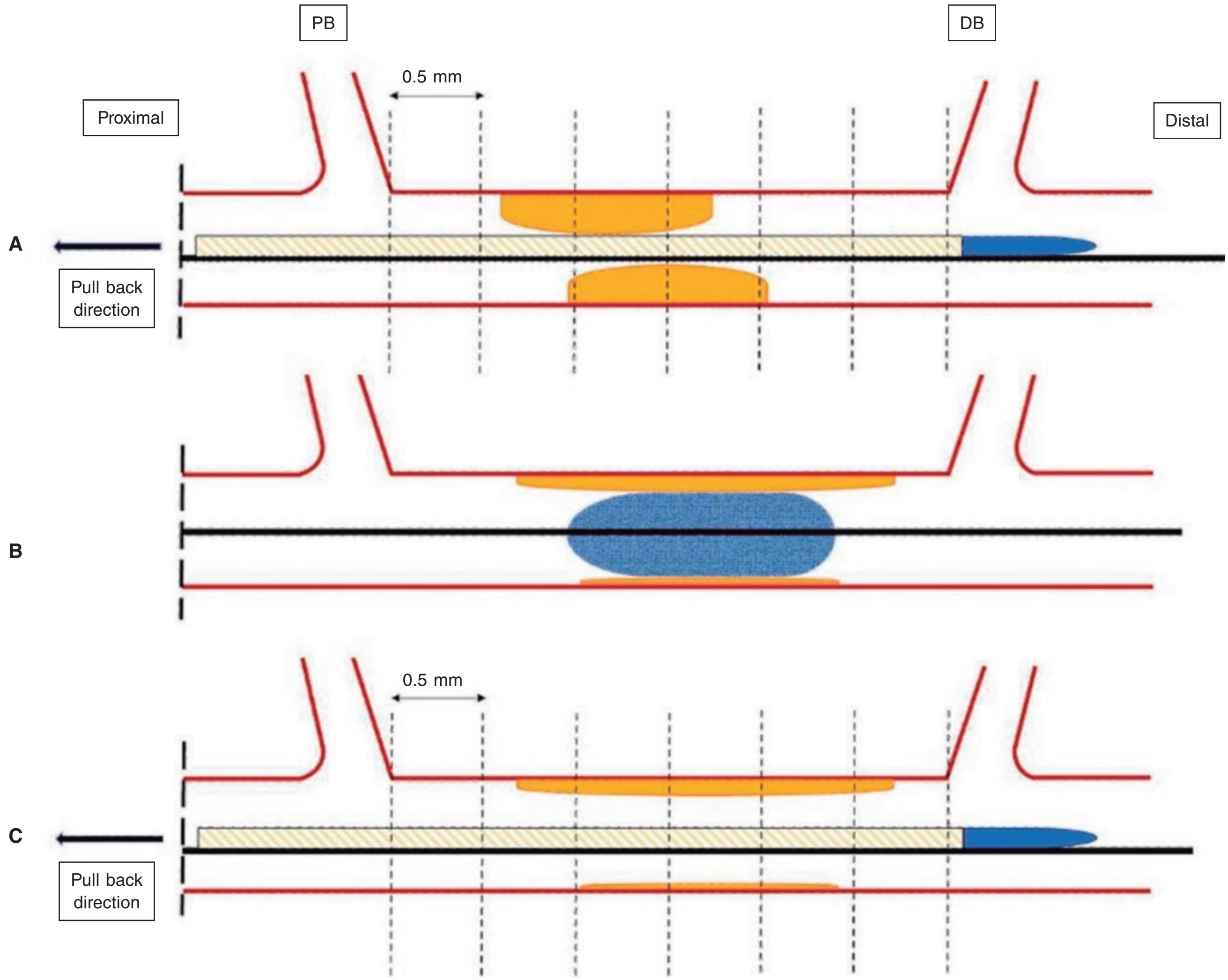

Figure 2. Schematic representation of IVUS acquisition. The IVUS images will be acquired before (A) and after (C) DCB-PCI (B) at 30 frames per second with an automatic transducer pull back (at 0.5 mm/second) to the proximal reference vessel lesion. The same anatomic slice will be analyzed before, after, and at 3 months of follow-up after the PCI by using reproducible landmarks (side branches). The first frame analyzed will be the distal point of the treated vessel before the exit of the DB (represented by the rightmost dotted line), and the last frame analyzed will be the proximal point of the vessel before the split of the proximal branch. DB, distal branch; DCB-PCI, drug-coated balloon percutaneous coronary intervention; IVUS, intravascular ultrasound; PB, proximal branch.

(POBA) generates an increase in luminal area that is mainly due to an expansion of the EEM, mainly attributed to the elastic properties of the vessel rather than to plaque compression or removal.[20] Subsequently, within the first few minutes after PCI, there is an "acute recoil" due to the elastic properties of the arterial wall. In the chronic phase, IVUS data indicate that luminal loss is mainly due to a progressive reduction in EEM rather than an increase in atherosclerotic plaque volume. Unlike the acute phase where loss of area is solely due to elastic properties, "chronic recoil" leading to the loss of area also involves a combination factors such as fibrosis, apoptosis, and changes in the extracellular matrix.[19,21] Interestingly, not all patients show negative remodeling with a decrease in EEM; around 25% show a persistent increase in EEM, which is correlated with a reduced restenosis rate. Consequently, restenosis appears to be primarily due to the direction and magnitude of changes in arterial remodeling,[19] although neointimal hyperplasia also plays a role .

Nevertheless, the existing evidence is based on analysis after the use of traditional balloons. With DCB-PCI, late lumen enlargement has been observed compared with POBA.[20] Although this finding has been partly attributed to the inhibition of neointimal proliferation by antiproliferative drugs,[22] the role of plaque modification or vessel healing phenomena in influencing this process cannot be excluded. A previous study showed that late lumen enlargement was higher in areas with the highest plaque burden; however, that study was a retrospective assessment and used a quantitative coronary angiography protocol.[23] It could be hypothesized that, by inducing controlled damage to the artery wall, together with the antiproliferative effect of DCB, positive vessel remodeling might be achieved, reducing restenosis rates without the need for DES. Therefore, with DCB-PCI, we are able to treat coronary stenosis not only from a mechanical point of view, but can also change the natural history of the disease and restenosis. In this regard, IVUS analysis will be essential to evaluate the reasons behind the gain or loss of luminal area. The dynamic changes produced after PCI are depicted in figure 3.

The DCB that will be used in our study, paclitaxel, has been extensively analyzed as a balloon-coating drug due to its lipophilic properties and its ability to elute into the vessel wall.[24] Moreover, the available paclitaxel-DCB have shown good results in patients undergoing PCI for native vessel disease.[25] In contrast, because

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patient with CAD undergoing PCI with DCB with no limitation to vessel size	Age < 18 years
	Cardiogenic shock
	ST-segment elevation myocardial infarction
	Use of mechanical circulatory support
	Complex coronary lesions* including chronic total occlusions, bifurcation lesions, left main coronary artery disease, severe calcified lesions, graft interventions and in-stent restenosis
	Inability to provide informed consent
	Unable to understand and follow study-related instructions or unable to comply with study protocol
	Currently participating in another trial
	Pregnant women

CAD, coronary artery disease; DCB, drug-coated balloon; PCI, percutaneous coronary intervention.
* Complex coronary lesions as defined in Lawton et al.[11]

of the hydrophobic characteristics of sirolimus, maintaining an adequate percentage in the wall over the mid-term poses technical challenges. However, advances in the formulation of the new generation of sirolimus DCB are anticipated to address this issue by facilitating adequate drug release into the vessel wall.[24]

As previously mentioned, the coronary microcirculation is closely related to proper coronary functioning and the pathophysiology of coronary artery disease. While it is believed that the performance of PCI, as well as the injury and healing of the coronary artery, may affect the coronary microcirculation, the evidence regarding DCB-PCI is scarce. Moreover, the plaque rupture, intimal dissections and thrombus formation that occur during balloon angioplasty are a potential source of embolism to the microvascular bed.

Since direct visualization of the microcirculation is not feasible in clinical practice,[26] its assessment relies on parameters reflecting its functional status, usually coronary flow reserve and the IMR. Coronary flow reserve is defined as the ratio between hyperemic flow in response to nonendothelial vasodilation and resting blood flow. It is crucial to exclude epicardial stenosis before using coronary flow reserve, as it provides an integrated measurement of both epicardial and coronary microcirculation.[26] IMR is calculated as the product of distal coronary pressure at maximal hyperemia multiplied by the hyperemic mean transit time.

In our study, we will perform a noninvasive, nonhyperemic assessment of the coronary microcirculation using IMRangio. This approach aims to characterize the baseline status of the microcirculation and assess the microvasculature changes induced by PCI and their variation over a 3-month period.

By monitoring IMRangio before and after treating the stenotic epicardial lesion, we will be able to assess the effects of acute fracture of the atherosclerotic plaque and injury to the arterial wall in the microvascular bed. We also aim to investigate whether these collateral harmful changes provoked during angioplasty remain consistent or vary significantly at 3 months of follow-up. In this same context, the analysis of IVUS during follow-up will allow us to correlate the changes in the arterial wall and atherosclerotic plaque after DCB-PCI with microcirculation physiology. To date, no insights into the anatomical and physiological process of healing of the injured arterial wall after DCB-PCI have been available in the published literature.

CONCLUSIONS

The PLAMI study is a first-in-man pilot study that aims to provide new information on the modification of atherosclerotic plaque assessed by intracoronary imaging in patients with de novo lesions undergoing PCI with DCB.

FUNDING

None reported.

ETHICAL CONSIDERATIONS

The study has been approved by the hospital ethics committee on research involving medical products. Eligible patients will be

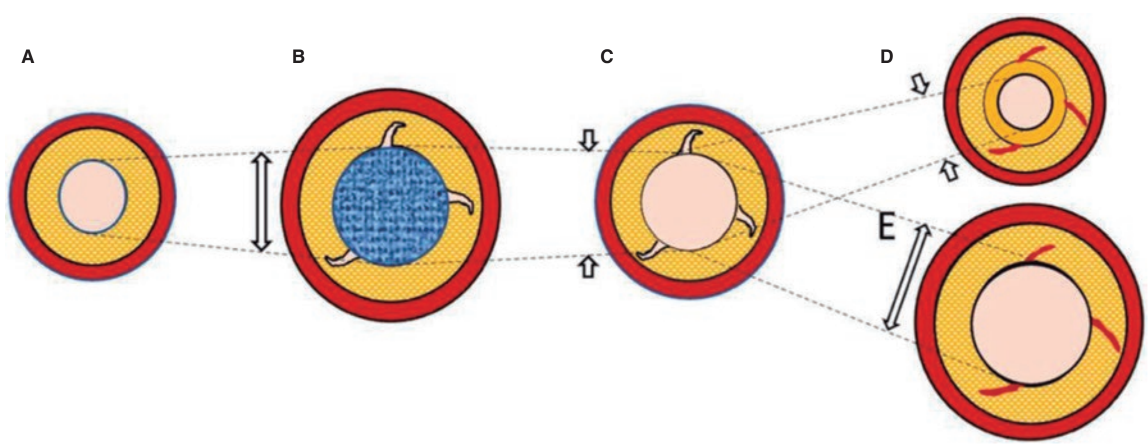

Figure 3. Central illustration. Schematic representation of timeline of DCB-PCI and lumen variation. **A**: pre-DCB-PCI de novo lesion. **B:** DCB-PCI (blue), generating injury to the vessel wall and an increase in lumen and EEM CSA. **C:** acute recoil. **D,** chronic recoil with decrease in EEM and neointimal hyperplasia. **E.** LLE due to maintenance of EEM area and no neointimal hyperplasia. The dotted lines represent the variations of the luminal area throughout the process. The image exemplifies how changes in luminal area, as well as plaque burden, are mainly due to variations in EEM rather than plaque compression. CSA, cross-sectional area; DCB-PCI, drug-coated balloon percutaneous coronary intervention; EEM, external elastic membrane; LLE, late lumen enlargement.

informed about the study and must provide written informed consent prior to inclusion in the study. Possible gender/sex biases have been considered.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

J.A Sorolla Romero, A.Teira Calderón, J. Sanz Sánchez and H.M. Garcia-Garcia contributed to the conception, design, drafting and revision of the article. J.P. Vílchez Tschischke, P. Aguar Carrascosa, F.Ten Morro, L. Andrés Lalaguna, L. Martínez Dolz and J.L. Díez Gil contributed to the critical revision of the intellectual content.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- DCB have proven clinical effectiveness in cases of in-stent restenosis and de novo lesions involving small vessel coronary artery disease.
- Several studies in small vessel coronary artery disease have shown a benefit of DCB in the vessel wall, with late lumen enlargement during follow-up.
- However, there is little evidence of their use in larger vessels.
- In addition, the impact of DCB on the coronary microcirculation has not been evaluated to date.

WHAT DOES THIS STUDY ADD?

- The PLAMI study aims to characterize vessel healing using IVUS after DCB-PCI in patients with native vessel disease and to correlate these findings with the impact on microcirculation.

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Original article

The PULSTA valve in native right ventricular outflow tract: initial experience in 3 Spanish hospitals

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ABSTRACT

Introduction and objectives: Surgery for congenital heart defects with right ventricular outflow tract (RVOT) stenosis often results in significant pulmonary regurgitation, requiring pulmonary valve replacement in the long term. Despite the development of balloon-expandable prostheses, the native RVOT frequently dilates beyond the maximum diameters allowed for these valves. To allow percutaneous pulmonary valve implantation (PPVI) in these patients, clinical trials have been initiated with self-expanding prostheses, including the PULSTA valve. The aim of this study was to report the initial experience with this valve at three Spanish hospitals.
Methods: Descriptive study presenting the results of PPVI with the PULSTA prosthesis in patients with native RVOT and pulmonary regurgitation.
Results: We included 10 patients with a mean age of 15 ± 2.8 years. The implantation was successful in all patients, with no major complications occurring during the procedure. The mean length of follow-up was 18 [range, 2-35] months. In 8 patients, cardiac magnetic resonance was performed at 6 months, revealing a reduction in mean end-diastolic volume (131.7 ± 31.7 mL/m^2 vs 100.3 ± 28.9 mL/m^2) and end-systolic volume (68 ± 20.8 mL/m^2 vs 57 ± 18.5 mL/m^2).
Conclusions: The PULSTA prosthesis offers a safe, feasible, and effective alternative for PPVI in patients with native dilated RVOT. Due to the limited available follow-up data, further studies are needed to assess its long-term safety and durability.

Keywords: Congenital heart disease. Tetralogy of Fallot. Pulmonary regurgitation. Native right ventricular outflow tract. Transcatheter valve implantation, PULSTA valve.

Experiencia inicial con la prótesis PULSTA para el tracto de salida del ventrículo derecho nativo en tres centros españoles

RESUMEN

Introducción y objetivos: La cirugía de las cardiopatías congénitas con estenosis del tracto de salida del ventrículo derecho (TSVD) suele producir insuficiencia pulmonar con necesidad de recambio valvular a largo plazo. Pese al desarrollo de las prótesis expandibles con balón, los TSVD nativos corregidos con parche de ampliación pueden dilatarse por encima de los diámetros máximos admitidos para estas válvulas. Para posibilitar el implante percutáneo de válvula pulmonar (IPVP) en estos casos se están desarrollando prótesis autoexpandibles, entre las que se encuentra la PULSTA. El objetivo de este trabajo es presentar la experiencia inicial con esta válvula en 3 centros españoles.
Métodos: Estudio descriptivo de los resultados del IPVP con la prótesis PULSTA en pacientes con insuficiencia pulmonar sobre TSVD nativo.
Resultados: Se incluyeron 10 pacientes con una media de edad de 15 ± 2,8 años. En todos los casos se consiguió el implante sin complicaciones durante el procedimiento. El tiempo medio de seguimiento fue de 18 meses [rango 2-35 meses]. A 8 pacientes se les realizó una resonancia magnética cardiaca a los 6 meses, donde se observó una reducción de los volúmenes medios telediastólico (131,7 ± 31,7 frente a 100,3 ± 28,9 ml/m^2) y telesistólico (68 ± 20,8 frente a 57 ± 18,5 ml/m^2).

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Conclusiones: La prótesis PULSTA ofrece una alternativa factible, segura y eficaz para el IPVP en pacientes con TSVD nativos dilatados. Son necesarios más estudios para evaluar su durabilidad y seguridad a largo plazo, ya que los datos de seguimiento son limitados.

Palabras clave: Cardiopatías congénitas. Tetralogía de Fallot. Insuficiencia pulmonar. Tracto de salida del ventrículo derecho nativo. Implante valvular percutáneo. Válvula PULSTA.

Abbreviations

CMR: cardiac magnetic resonance. **LVEF:** left ventricular ejection fraction. **PPVI:** percutaneous pulmonary valve implantation. **RVOT:** right ventricular outflow tract.

INTRODUCTION

Congenital heart diseases involving right ventricular outflow tract (RVOT) stenosis require surgical procedures that often compromise the function of the pulmonary valve. The main example of this is RVOT enlargement with transannular patch correction in Tetralogy of Fallot. Because of these patients' current high survival rates (> 90% 25 years after surgical repair),[1] they tend to develop hemodynamically significant pulmonary regurgitation, with an indication for valve replacement due to symptom onset or right ventricular dilatation or dysfunction, which is sometimes asymptomatic.[2,3] To avoid the morbidity and mortality risk associated with repeat surgical procedures, percutaneous pulmonary valve implantation (PPVI) techniques have grown exponentially over the past 20 years, with excellent long-term results.[4-6] These techniques have become the procedure of choice, and surgical aortic valve replacement is now reserved to anatomies ineligible for percutaneous approaches. In some patients with native RVOT, the volume overload due to pulmonary regurgitation leads to RVOT dilatation beyond the maximum diameters allowed for balloon-expandable valves—22 mm for the Melody TPV (Medtronic Inc., United States) and 29 mm for the Edwards SAPIEN XT THV and S3 (Edwards Lifescience, United States)—resulting, in recent years, in several clinical trials of self-expandable pulmonary valves with larger diameters to broaden the indications for PPVI to larger native RVOTs.[7,8] The PULSTA valve (Taewoong Medical, South Korea) belongs to this new generation of self-expandable valves with promising initial results in small series in South Korea[9,10] and Turkey.[11] The objective of this study was to present the initial experience with this new valve in patients with dilatated native RVOT in 3 Spanish centers in Madrid, Spain.

METHODS

Patient selection

Hospitals La Paz and Gregorio Marañón are participating centers in the international multicenter clinical trial The PULSTA transcatheter pulmonary valve (TPV) pre-approval study (NCT03983512). The trial has just completed its enrollment phase and is currently analyzing the initial data. Of the 10 patients included in the present study, 8 are enrolled in this clinical trial, while the remaining 2 received the valve via compassionate use—1 at Hospital Universitario La Paz after the trial enrollment phase, and the other at Hospital Universitario 12 de Octubre.

We included participants with at least moderate pulmonary regurgitation after RVOT surgery due to initial obstructive lesions. The inclusion criteria were *a)* age ≥ 10 years and weight ≥ 30 kg; *b)* at least moderate pulmonary regurgitation in native RVOT with indications for valve replacement due to symptoms, worsening functional class, or progressive right ventricular dilatation or dysfunction on cardiac magnetic resonance (CMR); and *c)* pulmonary trunk measurements ≥ 16 mm and ≤ 30 mm as seen on the transthoracic echocardiogram, CMR, or computed tomography.

Table 1. Echocardiographic quantification criteria of pulmonary regurgitation

Degree	Echocardiographic parameters
Mild	Narrow jet (≤ 1/3 of the pulmonary valve annulus diameter), weak continuous Doppler signal with slow deceleration
Moderate	Intermediate-sized jet (1/3 to 2/3 of the pulmonary valve annulus diameter), dense continuous Doppler signal
Severe	Wide jet (≥ 2/3 of the pulmonary valve annulus diameter), dense continuous Doppler signal with rapid flow deceleration or cessation in mid-to-late diastole, diastolic flow reversal in the pulmonary branches

The degree of pulmonary regurgitation was assessed by both transthoracic echocardiography (table 1) and CMR, while considering the fraction of pulmonary regurgitation (< 20% mild, 20% to 40% moderate, and > 40% severe).

After the study was approved by the local ethics committees, the participants and their families were informed of the nature of the study, and gave their written informed consent to the indication and type of procedure. Ethical principles regarding privacy and confidentiality, as outlined in the Declaration of Helsinki of the World Medical Association revised in October 2013, were observed throughout the study.

The PULSTA Valve

The PULSTA is a 3-leaflet porcine pericardial valve (decellularized and treated to prevent calcification) knitted to a self-expandable nitinol stent also covered with porcine pericardium, except for its proximal and distal portions, with radiopaque markers outlining the covered area (figure 1). The whole system has a diabolo-shaped configuration. The available diameters range from 18 mm to 32 mm—always in relation to the narrowest central area—with 2 mm

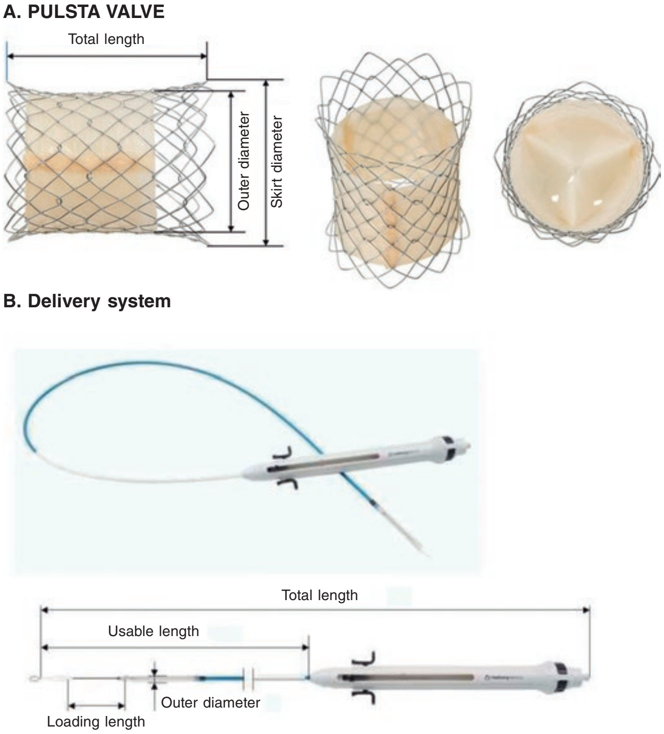

Figure 1. Image of the PULSTA valve showing its diabolo-shaped configuration and covering with its two ends uncovered (**A**) and the delivery system (**B**).

increments. The diameter at the borders is always 4 mm larger, and total length varies between 28 mm and 38 mm and is diameter-dependent, with 1 row of uncovered proximal cells and 2 rows of distal cells to avoid obstructing flow through the pulmonary branches.

The length of the transport system (figure 1) is 110 mm, and its gauge for diameters of up to 28 mm and larger diameters is 18-Fr and 20-Fr, respectively. It requires simple pre-crimping at room temperature using a specific device, but no accessory sheaths to insert and navigate the system that would increase costs. The valve remains attached to the transport system through 3 small protrusions hooked on to the proximal cells. Once in position at the site of choice, the system is deployed by removing the covering portion, for which the proximal portion has a button that allows very fine movements and a trigger that releases the final portion. It reaches nominal diameters when nitinol reaches blood temperature. The valve is retrievable until the distal third is opened.

Valve implantation procedure

All procedures were performed under general anesthesia, while the patient remained on invasive mechanical ventilation and complete heparinization with a bolus of 100 IU/kg of sodium heparin. Two venous femoral vascular access es and 1 arterial access were cannulated. An initial hemodynamic study was conducted, with measurements of pressures on the right side and pulmonary angiography (figure 2) in several views (always with lateral and right anterior oblique views 30° more cranial), including sizing and examination of the pulmonary trunk dynamic behavior using a 34 mm AGA cutting balloon (AGA Medical Corporation, United States). A high-support guidewire (Lunderquist Cook, Denmark) was placed distal to the right or left branch, as appropriate, for navigation. The inflation of the measuring and sizing balloon was coordinated with selective coronary angiograms to rule out the risk of compression. Although the pre-CMR and quantitative angiography images supported the process, the angiographic measurement obtained with the cutting balloon had a more specific weight in the decision-making process. The manufacturer's recommendation is to use valve sizes that should be 2 mm to 5 mm larger than the narrowest region of the pulmonary trunk. However, the final decision depends on the behavior and pulsatility of such region, the mean values of the entire length of the tract, the smaller diameter of the region, and the pre-bifurcation distal architecture of the branches. Each decision was made individually, considering other factors such as the presence of calcium in the RVOT enlargement patch, the patient's weight, the caliber of the delivery system, and the proctor's recommendations when available.

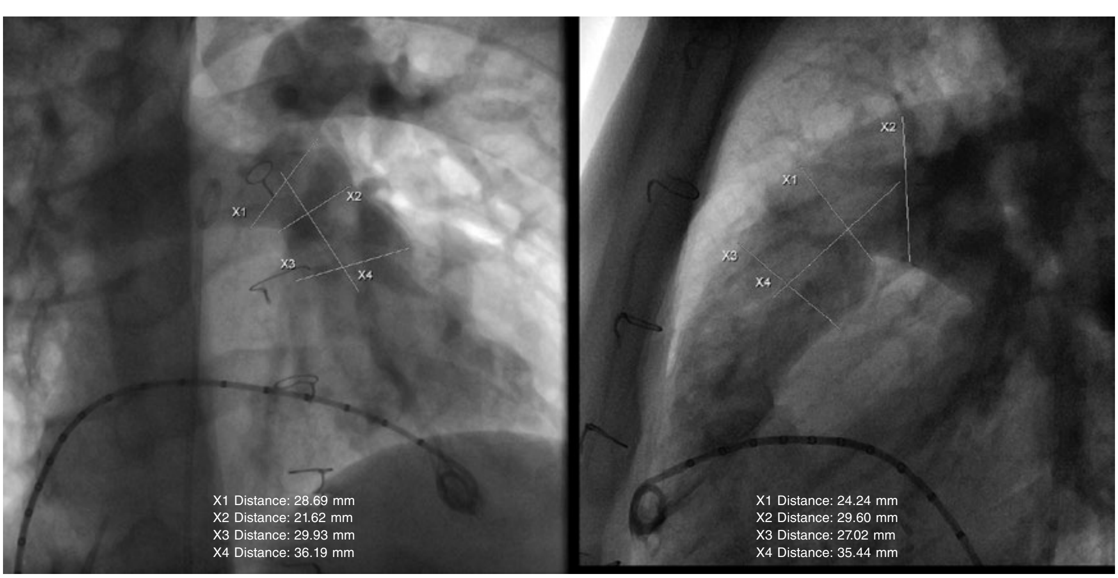

Figure 2. Pulmonary angiogram showing measurements during the pre-implantation assessment.

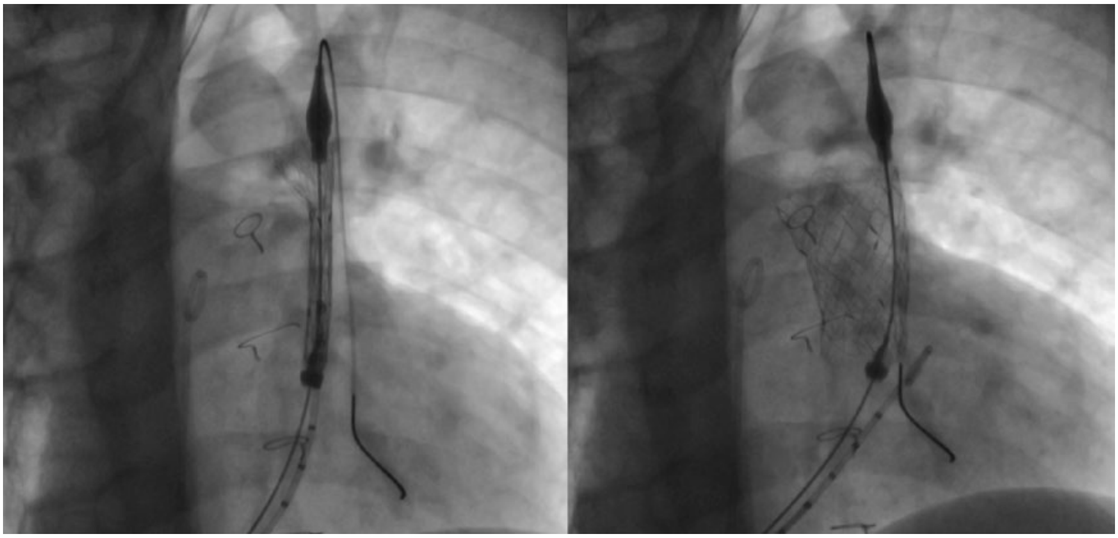

Figure 3. Sequence illustrating the gradual release of the valve inside the pulmonary trunk.

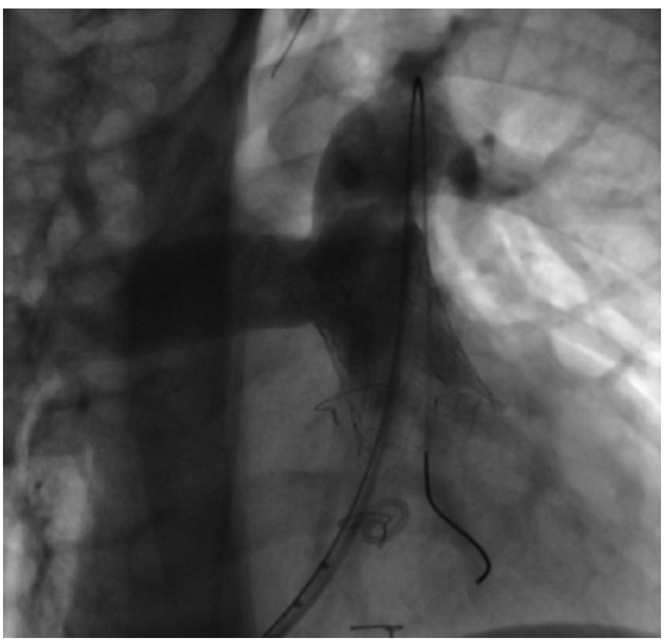

Figure 4. Final angiogram showing the valve implanted in the pulmonary trunk and absence of pulmonary regurgitation.

While mounted on the delivery system, the selected valve is moved toward the pulmonary trunk, its position is angiographically confirmed in the region of interest, and its cover is carefully removed (figure 3; videos 1 and 2 of the supplementary data). Correct positioning is facilitated by radiopaque markers. Once implanted, new measurements of right-sided pressures and a final pulmonary angiogram with a pigtail catheter in the same views are obtained to confirm the proper functioning of the valve (figure 4; video 3 of the supplementary data).

The procedure was considered successful when the device of the previously selected size was implanted, no acute complications occurred requiring removal such as coronary compression, or migration, and the final angiogram showed trivial or no pulmonary regurgitation.

The Perclose Pro-Glide system (Abbott, United States) was used to close the vascular access es through which the delivery system sheath was advanced. Simple compression was applied to all the remaining accesses.

Statistical analysis

In the descriptive analysis, continuous variables are expressed as mean ± standard deviation, or range, and categorical variables as frequencies and percentages. An exact permutation test was used to compare the variables at baseline and at 6 months after valve implantation. The analyses were performed using the STATA software package, version 17.0 (StataCorp-LLC, United States).

RESULTS

All 10 included patients met the inclusion criteria and received a PULSTA pulmonary valve in 1 of the 3 participating Spanish centers (Hospital Universitario La Paz, 6 patients; Hospital Universitario Gregorio Marañón, 3 patients; Hospital Universitario 12 de Octubre, 1 patient) from December 2019 through November 2022. Table 2 illustrates the participants' baseline characteristics. The mean age and weight were 15 ± 2.8 (range, 13-23) years and 55.2 ± 19.5 (range, 30-87.8) kg, respectively. Eight of these patients (80%) were men. In most cases (80%), pulmonary regurgitation was secondary to transannular repair due to Tetralogy of Fallot, with 2 cases being due to pulmonary valve stenosis (1 associated with supravalvular pulmonary stenosis) that also required transannular RVOT enlargement. Two patients showed heart disease in a syndromic context: 1 had trisomy 21 and Tetralogy of Fallot, and the other had Noonan syndrome and pulmonary valve stenosis.

According to the CMR, the mean right ventricular volumes were 131.7 ± 31.7 mL/m^2 (end-diastolic) and 68 ± 20.8 mL/m^2 (end-systolic), and the mean right ventricular ejection fraction (RVEF) was 49% (range, 40% to 60%). The mean pulmonary regurgitant fraction was 46% (range, 35.6% to 70%). The mean maximal oxygen consumption was 32.1 ± 7.7 mL/kg/min, and 4 of the 5 patients who underwent ergospirometry showed oxygen consumption < 80% of the expected level for their age and weight.

Table 2. Patients' baseline characteristics

Patient	Sex	Age (years)	Weight (kg)	Diagnosis	Valve indication	FC	Echo PR	CMR data				VO_2 peak (mL/kg/min)	% VO_2 theoretical peak
								RV EDV (mLm²)	RV ESV (mLm²)	RVEF (%)	PRF (%)		
1	M	16	59.3	T. Fallot	PR + RV dilatation	I	Severe	158.7	83.1	47.7	44.9	32.1	68
2	M	16	49.3	T. Fallot	PR + clinical signs	II	Severe	100.8	60.5	40	42.3	21.3	49
3	M	14	37.5	T. Fallot	PR + RV dilatation	I	Severe	166	97	41.7	70	38.9	80
4	M	13	30	T. Fallot (Down Sd.)	PR + clinical signs	II	Severe	126.6	60.7	52.03	40.9	-	-
5	M	14	56.4	Valvular and supravalvular PS	PR + clinical signs	II	Severe	83.3	36.8	55.8	35.6	39.8	69
6	W	14	87.8	T. Fallot	PR + clinical signs	II	Severe	108	43	60	36	28.4	100
7	W	15	47	Valvular PS (Noonan Sd.)	PR + RV dilatation	I	Severe	115	-	53	47	-	-
8	M	13	35	T. Fallot	PR + RV dilatation	I	Severe	165.7	93.9	43	47	-	-
9	M	15	67.5	T. Fallot	PR + RV dilatation	I	Severe	120	69.8	42	51	-	-
10	M	23	82	T. Fallot	PR + RV dilatation	I	Severe	173	67	55	45	-	-

CMR, cardiac magnetic resonance; echo PR, echocardiographic assessment of pulmonary regurgitation; EDV, end-diastolic volume; FC, functional class; M, man; PR, pulmonary regurgitation; PRF, pulmonary regurgitation fraction; PS, pulmonary stenosis; RV, right ventricle; RVEF, right ventricular ejection fraction; Sd, syndrome; T, tetralogy; VO_2: oxygen volume; W, woman.

Table 3 illustrates the hemodynamic and angiographic measurements and procedural data. None of the patients had significant residual RVOT stenosis, although an AndraStent 30 XL stent (Andramed, Germany) had been previously implanted in the left pulmonary artery in 1 patient due to stenosis. The mean RVOT-pulmonary artery pressure gradient was 7.2 ± 4.7 mmHg. Valve size was 26 mm in 1 patient, 28 mm in 2 patients, 30 mm in 6 patients, and 32 mm in 1 patient. In 1 patient, the valve was placed inside a stent previously implanted in the RVOT (CP 10 ZIG 50 mm stent, NuMED, United States) and was dilated with a high-pressure balloon up to 30 mm. In all patients, implantation was performed via femoral vascular access. The mean procedural and fluoroscopy times were 165 (range, 122 to 233) minutes and 30 (range, 18 to 50) minutes. All valves were successfully implanted with no acute complications during the procedure. The pulmonary regurgitation seen on the final angiogram was trivial or nonexistent.

Four patients (40%) experienced adverse events after implantation: 2 developed chest pain the evening following the procedure. In both patients, an ECG was performed showing no changes compared with the baseline values (both showed repolarization changes in precordial leads due to pre-existing right bundle branch block), preserved biventricular function without segmental contractility alterations and no pericardial effusion. Thoracic computed tomography ruled out the presence of coronary compression, and the blood test results showed no elevation of troponin levels. Pain subsided with standard analgesia (IV metamizole), and the patients remained asymptomatic. A third patient developed monomorphic ventricular extrasystoles without clinical repercussions a few hours after the procedure, and treatment with atenolol was initiated, resulting in good control. Treatment was discontinued at 6 months, with no recurrence of extrasystoles. The fourth patient experienced self-limiting mild hemoptysis that required no treatment. All patients were discharged 24 to 72 hours after the procedure on antiplatelet doses of aspirin.

Follow-up data after implantation are shown in table 4. The median length of follow-up after the procedure was 18 (range, 2-35) months. Eight out of the 10 participants underwent a follow-up CMR at 6 months that showed reduced mean end-diastolic (131.7 ± 31.7 mL/m^2 before vs 100.3 ± 28.9 mL/m^2 at 6 months) and end-systolic volumes (68 ± 20.8 mL/m^2 before vs 57 ± 18.5 mL/m^2 at 6 months). However, this reduction was not statistically significant (P = .065 and P = .49, respectively).

The 6-month follow-up ECG revealed moderate intraprosthetic pulmonary regurgitation suggestive of valve dysfunction in 1 patient. This finding was later confirmed by a CMR showing a 32.7% regurgitant fraction (compared with the 70% found prior to valve implantation). Since the patient remained asymptomatic and right ventricular volumes had reduced, a wait-and-see approach was adopted. In this patient, pulmonary regurgitation remained moderate 33 months after implantation. Among the remaining patients, 6 showed no pulmonary regurgitation and 3 showed mild regurgitationin the last follow-up ECG. Three out of the 4 patients with exercise deterioration improved to functional class I, and 1 remained in functional class II.

None of the patients died during follow-up, and there were no serious device malfunctions requiring replacement. Although stent fractures were unlikely due to the relatively short follow-up and design of the valve that used a nitinol mesh with interlacing cells rather than welding, making it more resistant to this complication, chest x-rays were obtained from 8 patients 6 months after implantation. No abnormalities were found. No cases of infective endocarditis or ventricular arrhythmias were reported beyond the immediate postoperative period.

DISCUSSION

In our series of patients with a history of right sided obstructive congenital heart disease and pulmonary regurgitation in the native RVOT, the initial results with the PULSTA valve are promising.

Table 3. Hemodynamic and angiographic measurements and procedural data

Patient	Initial angio PR	Initial PG RV-PA (mmHg)	Previous stents	PT measurement (mm)	Measurement cutting balloon (mm)	PULSTA valve size (mm)	Proc t (min)	Fluoro t (min)	Final angio PR	Final PG RV-PA (mmHg)	Post echo PR
1	Severe	14	No	26.6	26	30	145	22	No	0	No
2	Severe	0	AndraStent 30 XL in RPB	23	28	28	135	18	No	6	No
3	Severe	3	No	30	25	30	140	28	Trivial	2	Mild
4	Severe	12	No	30.1	27.5	28	195	40	Trivial	7	No
5	Severe	9	No	27.6	24	30	170	24	No	6	No
6	Severe	8	CP 10 ZIG 50 mm in PT	26	28	30	160	29	No	6	No
7	Severe	7	No	31	24.5	30	159	50	No	2	No
8	Severe	10	No	26	18.6	26	122	26	No	4	No
9	Severe	2	No	27	25	32	233	37	No	3	No
10	Severe	0	No	29	30	30	195	28	Trivial	5	Mild

angio PR, angiographic assessment of pulmonary regurgitation; fluoro t, fluoroscopy time; PG RV-PA, peak pressure gradient right ventricle-pulmonary artery (invasive measurement); post echo PR, pulmonary regurgitation in the first ECG after the procedure; proc T, procedural time; PT, pulmonary trunk.

Table 4. Follow-up data

Patient	Foll t (months)	RV EDV (mL/m^2)		RV ESV (mL/m^2)		FC		Last echo PR	Last echo PF RV-PA (mmHg)	Complications
		Pre	Post	Pre	Post	Pre	Post			
1	26	158.7	102	83.1	57.9	I	I	No	12	Self-limiting chest pain
2	35	100.8	74.7	60.5	41.2	II	I	No	15	No
3	33	166	125.8	97	78.7	I	I	Moderate	15	Self-limiting chest pain
4	25	126.6	80	37	37	II	I	Mild	11	No
5	12	83.3	70.5	36.8	37.9	II	I	No	11	No
6	3	108		43		II	II	No	13	No
7	25	115	81			I	I	No	14	Self-limiting mild hemoptysis
8	6	165.7	151.1	93.9	74.5	I	I	Mild	14	Ventricular extrasystole treated with atenolol
9	9	120	117.2	69.8	73.3	I	I	No	15	No
10	2	173		67		I	I	Mild	-	No

EDV, end-diastolic volume; ESV, end-systolic volume; FC, functional class; foll t, follow-up time; PG RV-PA, peak pressure gradient right ventricle-pulmonary artery; PR, pulmonary regurgitation; RV, right ventricle.

The implantation success rate was 100%, there were no serious acute complications, and right ventricular volumes decreased on CMR 6 months after the procedure.

Two patients experienced nonspecific chest pain a few hours after implantation, with no signs of coronary compression, ECG changes or elevated troponin levels. In both patients, the chest pain was resolved with standard analgesia This symptom has already been reported in previous series,[9-11] and is attributed to device-induced distension of the pulmonary arterial wall.

One patient developed moderate intraprosthetic pulmonary regurgitation 6 months after implantation but has remained stable ever since without symptoms or right ventricular dilatation on imaging modalities. No previous series have reported the development of significant pulmonary regurgitation during follow-up,[9-11] highlighting the need for further studies with a larger number of patients and longer follow-up periods to assess the durability of the PULSTA valve.

Pulmonary regurgitation is a common residual lesion in patients undergoing surgery for right heart obstructive lesions, with long-term effects on right ventricular function and exercise capacity.[12] Although balloon-expandable pulmonary valves have yielded good international results, patients with large native RVOTs have historically been excluded from PPVI.[13] To address this limitation, several large-diameter self-expandable pulmonary valves, including the PULSTA, are currently in the pipeline.

The Venus P-Valve (Venus Medtech, China) is another self-expandable pulmonary valve designed for native RVOTs and already has the CE marking. Initial series have reported high implantation success rates and good short- and mid-term results,[14-16] similar to the PULSTA valve. The advantage of both devices is that they can be implanted in a single procedure after the initial diagnostic assessment because they do not require previous stent implantation to create a scaffold for valve implantation, as is the case with balloon-expandable valves. In our opinion, the PULSTA valve is particularly suitable for the pediatric population due to its slightly smaller profile (maximum length, 38 mm), which facilitates navigation and implantation in the curved anatomy of the RVOT, and smaller delivery system (18-Fr or 20-Fr compared with the 22-Fr or 24-Fr of the Venus P-Valve), which reduces the risk of vascular injury in smaller patients. However, there are currently no studies that compare the 2 self-expandable valves.

Limitations

The main limitations of this study are its small sample size and relatively short follow-up, limiting its statistical power and ability to detect rare adverse events, or long-term occurrences. Possible sex and gender variables in accordance with the SAGER guidelines have also not been taken into account.

CONCLUSIONS

Based on our initial experience, the PULSTA valve is a feasible, safe, and effective alternative to PPVI in most patients with dilated native RVOTs who would have otherwise required surgery. However, more studies are needed to evaluate its long-term durability and safety profile since the current follow-up data are still limited.

FUNDING

Eight out of the 10 study participants are enrolled in the PULSTA transcatheter pulmonary valve pre-approval study (registration no. NCT03983512) funded by Taewoong Medical (South Korea).

ETHICAL CONSIDERATIONS

The Ethics Committees of La Paz and Gregorio Marañón Hospitals approved the inclusion of patients in the study. Informed consents were obtained from the patients after receiving information adapted to their age, and from the parents in those cases under 18 years of age.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used for the development of this study or writing of the manuscript.

AUTHORS' CONTRIBUTIONS

All the authors participated in the treatment and follow-up of the included patients. D. Salas-Mera, A. Sobrino, and F. Sarnago collected data from each participating center. D. Salas-Mera, E. Balbacid, C. Abelleira, and F. Gutiérrez-Larraya analyzed the data and drafted the manuscript. All authors participated in the data interpretation, critical review process, and final approval of the manuscript.

CONFLICTS OF INTEREST

D. Salas-Mera, C. Abelleira, E. Balbacid, A. Sobrino, J.L. Zunzunegui, and F. Gutiérrez-Larraya are participating investigators in the international and multicenter PULSTA transcatheter pulmonary valve pre-approval study. The remaining authors declare no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- Pulmonary regurgitation is a common residual lesion after the surgical repair of congenital heart diseases involving obstructive lesions of the right ventricular outflow tract. Despite successful international experiences with balloon-expandable valves for percutaneous pulmonary valve replacement, the native outflow tract often dilates beyond the maximum diameters allowed by these valves. To enable percutaneous valve implantation in these cases, a new generation of self-expanding valves is currently in the pipeline.

WHAT DOES THIS STUDY ADD?

- We report the first series of patients who received the PULSTA self-expanding pulmonary valve in Spain. The good initial results in terms of safety and efficacy make it an attractive option for percutaneous pulmonary valve implantation in patients with pulmonary regurgitation and dilated native right ventricular outflow tracts.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000402.

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Original article

Cardiac catheterization activity in pediatric cardiac transplantation. Can catheterization needs be predicted?

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ABSTRACT

Introduction and objectives: Although cardiac catheterization (CC) has become a routine practice in pediatric heart transplantation (HT), there is still a shortage of widely used protocols and strong evidence on the number of procedures required and their impact on HT outcomes, as well as the need for further CC. This study aimed to analyze CC activity in pediatric HT recipients in a tertiary center and describe risk factors for a higher number of post-HT procedures.
Methods**:** This retrospective study obtained data from medical reports and image files. The sample was composed of patients with cardiomyopathies and congenital heart diseases (CHD). Risk factor analysis for CCs was conducted with linear regression and the ANOVA test.
Results**:** The sample included 61 children (36.07% with CHD). The CHD group had a higher mean number of CCs prior to HT. The most frequent activities prior to HT were diagnostic catheterizations, followed by endomyocardial biopsies for cardiomyopathies and aortopulmonary collaterals in CHD patients. There were 389 post-HT CCs (608 procedures). Most CCs were performed for rejection surveillance, accounting for 92.75% of procedures. The univentricular CHD subgroup was associated with a higher number of CC after HT ($P = .03$).
Conclusions**:** Despite long life expectancy, pediatric HT recipients have substantial morbidity due to these procedures. Therefore, it is necessary to establish protocols for follow-up and rejection surveillance to minimize the interventions required by these patients.

Keywords: Pediatric heart transplantation. Cardiac catheterization. Graft rejection. Endomyocardial biopsy.

Actividad de hemodinámica cardiaca en trasplante cardiaco pediátrico. ¿Es posible predecir las necesidades de cateterismo?

RESUMEN

Introducción y objetivos: A pesar de que el cateterismo cardiaco (CC) se ha convertido en una práctica habitual en el trasplante cardiaco (TxC) pediátrico, hay escasez de protocolos globales y de evidencia robusta sobre los procedimientos requeridos y el impacto que tienen en la evolución del propio trasplante y los futuros CC. Este estudio tiene como objetivo analizar la actividad de CC en niños receptores de trasplante cardiaco en un centro terciario y describir los factores de riesgo para un mayor número de procedimientos.
Métodos: Estudio retrospectivo con datos obtenidos de los informes médicos y los archivos de hemodinámica. La muestra se dividió en miocardiopatías y cardiopatías congénitas (CAC). El análisis de los factores de riesgo para CC se calculó con regresión lineal y ANOVA.
Resultados: Conformaron la muestra 61 niños (36,07% CAC). Las CAC muestran una mayor media de CC antes del TC. Los cateterismos diagnósticos son la actividad más frecuente previa al TxC, seguidos por las biopsias endomiocárdicas en las miocardiopatías y el cierre de colaterales aortopulmonares en las CAC. Hubo 389 CC tras el TC (608 procedimientos), la mayoría (92,75%) por vigilancia del rechazo. El subgrupo de CAC univentriculares tuvo significativamente un mayor número de CC tras el TxC (p = 0,03).
Conclusiones: A pesar de su larga expectativa de vida, los niños receptores de TxC sufren una morbilidad importante debido a los CC, por lo que es necesario establecer protocolos de seguimiento y vigilancia del rechazo para minimizar las intervenciones que necesitarán.

Palabras clave: Trasplante cardiaco pediátrico. Cateterismo cardiaco. Rechazo injerto. Biopsia endomiocárdica.

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Abbreviations

CC: cardiac catheterization. **CHD:** congenital heart disease. **EMB:** endomyocardial biopsy. **HT:** heart transplant. **IVUS:** intravascular ultrasound.

INTRODUCTION

Heart transplant (HT) in children is an uncommon but complex procedure that entails close chronic monitoring. HT involves not only major surgery and challenging postsurgical recovery but also requires lifelong rejection surveillance and review of anastomosis or surgical complications. The latter can be assessed through cardiac catheterization (CC) studies, which have become an indispensable practice in HT follow-up.

Some authors have studied whether the underlying disease can influence the course of post-HT surgery. Although the literature reports discrepant controversial results, it is generally observed that patients with congenital heart diseases (CHD) have higher rates of post-HT procedures regardless of the number of previous CCs. This could be because diagnostic procedures are rare in pediatrics, and therefore, the therapeutic catheterizations reported were mainly performed in patients with congenital disease. It is also well-known that younger recipients (especially if aged < 1 year) and those with hypoplastic left heart syndrome (HLHS) require a larger number of interventions.[1-3]

Globally, endomyocardial biopsy (EMB) is the most frequently performed diagnostic procedure. EMB is the gold standard test for diagnosing rejection, as noninvasive tests are not currently available. Coronary angiography allows monitoring for coronary allograft vasculopathy (CAV), which is a marker of chronic rejection, the leading cause of death beyond the third year post-HT. Coronary intravascular ultrasound (IVUS) is an advanced complementary tool for the detection and grading of CAV.[4,5]

Reported interventions after HT mainly include the treatment of aortic arch and systemic vein connection to right atrium stenosis. The latter is mainly associated with lower weight, a greater donor-recipient size discrepancy, and more frequent complex anatomies.[6,7]

Other indications for CC include haemodynamic assessment for congestive symptoms and diagnosis of pulmonary hypertension, which are of the utmost importance as they are markers of the need for retransplantation.[8,9]

Due to the rarity of pediatric HT, most centers are developing protocols for the frequency at which these CCs should be performed and how the technique should be applied, with the aim of establishing common practice and achieving better results. Therefore, knowledge of the procedures performed is essential.

The objective of the present study was, in first instance, to determine CC activity after pediatric HT and, second, to study the risk factors for higher post-HT CC requirements, based on the medical history and previous procedures.

METHODS

This retrospective study included all pediatric HT recipients aged < 18 years at the time of HT who underwent at least 1 post-HT CC in a university tertiary hospital from 2002 to 2021. The study was approved by the local ethics committee, with consent form exemption, and was performed in accordance with the principles of the Declaration of Helsinki.

The data reviewed include patients' medical history on previous CCs and surgical interventions, demographic information, and complications during the HT surgery. For all post-HT CCs, we collected data on the material used, timing, specific procedures, and diagnoses for each participant. Due to differences in their presentation and progression, patients with cardiomyopathies and CHD were analyzed separately in some of the analyses. A procedure was defined as any intervention/technique performed, while each visit to the catheterization laboratory was considered a separate CC.

Given the retrospective nature of the study and the patient age group, the patients' gender was extracted from the documented sex assigned at birth or from their medical history.

Qualitative data are expressed as percentages, while the mean and standard deviation (SD), or median and interquartile range (IQR) are used for quantitative variables. Differences were analyzed by the Fisher, Chi-square, Mann-Withney U or T-students tests, depending on the type of variable. Risk factors for increased post-HT requirements were examined using linear regression or ANOVA tests. Statistical significance was set at $P < .05$.

The number of CCs required for each patient followed the protocol established by the Pediatric Cardiology Unit. This protocol mandates EMB at specific time points: 10 to 14 days after HT, at 1, 3, 6, 12, and 24 months post-HT, and subsequently every 2 years. Additional CCs are performed if rejection is suspected. If rejection is confirmed (grades ≥ 2 cellular and ≥ 1 humoral), a follow-up EMB is performed 2 weeks later, following appropriate treatment. The EMB samples are obtained from the right side of the interventricular septum using a 6-French bioptome, via the right jugular vein. Coronary angiography is routinely performed in the first 3 to 6 months, and subsequently every 2 years together with EMB. Coronary intravascular ultrasound (IVUS) is carried out in the anterior descending artery and is associated with coronary angiography in patients weighing > 20 kg. Pathological findings are defined as intimal layer measurements ≥ 0.5 mm.

RESULTS

Demographic and heart transplant data

A total of 61 participants were included, of whom 37 (60.66 %) were boys. The underlying disease was CHD in 22 patients (36.07%) and cardiomyopathy in 39 (64.93%). Five participants (8.20%) were categorized as having hypoplastic left heart syndrome (HLHS). All patients with CHD had undergone at least 1 cardiac surgical intervention before HT.

The mean age at HT was 96.24 ± 89.47 months, with no differences between groups. A higher proportion of the CHD group required

Table 1. Demographic and heart transplant data

Demographic and heart transplant variables	Total	Cardiomyopathy	Congenital heart disease	*P*
Number of patients	61	39	22	
Male sex	37 (60.66)	23 (58.97)	14 (63.64)	.403
Patients with 1 previous cardiac surgical intervention	27 (44.26)	25 (64.10)	2 (10)	.029*
Patients with 2 previous cardiac surgical interventions	18 (29.51)	0 (0)	18 (81.81)	< .001*
Univentricular physiology	10 (16.39)	0 (0)	10 (50)	< .001*
Hypoplastic left heart syndrome	5 (8.20)	0 (0)	5 (22.73)	.02*
Patients with cyanosis	9 (14.75)	0 (0)	9 (45)	< .001*
Pulmonary hypertension	17 (27.87)	7 (17.95)	10 (50)	.377
Number of treatments for pulmonary hypertension	0 (0)	0 (0)	1.5 (0-4)	.075
Age (months) at transplant	74.00 (20.00-168.00)	72.00 (20.00-127.00)	77.50 (24.25-169.50)	.440
Weight (kg) at transplant	31 (11.80-45.00)	22.00 (10.85-40.50)	35.00 (17.50-56.00)	.067
Patients requiring posttransplant ECLS	12 (19.67)	4 (10.26)	8 (40)	.005*
PICU days after transplant	15.5 (10.75-30)	14.00 (9.75-24.50)	26.50 (12.75-76.25)	.035*

ECLS, extracorporeal life support; IQR, interquartile range; PHT, pulmonary hypertension; PICU, pediatric intensive care unit.
Qualitative data are expressed as absolute number and percentage and quantitative variables as the median and interquartile range.
* Statistical significance for the student t or chi-square tests.

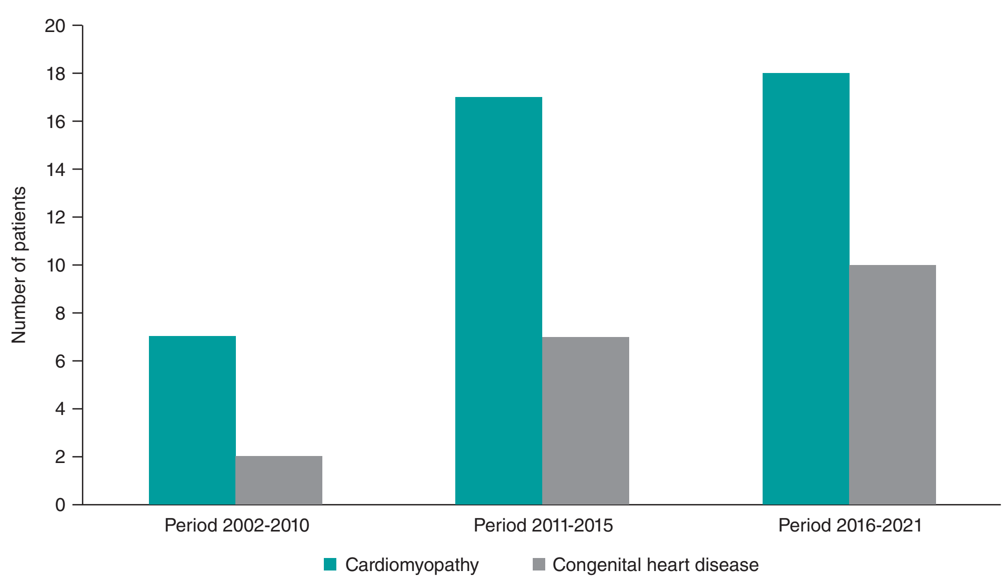

Figure 1. Distribution of underlying heart disease over time periods.

extracorporeal life support (ECLS) after HT than the cardiomyopathy group (40.00% vs 10.26%; $P = .005$) and had longer admissions to the pediatric intensive care unit (PICU). In both groups, New York Heart Association functional class before HT remained between grades 3 and 4.

Dividing the study years in time periods (2002-2015, 2016-2021) revealed that the number of HT recipients increased over the years. Although cardiomyopathy was the most common underlying disorder in all time groups, patients with CHD showed a nonstatistically significant increase, representing 22.23% of patients in the first period, and 35.71% in the final 5-year period ($P = .722$). See table 1 and figure 1 for further demographic and transplant data.

Cardiac catheterizations performed prior to heart transplant

The number of patients with at least 1 CC did not differ between the CHD and cardiomyopathy groups ($P = .07$). However, the mean number of previous CCs was significantly higher in patients with CHD (P = .014). CC was mainly performed for diagnostic purposes in the cardiomyopathy group (45.00%), followed by EMB (16.70%) and by atrioseptostomy with stent for left cavity unloading in ECLS (15%). There were 8 coronary angiograms and 1 IVUS, as well as 2 coronary balloon angioplasties and 3 coronary angioplasties with stent, in OM1 and circumflex arteries. The coronary angiography-related procedures were performed in a single patient, who had previously undergone HT.

In the CHD group, CCs were mostly performed for diagnostic purposes, accounting for 57.30% of the procedures, followed by major aortopulmonary collateral closure (11.0% of the activity), and by pulmonary artery angioplasty with stent (10.26%).

A higher percentage of diagnostic procedures were unrelated to rejection surveillance in the CHD group but this difference was not statistically significant. Nonetheless, there was a significantly higher predominance of rejection surveillance in the cardiomyopathy group (57.3% CHD vs 75.0% cardiomyopathy).

When we divided the study in 2 time periods, 2002 to 2014 and 2015 to 2021, there was a median of 0 [IQR, 0-2] procedures per person in the first period, and 2 [IQR, 0-3.25] in the recent period, showing a tendency to nonsignificant growth in activity (see table 2 for further information).

Table 2. Data on pretransplant cardiac catheterizations

Pretransplant procedures	Cardiomyopathy (n = 39)	Congenital heart disease (n = 22)	*P*
Patients with previous CC	17 (43.59%)	18 (81.82%)	.282*
1 CC	12	6	0
2 CC	2	1	0
3 CC	2	5	0
4 CC	1	1	0
5 or more CC	0	5	0
CC per person; median (IQR)	0 (0-1)	2.5 (1-3.75)	.014*
Number of previous procedures	60	82	0
Number of therapeutic interventional procedures (n)	15	35	0
Balloon atrioseptostomy	2	0	0
Atrioseptostomy with stent	5	3	0
Coronary angioplasty with stent	3	0	0
Interatrial stent redilatation	2	0	0
Balloon coronary angioplasty	2	0	0
IVUS	1	0	0
Collateral artery closure	0	9	0
Pulmonary branch angioplasty with stent	0	9	0
Cavopulmonary anastomosis balloon angioplasty	0	2	0
Cavopulmonary anastomosis angioplasty with stent	0	1	0
Aortic valvuloplasty	0	3	0
Ventricular septal defect closure	0	2	0
Coronary fistula embolization	0	2	0
Pulmonary trunk angioplasty with stent	0	1	0
Superior cava vein balloon angioplasty	0	1	0
Iliac stent dilatation (previous migration)	0	1	0
Fontan fenestration (failure)	0	1	0
Diagnostic procedures (percentage of total procedures)	45 (75.0%)	47 (57.3%)	.029*
Coronary angiography	8	4	0
Endomyocardial biopsy	10	0	0
Diagnostic catheterization	27 (45.0%)	43 (52.4%)	.380

CC, cardiac catheterization; ECLS, extracorporeal life support; IVUS, intravascular ultrasound.
Qualitative data are expressed as absolute numbers and percentages and quantitative variables as median the and interquartile range.
* Statistical significance.

Postheart transplant surgery cardiac catheterization

After the HT surgery, a total of 389 CC were obtained, corresponding to 608 procedures. The mean number of procedures per CC was 1.37 ± 0.83. The mean number of CCs per person was 6.71 ± 4.13.

The median number of procedures per person was 13 [IQR, 9-17] in the first period (2002-2015), which decreases to 8 [IQR, 2-9.25] in the second period (2016-2021), given the shorter follow-up time in the latter period.

Rejection surveillance

Most CCs were performed for rejection surveillance: EMBs represented 63.10% of post-HT activity, coronary angiograms up to 18.29%, and IVUS 11.53%. The proportion of rejection surveillance studies was significantly higher in patients with cardiomyopathy than in those with CHD. EMB was positive in 7.39% of cases for cellular rejection, and in 3.17% for humoral rejection. Up to 9.40% of EMB were follow-up EMBs secondary to rejection found in a previous CC.

CAV was diagnosed in 6.71% of coronary angiograms. The most frequently involved coronary artery was the anterior descending artery, found in the 36% of positive studies, followed by the left ostium, circumflex and ramus intermedius, with 14% each. No differences were found between baseline heart disease groups, with cardiomyopathy having a positivity index of 29.07% and CHD 16.67%.

Among patients undergoing IVUS (n = 70), 31.43% met the criteria for positivity.

No differences were found in the positivity index depending on the baseline heart disease, with 29.07% in the cardiomyopathy group and 13.33% in the CHD group being positive.

The mean time to CAV diagnosis was 37.1 [IQR, 13-47.5] months after HT, corresponding to the fourth to 13th CC.

Interventional procedures

The most common techniques were superior cava vein and pulmonary artery balloon angioplasties, each representing 20.45% of the interventional procedures and corresponding to 18.03% (n = 11) of the patients for the superior cava vein and to 4 patients for the pulmonary arteries.

Cava vein angioplasty was performed at a median time of 2.5 [IQR, 0.75-6] months, and 6 (40%) of the procedures took place within the first 2 months after HT.

Diagnosis of stenosis was secondary to clinical symptoms in the superior cava vein in 2 patients and pericardial effusion in 1 patient. In 1 patient, signs of congestive hepatopathy led to the diagnosis of inferior cava vein stenosis. The remaining indications were driven by echocardiographic findings or observation during biopsy. Patients who underwent superior cava vein angioplasty, either with a balloon or with a stent, showed a tendency to lower mean age (63.6 vs 90.6 months) and weight at HT and higher discrepancies in weight ratios, but without statistically significant differences (P values .233, .243 and .605, respectively). This group did not have a higher number of previous surgical interventions (P = .460) or higher ECLS requirements (P = .253). We did not observe a higher proportion of patients with CHD in the cava stenosis group (P = .221). Three patients underwent more than 1 angioplasty due to restenosis.

Pulmonary angioplasty, either with a balloon or stent, was required mainly at the pulmonary branches. The median time from transplant to pulmonary angioplasty was 4 [IQR, 2-26] months, and 3 of them were performed during the first 2 months after surgery.

Coronary treatments were required only twice, one consisting of angioplasty with stent implantation, and the other in a thrombolysis.

Pulmonary artery angioplasty, whether with balloon (P < .001) or stent (P = .011), superior cava vein angioplasty with stent (P = .038), and right ventricle-to-pulmonary artery tube angioplasty (P = .037) were more frequent in CHD patients (see table 3 and figure 2 for a detailed description).

Generalities

The mean CC duration was 64.65 ± 38.02 minutes. When participants were divided into 2 periods (2002-2015 and 2016-2021), there were a significantly (P < .001) higher number of procedures per person in the first period, with a mean of 12.67 ± 7.55, than in the second period, with a mean of 6.54 ± 4.05.

Complications, both systemic and local and of all degrees severity, occurred in 2.80% of the total number of CCs. Systemic complications consisted of 1 ST-segment depression at initiation of the procedure that spontaneously disappeared, atrial flutter unresponsive to atrial overstimulation but that reverted with electrical cardioversion, 1 bronchospasm with anesthetic induction requiring PICU admission for elective extubation (performed after 24 hours), 2 right coronary spasms that reverted with nitroglycerine, a second and a third degree temporary atrioventricular blockage, which required a dose of epinephrine, 1 pulmonary hypertension crisis treated effectively in the catheterization laboratory, 1 moderate tricuspid valve regurgitation, and 1 posterior reversible encephalopathy syndrome. Local complications consisted of 1 puncture site hematoma and 1 femoral artery vasospasm.

Distribution according to time period revealed that the complication rate was 1.91% in the first period (2002-2015) and 1.64% in the second (2016-2021). ECLS-supported patients corresponded to 1.60% of the activity. In the first 6 months after HT, ECLS was being used in 47.56% of procedures (figure 3).

The mean patient follow-up was 6.48 ± 4.07 years. Survival at this point was 88.52%. No significant associations were found in the analysis of risk factors for mortality, in which we assessed the number of CCs before HT, the number of therapeutic procedures, the total number of CCs post-HT, and the number of patients who had undergone superior cava vein or pulmonary artery angioplasty.

Table 3. Posttransplant activity and comparison between underlying disease groups

Postheart transplant procedures	Total	Cardiomyopathy	Congenital heart disease	P
Superior cava vein balloon angioplasty	9	4	5	.125
Pulmonary artery balloon angioplasty	9	0	9	<.001*
Pulmonary resistance study	6	2	4	.066
Inferior cava vein balloon angioplasty	3	2	1	.957
Pulmonary artery angioplasty with stent	3	0	3	.011*
Cava vein thrombi-related procedures	3	1	2	.195
Innominate vein angioplasty	2	1	1	.582
Superior cava vein angioplasty with stent	2	0	2	.038*
Right ventricle-pulmonary artery conduit balloon angioplasty	2	0	2	.038*
Inferior cava vein angioplasty with stent	1	1	0	.493
Coronary angioplasty with stent	1	1	0	.493
Marginal coronary artery thrombolysis	1	1	0	.493
Pericardiocentesis	1	1	0	.493
Total	44	14	29	
Rejection surveillance activity				
Endomyocardial biopsy	383	255	128	.274
Coronary angiography	111	89	22	.001*
IVUS	70	55	15	.046*
TOTAL	564	399	164	

CC, cardiac catheterization; ECLS, extracorporeal life support; IVUS, intravascular ultrasound.
Qualitative data are expressed as absolute numbers and percentages and quantitative variables as the median and interquartile range.
* Statistical significance.

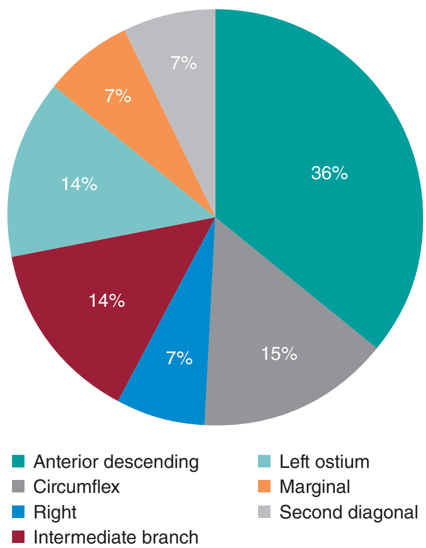

Figure 2. Distribution of the artery affected in coronary angiography.

Analysis of risk factors for greater requirement of procedures

In the analysis of factors associated with a higher number of CC procedures after HT, we found no association with the number of previous interventional procedures (P = .149) or CC (P = .059), or with having undergone at least 1 prior CC (P = .107). The subgroup with univentricular CHD required a significantly higher number of CCs after HT (P = .03). Weight and age at HT were not significantly associated with the need for subsequent CC. A greater donor-recipient weight discrepancy was not found to be a predictive factor. A higher need for interventional procedures was not associated with length of PICU stay, the number of days under mechanical ventilation, or a medical history of pulmonary hypertension or renal failure. Longer follow-up was associated with a larger number of CC procedures due to the longer amount of time studied (table 4).

DISCUSSION

In this study, we evaluated pediatric HT-related CC activity in a university tertiary hospital. There were 61 patients and 607 procedures. Most post-HT activity was performed for rejection surveillance, representing up to 92.75% of procedures. The most frequently performed procedure was EMB, followed by coronary angiography and intravascular ultrasound, which allowed diagnosis of chronic allograft vasculopathy (figure 4).

This distribution is in line with other publications. A multicenter study including almost 50 000 pediatric catheterization procedures in Philadelphia found that the most frequent HT-related diagnostic techniques were CCs, including EMB.[10]

IVUS clearly showed higher sensitivity for detecting coronary allograph vasculopathy, which is unsurprising as the technique allows a more detailed diagnosis than the imaging provided by coronary angiography. In our study, positive results were obtained in 6.71% of coronary angiograms vs 31.43% of IVUS studies. Therefore, IVUS provides a much earlier diagnosis and implementation of measures.

Rejection surveillance represented a statistically higher relative percentage of activity in patients with cardiomyopathy. This was because CHD participants also required other types of procedures secondary to previous surgical interventions or to the sequelae of

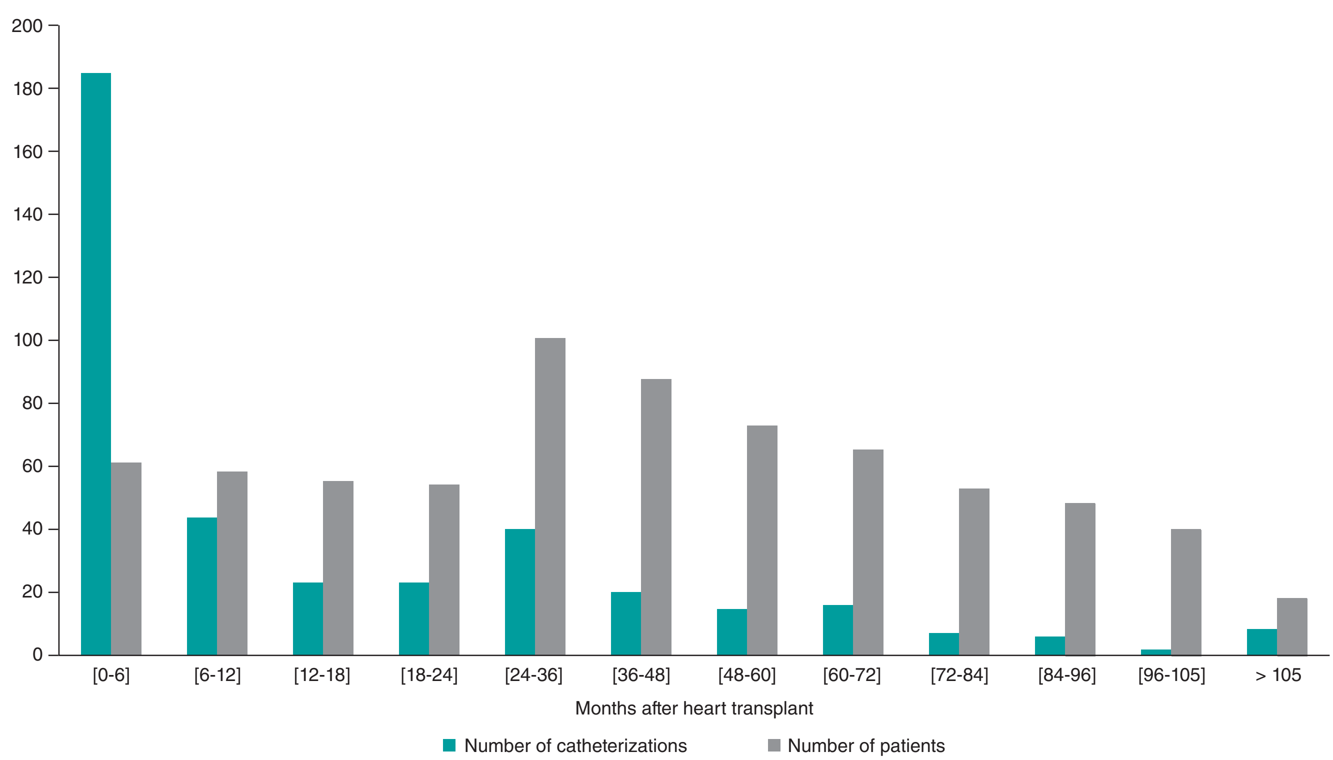

Figure 3. Variation in frequency of cardiac catheterization according to time from transplant and number of patients at follow-up.

Table 4. Study of factors associated with requirement for catheterization procedures after heart transplant

Variable	Test result	P
Type of heart disease	Mann-Whitney U test = 555.5	.142
Univentricular physiology	Kruskal Wallis test = 4.71	.030*
Previous surgery	Kruskal Wallis test = 2.52	.284
Pulmonary hypertension prior to HT	U Mann Whitney test = 281	.134
Number of pulmonary hypertension treatments	R^2 = -0.186; 95%CI, -0.419 - 0.069	.150
Number of previous cardiac catheterizations	R^2 = - 0.233; 95%CI, -0.460- 0.220	.073
Number of previous interventional procedures	R^2 = -0.19; 95%CI, -0.426 - 0.069	.149
Renal failure prior to HT	U Mann Whitney Test = 358	.755
Age at HT	R^2 = - 0.001; 95%CI, -0.388 - 0.109	.992
Weight at HT	R^2 = - 0.072; 95%CI, -0.183 - 0.318	.583
Weight differences (ratio between donor-recipient)	R2 = 0.0164; 95%CI, -5.39 - 1.93	.347
Length of stay in the pediatric intensive care unit	R^2 = 0.038; 95%CI, -0.249 - 0.319	.798
Mechanical ventilation days	R^2 = 0.140; 95%CI, -0.325 - 0.255	.348
Length of follow-up	R^2 = 0.394; 95%CI, 0.158 - 0.588	.002*

CI, confidence interval; HT, heart transplant; R^2, Pearson correlation.
* Statistical significance.

the CHD itself. An example could be the underdevelopment of pulmonary branches commonly found in cyanotic or univentricular patients with previous banding or systemic-pulmonary fistulae, which cannot be replaced in the HT surgery, or which are left untouched during the HT to shorten the surgical time and are delayed for a percutaneous approach.

Our protocol, described in the Methods section, is similar to the protocols of other centers, such as that of the Helsinki University Hospital, where they proceed to EMB at 1- to 2-weeks during the first 4 to 6 postoperative weeks in children aged > 24 months. Once the patient is discharged, EMB is performed at 3, 6, 12, 18 months and after that, on a yearly basis until the patient reaches adulthood. Coronary angiography is performed annually.[11] Although a third of their IVUS were positive for CAV, only 1 patient required coronary stenting. These results differ from data in adults, whose mature immune system plays a detrimental role.[12]

Regarding interventional catheterizations, more than half of therapeutic procedures were due to anastomosis stenosis, mainly of the superior cava vein and pulmonary arteries, predominantly at the level of the branches followed by the common trunk. Less frequently performed were inferior cava vein angioplasties and coronary treatments, including stenting and mechanical thrombectomy.

In our study, the percentage of superior cava vein obstruction accounted for 13.11% of the patients. Salavitabar et al.[5] reported a prevalence of superior cava vein obstruction in HT of 3.4%, diagnosed either clinically secondary to superior cava vein syndrome or chylous effusion, or by echocardiography. All of the patients underwent angioplasty in the first 10 months after surgery, and as many as two-thirds were performed within the first 2 months. Statistically significant risk factors for superior cava vein stenting included younger age, lower recipient weight, a history of congenital heart disease, and previous superior cavopulmonary anastomosis. In our cohort, we did not obtain statistically differences in these factors in the superior cava vein stenosis group. The authors propose measuring the pressure at the right atrium and high superior cava vein (SCV) in routine EMB in patients with these risk characteristics. In our center, right heart cavity pressures are measured in routine EMB. No cases of stent thrombosis were diagnosed in the study by Salavitar et al.[5] Their protocol includes enoxaparin for 3 to 6 months if a stent is placed. Sachdeva et al.[13] reported 5.1% of stented superior cava vein obstructions in a pediatric HT cohort, in contrast with our 13.11%. The median age at HT in these 7 patients was lower than in our cohort (9 vs 63.6 months) and their median weight was also lower (8.7 vs 10.5 kg). Despite lower rates of superior cava vein obstruction than in our cohort, the median follow-up was shorter (48 months) than in our study (see figure 4 for a summary).

Tadros et al.[14] reported an incidence of 30% of superior cava vein stenosis, of which almost 6% had to undergo intervention. Risk factors for its development were smaller weight and younger age, as well as previous cavopulmonary surgery or cava procedures.

A probable explanation for the higher proportion of superior cava vein stenosis in our study than in other reports in the literature could be the complex anatomy of most of our HT recipients, who had congenital heart disease and several previous surgical interventions, as well as anomalous venous anatomies in some cases. The initial choice between performing a bare angioplasty or implanting a stent in pediatric patients is influenced by multiple factors, rather than solely by aiming for the best final procedural outcome. These factors include the small patient and stent sizes, the need for multiple consecutive balloon dilations to accommodate the patient's growth, the high risk of pulmonary leaflet entrapment during stent implantation in the pulmonary trunk, the strong possibility of future new HTs, and the goal of avoiding stent placement in sutures, among other considerations. These factors may lead to a modification of the initial stent implantation strategy in favour of a bare angioplasty approach, if the patient's anatomy is suitable, and when there is the possibility of achieving a sufficiently good final result.

Pulmonary stenosis represented 27.27% of the interventional therapeutic activity in this work, corresponding to 4 patients (6.55%). This percentage is higher than that in the single article found in the literature, which described rates of 1.44%.[2] A probable explanation for this discrepancy is that the present study included a higher number of patients with congenital heart disease.

Coronary interventions accounted for a few cases, as reported in other studies, such as the American and Canadian Pediatric Heart Transplant Study, in which revascularization was required in 0.90% of their patients.[15]

To our knowledge, this is the first study to analyze the predisposing and associated factors for a higher number of catheterizations after HT. The antecedent of univentricular physiology was statistically significant, while, in contrast, the number of interventional procedures or catheterizations prior to HT was not. No differences were found depending on patient age or weight at HT. Worse baseline status, such as patients with pulmonary hypertension or renal failure, or perioperative complications, such as longer PICU stay or mechanical ventilation support, were not significantly associated in our study. We did not perform a multivariate analysis due to the lack of significant univariate variables.

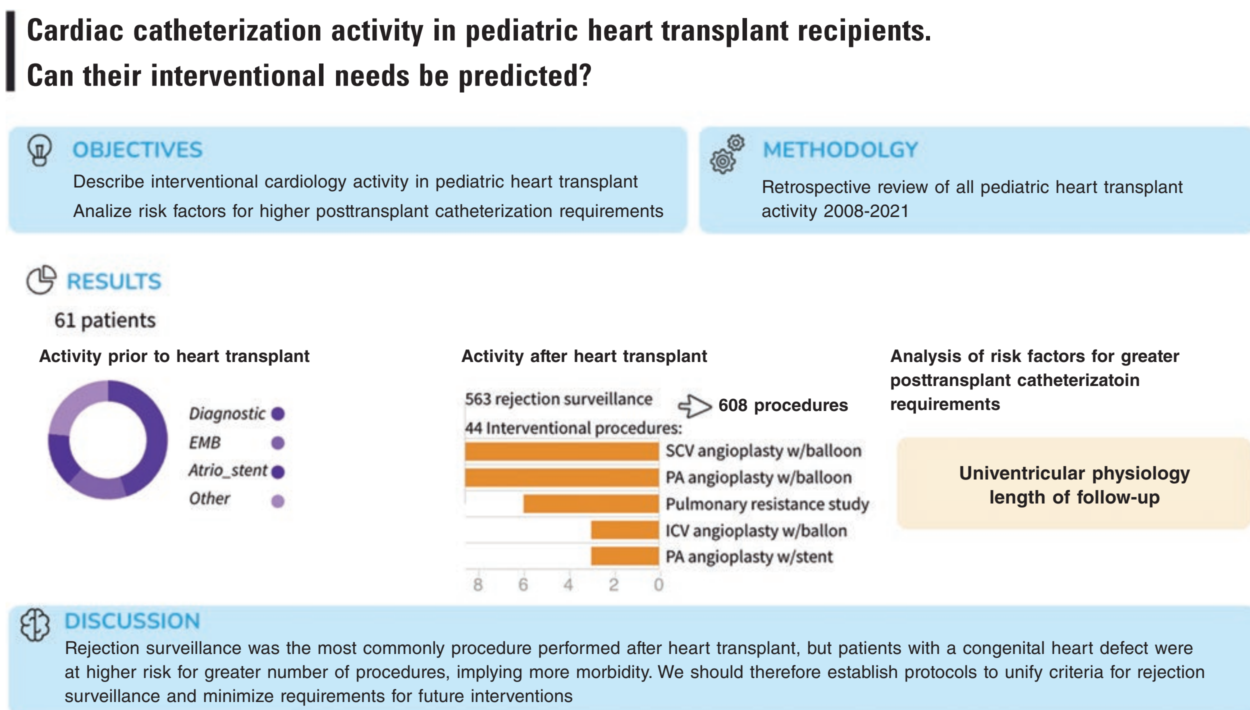

Figure 4. Central illustration. Key points of the article. Atrio_stent, interatrial stent; EMB, endomyocardial biopsy; ICV, inferior cava vein; PA, pulmonary arteries; SCV, superior cava vein.

HLHS is known to worsen the outcome of HT, as reflected in our study.[2] However, a publication by Miyamoto et al.[3] found no increased risk for pulmonary angioplasty in HLHS patients who had undergone bilateral pulmonary banding.

Limitations

The limitations of the study are those inherent to retrospective studies, although a rigorous and extensive database of the CCs performed exists in our center. Another limitation is that the study was performed in a single center and it would be advisable to obtain data in a multicenter study. Extending the follow-up time would have allowed wider and more accurate interpretation of the results, particularly regarding coronary allograph vasculopathy outcomes. In addition, further studies are needed on the risk factors than can increase the requirements for post-HT CCs. The retrospective nature of this work in a pediatric population means that gender was assigned according to that given at birth and documented in the medical history; hence we were unable to comply with the SAGER guidelines.

CONCLUSIONS

Although pediatric HT recipients have long-life expectancy, they considerable morbidity due to interventional procedures, mainly performed for rejection surveillance. Despite only finding statistical significance in univentricular physiology as an associated factor for a higher number of post-HT catheterizations, there was a tendency indicating that previous interventions and smaller patients are at higher risk.

Multicenter studies with a high volume of patients and long follow-up are needed to establish follow-up protocols for these patients.

FUNDING

No conflicts of interests or financial support are declared.

ETHICAL CONSIDERATIONS

This work was approved by the local ethics committee, with a waiver of informed consent form due to its retrospective methodology. The principles of the Declaration of Helsinki were followed throughout the study. Despite the authors agreeing with the SAGER guidelines, because of the retrospective nature of this work and its performance in a pediatric population, gender was assigned according to the sex assigned at birth and documented in the medical history.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence has been used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

A. Freixa-Benavente performed the data recollection, analysis of results and manuscript writing. P. Dolader and F. Gran participated in the conception of the study, in providing guidance, and in reviewing the manuscript. P. Betrián-Blasco led the project, made the initial proposal, conceived the original hypothesis, led the research, and reviewed and approved the manuscript and analysis.

CONFLICTS OF INTEREST

P. Betrián conducts personal advisory tasks on devices for Occlutech, not related to this work. No other conflicts of interest are declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– Pediatric HT recipients undergo a high number of CCs, involving multiple hospital admissions and significant morbidity.

– However, because HT is a rare procedure, there are a scarcity of protocols and information on how to perform rejection surveillance, which is the most common activity in the catheterization laboratory.

WHAT DOES THIS STUDY ADD?

– We provide a detailed analysis of the activity of the pediatric interventional cardiology unit in a tertiary center. Globally, the most frequently performed procedures were diagnostic catheterizations for rejection surveillance. The most frequent therapeutic interventional techniques were superior cava vein and pulmonary artery balloon angioplasties.

– Patients with univentricular physiology had a higher need for post-HT CCs, but no differences were found for other congenital diseases, age, weight, or longer intensive care unit admissions.

– There is a need to unify protocols across multiple centers.

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Special article

Diagnosis and treatment of patients with ANOCA. Consensus document of the SEC-Clinical Cardiology Association/SEC-Interventional Cardiology Association/ SEC-Ischemic Heart Disease and Acute Cardiac Care Association/SEC-Cardiovascular Imaging Association

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ABSTRACT

A substantial number of patients undergoing coronary angiography for angina or ischemia in noninvasive tests have coronary arteries without lesions or with nonsignificant stenosis. Many of these patients have nonobstructive myocardial ischemia (INOCA/ ANOCA), which is an entity with prognostic importance that significantly affects patients' quality of life. The absence of a proper diagnosis leads to inappropriate medical treatment, repeat diagnostic tests, and greater use of social and health resources. An adequate diagnostic strategy is required for individualized treatment that improves symptoms and quality of life. In this document from the SEC-Clinical Cardiology Association, SEC Interventional Cardiology Association, SEC-Ischemic Heart Disease and Acute Cardiac Care Association, and SEC-Cardiovascular Imaging Association of the Spanish Society of Cardiology, we provide simple and practical algorithms, with the aim of facilitating the early diagnosis and most appropriate treatment for patients with ANOCA.

Keywords: ANOCA. INOCA. Microvascular dysfunction. Vasospastic angina.

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Diagnóstico y tratamiento de los pacientes con ANOCA. Consenso SEC-Asociación de Cardiología Clínica/ SEC-Asociación de Cardiología Intervencionista/SEC-Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares/SEC-Asociación de Imagen Cardiaca

RESUMEN

Un número importante de aquellos pacientes en quienes se realiza coronariografía por angina o isquemia presentan en pruebas no invasivas arterias coronarias sin lesiones o con estenosis no significativas. Muchos de estos pacientes tienen isquemia miocárdica de causa no obstructiva (INOCA/ANOCA), una condición con importancia pronóstica que afecta de manera considerable la calidad de vida. La ausencia de un diagnóstico que haga posible un tratamiento médico efectivo acarrea la repetición de pruebas diagnósticas y un mayor uso de recursos sociosanitarios. Es necesaria una estrategia diagnóstica adecuada para poder realizar un tratamiento personalizado, que mejore los síntomas y la calidad de vida. En este documento de la SEC-Asociación de Cardiología Clínica, SEC Asociación de Cardiología Intervencionista, SEC-Asociación de Cardiopatía Isquémica y Cuidados Agudos Cardiovasculares, y SEC-Asociación de Imagen Cardiaca, se establecen unos algoritmos sencillos y prácticos con el objetivo de facilitar el diagnóstico precoz y el tratamiento más adecuado de los pacientes con ANOCA.

Palabras clave: ANOCA. INOCA. Disfunción microvascular. Angina vasoespástica.

Abbreviations

ANOCA: angina with nonobstructive coronary arteries. **CFR:** coronary flow reserve. **IMR:** index of microcirculatory resistance. **INOCA:** ischemia with nonobstructive coronary artery disease. **PET:** positron emission tomography. **SEC:** Sociedad Española de Cardiología.

INTRODUCTION

Angina pectoris affects more than 100 million persons worldwide.[1-5] According to the OFRECE study, the prevalence of angina in Spain is around 2.6%, indicating that there are more than 270 000 affected individuals.[4] A significant number of stable patients referred for coronary angiography due to angina or a positive ischemia test do not have obstructive coronary artery disease.[1] Many of these patients have ANOCA (angina with nonobstructive coronary arteries), or INOCA (ischemia with nonobstructive coronary artery disease) of nonobstructive origin. These 2 entities are manifestations of the same disease, which is why the recommendations provided by this document are applicable to both.

Angina pectoris is more prevalent among women (50%-70%) than men (30%-50%), although its true prevalence remains unknown.[1-5] In these patients, angina or ischemia is produced by coronary vascular dysfunction due to vasomotor disorders of the epicardial vessels or arterioles, and/or coronary microvascular dysfunction.[6-8]

An important point is that, currently, angina pectoris is significantly underdiagnosed, and consequently many patients suffer its consequences without receiving potentially effective treatment. The reasons for this lack of diagnosis and treatment are various. First, there is the inertia associated with the paradigm that has dominated the diagnostic approach to patients with angina for decades focused on identifying coronary artery stenosis rather than vasomotor or coronary microvascular disorders. Additionally, patients with angina without coronary artery stenosis have generally been considered low-risk patients with poor response to conventional antianginal medical therapy.[9] Second, and partly related to the previous point, many noninvasive techniques are based on identifying the regional ischemia that is characteristic of coronary artery stenosis (dysregulated contraction or isotope uptake during exertion or stress), making them less sensitive and specific for the detection of nonobstructive ischemia. Third, most cardiologists have not had access to the invasive techniques that provide objective evidence of vascular dysfunction in their patients. These intracoronary techniques have been considered the sole domain of interventional cardiologists, who do not usually play a key role in the management and follow-up of patients with INOCA. These barriers prevent the valuable information provided by invasive techniques from being used in the clinical management of these patients. Finally, patients with ANOCA/INOCA often have extracardiac diseases and conditions that require a multidisciplinary approach, complicating follow-up for specialized cardiologists.

In 2019, the European Society of Cardiology guidelines on the diagnosis and management of patients with chronic coronary syndrome represented a significant advance in the recognition of microvascular angina and the value of specific diagnostic techniques. Therefore, in the diagnostic approach in patients with suspected coronary microvascular angina, the guidelines indicate that coronary flow reserve (CFR) and microcirculatory resistance should be measured through pressure-guided techniques in patients with persistent symptoms but angiographically normal coronary arteries, or moderate stenosis and a normal fractional flow reserve (recommendation IIaB). Even the remaining recommendations, such as the administration of intracoronary acetylcholine during coronary angiography, or the use of transthoracic Doppler echocardiography of the anterior descending artery, cardiac magnetic resonance (CMR), or positron emission tomography (PET) for the noninvasive evaluation of CFR, have a lower level of recommendation (IIbB). In patients with suspected vasospastic angina, the guidelines recommend intracoronary provocation testing to identify coronary artery spasm (recommendation IIaB).[10]

However, over the past few years, numerous studies have been conducted in patients with ANOCA to assess the efficacy profile of new invasive diagnostic tests for their specific diagnosis, as well as randomized clinical trials assessing symptomatic improvement with individualized therapies. These trials consistently suggest that individualized and multidisciplinary approaches to these patients help to relieve symptoms, reduce the number of medical visits and prescribed therapies, and lower the costs associated with this syndrome.[11-13]

OBJECTIVES OF THIS DOCUMENT

This document is endorsed by the Clinical Cardiology Association, and the Interventional Cardiology Association, Ischemic Heart Disease and Acute Cardiac Care Association, and Cardiovascular Imaging Association of the Spanish Society of Cardiology (SEC) and aims to:

1. Review the various causes of ANOCA syndrome and current methods for its diagnosis and individualized treatment.

2. Propose a diagnostic and treatment algorithm for the approach to these patients in compliance with the clinical practice guidelines of the European Society of Cardiology on the management chronic coronary syndrome and the latest evidence.

3. Encourage various health care entities to create multidisciplinary pathways for the diagnosis, treatment, and targeted follow-up of these patients.

This document was drafted based on the interpretation of the latest scientific evidence, with an eminently practical focus so that the recommendations can be effectively applied in our setting. Each Association of the SEC provided scientific evidence and their view of their respective fields. Afterward, through consensus, they all created a single document including practical recommendations. The selection of the members that would eventually draft the document was left to the presidents of these Associations and was based on their clinical experience and expertise in the field.

IMPORTANCE OF ANOCA IN ROUTINE CLINICAL PRACTICE

While it has been acknowledged for decades that angina without coronary artery lesions could constitute a separate nosological entity (initially called syndrome X), routine clinical practice has paid little attention to affected patients, primarily due to the widespread notion that their prognosis is good.[14] However, numerous subsequent studies in which the diagnosis of ANOCA was based on objective evidence of coronary vascular dysfunction, unlike that of syndrome X, consistently showed that nonobstructive ischemia has a significant prognostic impact. The risk of adverse coronary events in these patients is largely determined by factors such as plaque burden, demonstration of myocardial ischemia, microvascular dysfunction, and the presence of vasospasm or coronary endothelial dysfunction. For example, a study of 917 women with signs or symptoms of myocardial ischemia showed that the composite endpoint of myocardial infarction or cardiac death occurred in 6.5% of women without coronary artery disease, 12.8% of those with nonobstructive atherosclerosis, and 25.9% of those with obstructive coronary artery disease at 10 years of follow-up (figure 1).[15] A meta-analysis of 54 studies and 35 039 patients confirmed an increased risk of nonfatal myocardial infarction and death, with an incidence rate of 0.98 per 100 person-years in patients with ANOCA at 5 years of follow-up. The risk was higher in individuals with confirmed ischemia (vs those without ischemia) and patients with nonobstructive coronary artery disease (vs those with normal coronary arteries).[16]

Similarly, even in the presence of angiographically normal coronary arteries, microvascular dysfunction demonstrated by a reduced CFR has proven to be a powerful determinant of the risk of death and myocardial infarction in these patients.[17] Additionally, more cardiovascular complications, including stroke and heart failure,[18] have also been reported in these individuals, along with a higher prevalence of small vessel cerebral disease.[19] In conclusion, patients with coronary microvascular dysfunction, identified by an impaired CFR, have a higher risk of major cardiovascular events.[20]

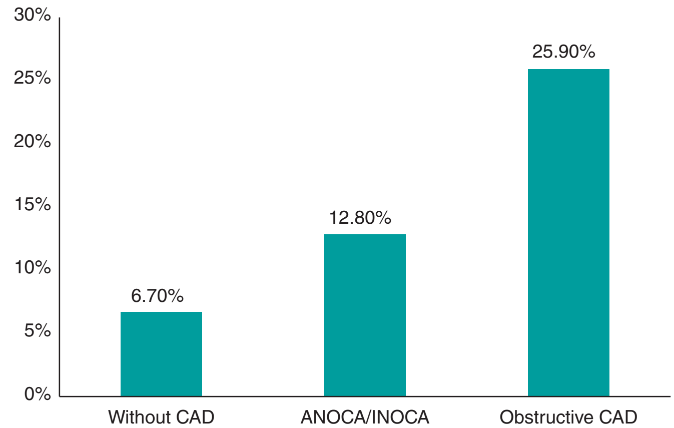

Figure 1. Risk of myocardial infarction or cardiovascular death at 10 years of follow-up in a cohort of women.[15] ANOCA/INOCA, angina/ischemia with nonobstructive coronary arteries; CAD, coronary artery disease.

Intracoronary acetylcholine provocation testing also allows coronary risk stratification. An abnormal response to intracoronary acetylcholine indicates vasomotor disorders due to endothelial dysfunction or smooth muscle cell hyperreactivity. In addition to causing vasospastic angina, coronary vasomotor disorders are associated with a higher long-term risk of cardiovascular events in patients with angina, especially when associated with increased coronary microcirculation.[13,21] Even moderate vasoconstrictor responses to acetylcholine can be predictive of a worse prognosis in this context.[20]

Additionally, patients with ANOCA often show persistent symptoms, partly due to the lack of an early diagnosis, thus leading to treatment delay. This is associated with a higher number of unnecessary diagnostic tests to rule out obstructive coronary artery disease, visits to the emergency room, hospital admissions, anxiety, impaired quality of life, episodes of sick leave, and higher direct and indirect health care costs.[16,22,23]

Diagnosing INOCA is essential to provide effective therapies to control angina symptoms. The CorMicA trial (Coronary microvascular angina) included 151 patients with ANOCA who underwent cardiac catheterization and invasive functional assessment (CFR determination, index of microcirculatory resistance, and fractional flow reserve) followed by acetylcholine vasoreactivity testing.[11] The patients were randomized to reveal their specific endotype, which would guide treatment based on the results (intervention group), vs standard treatment, which would be administered blind to the test results (control group). Targeted therapy was individualized based on the endotypes documented in the invasive study (vasospastic angina: smoking cessation, long-acting calcium channel blockers, long-acting nitrates, and lifestyle changes; microvascular angina: beta-blockers, lifestyle changes, possible angiotensin-converting enzyme inhibitors and statins; noncardiac chest pain: withdrawal of antianginal treatment). Targeted therapy was significantly associated with an improved angina-related quality of life at 6 months (measured using the Seattle Angina Questionnaire), disease perception, and treatment satisfaction, although no differences

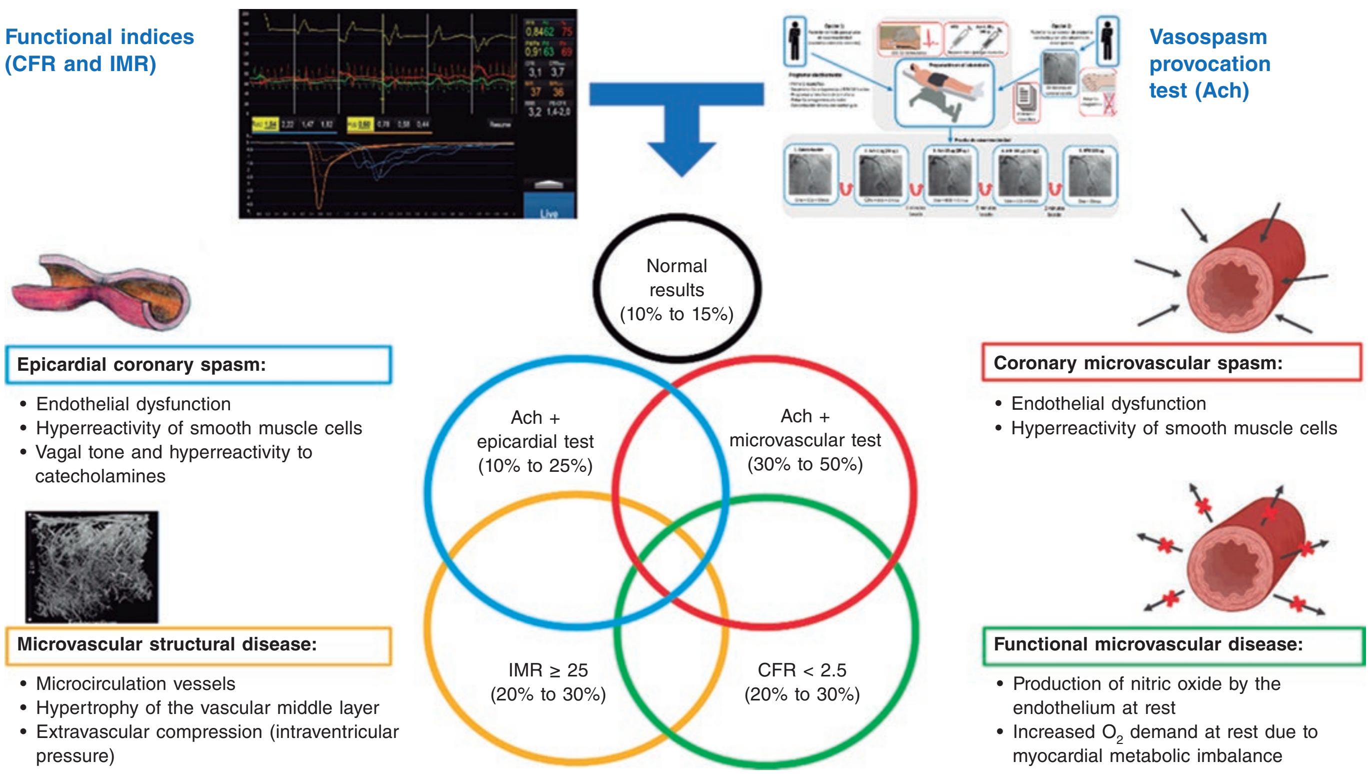

Figure 2. Possible results of an invasive functional study in a patient with ANOCA. Specific causes discovered to date with the pathophysiological mechanisms involved in their genesis. Ach, acetylcholine; ANOCA, angina with nonobstructive coronary arteries; CFR, coronary flow reserve; IMR, index of microcirculatory resistance. (Figure self-developed from Meeder et al.,[1] Jansen et al.,[3] Kunadian et al.,[7] Kunadian et al.,[34] and Hokimoto et al.[35].)

were reported in the risk of major adverse cardiovascular events. More antianginal drugs were prescribed in the intervention group (87.8% vs 48.7%; $P < .001$). While these results are very interesting, it is important to note that this was a single study with a limited number of patients.

ENDOTYPES OF PATIENTS WITH ANOCA

The specific causes of ANOCA are not yet fully described, and are likely multifactorial in most patients. Figure 2 illustrates the specific causes discovered so far and the pathophysiological mechanisms involved in their genesis. Of note, specific diagnostic techniques often do not allow us to differentiate among the various pathophysiological mechanisms. In fact, in many patients, these mechanisms overlap. Four pathophysiological mechanisms causing ANOCA have been described to date:

1. *Microvascular dysfunction due to structural changes to the microcirculation.* The density of microvessels in patients with hypertensive cardiomyopathy is lower than that in patients without this condition.[24] Remodeling of the coronary microcirculation has also been described, including arteriolar medial layer hypertrophy and induration in patients with hypertension, added to other cardiovascular risk factors, vascular infiltration by amyloid in cardiac amyloidosis, and reduced luminal caliber due to extrinsic compression in cases of ventricular hypertrophy or increased left intraventricular pressure.[3,7,25] These changes reduce microcirculatory conductance, resulting in increased microvascular resistances (index of microcirculatory resistance [IMR] ≥ 25). Elevated IMR values are associated with older age and left ventricular hypertrophy, with no clear difference between the sexes.[26,27]

2. *Functional microvascular disease.* An increase in resting coronary blood flow, leading to reduced CFR levels has been reported, especially in women with few risk factors and no objectively observable structural heart disease.[28] Although coronary flow is usually preserved at maximum hyperemia, many of these patients have a low exercise capacity. These patients may have an imbalance in oxygen availability (due to increased demand), with endothelial involvement being the main mechanism (due to increased nitric oxide synthesis).[29] In addition, these patients tend to have a greater number of associated ischemic abnormalities in organs such as the kidneys, retina, and central nervous system, suggesting systemic involvement.[30]

3. *Microvascular dysfunction due to microcirculatory spasm.* Microvascular dysfunction due to vasospasm is more common in women with cardiovascular risk factors, with endothelial dysfunction likely playing a significant role. It is a common finding in larger and medium-sized arterioles and manifests as paradoxical vasoconstriction in response to increased myocardial oxygen demand, which becomes apparent after intracoronary of acetylcholine administration.[3,7,19,31]

4. *Epicardial spasm.* Epicardial spasm is not usually associated with traditional risk factors, except for smoking. This type of vasospasm is believed to be caused by 2 main mechanisms: endothelial dysfunction and smooth muscle cell hyperreactivity. These 2 mechanisms respond differently to stimuli from the autonomic nervous system, depending on whether the stimuli are from the sympathetic system (such as exercise or a cold stimulation test), or whether the stimuli are from the parasympathetic system and provoke an exacerbated response (eg, nocturnal spasms).[19,32]

CLINICAL CHARACTERISTICS OF PATIENTS WITH ANOCA

The first step in identifying patients with ANOCA is diagnostic suspicion. Patients with microvascular angina often report angina-like chest pain, typically on exertion, but it can also occur at rest. ANOCA is more common in women, and affected individuals generally show poor response to short-acting nitrates. In some cases, instead of angina, patients may have angina equivalents such as exertional dyspnea or atypical symptoms such as nausea, vomiting, dizziness, or fatigue. In microvascular spasm, which is also more common in women, unstable angina can occur with a variable response to nitrates.[1-3]

Regarding angina due to coronary vasomotor disorders, the spectrum and clinical signs of these disorders are much more varied than the pattern of Prinzmetal's angina, which is a highly specific case of vasomotor disorder caused by an occlusive spasm of an epicardial vessel. However, this disorder is not representative of much more common substrates such as nonocclusive diffuse spasm and arteriolar or microvascular spasm. For example, in vasomotor disorders due to endothelial dysfunction, the dominant symptom is exertional angina, whereas in vasomotor disorders triggered by smooth muscle cell hyperreactivity of coronary vessels (such as in Prinzmetal's angina), angina tends to occur at rest or becomes unstable, especially at night. Nevertheless, it can also be associated with exertional chest pain and be triggered by specific stimuli such as stress, cold, or an increase in vasoconstrictor humoral factors. Angina can also be associated with other conditions such as migraines or Raynaud's phenomenon. Some anticancer drugs, such as 5-fluorouracil and capecitabine, among others, are known to be associated with vasospastic angina.[33] Similarly, the initial clinical manifestation of epicardial spasm can be myocardial infarction with nonobstructive coronary arteries (MINOCA).[19] This condition is often associated with smoking, unlike other traditional risk factors such as hypertension, diabetes mellitus, and dyslipidemia.[19,32]

NONINVASIVE DIAGNOSTIC APPROACH IN PATIENTS WITH ANOCA

The diagnostic approach to patients with ANOCA falls within the diagnostic process of chronic coronary syndrome as recommended by the current clinical practice guidelines and is initially noninvasive.[10] However, it is important to note that the available scientific evidence—sometimes scarce—has already been analyzed, and consequently some statements are based not only on clinical trials but also on consensus among the authors of the document.

After angina is suspected, the patient should be referred to the cardiology unit for basic symptom examination, including an electrocardiogram, echocardiogram, a complete blood count, and clinical response to initial antianginal treatment. A noninvasive strategy is advised for most patients with nonlimiting symptoms and a low or intermediate pretest risk of obstructive coronary artery. This strategy involves noninvasive imaging modalities, including functional studies, based on surrogates of myocardial blood flow and CFR, and/or anatomical studies, mainly coronary computed tomography.[3] The diagnostic tests performed will depend, among other factors, on the patient's exercise tolerance and the availability and experience of each center (figure 3).[1,3,7,34,35]

Of note, in many patients with ANOCA, noninvasive imaging modalities for detecting ischemia have low sensitivity for the diagnosis of most endotypes, especially those associated with coronary vasomotor disorders. In a registry of patients studied with noninvasive ischemia detection tests and invasive functional tests (considered the reference standard for diagnosis), only 50% of those with a low CFR showed abnormalities in the noninvasive imaging tests.[36] In fact, no noninvasive stress test can reliably detect the presence of microvascular spasms or coronary endothelial dysfunction and a negative stress test does not exclude the presence of vasomotor coronary dysfunction, especially in symptomatic patients.[7] The reasons for the low sensitivity of these techniques are diverse. However, an important reason is that they rely on visualizing regional differences among myocardial segments (nonuniform tracer uptake in single-photon emission computed tomography, differences in myocardial segment mobility in stress echocardiography). Given the characteristics of microvascular angina, in which ischemia can be widespread, it is difficult to find regional defects in noninvasive tests. Moreover, patients with vasospasms usually test negative in stress tests based on comparison between rest and hyperemia. Therefore, it is important to note that ANOCA should always be suspected in patients with suggestive chest pain and a normal coronary computed tomography scan, or without obstructive coronary artery disease (< 50% reduction in diameter), and in patients who test negative on noninvasive imaging modalities for ischemia detection. Currently, no imaging modality allows the direct anatomical visualization of coronary microcirculation in vivo in humans, which is why its evaluation relies on measuring parameters that reflect functional status, such as myocardial blood flow and myocardial flow reserve.[7]

However, certain ANOCA endotypes with low CFR and a high suspicion of microvascular angina can be diagnosed noninvasively through various imaging modalities such as PET, transthoracic Doppler echocardiography, contrast-enhanced transthoracic echocardiography, and CMR. CFR is defined as an increased flow between the resting state and maximum hyperemia. CFR values < 2 to 2.5 are considered pathological.[1]

PET allows determination of myocardial blood flow at rest and during hyperemia in absolute terms, which facilitates the calculation of CFR. Although PET is considered the reference noninvasive imaging modality and correlates well with invasive study (CFR < 2 is associated with a worse prognosis regardless of the severity of coronary artery disease),[37] its availability is highly limited in our setting,[3,38] due to its high cost and the need for specific cyclotron-produced radiation-emitting radiotracers, such as oxygen-15-labeled water, nitrogen-13-labeled ammonia, or rubidium-82, a potassium analog.

Transthoracic Doppler echocardiography allows for the measurement of baseline and hyperemic blood flow velocity (after adenosine administration) using pulsed-wave Doppler. CFR < 2.5 is considered diagnostic of microvascular dysfunction. However, this imaging modality requires highly trained personnel and can only be used in the left anterior descending coronary artery.[3,39] On the other hand, contrast-enhanced transthoracic echocardiography using microbubbles allows estimation of myocardial perfusion flow based on its degree of opacification. The latter imaging modality has shown good correlation with PET, although there may be significant interobserver variability, thus requiring further validation in studies.[40]

Finally, CMR can determine myocardial perfusion using stress and contrast agents (gadolinium) to calculate the myocardial perfusion reserve index, which is a surrogate parameter of CFR. This imaging modality is more widely available than PET, and has less interobserver variability than echocardiographic studies, making it the most suitable imaging modality for the study microvascular dysfunction in our setting. However, CMR is still pending validation in the remaining ANOCA endotypes.[3,41] Hyperemia or coronary vasodilation can be achieved through adenosine infusion, or the administration of a single bolus of regadenoson, and stress vs resting perfusion can be compared quantitatively. The diagnostic ability of stress CMR in microvascular dysfunction was demonstrated 2 decades ago.[42] A myocardial perfusion reserve index < 1.84 has shown sensitivity and specificity rates of 73% and 74%, respectively, to predict abnormalities in invasive coronary physiology studies, with an area under

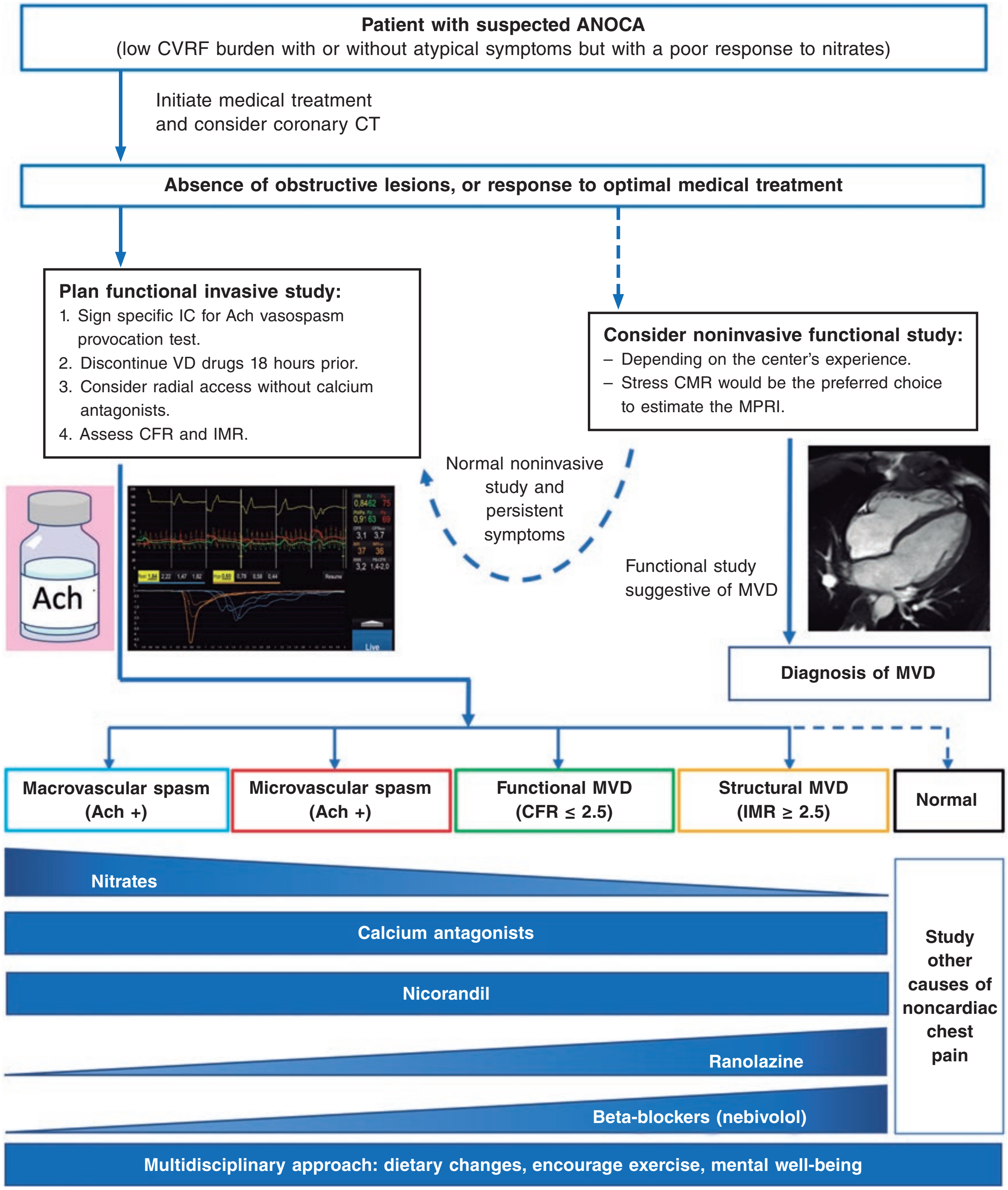

Figure 3. Diagnostic approach to patients with suspected ANOCA or INOCA. Ach, acetylcholine; ANOCA, angina with nonobstructive coronary arteries; IC, informed consent; CFR, coronary flow reserve; CT, computed tomography; CVRF, cardiovascular risk factors; IMR, index of microcirculatory resistance; INOCA, ischemia with nonobstructive coronary arteries; MPRI, myocardial perfusion reserve index; MRI, magnetic resonance imaging; MVD, microvascular dysfunction; VD, vasodilator. (Figure self-developed from Meeder et al.,[1] Perera et al.,[2] Jansen et al.,[3] Kunadian et al.,[7] Ang and Berry,[31] Kunadian et al.,[34] and Hokimoto et al.[35].)

the ROC curve of 0.78.[41] A quantitative assessment of stress perfusion studies showed an even stronger correlation with invasive studies in a series of 65 patients (50 with stable angina, 46% of whom had no coronary artery lesions, and 15 healthy volunteers) to distinguish multivessel disease from microvascular dysfunction, with an area under the ROC curve of 0.94 (P < .001) for the absolute quantification of myocardial flow during stress < 1.82 mL/g/min.[43] In this study, myocardial flow during stress correlated better with invasive measurements than with myocardial flow reserve. Additionally, its prognostic capability has also been demonstrated. In a series of 218 patients with angina and coronary arteries without epicardial lesions,[44], a myocardial perfusion reserve index ≤ 1.47 was associated with a 3-fold higher risk of major cardiovascular events compared with patients with values > 1.47 (hazard ratio, 3.14; 95% confidence interval, 1.58-6.25; P = .001). In another series of 395 patients, myocardial perfusion reserve improved the prognostic value vs the baseline model (age, sex, and late enhancement) of the primary endpoint defined as a composite of cardiac death, nonfatal myocardial infarction, aborted sudden death, or late revascularization, at 460 days of follow-up. Moreover, this study

Table 1. Diagnostic criteria for ANOCA

Endotype	Physiopathology	Criteria	Comments
Microvascular angina	Coronary microvascular dysfunction	Myocardial ischemia symptoms	• Exertional or resting angina • Angina equivalent (exertional dyspnea)
		Evidence of myocardial ischemia	• Positive ischemia detection test
		Absence of obstructive coronary artery disease	• FFR > 0.80 or stenosis < 50% • Confirmed by coronary CT or coronary angiography
		Impaired coronary microvascular function	• Adenosine test: CFR ≤ 2.0 (2.5 according to the method), IMR ≥ 25, HMR ≥ 1.9 • Microvascular spasm (spontaneous or acetylcholine test): angina, EKG changes, without epicardial spasm (lumen reduction < 90%)
Vasospastic angina	Epicardial spasm	Symptoms	• Angina, more at rest, especially nocturnal • Reduced exercise tolerance, especially in the morning • Response to nitrates and calcium antagonists
		EKG changes	• ST-segment changes (elevation/depression) ≥ 1 mV • New negative U waves
		Absence of obstructive coronary artery disease	• FFR > 0.80 or stenosis < 50% • Confirmed by coronary CT or coronary angiography
		Coronary spasm	• Vasoconstriction > 90% with angina and spontaneous EKG changes, or after provocation test (acetylcholine)
		Preserved coronary microvascular function	• Adenosine test: CFR > 2.0 (2.5 according to the method), IMR < 25, HMR < 1.9
Mixed	Microvascular angina and epicardial spasm	Absence of obstructive coronary artery disease	• FFR > 0.80 or stenosis < 50% • Confirmed by coronary CT or coronary angiography
		Microvascular angina	• Microvascular dysfunction • Adenosine test: CFR ≤ 2.0 (2.5 according to the method); IMR ≥ 25, HMR ≥ 1.9
		Coronary spasm	• Angina + EKG changes + epicardial vasoconstriction (> 90%)
Noncardiac chest Pain	None	Absence of obstructive coronary artery disease	• FFR > 0.80 or stenosis < 50% • Confirmed by coronary CT or coronary angiography
		Normal functional tests	• Adenosine test: CFR > 2.0 (2.5 according to the method), IMR < 25, HMR < 1.9 • Negative acetylcholine test

ANOCA, angina with nonobstructive coronary arteries; CFR, coronary flow reserve; CT, coronary computed tomography; EKG, electrocardiogram; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; IMR, index of microvascular resistance.
Table based on data from Meeder et al.,[1] Perera et al.,[2] Jansen et al.,[3] Kunadian et al.,[7] Mejia-Renteria et al.,[19] Ong et al.,[25] Ang and Berry,[31] Kunadian et al.,[34] and Hokimoto et al.[35].

confirmed that quantitative perfusion (defined as > 10% ischemic myocardium) was superior to qualitative perfusion (defined as perfusion defects in > 2 segments) in the assessment of ischemia.[45] Rahman et al.[46] also demonstrated that high-resolution CMR techniques using fully quantitative perfusion were properly accurate and outperformed visual assessment in detecting microvascular dysfunction.

Unfortunately, some of the tests that could help in the noninvasive functional diagnosis of patients with ANOCA/INOCA are not available in routine clinical practice in many centers in Spain, thus limiting the diagnostic approach in these patients.

Table 1 shows the diagnostic criteria for ANOCA, while figure 3 illustrates the complete diagnostic algorithm proposed for patients with ANOCA, specifying the initial strategy, when to schedule invasive studies, and the possible therapies based on the specific endotype.

INVASIVE DIAGNOSTIC APPROACH IN PATIENTS WITH ANOCA

Although these are very safe procedures, there are risks involved in the invasive assessment of patients with suspected ANOCA. Therefore, it is of paramount importance that the health professionals involved should have specific training in performing and interpreting various tests. Adequate pathways should also be implemented. Currently, the use of 2 functional tests is advised, consisting of a vasospasm provocation test with intracoronary acetylcholine infusion and a microvascular function test using a pressure-temperature sensor-tipped wire at rest and during maximum pharmacological hyperemia.[7,11,34,35]

Vasospasm provocation testing with intracoronary acetylcholine is advised. Since the technical data sheet of acetylcholine does not include its intracoronary use, the pharmacy department of the medical center must be contacted for prior authorization. In most cases, patients must provide their prior written informed consent for the off-label use of the drug.[47] This test has demonstrated high sensitivity and specificity rates (around 90% and 100%, respectively, depending on the patient's characteristics) for diagnosing micro- and macrovascular vasospastic angina, with very few complications.[47,48] Before the test is conducted, the use of long-acting vasodilator drugs should be avoided. A minimum of 18 hours without oral or topical vasodilator agents is advised to avoid false negatives. Although the use of beta-blockers may increase vasoconstriction after acetylcholine infusion, their discontinuation before the test is not advised if these drugs are deemed necessary. In procedures performed via the radial route, the use of calcium antagonists should also be avoided.[47] Essentially, the test involves the infusion of increasing acetylcholine doses while simultaneously assessing the reproduction of the patient's symptoms, changes in the 12-lead electrocardiogram, and the presence of spasms in the epicardial arteries > 90% of their baseline diameter. The Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology recently published a technical document on the performance and interpretation of this test.[47]

Microvascular function can be assessed using intracoronary Doppler, or pressure-temperature sensor-tipped wires. However, the only currently available guidewires are pressure-temperature sensor-tipped wires (Pressurewire X, Abbott, United States), which use the thermodilution method. Coronary thermodilution allows coronary flow values to be obtained at rest and during maximum hyperemia after the infusion of any microcirculation vasodilator agent (usually adenosine or its derivatives). These values are obtained after the infusion of 3 mL of physiological saline solution through the guide catheter and by measuring the transit time of this solution between the proximal segment of the artery and the distal segment, where the distal guidewire thermistor is located, both at rest and during maximum hyperemia. By obtaining flow data at rest and during maximum hyperemia, the CFR can be calculated, which under normal conditions should be > 2.5. CFR values ≤ 2.5 are considered diagnostic of microvascular dysfunction. Since the pressure of microcirculation perfusion (measured in the distal segment of the artery where the guidewire is located) can be obtained while performing the test during maximum hyperemia, the minimum microcirculation resistance (IMR) can be estimated. In studies performed in healthy patients, a cutoff value of 25 has been established. IMR values ≥ 25 are also indicative of microvascular dysfunction.[7,34,35]

There is another promising method in the invasive diagnosis of patients with ANOCA. Using the same pressure guidewire and a dedicated microcatheter (RayFlow, Hexacath, France), absolute coronary flow values (in mL/min) and absolute microcirculation resistances (in Wood units) can be obtained.[49] Since these are absolute values, they partly depend on the perfusion territory of the artery and the studied segment. Currently, research is underway to develop an indexed approach using this method.[50]

THERAPEUTIC APPROACH IN PATIENTS WITH ANOCA

General approach

In patients with ANOCA, treatment should focus on relieving symptoms and improving the risk profile, quality of life, and prognosis. In this regard, early diagnosis, identification of the pathophysiological mechanisms involved, and early initiation of treatment tailored to the INOCA endotype are key to achieving therapeutic success.[1,3,7,25,31,34,35,51-54] However, currently available studies of specific medical treatment for this condition are small, with heterogeneous methodologies and variable results, which makes it difficult to establish robust recommendations for the therapeutic management of these patients.

Lifestyle changes and control of cardiovascular risk factors

First, given the impact of cardiovascular risk factors on the development of coronary microvascular dysfunction and epicardial spasm, effective control of these risk factors is essential, including lifestyle changes (weight loss, physical exercise, smoking cessation, stress reduction), and appropriate pharmacological therapies.[10] To reduce the risk of coronary vasospasm, it is important to avoid triggering factors such as smoking and the use of certain drugs (cocaine and amphetamine).[10]

Statins are beneficial not only due to their effect on lipid profile, but also due to their positive effect on endothelial function and in preventing the development of coronary spasms.[55,56] Renin-angiotensin-aldosterone system inhibitors are beneficial to reduce blood pressure and improve endothelial function. In fact, these drugs have been reported to have positive effects on both coronary microvascular dysfunction and epicardial coronary vasospasm.[55-57] The role of aspirin in patients without known cardiovascular disease is controversial.[55,56] In the Japanese guidelines, aspirin is not advised in the absence of angiographically confirmed stenosis in patients with vasospasm (class IIIB indication).[35]

Antianginal treatment

Antianginal treatment is crucial for symptom relief. Preferential use of drugs that reduce myocardial oxygen consumption is advised in patients with a structural endotype of INOCA (microvascular dysfunction), such as beta-blockers or calcium channel blockers (ivabradine may also be considered in certain cases), along with other drugs such as ranolazine, trimetazidine, and nicorandil. On the other hand, calcium channel blockers, nitrates, nicorandil, or a combination of these, are advised in patients with a vasomotor endotype of INOCA (whether epicardial or microvascular spasm) (table 2).[1,3,7,25,31,34,35,51-54]

There is some evidence on nebivolol compared with other beta-blockers, due to its potential vasodilatory effect that targets the production of nitric oxide.[58] A beneficial effect of carvedilol has also been suggested by improving endothelium-dependent dilation.[59] A randomized clinical trial of 81 patients demonstrated the benefit of ranolazine treatment in relieving symptoms in patients with CFR values < 2.5.[60] Diltiazem treatment shows no benefits in improving symptoms, quality of life, or coronary microvascular function in the randomized EDIT-CMD trial of 73 patients with ANOCA in a 6-week course of treatment, although there was a reduction in induced epicardial vasospasms.[12] Finally, there are promising potential benefits associated with drugs that have new therapeutic targets, such as cilostazol, a phosphodiesterase 3 inhibitor that targets coronary vasospasm,[61] or zibotentan, a selective endothelin A antagonist with benefits on microcirculation and endothelial dysfunction,[62] or fasudil, a rho-kinase enzyme inhibitor capable of reducing the IMR in patients with a positive vasospasm provocation test and elevated IMR.[13]

Treatment for resistant angina

The use of drugs such as low-dose tricyclic antidepressants (which modulate norepinephrine uptake and have anticholinergic effects, which can induce analgesia), or neurostimulators that block the transfer of pain at the spinal cord has been proposed in patients with resistant angina, and even coronary interventions in the case of vasospastic angina refractory to medical therapy.[51]

Patient follow-up

The follow-up of these patients should be coordinated between primary care physicians and cardiologists, and once symptoms are under control, follow-up should preferably be conducted in primary care units, with referrals to cardiology if there is decompensation. In addition, given the particularities of ANOCA, it is essential to inform patients about their disease and its implications. A

Table 2. Therapeutic approach for patients with ANOCA or INOCA

General treatment			
Lifestyle changes	• Mediterranean diet • Physical exercise • Weight control • Stress reduction		
Cardiovascular risk factor control	• Hypertension • Dyslipidemia • Diabetes • Smoking cessation		
Aspirin	• With previous CVD • Without previous CVD, its use is controversial		
ACEI or ARA II	• Blood pressure reduction • Improvement in endothelial function: possible benefit in microvascular coronary dysfunction and coronary vasospasm		
Statins	• Reduction in total cholesterol and LDL • Improvement in endothelial function • Possible benefit in vasospastic angina		
Anti-anginal drugs	**Microvascular angina**	Beta-blockers	• Decreased myocardial oxygen consumption*
		Calcium antagonists	• Decreased myocardial oxygen consumption • Vascular smooth muscle relaxation
		Ranolazine	• Improvement in microvascular perfusion reserve
		Trimetazidine	• Increased cellular tolerance to ischemia
	Vasospastic angina	Calcium antagonists	• Decreased myocardial oxygen consumption • Decreased coronary spasm via relaxation of vascular smooth muscle
		Nitrates	• Decreased myocardial oxygen consumption • Decreased coronary spasm via relaxation of vascular smooth muscle
		Nicorandil	• Coronary vasodilator effect
	Microvascular angina + vasospastic angina	Calcium antagonists, nitrates, ranolazine, trimetazidine, nicorandil	

* Consider the use of nebivolol due to its antioxidant properties through nitric oxide.
ACEI, angiotensin-converting enzyme inhibitors; ANOCA, angina with nonobstructive coronary arteries; ARA II, angiotensin II receptor antagonists; CVD, cardiovascular disease; INOCA, ischemia with nonobstructive coronary arteries; LDL, low-density lipoproteins.
Table based on data from Meeder et al.,[1] Jansen et al.,[3] Kunadian et al.,[7] Kobayashi et al.,[26] Ang and Berry,[31] Kunadian et al.,[34] Hokimoto et al.,[35] Beltrame et al.,[51] Mehta et al.,[52] Seitz et al.,[53] and Abouelnour et al.[54].

multidisciplinary approach is necessary since other health professionals, such as psychologists, internists, and pain clinics, may sometimes be required.

Future lines of research

Finally, ongoing clinical trials are currently exploring whether intensive treatment of coronary atherosclerosis with high-intensity statins, renin-angiotensin-aldosterone system inhibitors, and low doses of aspirin improves angina and ischemia. The WARRIOR trial (NCT03417388) is studying whether such treatment improves outcomes, and the MINOCA-BAT trial (NCT03686696) is investigating whether the combined use of beta-blockers and renin-angiotensin-aldosterone system inhibitors reduces major cardiovascular clinical events.

CONCLUSIONS

Patients with suspected ANOCA exhibit a wide array of presentations that can currently be diagnosed and treated with effective individualized therapies. It is important for clinical cardiologists to become familiar with the various abnormalities in patients with ANOCA, and the currently available diagnostic and therapeutic tools. Invasive diagnostic tests constitute a new option requiring specific training for their correct performance and interpretation, as well as CMR with adenosine or regadenoson for myocardial perfusion calculation. In conclusion, specific actions need to be taken by all health centers to create diagnostic and therapeutic protocols for the management of these patients.

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Artificial intelligence has not been used in the preparation of this document.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the conception, literature search, development, drafting, reading, and final approval of the manuscript. C. Escobar served as the consensus coordinator.

CONFLICTS OF INTEREST

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Review article

Coronary obstruction following transcatheter aortic valve replacement. Risk evaluation and preventive strategies

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ABSTRACT

Coronary obstruction (CO) is a rare but potentially fatal complication of transcatheter aortic valve implantation (TAVI). The present article aims to summarize the evidence on CO risk factors and provide an overview of preventive strategies. We performed a comprehensive literature review focused on these items. The analysis included studies addressing patient-specific characteristics, procedural aspects, and the effectiveness of various prevention techniques in mitigating CO risk. Specific risk factors for CO, which can be assessed by evaluating patient characteristics using computed tomography, are described. Procedural factors associated with an increased risk of CO are discussed. Preventive techniques, including the chimney stent and bioprosthetic aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA), are also described, highlighting the advantages and disadvantages of each method. The present review also provides an overview of emerging dedicated devices designed to address this complication. In conclusion, identifying patients at risk for CO is crucial for optimizing TAVI outcomes. Comprehensive imaging assessment and appropriate preventive strategies, such as the BASILICA technique, can mitigate the risk of CO and improve patient outcomes. Further research is needed to validate emerging dedicated devices.

Keywords: Transcatheter aortic valve replacement. Coronary artery obstruction. Coronary protection techniques.

Oclusión coronaria posterior al implante percutáneo de válvula aórtica. Evaluación del riesgo y estrategias preventivas

RESUMEN

La obstrucción de las arterias coronarias (OC) es una complicación rara, pero potencialmente fatal, del implante percutáneo de válvula aórtica (TAVI). El objetivo de esta revisión es resumir la evidencia sobre los factores de riesgo de OC y las estrategias preventivas. Se realizó una revisión integral de la literatura centrada en estos aspectos. El análisis consideró estudios que abordaran las características del paciente, los factores procedimentales y la efectividad de diferentes técnicas preventivas para reducir el riesgo de OC. Se describen los factores relacionados con el paciente y del procedimiento que condicionan un mayor riesgo de OC. A lo largo del texto se detallan las técnicas para disminuir el riesgo de OC, incluidos el *stent* en chimenea y la técnica BASILICA. Además, se aporta una descripción general de los dispositivos diseñados para abordar esta complicación. En conclusión, la identificación de los factores de riesgo de OC es crucial para optimizar los resultados del TAVI. La evaluación exhaustiva mediante imagen multimodal, junto a estrategias preventivas apropiadas, como la técnica BASILICA, pueden mitigar el riesgo de OC y mejorar los resultados. Aún se requiere más investigación para validar los dispositivos emergentes.

Palabras clave: Implante percutáneo de válvula aórtica. Obstrucción de arterias coronarias. Técnicas de protección coronaria.

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Abbreviations

BSV: biological surgical valve. **CO:** coronary obstruction. **SAVR:** surgical aortic valve replacement. **SOV:** sinus of Valsalva. **STJ:** sinotubular junction. **TAVI:** transcatheter aortic valve implantation. **THV:** transcatheter heart valve. **VTC:** valve to coronary distance.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has evolved rapidly, achieving substantial safety and efficacy.[1,2] However, complications such as conduction disturbances, access site-related complications, and coronary obstruction (CO), remain concerning due to their morbidity and mortality. CO is a rare (0.5-8%) but potentially lethal complication during TAVI.[3-5] The reported in-hospital to 30-day mortality rate associated with this event is about 30% to 50%.[6-8] CO can occur in an acute setting during valve implantation, before the patient has left the operating room, or it can be delayed, occurring after the patient left operating room following a successful TAVI. Delayed CO can be classified as early (0-7 days) or late (> 7 days).[9]

There are 2 main mechanisms of CO. The first is direct obstruction by displacement of a native or degenerated prosthetic leaflet caused by the transcatheter heart valve (THV). This is most common in patients with low coronary takeoff, accompanied by a narrow sinus of Valsalva (SOV).[4] The second mechanism involves indirect obstruction wherein the leaflet is also displaced, occluding the sinotubular junction (STJ), with consequent sinus sequestration. This is more frequent with a low and narrow STJ. Most COs occur at the level of the coronary ostium (92%) and primarily on the left coronary artery (78%).[4] Other causes of CO include embolization and direct obstruction of the coronary ostia by the TAVI prosthesis.[3-5,7,10-12]

After a thorough assessment, high-risk anatomical characteristics could favor surgical aortic valve replacement (SAVR). Nonetheless, if the surgical risk is prohibitive, it is necessary to proceed with TAVI. In such situations, coronary artery protection techniques are essential to enhance safety and minimize risks.[13,14]

The present review aims to summarize and analyze the predictors of CO, as well as the current techniques and strategies used to prevent this complication in the setting of TAVI procedures.

ASSOCIATED FACTORS IN CORONARY ARTERY OBSTRUCTION AFTER TAVI

Meticulous planning of TAVI and a comprehensive understanding of the underlying mechanisms that predispose to complications are imperative to improve outcomes. Computed tomography (CT) is crucial in evaluating TAVI candidates, including estimating possible complications.[15] The main predictors of TAVI-related CO are summarized in table 1.

Anatomical factors contributing to CO in patients with native aortic valves

The main predictor is a low coronary ostia height, measured by CT from the plane of the aortic annulus. A previous expert consensus suggested a cutoff height of < 10 mm as indicative of maximum risk.[16,17] However, data from a multicenter registry found that about 80% of the patients with CO had a left main (LM) coronary ostium height < 12 mm (mean height of 11 mm).[3] Furthermore, Ribeiro et al. reported that approximately 60% of the patients with CO had a coronary ostia height > 10 mm, suggesting that the cutoff should be increased to 12 mm.[18] The right coronary artery (RCA) ostium was affected only in 11% of all cases of CO in a previous registry.[3]

Table 1. TAVI-related coronary artery occlusion-associated factors

Predictors	Commentary
Anatomical factors	Coronary ostia height < 12 mm (< 10 mm: maximum risk)[a]
	Sinus of Valsalva diameter < 30 mm[a]
	Cusp height > coronary height
	Low STJ height and narrow STJ diameter
	VTC ≤ 4 mm
	Culprit leaflet calcification > 600 mm^3
Valve-in-valve TAVI	VTC ≤ 4 mm[a,b]
	Stentless BSV or stented BSV with externally mounted leaflets[b]
Female sex	Probably related to smaller anatomy in women
THV and procedural factors	Balloon-expandable valves associated with a higher rate of acute CO
	Self-expanding valves associated with delayed CO
	Extended sealing cuff
	High implantation

BSV, biological surgical valve; CO, coronary obstruction; STJ, sinotubular junction; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; VTC, valve-to-coronary distance.
[a] Estimated using computed tomography.
[b] Valve-in-valve TAVI itself has been associated with higher risk; however, these factors increase the probability of CO.

This is due to the higher takeoff of this artery compared with LM in most cases,[19] underscoring the importance of these measures.

Another risk factor is a narrow aortic root with a SOV diameter < 30 mm.[7,11] The valve-to-coronary (VTC) distance is the distance from the coronary ostia to the anticipated final position of the displaced bioprosthetic leaflets after TAVI.[15] To calculate VTC using CT, a virtual cylinder representing the THV is used and the horizontal distance between this cylinder and the coronary ostia is measured.[15] If the VTC is > 6 mm, the risk of CO is low; between 4 and 6 mm, the risk is borderline; and at < 4 mm, the risk is maximum.[7,15] However, VTC measurements are not 100% specific. This might be related to the differences between the estimated and observed VTC that have been described by Tzimas et al.[20]

The relationship between aortic cusp height and coronary height is a relatively novel criterion. Cusp height is the vertical distance from the annular plane to the top of the cusp commissural attachment. This measurement is likely more reproducible than leaflet length.

The risk of indirect CO by sinus sequestration is higher when the annular diameter is larger than the STJ diameter, and the cusp height is higher than the STJ height.[21] Similarly to VTC, the virtual distance from the THV to the STJ (VTSTJ) distance should be calculated. Figure 1 shows a schematic representation of the measures related to a predictive value for CO.

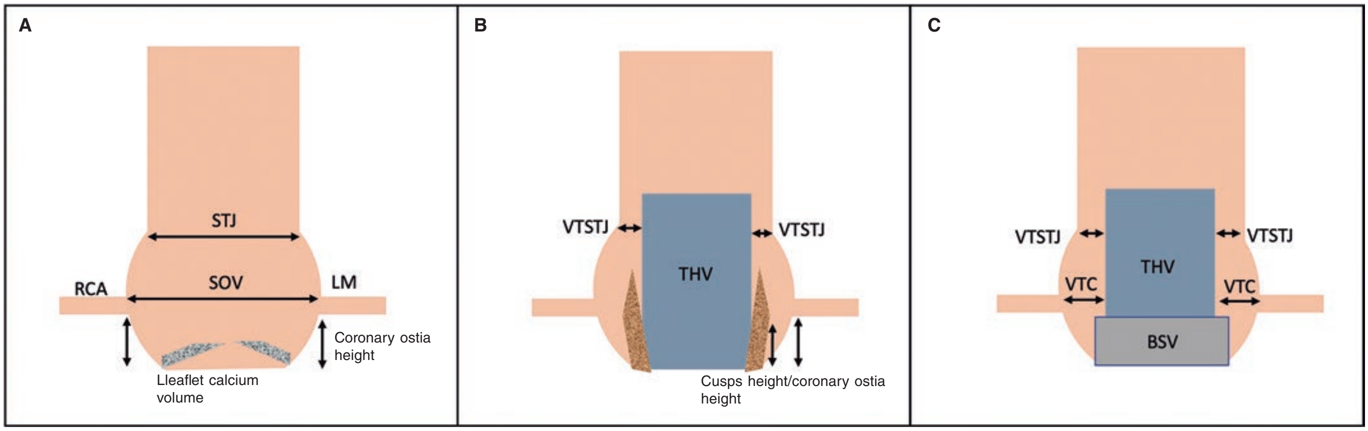

Figure 1. Schematic representation of the aortic root and CO predictors. **A:** native aortic valve. Coronary ostia height and the width of the SOV are predictors for CO. Leaflet calcium volume could also influence outcomes in this setting. **B:** displaced cusps of a native aortic valve displaced by a THV are represented in this figure. A narrower VTSTJ and a greater height of the cusps in relation to the height of the coronary ostia have been related to the risk of CO. **C:** aortic root with a BSV. ViV TAVI is a risk factor *per se* for CO; however, this is increased with shorter VTC distances. On the other hand, a tight STJ has been suggested as another factor contributing to the risk of CO. BSV, biological surgical valve; LM, left main; RCA, right coronary artery; SOV, sinus of Valsalva; STJ, sinotubular junction; THV, transcatheter heart valve; VTC, valve to coronary; VTSTJ, virtual distance from the THV to the STJ.

Khan et al. have developed a predictive algorithm to assess the risk of CO.[4] The algorithm considers cusp height greater than coronary height and either VTC ≤ 4 mm or culprit leaflet calcium volume > 600 mm^3. The model exhibited excellent performance in predicting LM and RCA ostia obstruction. Figure 2 shows a flowchart for assessing the risk of CO in patients with native aortic valves.

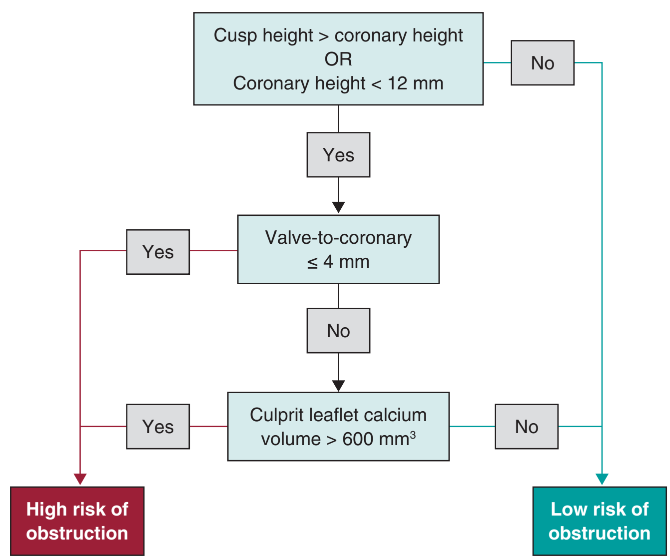

Figure 2. Evaluation of coronary obstruction risk in patients undergoing TAVI for native aortic valves.

Patient characteristics associated with CO

Female sex has been associated with a higher incidence of CO. Approximately 80% of the patients in the CO registries are women.[18] This association is likely due to the anatomical differences between the sexes. Women tend to have a smaller aortic root, smaller SOV dimensions, and a lower coronary ostia height.[19]

Regarding patient history, prior coronary artery bypass has been associated with a lower incidence of symptomatic CO due to the "protective effect" of providing alternative blood flow.[18] However, graft patency should always be evaluated before the TAVI procedure.[22]

Procedural factors affecting CO

THV type may be related to outcomes. Balloon-expandable valves are associated with a higher risk of acute CO than self-expandable valves.[11,18] This difference could partly be explained by the frame characteristics and the implantation mechanism.[18] However, a later registry assessing delayed CO showed that self-expandable valves were associated with higher rates of this complication than balloon-expandable valves. This is likely because self-expandable valves are nitinol-based and continue to expand after initial deployment.[9] Other factors that could contribute to CO in this setting are flow stagnation and device micromigration. Jabbour et al. have postulated that endothelialization and thrombus embolization could be implicated in late delayed CO.[9]

Bioprosthetic surgical valves and valve-in-valve TAVI

TAVI have become a new alternative to SAVR in patients with a failed biological surgical valve (BSV) and high or prohibitive perioperative risk.[1,2] Valve-in-valve (ViV) TAVI accounts for approximately 5% of all TAVI procedures in the United States.[23] The CO rate is 4- to 6-fold higher in ViV procedures than in native valves.[9] The higher CO risk is probably related to the supra-annular design of most BSVs, lowering coronary ostia height, while valve suturing draws the coronaries closer, with a consequent reduction in sinus width.[24]

Comprehensive preprocedural report must be obtained.[23] The details of the previous intervention must be investigated, including the exact model and size of the BSV.[25] This differentiation is crucial because stentless (eg, Freedom [Sorin Biomedica, Italy], Toronto SPV [St Jude Medical, United States], Freestyle [Medtronic, United States]), and stented valves with externally mounted leaflets (eg, Mitroflow [Sorin Biomedica, Italy], Trifecta [St Jude Medical, United States]) have a higher risk of CO.[25] Ribeiro et al. have reported a significantly higher incidence of CO in patients with stentless valves (3.7%) and stented vales with externally mounted leaflets (6.4%), compared with those with stented valves with internally mounted leaflets (0.7%). Furthermore, in the same registry, the presence of these types of valves was demonstrated to be an independent predictor for CO.[7]

The VTC distance estimated by CT is one of the most accurate predictors of CO following a ViV TAVI.[7,26] The coronary ostia height and the mean diameter of the SOV must be considered.[3,7,15] Another potential anatomical risk factor for CO in a ViV procedure is a narrow STJ, as well as supra-annular position and high leaflet profile of the BSV.[27,28]

Redo-TAVI. Implications for coronary artery obstruction

The current trend in the treatment of aortic disease suggests that shortly, patients with longer life expectancies will undergo TAVI instead of SAVR.[29] Thus, redo-TAVI will probably play a central role in treating patients with failed THV. However, data on predictors to avoid complications in this setting are still scarce.

In some of the first registries and systematic reviews assessing redo-TAVI or TAVI-in-TAVI, researchers reported very low rates of periprocedural complications, ranging from zero to only 0.9% of CO.[30-32] This is likely due to the careful evaluation of the anatomy with knowledge of the predictive factors discussed above, ruling out patients at higher risk and leading to selection bias.

Redo-TAVI procedures could be related to CO risk and impaired coronary access.[33] The implantation of a second THV overlaps the stent frames of the 2 prostheses, with possible compression of the leaflets of the first THV, creating a covered cylinder up to the edge of the leaflets.[34] Overlapping of the stent frame and loss of free flow can impair both coronary flow and the possibility of cannulation.

In patients undergoing TAVI-in-TAVI, the STJ is critical in accessing the coronary arteries and acts as an anatomical bottleneck: a higher and broader STJ will leave more space between the first THV and the aortic wall and, therefore, easier access to coronary ostia and a lower probability of flow impairment.[34] The height of the leaflets of the first THV implanted also could affect access and flow. Previous THV with supra-annular leaflets and THV with high implantation could lead to a higher risk of interaction with the STJ and impairment of the flow in the case of a second THV.[34,35] Therefore, it was suggested that the VTSTJ should be calculated, especially in TAVI-in-TAVI and ViV TAVI.[36]

Tarantini et al. suggested an algorithm to predict the risk of CO and the feasibility of future coronary access. These authors considered CT evaluation of the coronary ostia height in relation to the first THV, a distance of 2 mm from the THV to the aortic wall, and confirmation of feasible coronary cannulation with the prior valve in place. If the coronary ostia are below the risk plane of the prior THV, the distance to the aortic wall is < 2 mm, and coronary cannulation is not possible, then TAVI-in-TAVI is considered unfeasible.[33,37] The width of the aortic root again shows its importance in the risk of CO in this setting.

Redondo et al. have also highlighted another aspect to consider in the planning and execution of a TAVI-in-TAVI procedure: the alignment of the commissural posts of the previous THV with the actual localization of the coronary ostia. If a patient with a previous TAVI has a high risk of CO, intentional laceration of the bioprosthetic or native aortic scallop can be applied to prevent iatrogenic coronary artery obstruction during the TAVI (BASILICA) technique and mitigate the risk. This strategy, which consists of lacerating the previous leaflet to allow normal coronary flow and will be more fully described below, can be ineffective if there is inadequate alignment of the coronary ostia in relation to the commissural posts of the first THV. This can be caused by an eccentric location of the of the coronary ostia.[38]

STRATEGIES TO PREVENT CORONARY ARTERY OBSTRUCTION AFTER TAVI

As we have repeatedly emphasized, the first and most crucial step for preventing periprocedural TAVI complications is an exhaustive imaging evaluation and adequate planning. If CO is considered highly likely to occur, a risk reassessment could favor SAVR. An excessive surgical risk that mandates continuing with the transcatheter strategy requires coronary protection techniques.[22]

Coronary wire protection

This is the simplest protection technique in the setting of TAVI with a high risk of CO and was one of the first protective strategies reported. The technique involves placing a 0.014-inch coronary guidewire in one or both arteries through guiding catheters after crossing the aortic valve with the stiff wire. Depending on the operator's preferences, an angioplasty balloon ranging from 2.5 mm to 3.5 mm in diameter is advanced through the coronary wire to prepare a dilatation if there is a sudden occlusion.[14,39,40] If acute CO occurs, the coronary wire is be used to perform an ostial angioplasty with a balloon or the implantation of a stent to recover coronary flow.

The safety and feasibility of this technique have been demonstrated in previous reports.[13,14] However, there is a need for more evidence from randomized clinical trials, which may hinder the generalizability of the effectiveness of this approach. In addition, the absence of standardized procedural guidelines can contribute to variability in its application and outcomes. Despite these challenges, the most significant concern remains the persistent risk of occlusion even after the wire has been removed, as demonstrated in the Spanish Society of Cardiology registry.[5]

Chimney/snorkel stent technique

The chimney stent technique is a strategy involving the placement of a coronary guidewire with an undeployed stent in one or both coronary arteries, implanting the stent if CO occurs, so that it protrudes outside and above the coronary ostium, resembling a "chimney" or a "snorkel." First reported by Chakravarty et al., this strategy was initially used to treat an anticipated acute CO of the LM coronary artery in a patient with a degenerated BSV.[41] Several cases reports have shown its effectiveness and safety.[42,43]

Clinical follow-up has found acceptable mid-term outcomes (follow-up time of 612 days, interquartile range: 405-842 days) in a registry, with only 1 case of stent failure and 1 case of possible late stent thrombosis.[44] Longer follow-up results are required to respond to concerns about stent-related outcomes. Difficult coronary re-access through the "snorkel" is to be expected, which raises doubts if there are subsequent coronary complications. Potential mechanisms for eventual stent failure include persistent turbulent flow across the THV and the stent, galvanic corrosion, and local inflammatory processes.[10]

Procedural details

The chimney technique involves a series of critical steps. These steps, which may vary slightly across different cath-labs, are based

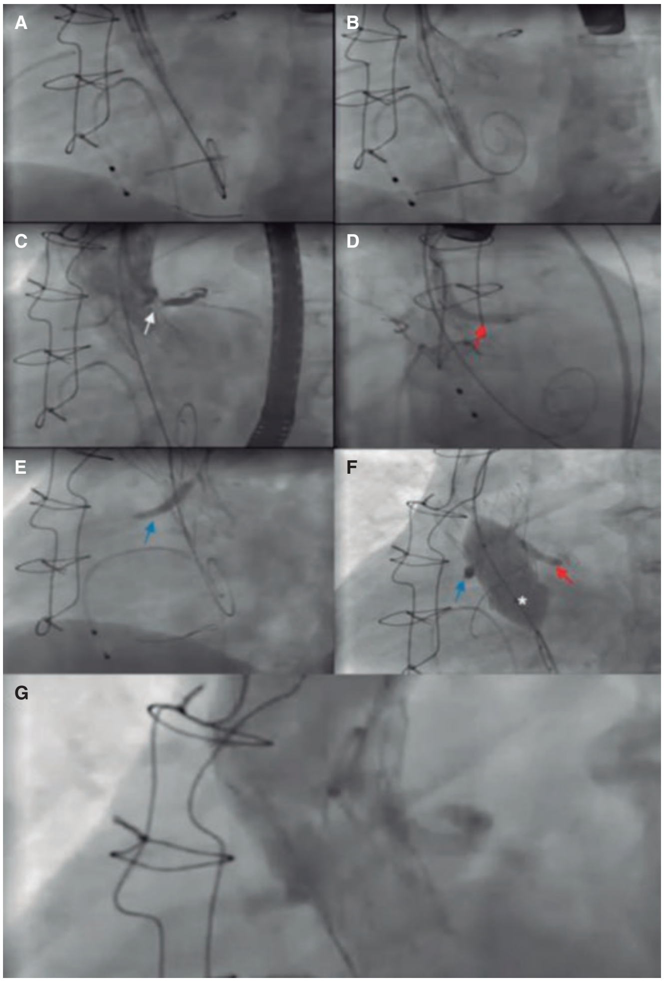

Figure 3. Main steps of a valve-in-valve (Freedom valve [Sorin Biomedica, Italy]) transcatheter aortic valve implantation in which a bilateral chimney technique is used to protect both coronary arteries. **A:** before valve implantation, undeployed drug-eluting stents were positioned in the right coronary artery (3.5 × 28 mm) and the LM (4 × 33 mm) in preparation for percutaneous coronary intervention in case of acute coronary obstruction. **B:** then a Portico valve (Abbott Vascular, United States) is advanced, and deployment is started. **C:** during valve deployment, contrast injections were performed to assess coronary ostia patency. The moment of the occlusion of the LM ostium is observed (white arrow). **D:** given the acute coronary obstruction, the stent of the LM is implanted (red arrow). **E:** posteriorly, due to the high risk, the stent of the right coronary artery is also implanted (blue arrow). **F:** postdilatation with a valvuloplasty balloon (*) was chosen to improve the expansion of the transcatheter heart valve. To avoid compression of the stents, the balloons of the stents were inflated at the same time as the aortic balloon. **G:** final angiographic follow-up shows both ostia patency and the absence of aortic regurgitation. LM, left main.

on existing literature and experience. As with any complex procedure, it must be performed by an experienced interventional team. Figure 3 shows an example of a real case using the chimney/snorkel technique to protect a patient at high risk of CO.

First step: patient assessment

- A thorough preprocedural evaluation is crucial. The procedure should be performed after the patient is discussed in a Heart Team composed of clinicians, interventional cardiologists, and cardiac surgeons with sufficient expertise.

Second step: vascular accesses

- Obtain radial access for the secondary access (Pigtail catheter). When protecting both coronaries, guiding catheters may be used for contrast injections to direct THV implantation and assess ostia patency.
- Common femoral artery access for THV implantation or alternative access if needed.

Use the contralateral femoral artery to access a guiding catheter for coronary protection. Ideally, a 7-Fr catheter (Extra back-up [EBU] or Judkins left [JL] for the LM, and Judkins right [JR] for the RCA).

- Obtain venous access for the pacemaker, if required.

Third step: preparation of coronary protection and THV deployment

- Cross the aortic valve and position the TAVI guidewire in the left ventricle (LV).
- Position the 0.014-inch coronary guidewire in the artery at risk.
- Advance stents over the coronary guidewires, ensuring they are long enough to anchor and protrude above the THV leaflets. A guiding catheter extension may be used to protect the stent from interacting with the THV.
- Perform valvuloplasty, if needed, and assess coronary flow during the process.[8,42]
- Advance the THV through the LV wire and deploy it, monitoring coronary flow using contrast injections.

Fourth step: stent deployment and postprocedure evaluation

- If the coronary flow is affected during THV implantation, pull up the undeployed stents protruding into the aorta, and deploy them.
- Maintain a low threshold for stent implantation, as recrossing the THV structure can be challenging.
- Consider flaring the proximal segment of the stent with a balloon to improve the possibility of reaccessing the coronary arteries.
- Perform postdilatation if needed, using a "kissing balloon" technique to avoid coronary stent crushing.[43]
- Conduct a final echocardiographic and angiographic evaluation to confirm successful results before ending the procedure.

Postprocedural treatment

The optimal antiplatelet therapy for these patients is uncertain. Maintaining dual antiplatelet therapy (aspirin plus clopidogrel) for at least 6 months is generally recommended. However, in the elderly population with comorbidities, bleeding risk should be considered. For patients on anticoagulants, triple therapy may be used for 1 week, followed by dual therapy (clopidogrel plus anticoagulant) for 3 to 6 months before continuing with the anticoagulant alone. More evidence is needed to determine the best strategy in these cases.

The BASILICA technique

The BASILICA technique is another strategy suggested to prevent CO. This strategy was developed as a pre-emptive measure before THV implantation, lacerating the leaflets to prevent their compression against the coronary ostia, which could lead to acute occlusion.[24,45] Creating a "triangle of flow" facilitates blood flow to the coronary artery.[46] BASILICA was designated as an alternative to stent-based techniques, which may have limitations such as potential extrinsic compression, unknown long-term thrombosis risk, and challenges in coronary access.[10]

Khan et al. reported 30-day outcomes for 30 patients who underwent BASILICA, with no CO reported and successful procedures in 28 patients. Safety outcomes, including major cardiovascular complications, stroke, kidney injury, and death, were reported in 70% of patients but were unrelated to BASILICA.[36] Recently, we demonstrated that this procedure can be performed with a very low risk of major cardiac adverse events and a high success rate in patients with native and prosthetic aortic valves.[47] Hemodynamic instability after valve laceration was rare and resolved after THV implantation. The unsuccessful procedures were probably due to significant calcification of the leaflets, avoiding their perforation before splitting.[45] One-year follow-up results indicated no additional strokes or myocardial infarctions, with only 2 more deaths.[48] Kitamura et al. reported even better results, with no major vascular complications, need for mechanical circulatory support, stroke, or mortality at 30 days.[49] The applicability of the BASILICA technique to failed THV is limited due to the design of some THV types and commissural alignment. Benchtop models found that leaflet splitting was effective in older generation Sapien XT valves but was less effective in the newer Sapien 3 (Edwards Lifesciences, United States) and EVOLUT (Medtronic, United States) valves.[50] Furthermore, even in the case of a feasible laceration, the new THV commissures might align unfavorably. In addition, positioning the new THV skirt too high may obstruct the lacerated leaflet.

Contraindications have yet to be clearly defined, but the technique may be ineffective in cases with extremely narrow SOV, eccentric coronary ostia, or highly calcified cusps. Additionally, it should be avoided in cases of endocarditis or valve thrombosis.[46] Regarding eccentricity, this could be one of the most important obstacles for an effective protection of the coronary ostia, especially in patients undergoing a TAVI-in-TAVI procedure, as Redondo et al. have suggested in a previous publication. In these cases, if the coronary ostia are located in an eccentric position within the SOV, the laceration will probably not be aligned with the ostia, suppressing its efficacy.[38]

Procedural details

The procedure should be performed with transesophageal echocardiographic (TEE) guidance to ensure the best outcomes and facilitate the approach, and general anesthesia is mandatory. Some operators prefer the use of intracardiac echocardiography and in these cases general anesthesia is not necessary. Figure 4 shows a ViV TAVI procedure using the BASILICA technique to protect the LM due to the high risk of occlusion.

First step: patient assessment

- Careful assessment must always be conducted for patients undergoing a TAVI procedure. Procedural planning must involve multi-imaging assessment, with CT images playing a central role.

Second step: vascular accesses

- Initially, at least 3 arterial accesses are needed for this technique (figure 5).[24]

- A 14-Fr sheath (at least) is used for the primary access. A Dryseal sheath (GORE, United States) is recommended as it can accommodate 2 guiding catheters and maintain hemostasis. One guiding catheter (7-8F) is used to perforate the leaflet, and the other is a pigtail placed in the LV.

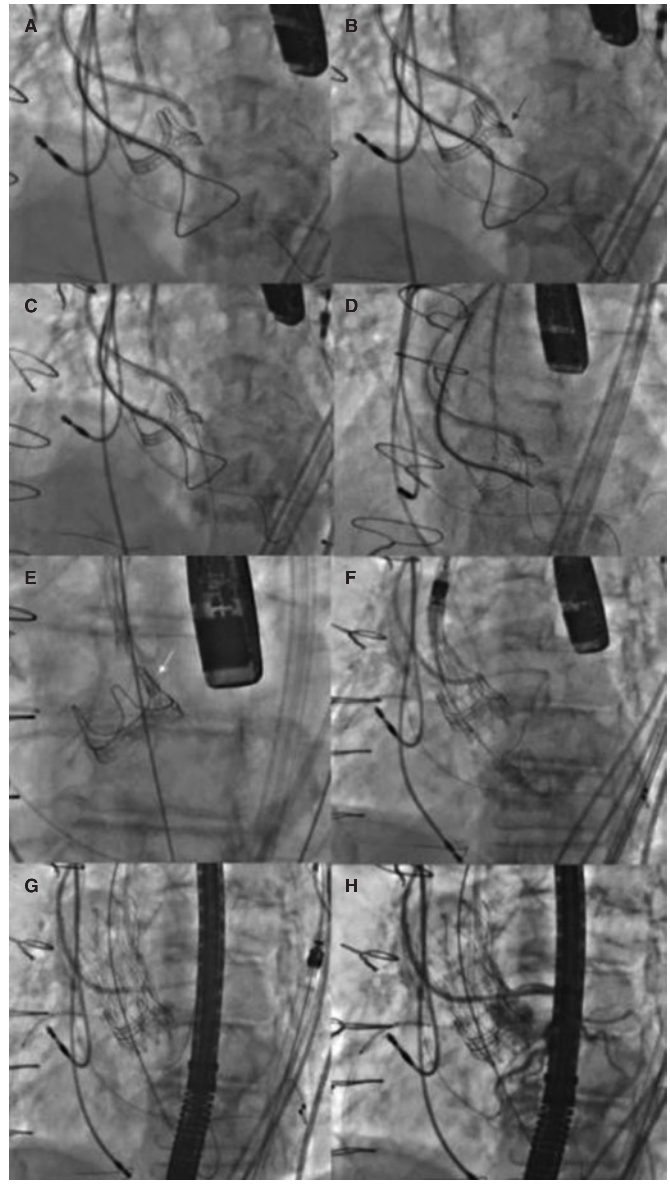

Figure 4. Main steps of a valve-in-valve transcatheter aortic valve implantation with BASILICA technique. **A:** first, a guiding catheter JR (8-Fr) was placed in the left ventricle with a snare, and a pigtail in the ascending aorta for an aortogram. A diagnostic JR (5-Fr) inside a guiding catheter AL 3 (8-Fr) was placed above the aortic prosthesis leaflet with a Finecross 130 microcatheter and an Astato XS 20 guidewire (Asahi Intecc, United States) inside. **B:** once the optimal perforation spot in the left cusp was identified using echography and angiography and the guidewire was correctly positioned, it was electrified, and the leaflet was perforated (red arrow). **C:** then, the wire was trapped with the snare placed in the left ventricular outflow tract, and it was pulled inside the guide catheter JR **(D, E)** before the externalization of the wire; a "V-shape" was performed in the middle part of the wire. Then, it was advanced, and when the "V-shape" contacted the leaflet (E, white arrow), the wire was electrified again while it was pulled at both ends, lacerating the leaflet. **F, G:** a self-expandable transcatheter heart valve was implanted, and coronary patency was finally confirmed **(H)**. BASILICA, bioprosthetic aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction; JR, Judkins right.

- If the iliofemoral anatomy is complex, we recommend using a femoral sheath that can be deployed to advance the THV. By doing this, the interventional cardiologist can ensure that the THV advances smoothly after lacerating the leaflet.

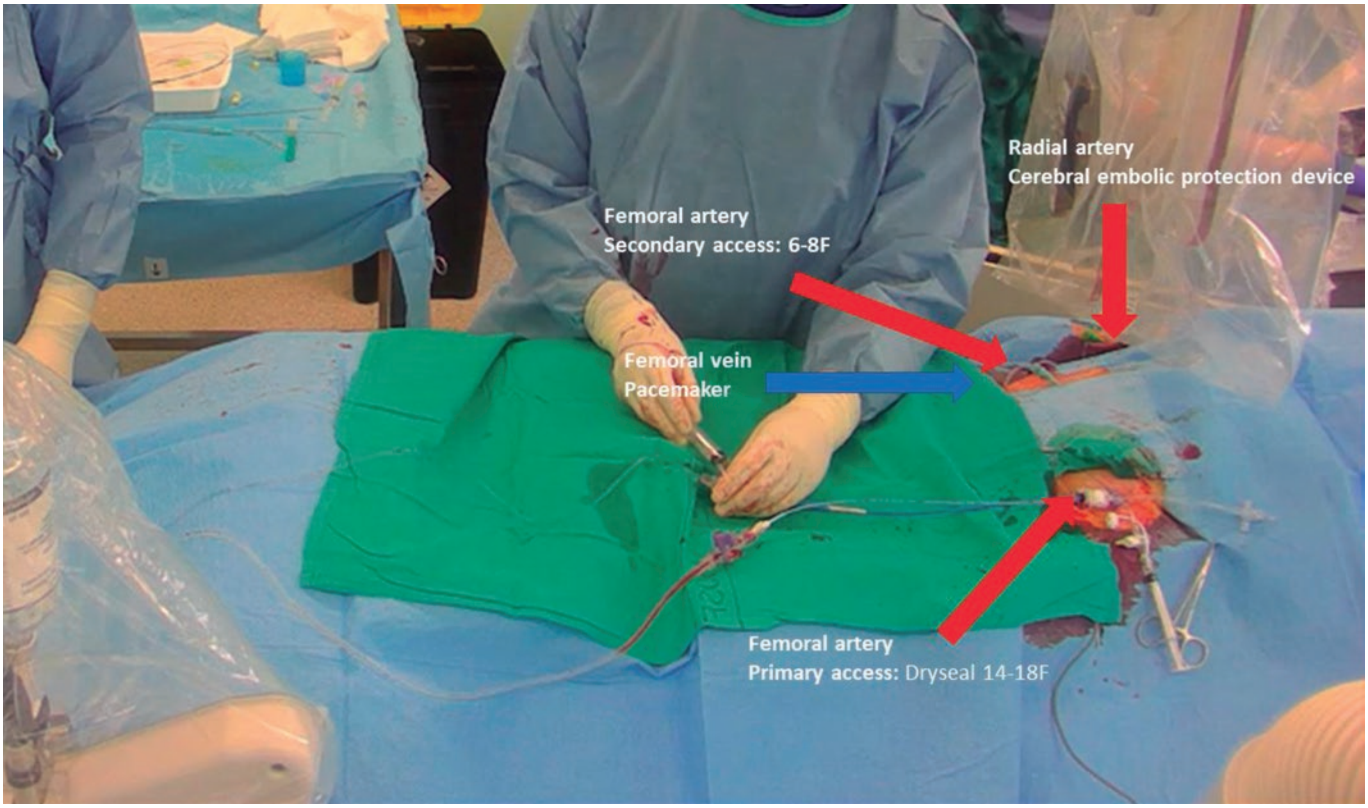

Figure 5. Patient setup with 3 arterial accesses —right radial for cerebral embolic protection device and 2 femoral— and 1 venous access for temporary pacemaker.

- The second access is placed in the contralateral common femoral artery to insert a catheter which is used to position a snare in the LV.
- The third access is inserted in the radial artery to place a cerebral embolic protection device (Sentinel [Boston Scientific, United States]).
- If needed, venous access should be obtained to implant a temporary pacemaker.

Third step: leaflet perforation

- The aortic valve should be crossed, and a 6-Fr multipurpose (MP) guiding catheter is placed in the LV outflow tract (LVOT). Using the MP, a goose neck snare with the size of the LVOT (20-30 mm) is positioned in the LVOT. Parallel to the snare, using the same MP catheter, a 0.018 wire is placed into the LV, reaching the apex; this wire allows the snare to be redirected into the LV if it is pulled out. Instead of an MP, a 6-Fr JR could be used, depending on the angulation of the anatomy.
- Subsequently, different catheters should be chosen, ideally, a 7-8F, depending on the cusp that needs to be lacerated. To approach the left cusp, an Amplatz left (AL) 3 is the first option; however, depending on the aortic root anatomy, an AL1, AL2, AL4, EBU 3.5, and 4, can also be used. For the right cusp, an MP is usually used, or a JR if the aorta is angulated.
- To perforate the left cusp, a diagnostic long 5-Fr catheter is typically needed inside the 8-Fr catheter (mother-and-child). The first option is a 125 cm diagnostic internal mammary or JR 4 catheter.
- With a telescope of devices, a 300 cm wire (suggested: Astato XS 20 300 cm [Asahi Intecc, United States]) with a microcatheter, both inside the 5-Fr internal mammary and the 8-Fr guiding catheter.
- The telescope of devices is oriented toward the base of the target cusp, with the correct orientation to avoid undesired perforations guided by fluoroscopy and TEE. The target leaflet should be projected in 2 fluoroscopic angles, "front view" and "side view". These projections, estimated using CT assessment, help achieve an accurate approach to the leaflet. Contrast injections can further assist in estimating the spatial relationship of the valve (figure 6).
- Once an optimal position of the "telescope" with a correct "attack angle" is achieved, leaflet perforation is attempted. The catheters and wire complex are propped, and the microcatheter is brought closer to the leaflet. The wire is then electrified to perform perforation.
- To electrify the wire, its back is scraped about 1 to 3 cm with a scalpel blade until the metal part is exposed, then connected to an electric pencil with a mosquito clamp. The electrosurgical generator is set to "pure cut" mode, and the power is set according to the leaflet; 30 watts for porcine, 50 watts for bovine or native, and 70 watts for severely calcified leaflets. Electrification should be brief (less than a second) and stopped immediately after the wire crosses the leaflet.[46]
- After perforation, the 300 cm wire is positioned in the LVOT, attempting to cross it through the snare. Snaring should be performed high in the LVOT to prevent mitral valve injury.

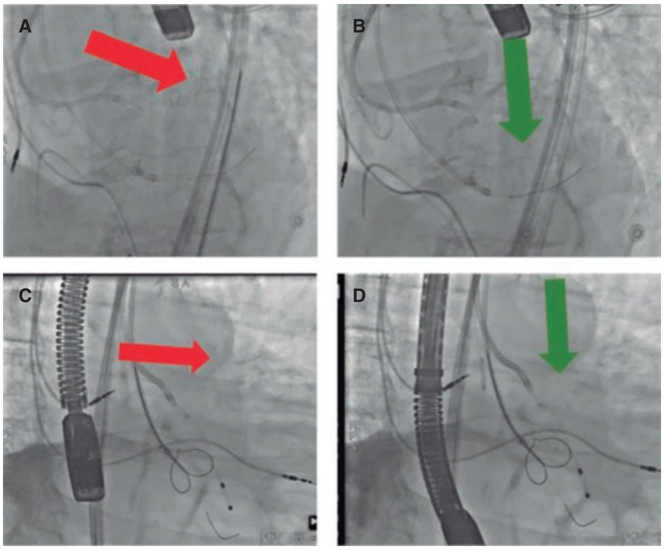

Figure 6. Catheter orientation for leaflet perforation. **A:** side view with off axis direction. **B:** side view with correct direction. **C:** en-face view with off axis direction. **D:** en- face view with correct direction.

Once snaring is achieved, the 300 cm wire is pulled inside the snare guide without externalizing the wire.

- TEE guidance should be used to ensure that the wire is not entangled with the mitral apparatus.

Fourth step: THV preparation

- After perforating the leaflet and before performing the laceration, prepare the THV to ensure it is ready for prompt implantation once the leaflet has been modified, as leaflet perforation can be time-consuming. The valve cannot remain crimped for an extended period, which could increase the risk of THV damage.

- Once the leaflet has been perforated, the aortic valve should be recrossed to position a pigtail catheter from the arterial main access to proceed quickly with THV implantation if there is hemodynamic instability after the leaflet laceration.

Fifth step: leaflet laceration

- Before the externalization of the 300-cm wire, a "V-shape" must be created in the middle part of the wire. To create this V-shape, the wire must be kinked and denuded with a scalpel blade of about 10 mm in the kinked part (figure 7). Then, the wire is advanced until the V-shape is in contact with the leaflet.

- The microcatheter position is fixed with a torque device to identify the "flying V".

- Once the V-shape is in the correct place, the wire is pulled at both ends, coinciding with a new electrification of the wire with the pencil connected in the same place as that used for perforation. The power to be applied is higher this time and varies depending on the type of leaflet; 50 watts for a porcine valve, 70 watts for a bovine or native valve, and 100 watts for a severely calcified leaflet.

- Dextrose solution injection in each guide catheter may be performed simultaneously with the laceration. However, if the dextrose is not used, the catheters should be flushed before laceration to remove all blood content.

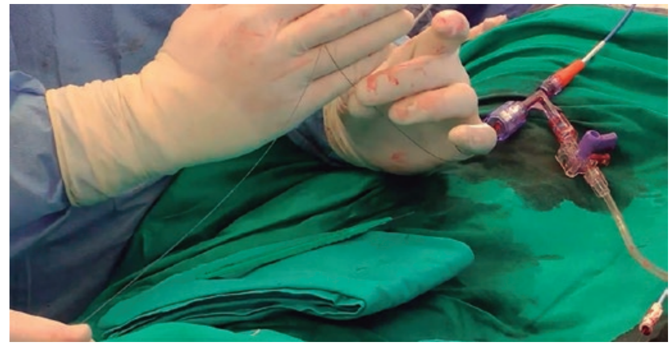

Figure 7. Astato XS 20 (Asahi Intecc, United States) with flying V for leaflet laceration.

- To avoid hemodynamic instability caused by prolonged laceration of a leaflet without THV implantation, both leaflets must be addressed simultaneously to protect both coronary ostia, if needed. This requires additional vascular accesses, such as using a 14- to 18 Fr sheath in 1 femoral artery for 1 leaflet and double access with 2 sheaths (6-8 Fr) in the other femoral artery or using another large sheath (14-18F) in the other femoral, but with increased bleeding and vascular risk.

Sixth step: THV implantation and postdilatation

- The THV should be implanted promptly after laceration. The catheters used for laceration are removed, and the pigtail placed in the LV is then used to advance the stiff wire for the THV implantation. The height of implantation should be balanced between the risk of high gradients with a low position and the risk of CO with implantation that is too high. Too high implantation can result in the skirt covering the "triangle of flow".[46] Recommendations for each kind of THV should be followed, attempting to keep the lower range of recommended depth, eg, for an EVOLUT Pro+ valve, (Medtronic, United States) 3 mm deep using cusp overlap projection. This is of particular importance in supra-annular THV.

- Operators should be highly cautious with postdilatation and BSV ring fracture in BASILICA procedures as they can increase the risk of CO.

- If the risk of CO is considered too high, operators can protect the coronary arteries with guidewires and undeployed stents at their discretion.[24]

- After THV is implanted, the patency of the coronary ostia must be checked with intra-aortic injection (preferred instead of selective injection). In addition, a TEE assessment would help to check the hemodynamic results and the absence of other potential complications.

- Like other TAVI, the procedure should conclude with proper hemostasis and checking of the accesses.

Splitting devices

The BASILICA technique has yielded promising results but is a complex procedure that requires a highly skilled team. The ShortCut (Pi-Cardia, Israel) was designed to simplify the laceration and splitting of the leaflets.[51] Initially intended for BSV, the devices comprise a handle, delivery system, and distal unit, introduced through a 16-Fr sheath to the common femoral artery. TEE guides its positioning, and it acts on the leaflet mechanically.[51]

Dvir et al. reported the findings of the preclinical and first-in-human experience using this device. These authors tested the device in 8 patients with failed BSV. In all patients, the TAVI procedure was successful without CO. They did not report any neurological events, and the patients were discharged with good clinical status.[51] although the initial results are promising, an evidence gap remains. The results of larger registries or even trials comparing it with the BASILICA technique could confirm the usefulness of this device in the future.

UNICORN procedure

The undermining iatrogenic coronary obstruction with radiofrequency needle (UNICORN) procedure is a novel technique aiming to address the CO risk in patients undergoing a TAVI-in-TAVI procedure. The first-in-man experience using this new strategy was reported by Chan et al. These authors used a coronary guidewire inside a telescoping system composed of a 7-Fr Amplatz left-1 guide catheter (Cordis, United States) and a 135-cm Navicross support catheter (Terumo, Japan) to traverse a prosthetic leaflet with the help of a radiofrequency impulse.[52] Once the leaflet was perforated, successive dilatations of the fenestration with balloons of increasing caliber were performed. The last step allowed a balloon-expandable valve to be advanced through the perforated leaflet and subsequently deploy the transcatheter valve.[52]

The implantation of the balloon-expandable valve through the fenestration finishes the laceration and entrapment of the previous leaflet, minimizing the risk of leaflet recoil obstructing the coronary ostium or embolization.[52] The first experience was successful and demonstrated the feasibility of this strategy; however, more data on long-term outcomes are needed.

CONCLUSIONS

To optimize outcomes in TAVI procedures, it is essential to identify patients at risk of CO. These patients can be best identified by a structured evaluation that includes specific CT measurements, such as cusp and coronary height, VTC distance, calcium volume, and other anatomical and procedural risk features. Coupled with appropriate preventive procedures, such as the BASILICA technique, this comprehensive patient assessment can mitigate the risk of CO. However, further research is needed to validate the different strategies and emerging dedicated devices that aim to prevent this complication. As TAVI procedures continue to expand, identifying and managing the risk of CO will remain an essential consideration for optimizing outcomes and improving patient safety.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used.

CONFLICTS OF INTEREST

A. Regueiro is a consultant for Abbott Vascular, Meril Life, and OpSens. X. Freixa is a consultant for Abbott Vascular outside the submitted work. M. Sabaté is a consultant for Abbott Vascular and iVascular outside the submitted work. None of the other authors have any conflict of interest to disclose.

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Review article

Atrial functional mitral regurgitation: was this new entity needed?

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ABSTRACT

Atrial functional mitral regurgitation (AFMR) has recently been the focus of numerous original articles and reviews. This entity has been highlighted by population aging, the increasing prevalence of heart failure with preserved ejection fraction and atrial fibrillation, and the advent of the transcatheter techniques for mitral valve repair. AFMR is phenotype of mitral regurgitation that presents specific diagnostic challenges and current guidelines do not provide strong recommendations for its management. Cumulative data show that the outcomes of patients with severe AFMR are poor if left untreated. However, new heart failure therapies and minimally invasive techniques may have a positive impact on the outcomes of these patients.

Keywords: Atrial functional mitral regurgitation. Diagnosis. Echocardiography. Edge-to-edge repair. Transcatheter mitral valve repair.

Insuficiencia mitral funcional auricular: ¿era necesaria esta nueva entidad?

RESUMEN

La insuficiencia mitral funcional auricular (IMFA) ha sido recientemente el foco de atención de muchos artículos y revisiones originales. El envejecimiento de la población, el aumento de la prevalencia de insuficiencia cardiaca con fracción de eyección preservada y fibrilación auricular así como el desarrollo de las técnicas transcatéter para la reparación de la válvula mitral han resaltado la IMFA, un fenotipo de insuficiencia mitral que presenta desafíos diagnósticos específicos y para el cual actualmente las guías no tienen recomendaciones sólidas para su tratamiento. Existe una importante acumulación de datos que sugieren que el pronóstico de los pacientes con IMFA grave es malo si no se tratan. Sin embargo, las nuevas terapias para la insuficiencia cardiaca y las técnicas mínimamente invasivas pueden tener un impacto positivo en el prognóstico de esos pacientes.

Palabras clave: Insuficiencia mitral funcional atrial. Diagnóstico. Ecocardiografía. Reparación de borde a borde. Reparación mitral transcatéter.

Abbreviations

AFMR: atrial functional mitral regurgitation.

The triad proposed by Prof. Carpentier is frequently used to characterize the mechanism of mitral regurgitation: etiology, lesion and dysfunction.[1] Fibroelastic deficiency, myxomatous disease, rheumatic heart disease and endocarditis are etiologies that directly cause lesions of the mitral valve, such as chorda rupture, excessive leaflet tissue, thickening and calcification of the leaflets, and subvalvular apparatus, and leaflet perforation. Consequently, the resulting mitral regurgitation has been classified as organic or primary mitral regurgitation. Ischemic heart disease, dilated cardiomyopathy and atrial fibrillation are etiologies that lead to mitral annulus dilatation and leaflet movement restriction. These lesions are considered secondary to the remodeling process of the left ventricle and atrium. Consequently, the resulting mitral regurgitation is considered secondary or functional. The approach to surgical repair has differed between primary and secondary mitral regurgitation. In primary mitral regurgitation, repair techniques have involved resection of the redundant scallop of the mitral leaflet, implantation of neochordae, the use of a pericardial patch

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(in leaflet perforation), and mitral annuloplasty to restore normal coaptation. In secondary mitral regurgitation, restrictive mitral annuloplasty is the mainstay technique.

The advent of transcatheter mitral valve repair techniques have underscored the importance of the assessment of the etiology of mitral regurgitation and characterization of the mitral valve apparatus, particularly focusing on mitral valve area, the leaflet length and motion, coaptation depth and length and location of the largest vena contract of the regurgitant jet.[2] These factors are key to select the patients with mitral regurgitation in whom a transcatheter edge-to-edge repair will be successful. Current guidelines outline the mitral valve characteristics that define the ideal, the challenging and the prohibitive anatomy of the mitral valve for successful transcatheter edge-to-edge mitral valve repair.[3] For patients with primary mitral regurgitation and anatomically suitable mitral valve apparatus who have high surgical risk or are deemed inoperable, transcatheter edge-to-edge mitral valve repair may be considered (class IIb). In patients with secondary mitral regurgitation and anatomically suitable mitral valve apparatus who have high surgical risk or are deemed inoperable and in whom coronary revascularization is not needed, transcatheter edge-to-edge mitral valve repair has a class IIa recommendation. In this last clinical scenario, there are currently many patients who have secondary mitral regurgitation due to atrial and mitral annulus dilatation and these patients are different from patients in whom the mitral regurgitation is caused by left ventricular dilatation and dysfunction. The surgical risk of patients with atrial functional mitral regurgitation (AFMR) is usually lower than the patients with ventricular functional mitral regurgitation and the evidence supporting the use of surgical vs transcatheter mitral valve repair remains elusive.

AFMR occurs in the setting of permanent atrial fibrillation or heart failure with preserved ejection fraction fraction[4-6] and is characterized by mitral annular dilatation, dysfunction, and the loss of atrial synchrony.[7] In patients with heart failure and preserved ejection fraction, left ventricular remodeling, characterized by concentric hypertrophy and increased stiffness, results in elevated left ventricular filling pressures that are transmitted to the left atrium. In response to these increased pressures, the left atrium undergoes dilatation as a compensatory mechanism to buffer the increased pressures and prevent their transmission to the pulmonary circulation. However, chronic left atrial remodeling leads to atrial dysfunction and mitral annulus dilatation, contributing to the failure of leaflet coaptation.[7]

The frequency of AFMR among patients with atrial fibrillation is reported to be up to 7%, while this figure can rise to 53% in patients with heart failure and preserved ejection fraction.[8] Furthermore, data from the large National Echocardiographic Database of Australia Registry reported frequencies of significant AFMR of 8% among patients with atrial fibrillation and no underlying structural heart disease, 28% in patients with long-standing atrial fibrillation, and 20% in those with heart failure and preserved ejection fraction.[9]

Based on various series, it is known that AFMR most commonly affects elderly female patients with a history of atrial fibrillation and arterial hypertension.[10] It is noteworthy that atrial fibrillation and heart failure with preserved ejection fraction often coexist, leading to greater remodeling, more symptoms, and worse clinical outcomes.[11] The diagnosis of AFMR is mainly performed with transthoracic and transesophageal echocardiography.[8] The main echocardiographic characteristics of AFMR include normal morphology and movement of the mitral leaflets with impaired coaptation due to mitral annulus dilatation, often with varying grades of calcification. Grading AFMR can be challenging as it is a dysfunction that depends on the patients' loading conditions. Additionally, the presence of atrial fibrillation adds complexity to AFMR grading due to beat-to-beat variability. It is crucial to consider the role of exercise echocardiography, which can reveal the presence of symptoms and detect severe AFMR during peak exercise. The induction of significant tricuspid regurgitation and pulmonary hypertension is also common during exercise. Exercise echocardiography may serve as the second step before other imaging techniques, such as cardiac magnetic resonance, to identify patients with severe AFMR.

The clinical implications of AFMR have been recently described.[8] The prognosis of severe AFMR under medical therapy is similar to that of left ventricular functional mitral regurgitation. Compared with patients with primary mitral regurgitation, AFMR was associated with worse survival and more heart failure hospitalizations. Importantly, patients with AFMR are less frequently referred to surgical mitral valve repair or replacement than patients with left ventricular functional mitral regurgitation or primary mitral regurgitation.[12] This is probably related to the pathophysiology of AFMR: guidelines recommend first to prescribe optimal medical therapy (in this case for heart failure with preserved ejection fraction) and achieve rhythm control (if atrial fibrillation is present) prior to intervention.[3] The evidence on the survival benefit of isolated surgical mitral valve repair for AFMR is scarce. Surgical mitral valve repair using complete rigid ring annuloplasty has shown a low reoperation rate and low recurrence of mitral regurgitation at 5 years of follow-up.[13]

Based on a large registry, machine-learning has identified 4 clusters of patients with mitral regurgitation undergoing transcatheter edge-to-edge mitral valve repair and with disparate clinical outcomes.[14] Patients in cluster 1 (isolated mitral regurgitation), characterized by dilated left atrium, preserved left ventricular ejection fraction, and 60% in atrial fibrillation showed the best survival while patients with cluster 4 (biatrial dilatation), characterized by extremely dilated left and right atria, left ventricular ejection fraction at the lower limit of normality and all of them in atrial fibrillation had the poorest outcomes.[14] These results were confirmed in an external cohort. However, the exact lesion of the mitral valve leading to mitral regurgitation remains unknown. Therefore, there may be patients with primary mitral regurgitation. Currently, there are no randomized clinical trials comparing the outcomes of surgical repair vs transcatheter edge-to-edge mitral valve repair for patients with AFMR.

The field of AFMR will attract significant attention since the prevalence of heart failure with preserved ejection fraction and atrial fibrillation, the main underlying pathophysiological etiologies of AFMR, will increase along with the aging of the population. New effective therapies such as sodium-glucose cotransporter-2 inhibitors,[15] glucagon-like peptide-1 agonist,[16] and early atrial fibrillation ablation techniques[17] may have an impact on the prevalence of AFMR. However, new trials focused on AFMR will be needed and, before then, we probably need to enhance the focus on this entity that has been largely neglected and considered as a bystander of other diseases. Precise diagnosis and characterization of AFMR are needed (figure 1). In addition, large registries reporting on the outcomes of AFMR under medical therapy and treated with surgical and transcatheter mitral valve repair techniques are needed to further delineate and design new randomized trials that will refine guideline recommendations. Therefore, establishing AFMR as a new entity was an unmet clinical need to provide the optimal, personalized treatment for each patient with mitral regurgitation.

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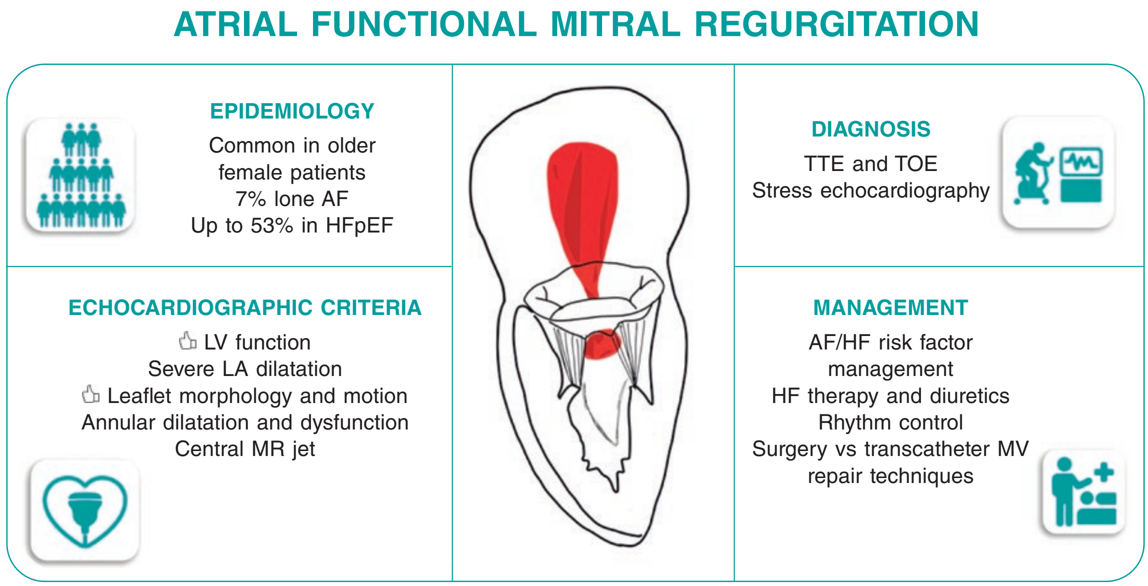

Figure 1. Characterization and management of atrial functional mitral regurgitation. AF, atrial fibrillation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; MR, mitral regurgitation; MV, mitral valve; TOE, transesophageal echocardiography; TTE, transthoracic echocardiography.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence-based tools have been used to draft this manuscript or to generate the figure.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows. Article conception and design: V. Delgado, S. Danojevic, M. De Raffele and L. Niro. Methodology: V. Delgado, S. Danojevic. Validation, M. De Raffele and L. Niro. Literature search: S. Danojevic, M. De Raffele and L. Niro. Writing—original draft preparation: S. Danojevic. Writing—review and editing: V. Delgado, M. De Raffele and L. Niro. Supervision: V. Delgado. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

V. Delgado has received speaker fees from Edwards Lifesciences, GE Healthcare, Novartis and Philips; consulting fees from Novo Nordisk, MSD, and Edwards Lifesciences. The remaining authors have no conflicts of interest.

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Debate. Ablation vs lithotripsy in calcified coronary lesions. Perspective from lithotripsy

A debate. Ablación frente a litotricia en lesiones coronarias calcificadas. Perspectiva desde la litotricia

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Question: Although we will discuss the aspects of 2 plaque modification techniques, please explain when you resort to intravascular imaging modalities in cases of calcified lesions and how that helps you.

Answer: Undoubtedly, intracoronary imaging modalities are an essential tool for interventional cardiologists in dealing with the assessment and treatment of calcified lesions. As we all know, revascularization of these lesions is associated with a higher rate of short- and long-term cardiovascular events, related to a greater risk of stent underexpansion and intraoperative complications.[1] In calcified lesions, simple angiographic assessment is insufficient because of its lower sensitivity in the detection of coronary artery calcification, and limitations in the identification of calcium distribution patterns.

In my opinion, since optimizing results is so important, the use of intravascular ultrasound or optical coherence tomography is mandatory in cases of moderate or severe calcification and helps us in several key aspects of the procedure. First, both intravascular ultrasound and optical coherence tomography have high sensitivity and specificity for calcium detection and its morphological characterization: pattern (nodular, parietal), angle, extent, and depth. With this information, we can select the best plaque modification technique for each case and evaluate its effect on the treated lesion. In recent years, several risk scores based on intracoronary imaging modalities have been developed, including decision algorithms for plaque modification systems based on calcium length, depth, and angle.[2]

Finally, imaging modalities allow us to be precise in selecting the size and length of the stent, as well as to assess its apposition and expansion, and rule out complications and residual disease. This aspect is crucial in the management of calcified lesions, where plaque modification devices can cause deep dissections and fractures, and we encounter more difficulties when trying to achieve adequate stent expansion.

Q.: In your opinion, what are the advantages and disadvantages of intracoronary lithotripsy?

A.: One of the main advantages for the implementation of intracoronary lithotripsy in the daily routine of cath labs is that it is technically simple and reproducible and does not require a long learning curve. The currently available intracoronary lithotripsy (ICL) system—Shockwave Medical, United States—consists of a specific semicompliant rapid-exchange balloon catheter with a 0.042-inch crossing profile, which is advanced inside the coronary arteries through a conventional 0.014-inch guidewire, and is compatible with a 6-Fr guide catheter. Once positioned in the lesion, the balloon is inflated to 4 atm with the sole intention of ensuring good contact between its surface and the vascular wall to facilitate energy transfer. Inside the balloon, there are 2 emitters that receive an electric discharge from the generator, vaporizing the liquid inside and generating sound waves that cause a local effect. The waves run through the soft tissues, causing selective calcium microfractures in the intimal and medial layers of the vascular wall. After pulse emission and the corresponding calcium modification, the balloon is inflated at 6 atm to maximize luminal gain.

On the other hand, compared with the limitations of noncompliant, very high-pressure, or cutting balloons, which in eccentric calcification can be directed toward noncalcified arterial segments with a risk of dissection at the fibrocalcific interface, ICL allows homogeneous calcium fracture. Another advantage is that ICL avoids the bias of having to follow the direction of the guidewire of rotational and orbital atherectomies, because it fractures calcium on superficial and deep layers circumferentially through acoustic pressure waves.[3]

Regarding complications, calcium fragmentation caused by the lithotripsy balloon remains in place, without distal embolization, thus reducing the incidence of slow-no reflow.[4]

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In terms of disadvantages, the main limitation of ICL is its crossing profile: it often requires lesion predilatation or combination with atherectomy techniques. Notably, the DISRUPT CAD III trial[5] reported ventricular captures during ICL pulses in 41.1% of the patients. Although the drop in systolic pressure is more common in patients in whom ICL induces ventricular capture, it has not been associated with the occurrence of adverse events, or sustained ventricular arrhythmias.

Q.: In which cases do you use intracoronary lithotripsy as a first-line approach?

A.: The available evidence on ICL comes from the DISRUPT CAD trials.[5-8] The most relevant of these trials, the DISRUPT CAD III,[5] is a prospective registry of 431 patients that assessed the safety and efficacy profile of the ICL balloon to treat calcified lesions. The 30-day rate of adverse cardiovascular events (death, myocardial infarction, or target lesion revascularization) was 7.8%, and the effectiveness rate (procedural success with in-stent stenosis < 50%) was 92.4%. This trial included patients with severely calcified de novo lesions and excluded those with acute myocardial infarction and aorto-ostial or bifurcation lesions.

As I mentioned previously, with the data provided by imaging modalities on calcium distribution and depth, we could consider ICL as the first-line approach to treat concentric calcified lesions with circumferential calcium distribution, especially in cases of deep calcium deposits, where ICL has proven more effective than other plaque modification techniques. Furthermore, ICL is effective in large-caliber vessels since balloons can be up to 4 mm in diameter.

One of the most common scenarios in which ICL is used in routine clinical practice is in calcified lesions that cannot be dilated with conventional or high-pressure balloons. This indication accounts for up to 75% of the cases in real-world registries,[9] with very good results, and a procedural success rate of 99%.

Q.: Which calcified lesions benefit most from intracoronary lithotripsy compared with rotational or orbital atherectomy?

A.: While we can't draw direct comparisons on the safety and efficacy results between ICL and rotational or orbital atherectomy because of the different inclusion criteria, stent types, and study endpoints among trials such as ROTAXUS[10] and DISRUPT-CAD, in clinical practice, we choose one technique over the other based on the characteristics of the lesion.

Although, as I will discuss later, both techniques are complementary, atherectomy is an excellent option to treat balloon-uncrossable calcified lesions. However, atherectomy targets superficial calcium shaving, less so the deep calcium deposits. Hence, ICL is a better choice for concentric calcified lesions with circumferential and deep calcium distribution.

Beyond the landmark studies, in recent years, numerous real-world experiences[11] have been reported, demonstrating the usefulness of ICL in specific and complex scenarios, such as:

- Calcified bifurcation lesions: information on the safety and efficacy profile of ICL in complex contexts is limited to case reports and short series of patients describing experiences in substrates such as bifurcation or aorto-ostial lesions with promising results. Unlike rotational or orbital atherectomy techniques, ICL is increasingly used because it allows us to work with 2 different guidewires easily and simplifies the procedure in this context.

- In-stent stenosis: Although this is an off-label use of ICL, there is growing evidence of the usefulness of ICL in both acute stent underexpansion and restenosis, especially in nondilatable lesions due to calcified neoatherosclerosis.[12] In the Spanish multicenter REPLICA registry[13] of 426 patients treated with ICL in routine clinical practice, a previously implanted stent was stenosed in 23% of the cases.

- Chronic occlusions: ICL can be useful to treat chronic occlusions with severe calcification, and its use has increased in recent years, as confirmed by a recently published subanalysis of the PROGRESS-CTO registry[14] with data from 82 patients (out of a total of 3301 included in the study [2.5%]) who underwent ICL. Indications were severe vessel calcification, or balloon nondilatable lesions. Technical success was achieved in 94% of the patients and procedural success in 90%.

- Acute coronary syndrome: available data on the use of ICL in calcified lesions in patients with acute coronary syndrome are scarce. These cases were excluded from the DISRUPT-CAD trials, and again, the experience reported in the medical literature is limited to short case series. However, as the REPLICA registry results show, where a high percentage of patients with calcified lesions treated with ICL presented with acute coronary syndrome (62.8%), this technique is commonly used in the routine clinical practice in this group of patients who require a quick and safe technique.

Q.: How do you integrate the 2 techniques into your protocol to treat calcified lesions?

A.: The combined use of the ICL balloon and other plaque modification techniques, such as rotational[15] or orbital atherectomy,[16] has shown promising results in short patient series, and seems to be a highly attractive strategy when the target lesion cannot be reached with the ICL balloon.

In my opinion, the combination of atherectomy and ICL techniques is a suitable option to treat diffuse, superficial, and deep calcium deposits. By combining the 2 techniques, we can leverage the advantages of each. On the one hand, atherectomy allows the advancement of the ICL balloon in long lesions with severe stenosis that prevent its passage. On the other, ICL is very useful in balloon nondilatable lesions after atherectomy. This combination of techniques can be particularly useful in one of the most complex scenarios: the management of calcium nodules.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in the preparation of this article.

CONFLICTS OF INTEREST

None declared.

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Debate. Ablation vs lithotripsy in calcified coronary lesions. The ablation perspective

A debate. Ablación frente a litotricia en lesiones coronarias calcificadas. Perspectiva desde la ablación

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Question: Although we will discuss the aspects of 2 plaque modification techniques, please explain when you resort to intravascular imaging modalities in cases of calcified lesions and how that helps you.

Answer: Intracoronary imaging modalities (optical coherence tomography [OCT] and intravascular ultrasound [IVUS]) allow us to optimize percutaneous coronary interventions, and their use in complex lesions improves the patient's prognosis.[1] They facilitate the following aspects:[2]

- Calcification detection and assessment: they have higher sensitivity and specificity than angiography for detecting calcium.[3] Also, they allow the evaluation of calcification characteristics, and various scores[4,5] have been developed that integrate variables associated with stent underexpansion.

- Selection of plaque modification technique: intracoronary imaging findings have an impact on the strategy used, which is why the use of advanced imaging modalities is advised in the presence of risk criteria for stent underexpansion.[2]

- Optimization of stent deployment: this is especially relevant in calcified lesions, which are the lesions most frequently associated with stent underexpansion, the parameter most often associated with stent failure.[2] Other parameters that should also be assessed are proper stent apposition, lesion coverage, the absence of dissection, and significant hematoma around the edges.[6]

Q.: In your opinion, what are the advantages and disadvantages of ablation, whether rotational or orbital?

A.: Ablation therapies, such as rotational atherectomy (RA), or orbital atherectomy (OA), and Excimer laser coronary angioplasty (ELCA), offer several advantages over intracoronary lithotripsy (ICL):

- Greater crossing ability: calcified lesions that result in very severe stenosis can be uncrossable with a balloon. In these lesions, the use of ablation techniques improves the rate of procedural success,[7,8] and probably, costs and safety.

- Ability to reduce plaque volume: an aspect that can be essential to optimize results.

- Treatment of long lesions and multivessel disease: ICL balloons are short in length, and display a maximum of 120 pulses per balloon. Also, balloons should be sized in a 1:1 ratio with respect to the vessel diameter, which complicates their use in multiple lesions. With RA, and especially with OA and ELCA, we can safely and effectively treat segments of different calibers without increasing costs.

The potential disadvantages of ablation therapies are:

- A longer learning curve: despite having specific technical aspects, ICL does not significantly differ from the plain old balloon angioplasty. Consequently, since it became available, the use of ICL has grown exponentially.[9] Ablation techniques require more operator (and nursing) training, which can limit their use.

- Need for specific angioplasty guidewires: ELCA can be used with 0.014-inch angioplasty guidewires, but both RA and OA require specific guidewires, whose characteristics have been improved to allow their use throughout the entire procedure, as with conventional guidewires. However, they can lead to more difficulties in directly crossing lesions and make the procedure more cumbersome due to their greater length and lower support.

- Side branch protection: although it can be performed using specific techniques, placing a side branch protection guidewire at a bifurcation during RA or OA is ill-advised. However, this is possible with ICL and ELCA.

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– Distal embolization: debris following the use of ablation techniques can be associated with slow-no reflow.

Q.: In which cases do you use ablation as a first-line approach? Are there any distinctions between rotational and orbital atherectomies?

A.: We usually use these techniques as the first-line approach in lesions so severely stenosed that they complicate balloon crossing or simply make it impossible (uncrossable lesions). The information provided by intracoronary imaging also plays a role in the decision to use ablation techniques as the first option. For some operators, the mere fact of being unable to cross the lesion with an IVUS or OCT probe is, *per se*, a criterion for using these ablation techniques. If intracoronary images are available, the presence of severity criteria, or the desire to reduce plaque volume encourages the use of advanced plaque modification therapies. Superficial concentric calcification with a very reduced luminal area would favor their use.

In terms of the differences among ablation techniques, in my opinion, the crossing ability of RA and ELCA is superior to that of OA, which therefore makes RA the preferred option to treat critical or uncrossable lesions. On the other hand, OA provides additional advantages over RA.[2,10] In the first place, we can treat vessels from 2.5 mm to 4 mm due to its mechanism of action (rotation associated with elliptical orbits) with a single 1.25 mm crown (compatible with 6-Fr) without increasing the size of the guide catheter. Also, the elliptical motion of this crown not only allows for superficial calcium shaving (like RA), but also exerts pulsatile forces against the wall that can modify deeper calcium deposits.[10,11] This orbital movement reduces wire bias compared with AR. Wire bias limits ablation, which is contact-dependent, to the vessel sector where the guide is located. In eccentric or nodular plaques, the guidewire may be displaced toward the opposite side of the vessel, thus minimizing the effect of RA on the plaque. Another interesting feature of OA is that the crown has a diamond coating across its entire surface (not just on the distal end, like RA crowns), allowing atherectomy to make forward and backward motions. The pullback mode modifies the ablation vector, potentially reducing wire bias even further. Furthermore, the debris produced by OA is theoretically smaller than those produced by RA. This, along with the fact that the crown does not impede coronary flow during atherectomy, reduces the risk of slow-no reflow and endothelial thermal injury.[10]

The main difference among ELCA, RA, and OA is that the former is the only ablation technique that is compatible with conventional coronary guidewires. Also, ELCA is compatible with 6-Fr guide catheters and allows for side branch protection. Also, it has beneficial effects in reducing thrombus and has proven to be safe and effective in peristent calcified lesions (restenosis or underexpansion).

Q.: Which calcified lesions benefit more from ablation compared with intracoronary lithotripsy?

A.: The calcified lesions that benefit the most from initial ablation rather than ICL are the most severely stenotic lesions, which are rarely crossable with a lithotripsy balloon as a first-line approach, and those with a large volume of plaque that we intend to reduce. Ablation techniques facilitate crossing these stenoses and are sufficient in many cases (when calcification is superficial, without significant thickness, and when calcified nodules are not involved) to allow adequate balloon or stent expansion, and complete the angioplasty. In addition, diffuse lesions in multiple segments, or vessels of different calibers can benefit more from ablation because they can be treated with a single RA, AO, or ELCA catheter.

Finally, although ICL can be safely performed in left main lesions, some patients (especially those with ventricular dysfunction or right coronary artery disease) can tolerate prolonged ICL balloon inflations poorly, and benefit from ablation techniques as a first option.

Q.: How do you integrate both ablation techniques into your protocol to treat calcified lesions?

A.: There are several algorithms for plaque modification techniques based on expert opinion. Evidence from comparative trials among the various techniques is scarce. Although randomized clinical trials are under way,[12] the lesion characteristics, clinical context, available resources, and operator capabilities should always be taken into consideration.

Intracoronary imaging modalities are essential to select the strategy. In general, it is useful to apply the rule of 5N:[2] advanced plaque modification techniques are advised to treat lesions where calcium occupies > 50% of the calcium arc (180°), extends longitudinally > 5 mm, is > 0.5 mm thick, or has calcified nodules. Additionally, the depth of calcium is important since some techniques, such as RA, can only modify superficial calcium.

Lesions that cause stenosis so severe that they cannot be crossed by IVUS or OCT probes will likely require RA, OA, or ELCA. RA may be the preferred choice for very stenotic lesions with superficial circumferential calcification, especially if they are uncrossable with a balloon and involve a nontortuous coronary segment. OA may be preferred to treat ostial, nodular lesions, or angulated segments. OA can also be useful in long lesions with significantly different proximal and distal vessel calibers. ELCA would be the preferred choice in lesions that cannot be crossed even with a microcatheter that allows exchange with RA or OA-specific guidewires. Also, ELCA could be the first option to treat peristent calcified lesions and those that combine calcium and thrombus.

ICL has the advantage of being a simpler technique and being able to modify deep calcium. ICL allows side branch protection without causing distal embolization of material. ICL can be the first choice if the lesion is crossable with a balloon, calcification is deep or thick, or it affects a true bifurcation. Additionally, ICL is an optimal technique for use in combination with ablation techniques when these do not allow adequate balloon expansion, or in complex lesions such as calcium nodules. Volume reduction and superficial calcium shaving with ablation techniques allows balloon ICL crossing. This completes plaque modification by fracturing deeper calcium deposits. This technique, initially described as rotatripsy[13] (RA and ICL), is increasingly being used. Combinations of ELCA and ICL,[14] or OA and ICL[15] are less common, but have also been reported.

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Artificial intelligence was not used in the preparation of this article.

CONFLICTS OF INTEREST

A. Jurado-Román is a proctor for Boston Scientific, Cardiovascular Systems, Inc., World Medica, and Philips-Biomenco.

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Scientific letter

Possible delayed effectiveness of intracoronary laser atherectomy

Posible efectividad retardada de la aterectomía láser intracoronaria

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To the Editor,

The excimer laser coronary angioplasty technique was first developed in the early 1980s. However, its safety and effectiveness have only improved in recent years, allowing its integration in an increasing number of cath labs. The technique has a triple mechanism of action: photochemical, photothermal, and photokinetic. When a mixture of hydrogen chloride and a noble gas such as xenon is exposed to a high-voltage electric field, an extremely unstable bond of chlorine and xenon atoms occurs. The separation of these atoms emits a photon which, when amplified, creates a high-energy laser.[1]

We report the cases of 3 patients, 2 with uncrossable lesions and 1 with rebel stent underexpansion, treated in our unit. Laser atherectomy, along with simultaneous intracoronary infusion of a physiological saline solution (using a 0.9 mm ELCA catheter, Spectranetics, United States), was unsuccessful at the first attempt. This was because, after its application, no other angioplasty devices (predilatation balloons, low-profile microcatheters, or rotational atherectomy guidewires) could be advanced in any of the uncrossable lesions. In the patient with underexpansion, effective dilatation with high-pressure noncompliant balloons after lithotripsy was also unfeasible. These are the only cases treated in our unit with failed laser therapy and a new angioplasty attempt in the culprit lesion. All patients signed a prior written informed consent form approved by the research ethics committee of our center and accepted to participate in the registry. The 3 patients were scheduled for lesion re-evaluation 7 to 8 days after the index procedure. Angiographic images showed a slight improvement in case #1 compared with the index procedure, unlike cases #2 and #3 whose angiographic images resembled those of the previous procedure. When we attempted to complete the coronary interventions, the previously uncrossable lesions proved perfectly accessible to treatment with rotational atherectomy, allowing the passage of the rotablator wire and use of appropriate plaque modification balloons. Both cases ended with successful drug-eluting stent implantation. In the case of stent underexpansion, effective postdilatation was performed with a noncompliant balloon (minimum luminal area gain from 4.7 mm^2 to 9.7 mm^2). The patients' good outcomes were confirmed using intracoronary imaging modalities. All the patients were eventually discharged the day after the procedure. The patients' clinical, anatomical, and baseline and follow-up procedural characteristics are shown in table 1. Figure 1 shows the angiograms and intravascular images of the 3 patients.

The hypothesis generated after these findings is that excimer laser therapy could induce a subacute molecular change (presumably due to the photochemical mechanism), which would cause internal changes to the plaque that would take a few days to fully establish and facilitate the subsequent treatment of the lesions with a failed first attempt at laser therapy.

Low-intensity laser therapy has demonstrated stimulating effects on various types of cells involved in wound healing and tissue regeneration through the photochemical mechanism. Although the onset of the process is immediate after tissue photon absorption, the cascade of biological responses triggered extends over time, with angiogenesis being an essential part of this process. Phototherapy has been extensively investigated to determine its effect on vessel formation. This therapy has demonstrated its ability to stimulate endothelial cells, fibroblasts, smooth muscle cells, and lymphocytes in vitro, in vivo, and in clinical settings. By triggering the activation of cytochrome c oxidase, leading to the production of nitric oxide, reactive oxygen species, and adenosine triphosphate in mitochondria, these molecules seem to act as secondary messengers that initiate the ERK/Sp1 and PI3K signaling pathways, which in turn leads to proliferation, migration, and proangiogenic factor synthesis.[2,3]

In the uncrossable lesions, changes were made to access in the second procedure (from radial to femoral access, and from a 6-Fr to a 7-Fr guide catheter in 1 procedure), which should have facilitated the advancement of materials (which would be the main limitation to the hypothesis raised in uncrossable lesions). However, in all 3 cases, the guide catheter support in the initial procedures was correct (aided in one of them with a Guideliner extension, Teleflex, United States). This, along with the limited relevance of support in the case of stent underexpansion, makes it unlikely that all the above can account for the dramatic change seen in the final outcomes.

In a recent registry of 126 uncrossable lesions treated with excimer laser,[4] primary success was achieved in 81.8% of cases and the success rate rose to nearly 90.5% when other techniques were used as bailout (mainly rotational atherectomy).[4] Similar success rates were reported in older registries,[5] where 90% seemed to be the

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Table 1. Clinical, anatomical, and procedural characteristics at baseline and at the follow-up

Patient	Case #1	Case #2	Case #3
Sex	Man	Woman	Man
Age (years)	54	72	72
Hypertension	Yes	Yes	Yes
Diabetes	Yes	Yes	No
Dyslipidemia	Yes	Yes	Yes
Smoking	Yes	No	Yes
Kidney disease	No (Cr, 0.82)	No (Cr, 0.41)	No (Cr, 1.26)
Indication	STEACS	Silent ischemia	Silent ischemia
Index procedure			
Vascular access	Radial 6-Fr	Radial 6-Fr	Femoral 6-Fr
Lesion location	Mid-right coronary artery	Mid-right coronary artery	Ostial right coronary artery
Initial TIMI grade flow	1	3	3
No. of laser pulses	38 812	11 780	28 654
Overall time of laser therapy (s)	501	169	365
Peak laser frequency and energy	80 Hz 80 mJ/mm²	80 Hz, 80 mJ/mm²	80 Hz, 80 mJ/mm²
Other plaque modification techniques	–	–	Noncompliant balloon Intracoronary lithotripsy (3.5 mm and 4 mm balloons)
Final TIMI grade flow	3	3	3
Follow-up procedure			
Days between procedures	7	8	7
Vascular access	Femoral 7-Fr	Femoral 6-Fr	Femoral 6-Fr
Initial TIMI grade flow	3	3	3
Other plaque modification techniques	Noncompliant balloon Cutting balloon Intracoronary lithotripsy (3.5 mm balloon) Rotational atherectomy (1.5 mm and 1.75 mm burrs)	Noncompliant balloon Rotational atherectomy (1.25 mm burr)	Noncompliant balloon
Intracoronary imaging modalities	OCT	IVUS	IVUS
After dilatation after stenting	Yes	Yes	Yes
Final TIMI grade flow	3	3	3

Cr, creatinine; IVUS, intracoronary ultrasound; OCT, optical coherence tomography; STEACS, ST-segment elevation acute coronary syndrome; TIMI, thrombolysis in myocardial infarction.

ceiling for the effectiveness of the technique, both alone and when used as part of a hybrid strategy. Other techniques have been described, such as applying laser therapy with simultaneous contrast injection instead of a physiological saline solution, to significantly increase the released energy. This can be useful in extreme cases like those reported above, although the risk of complications increases significantly.

Although the data referred to here may be considered of interest, they are, however, purely observational and are not based on previous experimental work, with their main value being their possible utility as hypothesis generators.

In patients with very unfavorable lesions and an apparently failed first attempt at laser atherectomy, it would be appropriate to consider a more conservative strategy (if allowed by the patient's clinical status), consisting of a second attempt at laser therapy, or another alternative plaque modification technique a few days later to achieve final procedural success. This could result in a lower risk of complications compared with some highly aggressive interventional procedures.

In addition, experimental and clinical trials should be conducted, with larger registries and even randomized clinical trials, in patients treated with failed attempts at the laser technique to confirm or refute the hypothesis raised.

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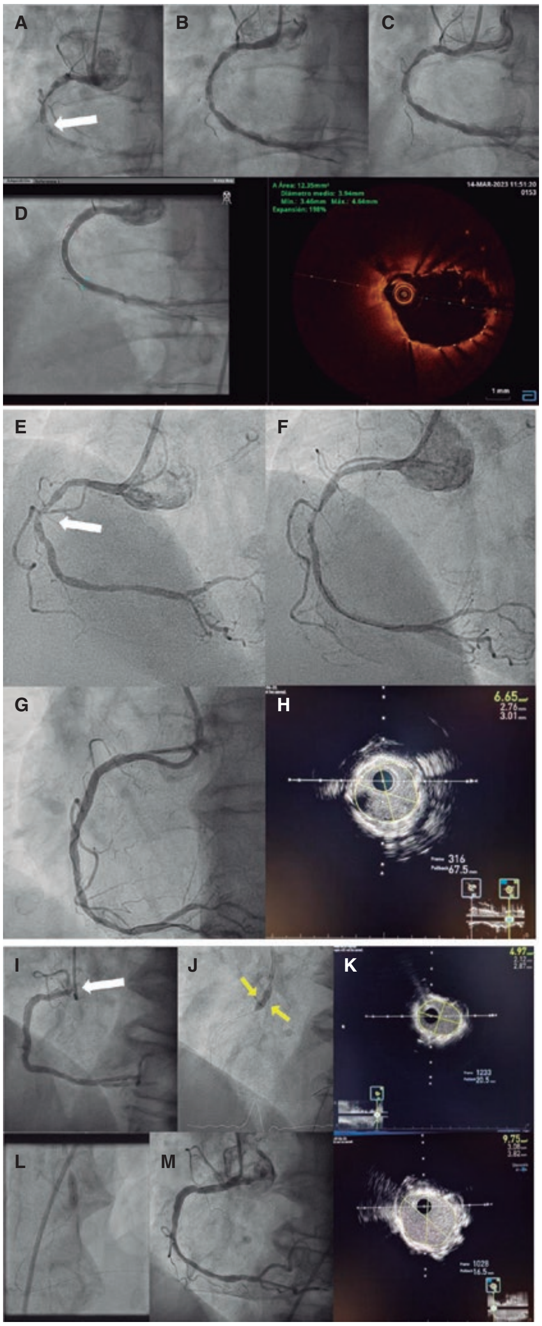

Figure 1. Case #1. **A:** extreme calcification of the right coronary artery with an uncrossable lesion in its middle third (white arrow). Initial angiograpm. **B:** angiogram after laser therapy and failed angioplasty during the index procedure. **C:** Initial angiogram of the second procedure. **D:** final angiographic and OCT results after the second procedure. Case #2. **E:** severely calcified uncrossable lesion in the middle of the right coronary artery (arrow). Initial angiogram. **F:** angiogram after laser therapy and failed index procedure. **G:** final angiographic result after the second procedure. **H:** final result according to intracoronary ultrasound. Case #3. **I:** significant stent underexpansion at the level of the right coronary artery ostium. Initial ostial lesion (arrow). **J:** after laser therapy in the index procedure, the noncompliant balloon failed to fully expand, showing a waist in its middle third (arrows). **K:** final result of the index procedure according to the intracoronary ultrasound, with a minimal luminal area of 4.97 mm² (50% expansion). **L:** complete expansion of the noncompliant balloon after the second procedure. **M:** final angiographic result after the second procedure according to angiography and intracoronary ultrasound, with an almost 2-fold increase of minimal luminal area compared with baseline and an expansion rate of nearly 100%.

ETHICAL CONSIDERATIONS

All patients signed the written informed consent forms approved by the research ethics committee of our center and accepted to participate in the registry. Possible biases related to sex and gender have been considered while drafting this manuscript.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in the development of this work.

AUTHORS' CONTRIBUTIONS

J. Valencia was the lead author of the manuscript. All the authors from Hospital General Universitario Dr. Balmis medical team contributed to the preparation of the case reports. A. Jurado-Román was also involved in critical review of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Scientific letter

Predictors of late pacemaker implantation following TAVI

Predictores de implante tardío de marcapasos tras TAVI

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To the Editor,

Transcatheter aortic valve implantation (TAVI) has become a safe and minimally invasive alternative to surgical aortic valve replacement, and its indications have expanded to include younger and lower surgical risk patients.[1] The development of advanced atrioventricular conduction disorders (AVCD) requiring permanent pacemaker implantation has been reported in 2.3% to 36% of patients, and is one of the major concerns associated with this technique, leading to higher mortality rates.[2] Specifically, late-onset AVCD can have fatal consequences. Its highly variable temporal definition hampers the identification of predictive factors. However, the appearance of complete left bundle branch block and baseline atrial fibrillation has been suggested.[3,4]

We conducted a study to assess whether electrocardiographic (ECG) changes can be predictors of late-onset AVCD requiring permanent pacemaker implantation within the first month after discharge following TAVI. This was a retrospective, observational, and cohort study of consecutive patients treated with TAVI from 2011 through 2022 at a tertiary referral center. We studied sociodemographic variables, atrial fibrillation, prior pacemaker implantation, baseline ECG abnormalities and within 24 hours after implantation, the need for pacemaker implantation during admission and after discharge, survival, and the length of stay. The diagnosis of late-onset AVCD and the indication for pacemaker implantation occurred through in-person consultations or visits to the ER. Due to the retrospective design and anonymous data handling, the research ethics committee deemed it unnecessary to require additional informed consent forms other than those obtained prior to the procedure.

The statistical analysis compared the baseline ECG abnormalities and those reported 24 hours after TAVI in the group requiring permanent pacemaker implantation after discharge vs the group with no such requirement. The chi-square test was used for qualitative variables, and the Student t-test for quantitative variables. Binary logistic regression was used, including statistically significant comparisons to identify the variables with the best predictive ability. Statistical tests were applied with a 95% level of confidence, and the IBM SPSS version 26.0 statistical software was used.

The study included a total of 448 patients with a mean age of 81.38 ± 6.1 years, 49.1% of whom were women. The device used was the Edwards-SAPIEN 3 valve (Edwards Lifesciences, United States), which was always implanted by the same operator. We excluded 49 patients (10.94%) who were chronic pacemaker carriers. Fifteen patients (3.8%) developed late-onset AVCD after discharge, requiring readmission for pacemaker implantation. No significant differences were reported in the baseline characteristics between the 2 study groups. The factors significantly associated with a higher rate of pacemaker implantation at discharge were baseline complete right bundle branch block (CRBBB) (P = .002), the presence of type I or Wenckebach and type II first- or second-degree atrioventricular block (AVB) at baseline (P < .001), the postoperative development of left anterior fascicular block (P = .005), CRBBB (P < .001), and first-degree transient AVB after implantation (P = .018) (table 1). Binary logistic regression was used to identify the best predictors of the need for pacemaker implantation after discharge, which were the combination of first- or second-degree AVB at baseline (odds ratio [OR], 2.008; 95% confidence interval [CI], 1.480-2.725), persistent CRBBB (OR, 10.53; 95%CI, 2.949-37.669), and second-degree transient AVB after implantation (OR, 8.15; 95%CI, 1.35-49.73).

This study reports a combination of ECG findings that can predict an increased risk of late-onset AVCD at discharge, a vulnerable time due to the cessation of ECG monitoring and discharge from hospital. Pacemaker implantation after discharge is associated with longer admissions, mainly due to closer and more prolonged ECG monitoring, which stresses the need for rapid decision-making following these ECG findings. In this study, the mean length of stay for the group that did not require pacemaker implantation was longer than that associated with this procedure at the present time,[5] mainly due to vascular complications in the first few years after the introduction of the procedure.

There is a discrepancy in the medical literature on the temporal definition of late blocks, their risk factors, and predictive ability. Only 1 study has considered late-onset AVCD as those occurring at discharge. The study was conducted by McCaffrey et al.,[6] who analyzed a series of 98 patients, 4 of whom required pacemaker implantation. This series was heterogeneous regarding the type of implanted valve and reported that predictors of late-onset AVCD after discharge were baseline CRBBB, longer QRS duration at baseline and at discharge, more than moderate aortic regurgitation, and atrial fibrillation.

The strength of our study lies in the uniformity of the valves, which were implanted by the same operator. However, it has the inherent limitations of a retrospective study, in addition to possibly underestimating events at discharge, including 5 deaths of unclear cause which could be associated with late-onset AVCD.

In conclusion, the presence of baseline CRBBB, first- or second-degree AVB at baseline, and the development of transient first or second-degree AVB should alert us to the possibility of late-onset AVCD.

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Table 1. Characteristics of the patients

Variables	PM implantation during admission (n = 37)	PM implantation after discharge (n = 15)	No need for PM implantation (n = 347)	*P* for PM implantation during admission	*P* for PM implantation after discharge
Women	12 (32.43)	11 (73.3)	206 (59.36)	.360	.866
Baseline CRBBB	9 (24.32)	7 (46.67)	39 (11.23)	.006	.002
Baseline CLBBB	3 (8.1)	0	38 (10.95)	.912	.130
Baseline LAFB	10 (27.02)	2 (13.33)	51 (14.69)	.003	.612
1st or 2nd-degree AVB at baseline	5 (13.51)	6 (40)	51 (14.69)	.702	< .001
Atrial fibrillation	16 (43.24)	8 (53.33)	164 (47.26)	.549	.683
Valve-in-valve	4 (10.81)	0	21 (6.05)	.079	.263
Persistent posterior LAFB	3 (8.1)	4 (26.67)	19 (5.47)	.356	.005
Transient posterior LAFB	0	0	1 (0.28)	.763	.815
Persistent posterior CLBBB	9 (24.32)	3 (20)	84 (24.2)	.444	.414
Transient posterior CLBBB	6 (16.21)	2 (13.33)	44 (12.68)	.220	.785
Persistent posterior CRBBB	1 (2.7)	7 (46.67)	14 (4.03)	.511	< .001
Transient posterior CRBBB	0	0	6 (1.73)	.458	.564
Persistent posterior 1st-degree AVB	8 (21.62)	4 (46.67)	34 (9.79)	.001	.517
Transient posterior 1st-degree AVB	1 (2.7)	3 (20)	14 (4.03)	.711	.018
Persistent posterior 2nd-degree AVB	1 (2.7)	1 (6.67)	0	< .001	.073
Transient posterior 2nd-degree AVB	6 (16.21)	1 (6.67)	19 (5.47)	.001	.069
Length of stay (days)	9.89 ± 8.89	12.03 ± 17.4	6.78 ± 7.98	< .001	.027

AVB, atrioventricular block; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; LAFB, left anterior fascicular block; PM, pacemaker.
Note: Qualitative variables are expressed as frequency, and quantitative variables as mean ± standard deviation.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

Due to the retrospective design and anonymous nature of data, informed consent was not deemed necessary by the research ethics committee. The SAGER guidelines were taken into consideration.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used.

AUTHORS' CONTRIBUTIONS

R. Muñoz-Rodríguez was involved in the design, data mining, analysis, and drafting of this manuscript. M. A. Rivero-García, and J.J. Castro-Martín were involved in data mining. G. Yanes-Bowden, and F. Bosa-Ojeda conducted the manuscript critical review process.

CONFLICTS OF INTEREST

None declared.

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Scientific letter

One-year outcomes with the Firehawk sirolimus-eluting stent and biodegradable polymer guided by intravascular ultrasound

Resultados a un año con stent Firehawk liberador de sirolimus y polímero biodegradable guiado por ultrasonido intravascular

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To the Editor,

Drug-eluting stents (DES) can show mechanical failure at implantation. Diagnosis of stent underexpansion through intravascular ultrasound (IVUS) seems to be the main mechanism of thrombosis and restenosis.[1] In the past, durable first-generation DES polymers have been associated with late adverse clinical events. The Firehawk stent (MicroPort Medical, China), is a cobalt-chrome structure with biodegradable sirolimus-containing polymer coating in abluminal grooves, designed to mitigate polymer load and to reduce drug concentrations in the vessel wall.[2] This third generation DES device has been tested in various studies.[3] The TARGET All Comers trial reported noninferiority in target lesion failure (TLF) at 1 year of follow-up with the Firehawk stent compared with SFA XIENCE (Abbott, United States) with durable polymer. Although the results have shown noninferiority, a 1.2% rate of definitive thrombosis was observed throughout the 12-month follow-up, which could be related to the lack of use of intravascular imaging to guide stent implantation. The use of this imaging modality leads to reductions in mortality, treated vessel-related myocardial infarction (MI) and clinically guided revascularization compared with procedures guided by angiography alone.

The aim of the present study was to assess the mid-term outcomes in real-world patients from a single center in Brazil who underwent Firehawk stent implantation guided by IVUS in nonselected coronary lesions.

This prospective, observational, nonrandomized, single arm pilot study included 100 patients with severe coronary artery disease treated with the Firehawk stent, guided by IVUS between May 2019 and December 2021 who were older than 18 years and had a wide range of clinical indications ranging from silent ischemia with positive functional tests and stable angina to acute coronary syndrome. Stent diameter and extension were selected based on IVUS data. Exclusion criteria were life expectancy less than 1 year, left ventricular ejection fraction < 40%, Firehawk stent implantation not guided by IVUS, and percutaneous coronary intervention (PCI) without at least 1 Firehawk stent. Following the consensus document of the European Association of Percutaneous Cardiovascular Interventions, stent expansion was defined as "the minimum stent cross sectional area either as an absolute measure (absolute expansion), or compared with the predefined reference area, which can be the proximal, distal, largest, or average reference area (relative expansion)". Considering this reference, a relative stent expansion > 80% was used as a predefined criterion. All patients completed 12 months of clinical follow-up. The study protocol was approved by the research ethics committee (n. 59849822.2.0000.0098) and all patients signed an informed consent form.

The patients' clinical characteristics and baseline angiographic lesions, procedural features and IVUS findings are shown in table 1. IVUS was used in all patients (100%), and 156 lesions were evaluated. IVUS diameter and the extension of these lesions were 2.88 ± 0.44 mm and 24.87 ± 7.21 mm, with these values being higher than those obtained through quantitative coronary angiography (2.45 ± 0.61 mm and 18.21 ± 7.14 mm, respectively). In total, 126 vessels (156 lesions) received 164 Firehawk DES (1.6/patient). The mean diameter and length of implanted DES were 3.0 ± 0.53 mm and 25.23 ± 8.35 mm, respectively.

Among the 164 DES assessed through IVUS after satisfactory angiographic results, 27 (16%) required reintervention for the following reasons: *a)* acute malapposition in 12 (44.5%); *b)* underexpansion in 10 (37%); *c)* edge dissection in 3 (11%); and *d)* plaque protrusion in 2 (7.5%). Considering the stent expansion criteria, the analysis of this cohort showed a mean stent expansion of 91.8% regarding the distal reference (table 1).

Table 2 provides a detailed description of all clinical events at 12 months of follow-up, patient-oriented composite endpoints (PoCE), and device-oriented composite endpoints (DoCE)-TLF. PoCE were observed in 6% of patients (6 events in 5 patients), all-cause death in 1% (1 patient), MI in 1% (1 patient), and target vessel revascularization (TVR) in 4% (4 patients). DoCE-TLF were observed in 1% (1 stent with 3 events: non-Q-Wave MI in 1.00%, target vessel MI in 1% and ischemia-driven TLR in 1%), and cardiac death in 0%. The description of events is as follows: patient No. 1: TVR. A lesion was found on follow-up angiography when a new intervention was planned for second vessel disease. Patient No. 2: TVR and TLR. A lesion was found on follow-up angiography when a new intervention was planned for second vessel disease. Patient No. 3: NSTEMI, TVR and TLR. Patient No. 4: TVR with ischemic perfusion test. Patient No. 5: noncardiac death. There was no stent thrombosis. The relationship between IVUS final minimum sent area and clinical events is shown but the analysis is clearly underpowered.

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Table 1. Patients' clinical characteristics and baseline angiographic lesions, procedural features, and IVUS findings

Clinical, angiographic, and procedure findings	N = 100	Clinical, angiographic, and procedure findings	N = 100
Male sex	71 (71)	Lesion classification* B2/C	95 (61)
Diabetes mellitus	53 (53)	Syntax score	18.5 ± 9.34
Previous PCI	37 (37)	QCA, vessel reference diameter (mm)	2.45 ± 0.61
Previous CABG	9 (9)	QCA, lesion extension (mm)	18.21 ± 7.14
Previous MI	21 (21)	Predilation due to lesion	134 (85)
Baseline clinical diagnostic		Lesion predilation with CB or PTCRA	14 (10)
Q-wave MI	7 (7)	Procedural success	100 (100)
Non-Q-wave MI	16 (16)	*Pre- and post-PCI IVUS*	N = 156/164
Unstable angina	28 (28)	Evaluation based on pre-PCI IVUS	156 (100)
Stable angina	26 (26)	Fibrolipid plaque	81 (53)
Atypical angina	5 (5)	Calcified plaque	38 (24)
Silent ischemia	15 (15)	Fibrotic plaque	26 (17)
LVEF	62.8 ± 7.4	Intrastent restenosis	10 (6)
Multivessel disease	67 (67)	Stenosis diameter	80.82 ± 6.21
Treated vessels	N = 126 (100)	Reference diameter, mm	2.88 ± 0.44
Left main coronary artery	9 (5)	Lesion extension, mm	24.87 ± 7.21
Left anterior descending coronary artery	67 (41)	Lesion with extension > 28 mm	48 (31)
Left circumflex coronary artery	34 (21)	Stents implanted per lesion	1.6 ± 0.84
Right coronary artery	54 (33)	Diameter of implanted stent, mm	3.0 ± 0.53
Treated lesions	N = 156 (100)	Extension of implanted stent, mm	25.23 ± 8.35
De novo lesions	146 (94)	Final evaluation through post-PCI IVUS	164 (100)
Intrastent, restenosis	10 (6)	Post-IVUS reintervention	27 (16)
Total oclusion	8 (5)	Mean stent expansion, (%) (distal reference)	91.8
Bifurcation	55 (35)		

BP, blood pressure; CABG, coronary artery bypass graft surgery; CB, cutting balloon; IVUS, intracoronary ultrasound; LDL, low-density lipoproteins; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PTCRA, percutaneous transluminal rotational atherectomy; PCI, percutaneous coronary intervention; PCI, percutaneous coronary intervention; QCA, quantitative coronary analysis.
* According to the ACC/AHA.
Data are expressed as No. (%) or mean ± standard deviation.

The present study reports our initial experience of using the Firehawk stent with routine use of IVUS before and after PCI. Safety and efficacy were demonstrated by the low PoCE and DoCE at 12 months of clinical follow-up, highlighting the absence of stent thrombosis. Some studies have identified stent underexpansion, geographical miss, and dissection of stent edges as independent causes of intrastent thrombosis.[4] All these predictors can be detected and properly treated through IVUS. According to the final IVUS analysis, this study showed that reintervention for optimization was required in 16% of the cases. All patients in this database received dual antiplatelet therapy for at least 12 months. These 2 factors can be closely linked to lack of thrombotic events in the assessed population.

The main limitations of this prospective study are its population size, due to its observational and nonrandomized nature. However, its value lies in the fact that it represents one of the main clinical experiences in Brazil with Firehawk stent implantation guided by IVUS, at all procedure stages, showing favorable performance after 12 months of follow-up. These findings and the data available in the literature, provide clinical support for the use of the fully biodegradable sirolimus-containing polymer-coated Firehawk stent.

FUNDING

No funding sources.

ETHICAL CONSIDERATIONS

The study protocol was approved by the research ethics committee (n. 59849822.2.0000.0098). All patients signed the informed consent form.

Considering the small size of the group of patients analyzed and that the percentages of both genders reflect those observed in our daily practice, the authors believe that there was no reason to carry out a sex/gender analysis.

Table 2. Clinical outcomes at 12 months of follow-up in 100 patients

	N = 100	
Primary endpoints		
PoCE	6 (6)	
All-cause death	1 (1)	
All MI	1 (1)	
All revascularization	4 (4)	
TVR	4 (4)	
Secondary endpoints		
DoCE (TLF)	1 (1)	
Cardiac death	0 (0)	
Q-wave MI	0 (0)	
Non-Q-wave MI	1 (1)	
Target vessel-related MI	1 (1)	
Ischemia-drivenTLR	1 (1)	
Definitive/probable thrombosis (acute or late)	0 (0)	
Clinical events analysis considering IVUS final luminal area	≤ 5.5 mm² (51 stents)	> 5.5 mm² (113 stents)
DoCE (TLF)	0 (0)	1 (0.88)
Cardiac death	0 (0)	0 (0)
Q-wave MI	0 (0)	0 (0)
Non-Q-wave MI	0 (0)	1 (0.88)
Target vessel-related MI	0 (0)	1 (0.88)
TLR	1 (1.96)	1 (0.88)
Ischemia-driven TLR	0 (0)	0 (0)
Definitive/probable thrombosis (acute or late)	0 (0)	0 (0)

DoCE, device-oriented composite endpoints (secondary endpoints), composite of cardiac death, target vessel myocardial infarction, ischemia-driven target lesion revascularization, and definite or probable (acute or late) thrombosis; MI, myocardial infarction; n, number; PoCE, patient-oriented composite endpoints (primary endpoints), composite of all-cause death, any myocardial infarction, and any target vessel revascularization; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization.
Data are expressed as No. (%).

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The authors confirm that artificial intelligence was not used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

C.R. Costantini, M.A. Denk, S.G. Tarbine: study idea, and data mining and analysis. C.O. Costantini, V. Shibata, R.M. De Macedo: manuscript review and edition.

CONFLICTS OF INTEREST

The authors declare no conflict of interest related to the present manuscript.

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Image in cardiology

Closure of a percutaneous tricuspid paravalvular leak with the Amplatzer Muscular VSD device

Cierre percutáneo de fuga perivalvular tricúspide con Amplatzer Muscular VSD

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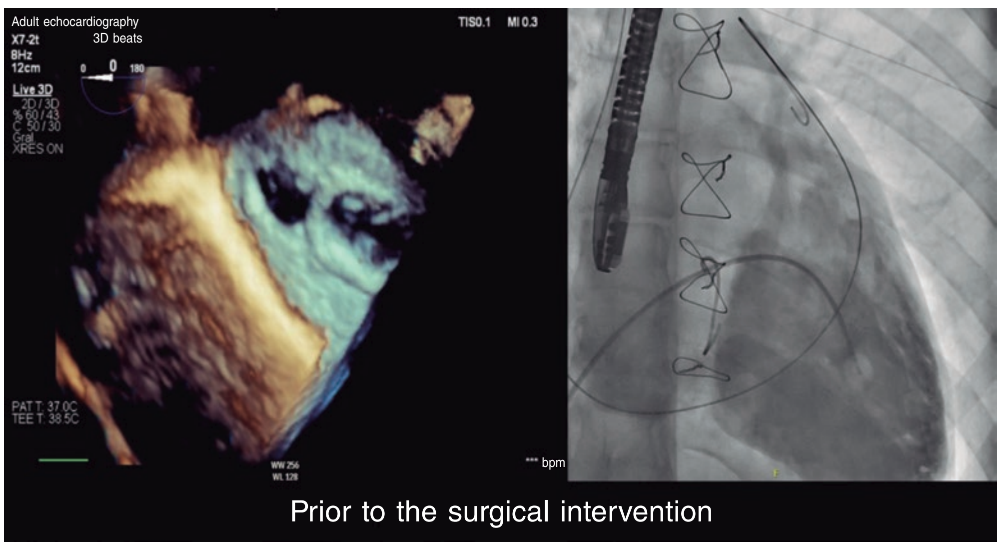

Figure 1.

We present the case of a 16-year-old girl with a prenatal diagnosis of Ebstein's anomaly and an atrial septal defect with severe tricuspid regurgitation.

In 2020, the patient was referred due to functional deterioration. Surgical repair included the implantation of a 26-mm Contour 3D tricuspid annuloplasty ring (Medtronic, United States) with the cone reconstruction technique and closure of the atrial septal defect. During the postoperative follow-up, the patient developed moderate paravalvular leak lateral to the ring that progressed to severe regurgitation with moderate right ventricular dilatation without dysfunction a year and a half later. The patient experienced no episodes of heart failure until 2 years after surgery.

Cardiac catheterization was performed via transjugular and right femoral access under general anesthesia and transesophageal echocardiography guidance, revealing the presence of a 13 mm × 10 mm leak posterolateral to the tricuspid annuloplasty ring that appeared as a 15 mm leak on ventriculography (figure 1). The first closure attempt with a 14-mm Konar MF device (Lifetech, China) did not achieve complete closure or attachment at the defect. Therefore, a second attempt was made with an 18-mm Amplatzer Muscular VSD device (Abbott, United States), which achieved proper attachment and almost complete occlusion (figure 2). After release, minimal residual regurgitation was confirmed by transesophageal echocardiography (figure 3 and video of the supplementary data). There were no irregular heart rhythms or repolarization abnormalities.

The patient was discharged 24 hours after the procedure, with the initiation of aspirin therapy. Follow-up revealed a normal electrocardiogram, with minimal residual regurgitation, and no hemolysis. The patient reported improvement during exertion.

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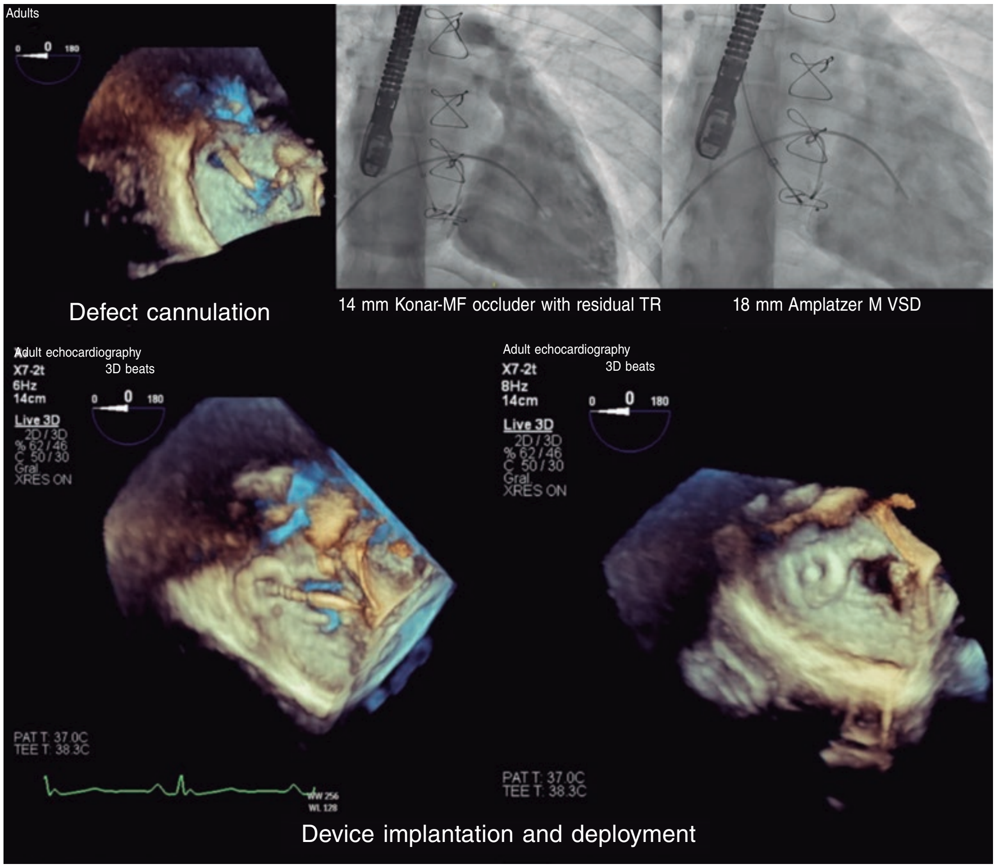

Figure 2.

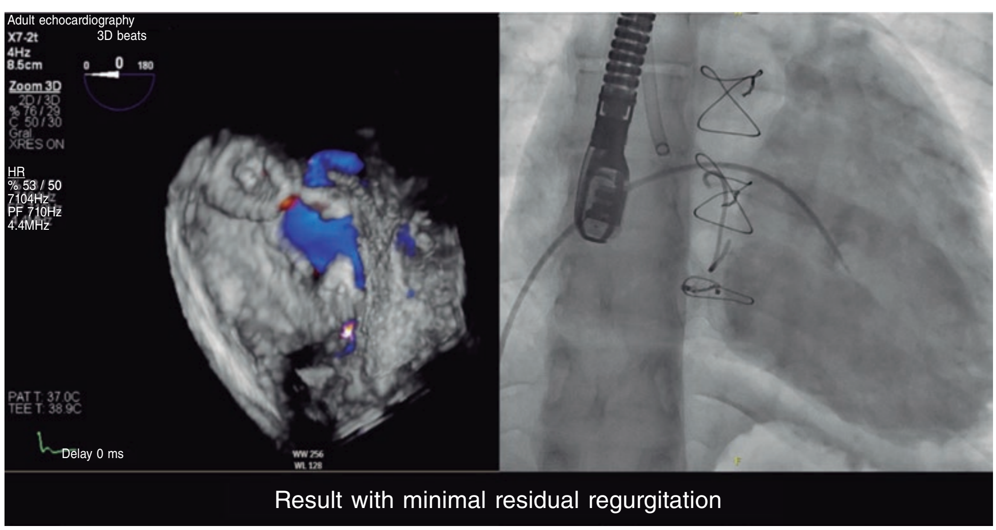

Figure 3.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This case was approved for publication by the pediatric cardiology unit, and did not require further evaluations by the research ethics committee. The parents of the minor and the mature minor herself gave their prior written informed consent. Because this is a presentation of an isolated case, the SAGER guidelines did not need to be followed.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool has been used during the preparation of this work.

AUTHORS' CONTRIBUTIONS

All authors participated in the procedure, image review, and manuscript drafting.

CONFLICTS OF INTEREST

None declared.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000411.

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Image in cardiology

Severe postransplant tricuspid regurgitation: treatment with the PASCAL system

Insuficiencia tricuspídea grave postrasplante: tratamiento con dispositivo PASCAL

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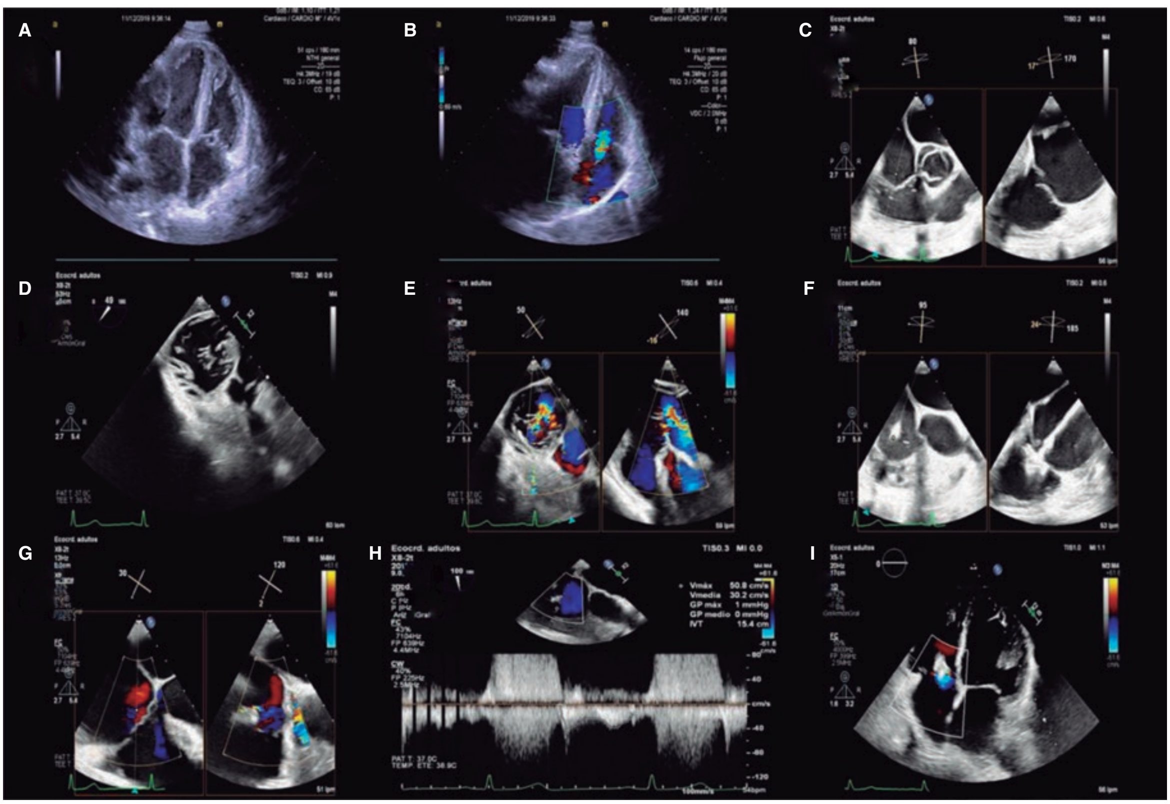

Figure 1.

We report the case of a 43-year-old man with a past medical history of heart transplantation in 2017 due to ischemic dilated cardiomyopathy. One month after the transplant, after routine endomyocardial biopsy, a follow-up transthoracic echocardiogram revealed the presence of moderate tricuspid regurgitation (TR). As a result, clinical and echocardiographic monitoring was initiated.

Four years later, the patient's functional class progressed to NYHA FC III-IV with signs of congestion. Transthoracic echocardiography showed good biventricular function, dilated right chambers, and severe TR with a vena contracta width of 12 mm, and an effective regurgitant orifice of 0.45 cm² due a prolapsed septal leaflet (figure 1A,B and videos 1-2 of the supplementary data). A transesophageal echocardiogram confirmed that the severe TR was due to a prolapsed septal leaflet in the portion proximal to the posteroseptal commissure,

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with signs of ruptured chordae tendineae (figure 1C,E; videos 3-5 of the supplementary data). The case was discussed with the heart team, which decided to perform a percutaneous edge-to-edge repair due to the high surgical risk. Due to its availability in our center, a PASCAL Ace device (Edwards Lifesciences, United States) was successfully implanted between the septal and posterior leaflets at the site of the prolapse (figure 1F,H; videos 6-7 of the supplementary data) under general anesthesia and transesophageal echocardiography guidance, with mild residual TR. Three months later, the patient remained asymptomatic, with minimal residual TR on transthoracic echocardiography (figure 1I; video 8 of the supplementary data). To our knowledge, this is the first reported case of severe iatrogenic TR after heart transplantation treated with a PASCAL device.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The patient's prior written informed consent was obtained for the publication of his case. Since consent had already been obtained and the procedure is routinely performed in clinical practice, the research ethics committee of our center does not require this kind of publication to be submitted for approval. The possible sex and genre variables were taken into consideration.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool has been used during the preparation of this work.

AUTHORS' CONTRIBUTIONS

All the authors participated in the drafting and revision of this manuscript, and agreed on its content.

CONFLICTS OF INTEREST

S. Ojeda is associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure the impartial handling of the manuscript has been followed. M.D. Mesa Rubio, M. Pan Álvarez-Ossorio y S. Ojeda have received small compensations from Edward's under presentations. The rest of authors do not have any conflict of interests.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000413.

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Image in cardiology

Impella-supported MitraClip implantation in acute mitral regurgitation

Implante de MitraClip con Impella en insuficiencia mitral aguda

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Finalist case in the ACCIS 2023 Madrid course

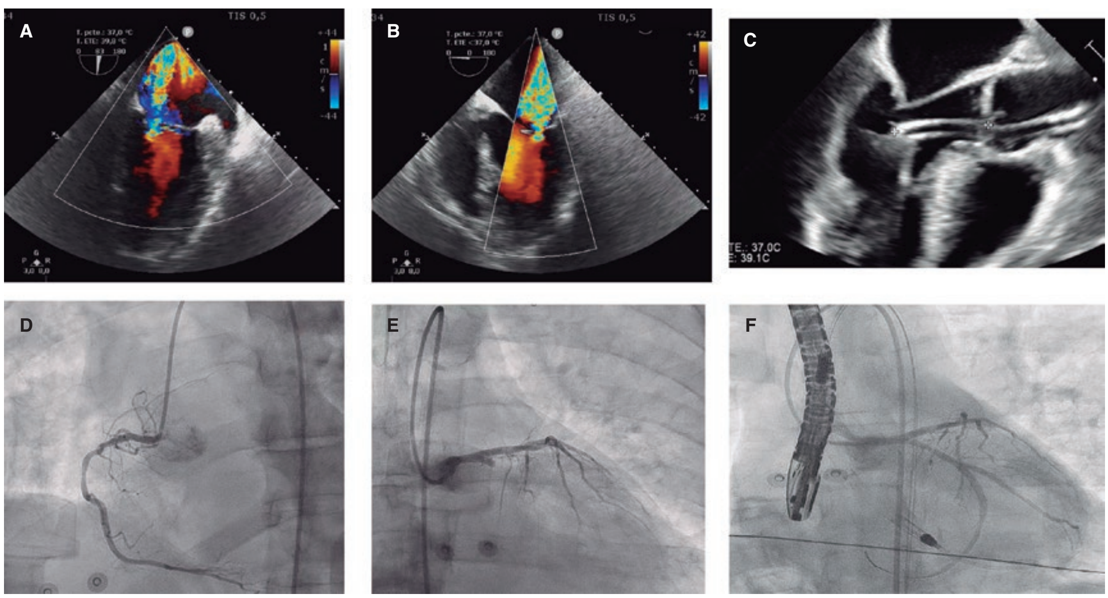

Figure 1.

A 59-year-old man was admitted to the cardiac intensive care unit (CICU) due to evolved inferior-posterior ST-segment elevation myocardial infarction complicated by cardiogenic shock. Upon arrival, transesophageal echocardiography revealed severe mitral regurgitation (MR) secondary to posterior leaflet restriction (figure 1A,B). After rupture of papillary muscles was ruled out, the patient was transferred to the cath lab, where a 100% thrombotic lesion was observed in the proximal left circumflex artery (figure 1D-E). Due to hypotension, we decided to support the angioplasty with the Impella CP device (Abiomed, United States) (figure 1C). Flow was finally restored (figure 1F).

Five days later, the patient was hemodynamically stable with Impella at P6, but developed multiple complications, including acute kidney failure, significant bleeding, and hemolysis. Three-dimensional echocardiography showed MR without changes. At this point, spontaneous improvement of MR seemed unlikely, and the risk of heart transplant or surgery was unacceptable. Finally, we decided to implant a MitraClip (Abbott, United States) supported by Impella.

The first MitraClip NTW (Abbott, United States) was placed between P2 and A2, with significant posterior-medial regurgitation (figure 2A-C). The second MitraClip NT (Abbott, United States) was implanted nearby. Residual MR was mild (figure 2D,E, video 1 of the supplementary data).

The patient was extubated after the procedure and the Impella device was removed the following day. He left the CICU 10 days later.

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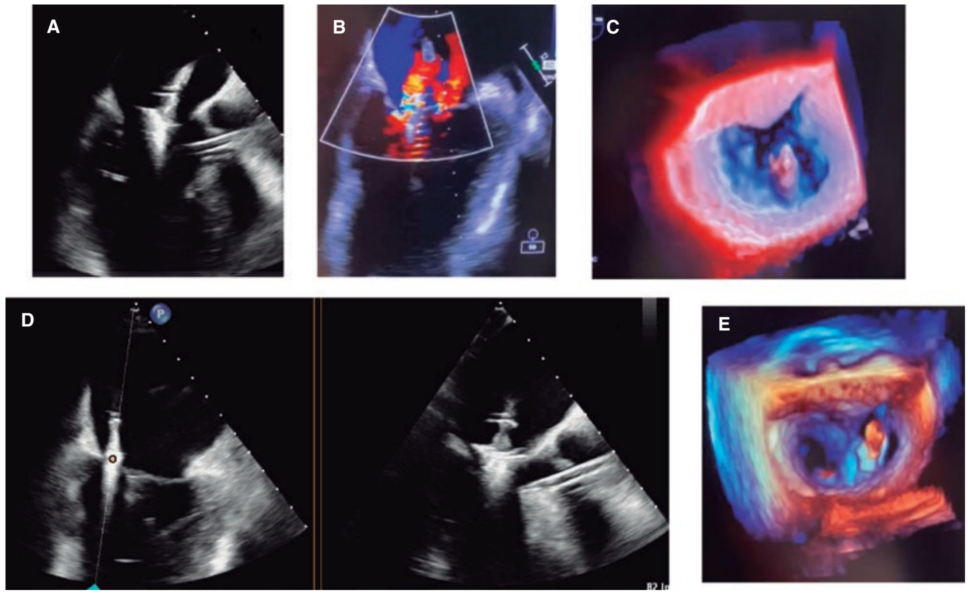

Figure 2.

This case is in line with other case reports suggesting that MitraClip, supported by Impella CP, could be an effective strategy in patients with severe functional MR. In this case, hemodynamic support by Impella CP was used to complete the primary percutaneous coronary intervention during CICU admission and during edge-to-edge mitral valve repair. Informed consent was obtained from the patient to publish this manuscript.

FUNDING

None.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the patient to publish this properly anonymized manuscript. Because this is a single case report, approval from ethics committee was not required and gender considerations were not applicable.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence software was used to write this manuscript.

AUTHORS' CONTRIBUTIONS

All authors contributed to data collection, drafting, review, and approval of the manuscript.

CONFLICTS OF INTEREST

I. Pascual Calleja: payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for Abbot Vascular. C. Garrote Coloma: proctor for MitraClip implant, Abbot. J.M. de la Torre-Hernández: grants or contracts from Abbot, Amgen, Boston SCI; consulting fees from Medtronic, Boston SCI, Abbot; support for attending meetings from Medtronic, Abbot, Boston SCI.

J.M. de la Torre-Hernández is also editor-in-chief of REC: Interventional Cardiology. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed.

The remaining authors have no conflicts of interest.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M23000414.