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ARGENTINIAN COLLEGE OF INTERVENTIONAL CARDIOLOGISTS

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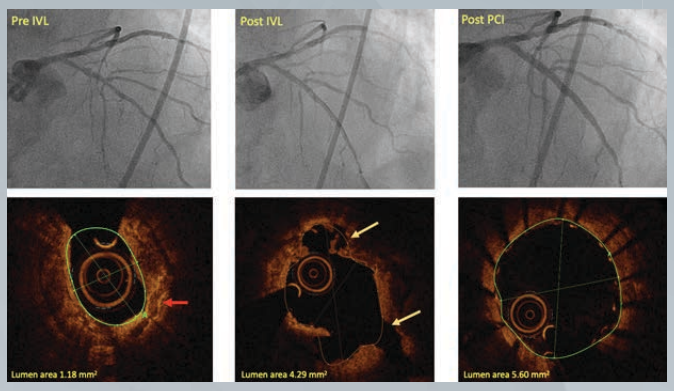
April - June 2022 | Year 13 | Number 2



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April - June 2022 | Year 13 | Number 2

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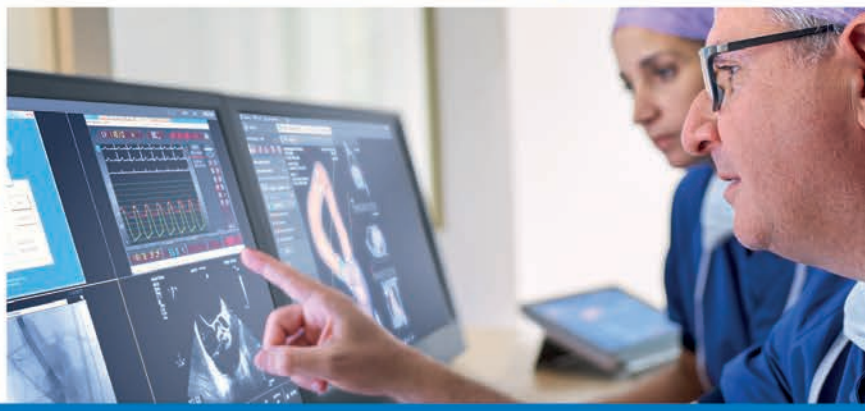
Summary

Sumario

Revista Argentina de Cardioangiología Intervencionista 2022;13(2):51. https://doi.org/10.30567/RACI/202202/0051-0051



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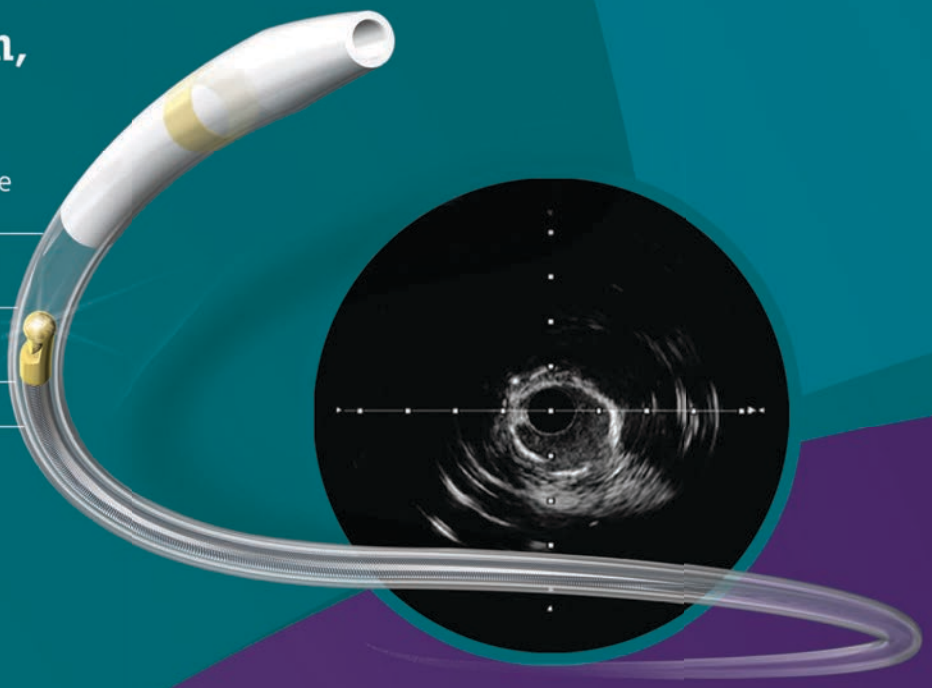

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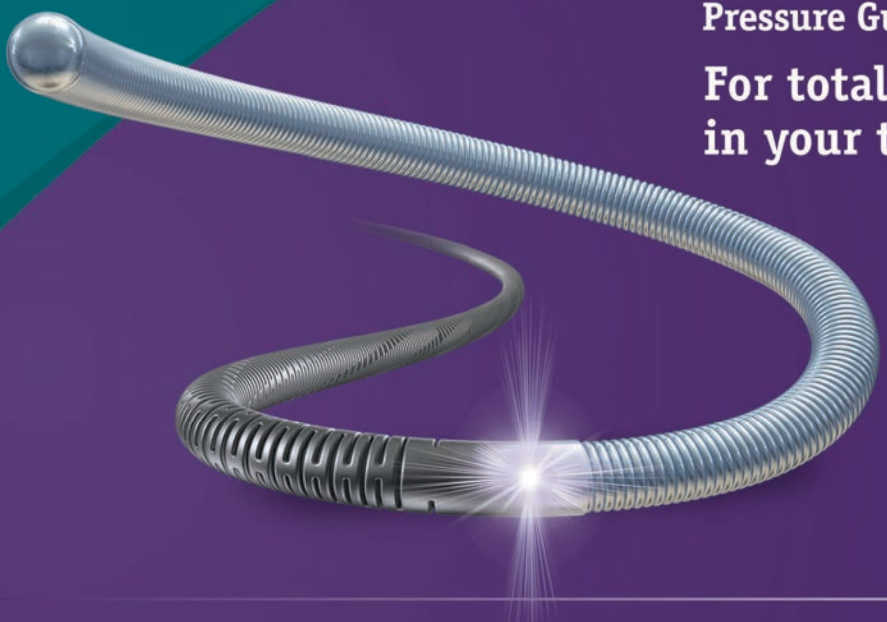

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At 5 years, outcomes of patients treated with VIVO ISAR compared with durable polymer based ZES were similar in sub group of Diabetes.

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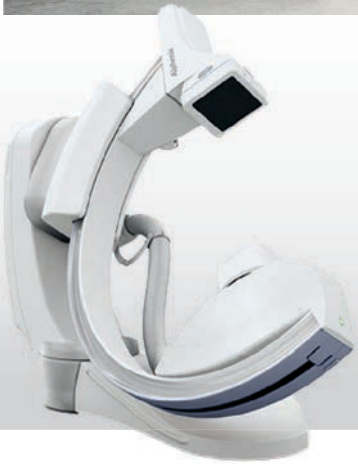

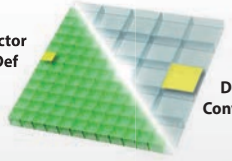

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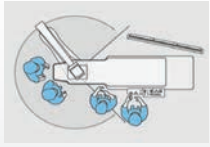

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Analytical Summary

Sumario analítico

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EDITORIAL / EDITORIAL

THE ORIGINS OF INTERVENTIONAL CARDIOLOGY IN CORONARY ARTERY DISEASE AND BEYOND

Rubén Piraino

Most healthcare workers think of interventional cardiology as a well-established medical specialty. However, it would be good to reflect on its true origin because for those who were already part of it even before our specialty was born, the present time is just another step in the timeline of interventional cardiology. Today, interventional cardiology has reached its peak after 40 years in the making. I would say that the revolution of this medical specialty started with the arrival of therapeutic procedures. There is no doubt that the pioneer of this specialty was Dr. Andreas Grüntizg, who surprised the entire world with the very first coronary angioplasty.

REVIEW ARTICLES / ARTÍCULOS DE REVISIÓN

CRISPR-CAS9 AS PROTECTION THERAPY AGAINST CARDIOVASCULAR DISEASE

David Vetcher

The use of CRISPR technology for gene editing has started a new era in biology and medicine. CRISPR technologies can modify the genome of any eukaryotic cell in an easy, fast, cost-effectively, and precise way. This new modality offers a promising therapeutic approach for heart disease protection and treatment by rewriting the genetic basis of disease.

THE EMERGENCE OF CORONARY INTRAVASCULAR LITHOTRIPSY

Sukhdeep Bhogal, Hayder Hashim, Ron Waksman

The presence of coronary artery calcification is an independent predictor of poor procedural outcomes. Several techniques, such as cutting or scoring balloons, rotational and orbital atherectomy devices, and excimer laser, are available for plaque modification in the modern catheterization laboratories; however, their use has been associated with increased risk of complications such as vessel dissection, slow or no flow, perforation, or occlusion. Lately, intravascular lithotripsy (IVL) has emerged as a safe and effective tool for the treatment of severely calcified coronary lesions. IVL utilizes spark-gap technology to transform electrical energy to mechanical energy, generating acoustic shock waves that travel transmurally and circumferentially, inducing a therapeutic field effect, and selectively causing fracture of superficial and deep vascular calcium, which is essential for optimal stent expansion. The purpose of this article is to review the mechanism of this novel technology and summarize the pertinent studies leading to its regulatory approvals.

CASE REPORTS / CASOS CLÍNICOS

ENDOVASCULAR RESOLUTION OF COMPLICATED PULMONARY PSEUDOANEURYSM AFTER RIGHT HEART CATHETERIZATION

Macarena Matus de la Parra, José María Milanesi, Agustín Hauqui, Raúl Solernó, Ricardo Aquiles Sarmiento

Right heart catheterization with a Swan-Ganz catheter is a commonly used method for the hemodynamic assessment of hospitalized patients in critical care units or else as part of the evaluation of pulmonary circulation in many different diseases. It is often considered a safe procedure with a low rate of complications. Pulmonary pseudoaneurysm is a rare complication although it is associated with a high mortality rate. This is the case of a pulmonary pseudoaneurysm that occurred as a complication associated with the use of a Swan-Ganz catheter and its resolution through percutaneous endovascular treatment.

INTRACORONARY LITHOTRIPSY FOR STENT UNDEREXPANSION RESOLUTION: UTILITY OF ENHANCED STENT VISUALIZATION OR STENTVIZ™

Juan Mieres, Carlos Fernández-Pererira, Diego Ascarrunz, Matías Rodríguez-Granillo, Alfredo E. Rodríguez

Percutaneous coronary intervention is always supported by elements of innovative technologyto create solutions to everyday problems that are complex like the management of severely calcified plaques, and a complication that is sometimes unexpected, which is stent underexpansion that can be truly challenging. We present three cases of stent underexpansion throughout different time periods, the first one presented in an acute form, and was solved within the first 24 hours. The second case was chronic stent underexpansion of several-month evolution that worsened due to the presence of acute coronary syndrome and that was solved in the same hospitalization. The last case was extremely challenging and involved the left main coronary artery that presented a slight stent underexpansion that, within a few months, became symptomatic and was successfully solved. All these cases were solved using intracoronary lithotripsy, a novel device that through ultrasound probes transmitted by a rapid exchange catheter breaks down coronary calcium. These were tested in de novo calcified plaques. We present patients who already had a previous stent and were guided by the stent enhancement technique, General Electric angio-

graphy systemStentViz™.It uses an algorithm to visualize the stent struts and allow detailed monitoring to achieve the proper stent expansion, which is associated with fewer cardiovascular events at follow-up.

CRITICAL LIMB ISCHEMIA: CASE PRESENTATION OF RETROGRADE ENDOVASCULAR APPROACH

Deysi Vanessa Cuadros Morales

Critical lower limb ischemia is a serious medical condition with a high risk of major amputation, disability, and death. Treatment of choice is percutaneous due to its low rate of complications. However, it poses a challenge when performing antegrade (femoral) revascularization in chronic total coronary occlusions with technical failure rates between 10% and 40%. For this reason, the retrograde approach ofinfrapopliteal vessels arises as an alternative with successful results, and a low risk associated with the puncture site. This is the case of a patient with critical ischemia who required unconventional access to achieve revascularization.

TRANSCATHETER AORTIC VALVE REPLACEMENT FOR FAILING HOMOGRAFT

José María Milanesi, Martín Oscos, Diego Grinfeld, Raúl Solernó, Ricardo Aquiles Sarmiento

Aortic valve replacement with homograft is a rarely used option due to the risk of late degeneration involved. Reoperation in patients with aortic valve replacement with homograft represents a high risk. Transcatheter aortic valve replacement is an established therapy for patients with severe aortic stenosis.However, its use in aortic homograft failure has been reported in very few publications. This is the case of transcatheter aortic valve replacement for failing homograft.

VENOUS THORACIC OUTLET SYNDROME, ANGIOGRAPHIC DIAGNOSIS

Jorge Cortez, Derwin Plazas Álvarez, Patricio Rattagan, Andrés E. Dini, Miguel Osvaldo Villegas

The thoracic outlet syndrome is an extremely rare entity. It is characterized by the compression of neurovascular structures(brachial plexus, subclavian artery and vein) being venous compression the second most common of all. Although diagnosis is suspected based on the patient's past medical history and physical examination, imaging studies are required to confirm the diagnosis. The most widely used imaging modalities are the ultrasound, the magnetic resonance imaging, and the computed tomography scan. This is the case of a patient with a past medical history of recurrent deep venousthrombosis (DVT) of right upper limb.Diagnostic certainty was achievedthrough dynamic venous angiography.

LETTER FROM THE PRESIDENT / CARTA DEL PRESIDENTE

LETTER FROM THE PRESIDENT OF CACI

Martín Cisneros

The origins of Interventional Cardiology in coronary artery disease and beyond

Los orígenes de la Cardiología Intervencionista en la enfermedad coronaria, y más allá

Revista Argentina de Cardioangiología Intervencionista 2022;13(2):58-60. https://doi.org/10.30567/RACI/202202/0058-0060

Most healthcare workers think of interventional cardiology as a well-established medical specialty. However, it would be good to reflect on its true origin because for those who were already part of it even before our specialty was born, the present time is just another step in the timeline of interventional cardiology.

ORIGINS

Today, interventional cardiology has reached its peak after 40 years in the making. I would say that the revolution of this medical specialty started with the arrival of therapeutic procedures. There is no doubt that the pioneer of this specialty was Dr. Andreas Grüntizg, who surprised the entire world with the very first coronary angioplasty. However, it was Dr. Alain Cribier the genius who revolutionized the field of valvular therapeutics. Dr. Cribier taught us how to treat aortic stenosis dilating the valve with a specially designed balloon. But let's focus on vascular diseases leaving other valvular conditions and structural problems of cardiology for some other time.

Some of the anecdotes that already out there are not well-known. For example, in 1974 in Frankfurt, in a congress held by Dr. Paul Lichten, a young radiologist called Dr. Andreas Grüntzig presented a poster on a brand-new technique called percutaneous transluminal angioplasty used in a dog's left anterior descending coronary artery. This would mark the beginning of a new clinical era just a year later.[1] In 1977, Dr. Grüntzig performed the very first angioplasty in a human being.

But even Dr. Andreas Grüntzig, who said that balloons were the solution to many heart conditions, also used to say that we would need much more if we really wanted to solve the problems posed by coronary obstruction. Dr. Grüntzig developed this technique in Switzerland. Afterwards, he moved to Emory, Atlanta, United States to work with Dr. Spencer King. Unfortunately, shortly after he started living in the United States, he died in a plane crash.

The next decade would witness the birth of multiple innovations, excellent some of them, others somehow weird to say the least. All sorts of lasers to burn, seal or perform selective ablations, hot-tip catheters, cooling devices and scrappers, and scaffolds we would eventually call *stents.*[2] The word "stent" came from a "dentist" who used some type of scaffold in his oral treatments. He used to call that scaffold *stent*. There is no translation for *stent* into Spanish. However, stents were the new hallmark to treat coronary obstructions treated with angioplasty. This new metal structure called *stent* met the requirement of placing a scaffold inside the artery to prevent "the walls from crumbling down". The Argentinian pioneer who started using stents for the first time was Dr. Julio Palmaz. He was a radiologist who had studied at La Plata School of Medicine, Buenos Aires, Argentina. Afterwards, he moved to the United States where he lives today. It was in the United States were here designed his *stent* back in 1987. The stent was designed to treat peripheral arterial diseases, especially of the lower limbs. His predecessor in the management of peripheral arterial diseases was Dr. Charles Dotter, a.k.a. "crazy Charles". At the time, he used a "telescopic" treatment to treat obstructions. He would place 2 gradually larger tubes inside the arteries to dilate the obstructions. The probably most implanted coronary stent at the time was called the *Palmaz stent*, which would later be called the *Palmaz Schatz stent* because Dr. Schatz added a 1 mm bridge between two 7 mm-stent segments. With this addition the stent became more flexible and navigated the coronary arteries much better. The stent was characterized by its significant radial strength which, unlike the other stent used at the time, the so-called *Gianturco Roubin stent* with little radial strength but very much used to contain dissections and prevent acute occlusion. Dr. Palmaz usually attends the meetings held in our country and often visits and is a member of our college. The first report on the use of stents in human beings dates back to March 29th, 1986. I was Dr. Ulrich Sigward who used them for the first time in Switzerland. Also, we should mention Dr. Paul Puech with a mesh-covered self-expanding stent called Wallsttent.[3]

I still can remember that when we started using *Palmaz stents* in human beings in Argentina we had to administer anticoagulant therapy, which was very complicated due to bleeding and the large number of thrombotic occlusions reported. The technique we used for implantation was to mount the stent "by hand" before the angioplasty by squeezing it firmly into the balloon so it would not move, which sometimes happened. Also, stent deployment happened at very low pressures, and stents were underexpanded at times, which is something that conventional angiographies would not capture at the time. These problems were closely associated with the massive use of coronary stents. But in 1995, Dr. Antonio Colombo developed a new stenting technique in Milan, Italy. It was published in *Circulation* that year. A multicenter study on this unique technique was published the next year with what were called the "MUSIC criteria".[4] This technique simply consisted in implanting stents at very HIGH pressure to later check their proper expansion using IVUS (intravascular ultrasound) by

completely covering the atherosclerotic plaque. With this correct expansion with good entry and exit of coronary flow and, above all, with the proper stent APPOSITION to the vessel wall, ANTICOAGULATION WAS AVOIDED and, consequently, all bleeding issues. Only dual ANTIPLATELET therapy was used. In addition, the proper expansion of the stent reduced acute occlusions dramatically.

We could say that: 1) Balloon angioplasty was "saved" by stent angioplasty, and 2) stent angioplasty was "saved" by Colombo with IVUS and high pressure.

Afterwards, in 1994 when the effectiveness of the stent was confirmed during coronary angioplasty, 2 multicenter studies were published with high rates of approval and massive use among interventional cardiologists. The STRESS trial was conducted in the United States, and the BENESTENT trial[5] in Europe and ARGENTINA. We felt honored to be asked to participate in the latter as representatives of our country. These studies gained the stent the approval it needed from international regulatory agencies.

However, we still had unfinished businesses with coronary stents like stent restenosis due to myointimal cellular proliferation. Basically 2 different research lines were created for the management of restenosis, one was intracoronary radiation and the other one was based on the use of drug-eluting stents. Intracoronary radiation was inferior compared to drug-eluting stents and fell into oblivion. Then, drug-eluting stents kept moving forward. Basically, different drugs were used like the antiproliferative drugs paclitaxel, and sirolimus. Sirolimus or rapamycin largely exceeded the effectiveness of paclitaxel. In 1999 the tremendous potential of rapamycin (sirolimus-eluting stent) had already been confirmed in the experimental work in animals conducted by Dr. Robert Falotico in Cordis headquarters based in New Jersey, United States.[6]

Back in 2002, the *NEJM* published the very first prospective, randomized, and multicenter study led by Dr. Marie-Claude Morice that compared rapamycin-eluting stents to regular stents with a 6-month follow-up to assess restenosis. The result of the RAVEL trial[7] conducted in Europe was devastating. Rapamycin-eluting stents had a rate of in-stent restenosis of 0% compared to non-pharmacological stents. The following year, 2003, a similar study called the SIRIUS trial was published in the United States with the same results. The very first rapamycin-eluting stent implanted in humans was performed by Dr. Edoardo Souza in Brazil back in 1999.

Parallel to rapamycin-eluting stents, other studies with paclitaxel-eluting stent were conducted called the TAXUS trials. In time, the effectiveness of sirolimus largely proved to be superior to paclitaxel, a drug not currently used for drug-eluting stents. Maybe the most important legacy that TAXUS trials left us was a score that was developed to know the morbidity and mortality rates of patients treated with stenting. It was conducted by Dr. Patrick Serruys and eventually referred to as the SYNTAX score.

After this first generation of stents, the second generation of stents starts what we would call "the stent war". It marked the appearance of different stents with different metal structures, new drugs all derived from sirolimus, different classes of polymers and deployment times. Currently, there are polymer-free stents available with 2 drugs, all with a proven safety and efficacy profile. It is obvious that bare metal stents contributed significantly to the management of coronary artery disease. Catheter-based revascularization procedures have now proven better compared to surgical revascularization.

ADVANCEMENTS IN THE DECISION-MAKING PROCESS: THE MULTI-SLICE COMPUTED TOMOGRAPHY

So far we have made a description of the advancements made in interventional cardiology from the beginning until present day.

However, the biggest question that still remains is what new breakthroughs will show up in this thriving specialty with the capacity to change the decision-making process. Well, it seems that new diagnostic methods will probably be perfected in the field of ischemic heart disease

The most important change that is present and future at the same time is multslice computed tomography, which will probably be replacing diagnostic coronary angiography. Cath labs where cardiac catheterizations are performed will be spared for therapeutic procedures alone. This means that in the coming future, decision-making regarding percutaneous coronary intervention or surgical revascularizations will be based on non-invasive images only.[8-11] Obviously, this prediction involves the disappearance of diagnostic cinefluoroscopy from conventional cath labs where cardiac catheterizations are performed, which in the future, will only be used as PCI capable cath labs.

Currently, numerous studies have been conducted to assess the decision-making process between the angiography and the computed tomography scan like the SYNTAX III Revolution clinical that compared decision-making process regarding revascularization between angiography and multi-slice computed tomography. However, once the computed tomography based decision-making process is behind us, the results of this decision-making are being assessed using multi-slice computed tomography. The ongoing Revolution CABG trial is conducting an ongoing investigation on planning and performing surgeries without previous cine coronary arteriography and multi-slice computed tomography guidance only. This will be an important first trial in humans that will be used to secure this concept.

RACE IS ON FOR THE CONQUEST OF OTHER TERRITORIES

Also, although we predicted some things would be lost, others will be gained too.

There are territories different from the coronary arteries that have already been conquered, some more consistently than others. Currently, the most important one is peripheral vascular territory—lower limbs mainly—which has been meticulously disputed by interventional radiologists mainly. However, this territory already has all the materials and resources nee-

ded to be handled correctly. The same thing happens with the management of aortic aneurysms, which is already part of structural heart diseases.

The "greatest" conquest of all for interventional cardiologists will be the cerebral territory, and they will be fighting this battle against interventional neurologists to treat strokes. Although the latter have already developed interventional procedures to treat **hemorrhagic strokes,** they don't have the experience needed for the management of **ischemic strokes**.[12] It is in this field that interventional cardiologists have already taken the lead since here one of the most important considerations to make is that patients need to be treated very fast. Interventional neurologists are not used to acting fast and still have not wrapped their minds around the fact that longer times equal more brain damage. The decade-long experience of treating acute myocardial infarctions has given interventional cardiologist the lead over interventional neurologists. Also, most of the elements used to treat ischemic strokes are perfectly well known by interventional cardiologists.

Interventional cardiology probably has other unfinished businesses we cannot anticipate today. However, the important takeaway is that this medical specialty does not begin and end in the management of coronary artery disease. A totally different thing are structural heart diseases, but I won't be referring to them in this Editorial.

I wouldn't want to go without leaving a final message on our medical specialty. This message revolves around the terms used to refer to our own specialty: interventional cardiology. This denomination is too encapsulated within the practice of heart procedures, which may have already shaped our mindset and thoughts tremendously. In turn, this may have limited us when our scope of action should go far beyond the coronary arteries since our playground is the entire human arterial tree. Therefore, this denomination should not be an obstacle to restrict our actions to coronary arteries alone. We already know how to treat cardiovascular diseases in the entire body, and this is what we should be doing. Also, we know how to handle different etiologies, not just etiologies of atherosclerotic origin. In the future our specialty will undoubtedly have to come to terms with other medical specialties dedicated to vascular procedures. Also, collaboration with interventional cardiologists, interventional radiologists, interventional neurologists, and vascular surgeons will be a common thing. This will eventually change our amazing specialty dramatically putting us, once again, in a new and different stage of evolution.

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CRISPR-Cas9 as protection therapy against cardiovascular disease

CRISPR-Cas9 como terapia de protección de enfermedades cardíacas

David Vetcher[1]

ABSTRACT

The use of CRISPR technology for gene editing has started a new era in biology and medicine. CRISPR technologies can modify the genome of any eukaryotic cell in an easy, fast, cost-effectively, and precise way. This new modality offers a promising therapeutic approach for heart disease protection and treatment by rewriting the genetic basis of disease.

Keywords: *CRISPR-Cas9 system, gene editing technology, cardiovascular gene therapy.*

RESUMEN

El uso de la tecnología CRISPR para la edición de genes ha iniciado una nueva era en biología y medicina. Las tecnologías CRISPR pueden modificar el genoma de cualquier célula eucariota especialmente humana, de una manera fácil, rápida, económica y precisa. Esta nueva modalidad ofrece un enfoque terapéutico prometedor para la protección y el tratamiento de las enfermedades cardíacas mediante la reescritura de la base genética de la enfermedad, corrigiendo los errores o defectos genéticos responsables.

Palabras clave: *sistema CRISPR-Cas9, tecnología de edición de genes, terapia génica cardiovascular.*

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INTRODUCTION

In February, 2017 we submitted the article *Impact and opportunity of CRISPR-Cas9 in Cardiology* to the Argentine Journal of Interventional Cardioangiology (RACI)—the official organ of the Argentine College of Interventional Cardiologists (CACI)— that was accepted in May 16 2017, and published in Issue #2 (April-June) of 2017.[1] Almost 5 years ago, neither we nor the editor-in-chief, Dr. Alfredo Rodriguez knew could anticipate the impact this article would have on our readers, especially because it dealt with a scientific area that is almost foreign to our own discipline with its own reading priorities.

Contrary to what we believed, this article drew much attention as other people who are more aware to what happens in other disciplines told us, as there was something new out there that was changing dramatically the world of DNA and RNA biology.

Today, after the 2020 Nobel Prize of Chemistry was awarded to Jennifer Doudna from the University of California at Berkeley (**Figure 1**), and Emmanuelle Charpentier from the University of Umea (Sweden) for the discovery in 2012 of a significant finding. The new and powerful Gene Editing technology CRISPR-Cas9. The first description that showed how to turn the natural machinery inside bacteria and archaea into a programmable editing tool that can be used to cut any DNA chain in vivo. Once again, we want to call the attention towards this system as a promising protection therapy for cardiovascular diseases.

We then anticipated that this gene editing technology, which turned upside down all molecular biology research laboratories, was Nobel Prize science and had started a race to achieve this goal.

Therefore, a new era in biology was inaugurated, one where we now could edit, correct, change, erase, insert or to put it more precisely, use insertion–deletion of specific base pairs, in the DNA cut site, and correct errors in the genes responsible for causing diseases.

We were witnessing a scientific revolution right in front of our eyes with the capacity of changing the genome sequence in all eukaryotic cells, especially human cells in an easy, accurate, and cost-effective way.

The possibilities of manipulating DNA sequences in a predictive way using CRISPR-Cas9 technology have multiple and innovative potentialities, and real applications for medicine. Reducing the risk of cardiovascular disease is its promising objective.

Cardiovascular disease (CVD) has a multifactorial, biologically complex etiology. I will clarify it, CVD is associated with metabolic, genetic, environmental, and behavioral risk factors that, combined, challenge our understanding of their etiopathogenesis.

Unlike cases where there is only a single mutation that causes the disease, cardiovascular diseases are caused by a variety of different mutations. Correcting the single mutation is easier. Breakthroughs in molecular biology make it possible to unravel more and more molecular pathways and genetic causes involved in cardiovascular disease.

Gene editing advances so fast that next-generation technologies are already surpassing CRISPR-Cas9 with a more accurate, second-generation technology called Base Editing. This new technology repairs the genetic defect by replacing only one base pair, thus correcting the mutation at one point. Also, it uses other tools that have recently been created in laboratories to insert

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and delete longer sequences, complete sentences instead of just letters, to the point of cutting and pasting whole genes.[2]

TERAPUTIC GENE EDITING WITH CRISPR-Cas9

Genome therapies seek to correct genetic errors or defects

The FDA has recently given its approval for clinical studies to be conducted with the objective of developing new therapies to approach cardiovascular disease in the 21st century using CRISPR-Cas9 Gene Editing to treat the leading cause of death worldwide.

Gene editing is a perfect tool for to control and cure cardio-specific genetic causes associated with cardiovascular disease. With the use of these technologies, it is possible to cure diseases that would otherwise require chronic treatment or have no treatment whatsoever (orphan diseases) accessible to pharmacological agents.

The therapeutic use of genes and base editors to treat genetic disorders corrects the cause of the disease directly instead of treating its symptom. It uses a gene editor to introduce a specific mutation to knockout gene activity thereby achieving loss of function. Altering genes associated with several cardiovascular diseases stimulates the generation, development, and accessibility of new safe drugs.

Researchers started proposing ways of correcting genetic disorders 50 years ago in the 1970s. Experiments in Gene Therapy started back the 1990s. The most important landmarks in that line of research were the FDA approval from 2017 of the first treatment for a genetic disorder that causes blindness.

The second approval was for the treatment of muscular atrophy disease (Zolgensme [Novartis]). First-generation gene therapy was Gene Transference Therapy and Gene Editing and, currently, new RNA-based drugs.

The therapeutic action of these drugs would not be that of a vaccine since the immune system is not involved here. However, the concept is similar, one single preventive therapy to provide lasting protection and possibly for life against cardiovascular diseases.

Gene inactivation has the capacity to reach permanent therapeutic benefits without the need for continuous treatment that requires the repeated administration of drugs. For example, with CRISPR there is this possibility of a single therapy by inactivating the PCSK9 gene permanently and, thus, reducing LDL-c for life.

The long-term objective is to be able to use CRISPR-Cas9 in patients and protect them from cardiovascular disease during their entire lives. The key to protecting the overall population could be in our own bodies. CRISPR-Cas9 has a lot to offer. It is possible to think of the benefits associated with the correction of genes associated with the risk of cardiovascular disease.

Using CRISPR-Cas9 to place those same mutations in normal people and protect them against cardiovascular disease. We are at the beginnings of this knowledge. Gene therapy offers new hope for people with genetic diseases. However, there is still a long way to go to reach its full therapeutic potential and make gene editing as safe and effective as possible.

PCSK9 THERAPEUTIC GENE EDITING

The relation between coronary artery disease and LDL-c has been demonstrated by a wide body of scientific information.[3] Research groups fed a group of mice with cholesterol-rich diets and another group with low cholesterol diets. The liver samples of these mice data were analyzed to see what genes seemed to be most affected by the addition of cholesterol to their diet. These genes coded proteins involved in the production of cholesterol.

When the liver detects that not enough cholesterol is entering the body through the diet, it has the capacity to take over, producing cholesterol molecules. And the other way around, if there is enough cholesterol in the body, the liver reduces its production.

These studies revealed that there was a gene that had never before been studied.

It was speculated that this gene could code an unknown protein involved in the production of cholesterol. They were on the look-out. They tracked down the protein that would be called convertase subtilisin/kexin type 9 or PCSK9.[4,5]

PCSK9 was discovered and identified in 2003 thanks to the research conducted with families with familial hypercholesterolemia (FH). They used a virus to take the gene to the liver of mice, which had the effect of increasing the production of the PCSK9 protein. They observed that the LDL cholesterol levels of mice skyrocketed as a response to the elevated protein level.

The more PCSK9 the more LDL cholesterol, which is equivalent to a higher risk of cardiovascular disease. Interest for developing therapies using the new gene editing technology and silencing the disease-causing genes grew.

Dr. Jonathan Cohen, and Dr. Helen Hobbs from the Southwestern Medical Center at the University of Texas published a historic study on PCSK9 in the *New England Journal of Medicine* with the finding that an increased PCSK9 activity caused familial hypercholesterolemia. Reference.[6,7]

They mapped a gene responsible in a particular region of chromosome 1 that had mutations in PCSK9 gene. This established that the patient's mutations that were causing familial hypercholesterolemia were making the protein work better than normal, that is, it was hyperactive. Mutations that make a protein be hyperactive and work better than normal are quite unusual. However, mutations that inactivate a protein are much more common.

Given that hyperactive mutations increased LDL cholesterol, they were expecting to find inactivating PCSK9 mutations in the population that would presumably reduce LDL cholesterol.

They sequenced PCSK9 gene in the 128 people with low LDL cholesterol in whom they identified two mutations without PCSK9 sense. They found 3% carried a copy of one of the mutations. This 3% not only had a 30% reduction in the LDL cholesterol levels, but also a 90% lower risk of coronary artery disease. Their PCSK9 mutations had given them a natural protection.

Several publications establish that CRISPR-Cas9 could work really well. Ding et al. obtained PCSK9 loss of function through the CRIPR-Cas9 system in humanized mouse livers to the point of reducing the LDL cholesterol levels from 35% down to 40%.[8]

Getting to knockout gene activity with CRISPR-Cas9 and reduce cholesterol levels obtaining the effect equivalent to

people who were born with a PCSK9 genetic mutation (in only one of the two copies) and who have very low levels of cholesterol that reduce the risk of CAD in nearly 90%.

If these results are translated into human beings, it would be similar to taking a statin pill every day for the rest of their lives to reduce cholesterol levels. In this case, it would possible to obtain the same therapeutic effect as statins with only one injection of the editing PCSK9 gene.

The PCSK9 protein in the bloodstream could be reduced to a large extent by silencing its genetic source in the liver with RNA interference; this should result in less LDL cholesterol and a lower risk of cardiovascular disease as seen with the PCSK9 mutations that occur naturally.

These people who lacked PCSK9 were healthy, suggestive that a drug targeted at silencing PCSK9 would be safe. This way they were seeking to achieve a similar effect by editing PCSK9 with CRISPR -Cas9 to benefit patients.

The strategy was simple: administer CRISPR-Cas9 to the liver, inactivate the PCSK9 gene permanently, see how the amount of PCSK9 proteins in the bloodstream decreases, how the levels of LDL cholesterol drop in blood (from 35% down to 40 %), and achieve reductions of approximately 90% in the risk of developing coronary artery disease. All that is required is to knockout the activity of the gene.

Mechanism of action

The PCSK9 gene is in chromosome 1 p32.3 and it is mainly expressed in the liver and the small intestine, which play a key role in cholesterol synthesis and regulation. Circulating PCSK9 binds to the LDL receptor (LDL-r) in the cell membranes of hepatocytes and reduces the number of LDL-r receptors of hepatic surface thus increasing the LDL-c plasma levels.

The increased production of PCSK9 degrades LDL receptors; this is associated with a decrease in receptor activity, which eventually results in elevated blood LDL-c levels.

On the contrary, it was demonstrated that lower productions of PCSK9 due to mutations with function loss are associated with lower LDL-c levels and a lower cardiovascular risk. Different groups of investigators started studying this specific gene. They started studying patients with extremely high LDL cholesterol levels that put people at risk of cardiovascular disease, particularly coronary artery disease that eventually causes heart attacks. These patients had high levels that were so high that they had been suffering heart attacks since their childhood. The condition seemed to be hereditary. Thus, they were eventually diagnosed with the disease known as familial hypercholesterolemia.

Familial hypercholesterolemia (FH) is a hereditary lipid metabolism disorder that starts with high LDL-c levels. FH is the most common monogenic disease in humans. In Argentina the study conducted by Corral et al. revealed a prevalence of heterozygous FH of 1:291 in the General Pueyrredon county by implementing clinical criteria for diagnostic purposes.[9]

FH is linked to gene mutation in LDL receptor. This receptor is the main responsible factor for LDL lipoprotein uptake. Such mutations will reduce the receptor's capacity to enter LDL from blood and into the cells reaching increased LDL-c levels from very early stages of development. Exposure to elevated LDL-c levels during their whole lives makes these patients develop coronary artery disease early.

FH carriers under 40 years showed a 100 times higher risk of having a cardiovascular event compared to the overall general population. Due to its high risk and chances of reducing it with the appropriate use of hypolipidemic drugs this condition has been the center of attention of several studies on iPCSK9, and it is considered that these drugs will be a great tool in the therapeutic armamentarium for the management of FH.

The pharmaceutical industry soon became interested and launched a development program around PCSK9. After a decade's work, the resulting drug, *inclisiran*, proved to have a very effective and safe profile reducing LDL cholesterol levels in clinical trials in patients with cardiovascular diseases. The drug seems to be on in the pipeline to being approved by the U.S. Food and Drug Administration.

Several companies decided to inhibit thee PCSK9 protein directly in the bloodstream, thus creating a new therapeutic option, the PCSK9 inhibitors. They created synthetic antibodies that capture PCSK9 and neutralize it following the model of natural human antibody that fight infections. Two of these monoclonal antibodies *Alirocumab* and *Evolocumab*, obtained FDA approval back in 2015.

In the coming years, large clinical trials showed that both drugs reduce risk of cardiac issues in high-risk patients. PCSK9 inhibitors are a new hypolipidemic group that plays a role reducing LDL-c and cardiovascular events. However, the cost-effectiveness analysis of these drugs is still controversial.[10] They have not become so popular as anticipated due to their high cost and administration regimen (drug needs to be injected subcutaneously, every few weeks, for the rest of the patient's life. An unappealing proposal compared to the daily intake of a pill as it occurs with statins, the typical way of reducing cholesterol levels.)

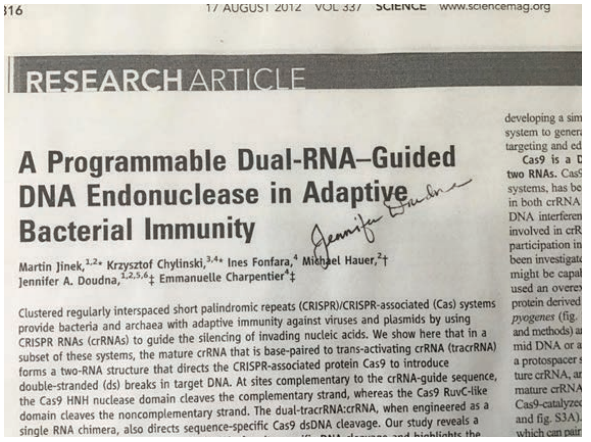
It is necessary to define what population of patients will benefit the most from PCSK9 inhibitors before adding a new drug to their treatment regime. The LDL-c threshold is a determining factor regarding drug indication, sparing this pharmacological resort for the group of highest-risk patients with the highest LDL-c levels. Its safety and efficacy profile has been demonstrated in clinical trials that support their use although long-term evidence is still scarce. Despite these problems, PCSK9 is widely considered a successful story in genetics: only twelve years passed between the discovery of the gene and the approval of drugs for patient use.

GEN *ANGPTL3* INACTIVATING MUTATIONS

There is another gene called *ANGPT3* located in chromosome 1. Protein coding occurs in the liver and is secreted into the bloodstream where it knocks out an enzyme that metabolizes triglycerides. When this gene is the carrier of inactivating mutations that silence protein activity, it explains the low levels of triglycerides and LDL and HDL cholesterol.

The members of a family with this beneficial hereditary condition—a hypobetalipoproteinemia with very low levels of LDL cholesterol, triglycerides, and HDL cholesterol—did not have a functional ANGPTL 3 protein due to their natural mutations (that geneticists call knockouts). This had a protective effect against coronary artery disease.

They had perfect health, no harmful effects of any kind because they did not have a functioning *ANGPTL3* gene. Unlike the PCSK9 in which mutations occur in 3% of the population, the *ANGPTL3* mutations are rarer. They reduce risk of coronary artery disease by one third. Also, there is



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RESEARCH ARTICLE

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]† Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems provide bacteria and archaea with adaptive immunity against viruses and plasmids by using CRISPR RNAs (crRNAs) to guide the silencing of invading nucleic acids. We show here that in a subset of these systems, the mature crRNA that is base-paired to trans-activating crRNA (tracrRNA) forms a two-RNA structure that directs the CRISPR-associated protein Cas9 to introduce double-stranded (ds) breaks in target DNA. At sites complementary to the crRNA-guide sequence, the Cas9 HNH nuclease domain cleaves the complementary strand, whereas the Cas9 RuvC-like domain cleaves the noncomplementary strand. The dual-tracrRNA:crRNA, when engineered as a single RNA chimera, also directs sequence-specific Cas9 dsDNA cleavage. Our study reveals a

developing a sim system to gener targeting and ed Cas9 is a D two RNAs. Cas9 systems, has be in both crRNA DNA interferen involved in crR participation in been investigat might be capal used an overex protein derived pyogenes (fig. and methods) a mid DNA or a a protospacer ture crRNA, a mature crRNA Cas9-catalyze and fig. S3A). which can pair

Figure 1. *Jinek M, Chylinski k, Fonfara I, Hauer M, Douda JA, Charpentier E. A programable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337(6096):816-21.*

evidence that these mutations minimize the risk of type 2 diabetes. A quadruple impact result: less cholesterol, lower triglyceride levels, less cardiovascular disease, and less risk of diabetes. Several companies have been actively developing therapies with ANGPTL3 to recreate these natural mutations, and to this date, their drugs have worked well in clinical trials reducing LDL cholesterol and triglyceride levels.[11]

HIV GENE

Yet another gene—HIV CCR5—is in the pharmacological target through inactivating mutation (deletion of both copies of the CCR5 gene). HIV binds to the surface protein CD4 of lymphocyte T to enter the cell. However, it also needs an additional factor to infect them, a surface protein called CCR5. A new way of fighting the virus is that, since CCR5 is completely gone from the surface of T cells, it brings high resistance against infections caused by the immunodeficiency virus.

CHAGAS DISEASE

It is possible to stop Chagas disease by genetically altering parasites in the laboratory like the trypanosome that causes the disease. Sequencing and gene studying *Trypanosome cruzi* is a way to eradicate the parasite and prevent trypanosomiasis through a new gene therapy. Chagas is a neglected diseases that constitutes a complete challenge for genetic research.[12]

There is this hypothesis of a crossed reactivity process among the parasite-dependent factors and the genetics of the host that triggers the disease. HLA gene studies indicate the existence of susceptibility to the infection and/or development of chagasic cardiomyopathy associated with patients' genetic components that create new opportunities to treat Chagas disease.

CARDIAC AMYLOIDOSIS

The genetic variation or hereditary transthyretin amyloidosis (hATTR) is caused by a protein called transthyretin. The offensive protein is produced by the liver only from a gene called TTR located in human chromosome 18 that is exported into the bloodstream. It is a rare, genetic disease caused by a mutation in the gene that codes transthyretin that prevents it from folding correctly and precipitates in the form of amyloid fibers.[13]

In some patients, transthyretin makes up lumps called amyloid while in blood to eventually be deposited in organs like the heart and peripheral nerves. As lumps build up in the organs, they can create potentially life-threatening issues. The heart becomes thickened by these amyloid lumps, the only recourse is heart transplantation. Other than that, there is no other way to treat cardiac amyloidosis. All that's left is treating its heart failure.

Transthyretin does not seem to play any essential role in the body. Therefore, if the TTR gene is silenced by RNA interference, there should not be any serious side effects. If the production of transthyretin is cut from the source, there is no transthyretin in blood meaning that no amyloid lumps will be found. Over time, lumps that are already in the heart can be eliminated. Even if that was to happen, treatment could stop or even revert the progression of the cardiac signs associated with hATTR amyloidosis thus preventing disease worsening. Pharmaceutical industry decided to develop drugs. After the data of the APOLLO clinical trial demonstrated that Patisiran would have the capacity to reduce the production of transthyretin and improve the patients' quality of life. It was approved by the FDA. It was the first RNA interference (RNAi) drug.[14]

HYPERTROPHIC CARDIOMYOPATHY

It is a hereditary disease that has a specific mutation in the MYBPC3 gene that causes the reference disease.

The team of reproductive biologist Shoukhrat Mitalipov from the Oregon Health & Science University in Portland, United States recruited a patient with severe hereditary hypertrophic cardiomyopathy injecting him with CRISPR-Cas9 and a synthetic DNA with the normal MYBPC3 sequence in the zygotes. In some of the resulting embryos, the patient's mutating MYBPC3 gene had corrected.[15]

In theory, genetically modified embryos could have been implanted in a mother's uterus, which, upon being born, would be free from the father's disease. However, embryos were destroyed within 2 weeks after fertilization, after the study, to guarantee that everything was ethical. Mitalipov thought that it would take 5 to 10 years before genetic editing of embryos would be ready for use to prevent diseases in babies.

By 2017, there were no scientific barriers to take genetically modified embryos from pregnancy to birth. Human embryo editing was already feasible (many researchers had already tried). The only thing that stopped the first genetically modified baby from being born was that no researcher was willing to cross that line. The case appeared on YouTube: *Dr. He Jiankui that his team have produced the first genetically modified babies. Twin girls Lulu and Nana, the first citizens of the CRISPR generation.* No one knew whether it was a historic scientific achievement or a fiasco. It turned out to be a hoax.

The main concern was that the capacity to modify the babies' genes would be within our reach. The objective was to make sure that it was not done prematurely and, if it were to be done someday, it should be done in a transparent, ethical, and safe way. An exciting direction is the use of CRISPR-Cas9-based technology in additional, non-cardiologic applications that we will report on herein as additional information.

Scientists are looking for genetic cures for diseases such as cystic fibrosis, Duchenne muscular dystrophy, sickle-cell anemia, and HIV by lowering the levels of infection or making them undetectable. Also, Alzheimer's and Parkinson's disease. Also, they're administering more effective inhibiting drugs against cancer with approval to conduct clinical trials whose objectives are cancer-involved genes like sotorasib, manufactured by Amgen. This drug deactivates the genetic mutation KRAS G12C that codes a protein responsible for lung, colon-rectal, and pancreatic cancer, type 1 hereditary tyrosinemia, human reproduction, and in the development of Covid-19 or ARDS diagnostic kits based on the CRISPR-Cas9 system.

Also using base editing researchers (Dr. Francis Collins, director of the U.S. National Institutes of Health, and Prof. David Liu from Harvard University) have successfully cured progeria in mice. This rare but devastating genetic syndrome is caused by mutation in a gene that codes a protein called Lamin A that plays a structural role in cell nucleus and causes fast premature aging in children.

To conclude, George Church, a remarkable Harvard geneticist had already anticipated: remember the word CRISPR. It allows us to change our relationship with nature. CRISPR can be really used in humans to change DNA. It actually allows us to change human evolution if we ever wanted to. It will make it possible to take human genome engineering to an unprecedented scale. The revolution has begun.

SUPPLEMENTARY DATA

Gene editing

It consists of double-strand breaks at the DNA target site. Tool used is CRISP-Cas9. Editing refers to a process through which a text is modified to eliminate errors, insert new fragments, erase words or paragraphs to achieve the desired writing. Editing is the act through which the writing or a text is modified. The same concept that we apply here can be used with the genetic code. The double DNA helix is broken, and a physical tear is created. However, the cell has the machinery to repair it and preserve the thread of life. It would be like a word processor for your DNA. You can think of it as a cursor you used in Microsoft Word. Wherever you make the cut on the DNA that is the equivalent of a cursor in the genome word processor. Right there you can write a new word.

CRISPR

It stands for Clustered Regularly Interspaced Short Palindromic Repeats. Term was first coined by Spaniard Francisco Mojica.[16] The first description of CRISPR was a new family of repetitive prokaryote sequences. In nature, the CRISPR-Cas9 system is used to cut viruses in bacterial and archea genomes. It is an immune system that provides bacteria with immunity against viruses, thus protecting the former from the latter. It is an adaptative immune response that makes them resistant to viruses. A record of past viral infections is stored in the bacterial genomic DNA. That information recorded is used to fight repeated infections by the same viruses.

When there is a new invader, bacteria can store part of the invading DNA in their own DNA (in the spacer, between repetitions). When the invader returns, bacteria make a copy of that spacer handing it over to protein Cas9. The latter looks for a match with the base sequence (of the virus) according to the instructions contained in the guide RNA molecule. Then, it makes a cut at that same spot. Nature invented CRISPR. How old is CRISPR? It is millions of years old. Cas proteins already participated capturing the sequences of invading viruses.

At the laboratory it has been used since 2013 in different ways: it can remove unwanted genes or insert new DNA at the location of choice, introduce specific changes in specific positions, correct errors in the genes responsible for causing diseases. A study conducted by Argentinean researcher Marraffini demonstrated that CRISPR-Cas9 targets a specific sequence of the DNA molecule. It was the first time ever researchers saw the potential application of this technology.[17]

Cas9 is a protein specialized in cutting DNA (molecular scissors). It can break strands in the nucleic acid chain. It is directed to a precise location by guide RNA. It looks for the specific sequence and then moves on to cut it. It carries the copy, looks for a match, and then cuts.

Guide RNA

It is a short, synthetic, personalized, programmable RNA, designed in vitro that is built with a specific base sequence of the desired target. Afterwards, it is released into the cells through various mechanisms. Its purpose is to direct the Cas-9 enzyme towards its target (GPS effect) into the DNA and then indicate the direction of the locus of interest where the cut should be made. It can be programmed, and easily exchanged for different sequences. Then, it is used to find and cut. A part of the sequence (the first 20 base pairs) should match that of the target DNA site. If it is necessary to change direction in the DNA these 20 base pairs are replaced with the wanted sequence. Any DNA can be cut out by just changing that small RNA part. This can be done at the lab in a test tube but also inside the cell.

CRISPR-associated Cas 9

It is a gene editing tool. Right now, it is the easiest method for genetic manipulation. Also, it is versatile, precise, and effective. It works by cutting any target double-strand DNA fragment with a matching target sequence. CRISPR-Cas9 has the capacity to treat cancer, muscular dystrophy, sickle cell anemia, recognize any pieces of DNA inside a cell and organism. It is basically a universal tool. It is often compared to a molecular pair of scissors or razor to cut DNA.

This gene selection system consists of two basic components in its machinery, a non-specific endonuclease enzyme known as Cas9 that interacts associated with CRISPER and a guide RNA. The Cas9 protein and a (guide) RNA are assembled in a unit that scans any double-strand DNA molecules with which it comes into contact. It works the same way as a modern word processor by correcting, inserting words or deleting others to program cell codes. If placed in the nucleus of a human cell, the machine will scan the 46 chromosomes of human genome.

When it meets the target sequence, it takes the first 20 pair bases with which the guide RNA is designed and tests whether the pair base sequence designed in the RNA matches the DNA base pair sequence at that location. If there is a perfect match (or an almost perfect sequence sometimes) the machine will cut out both DNA strands where the change is to be made, like some sort of GPS navigator that locates an address and the site where a change is to be made.

Natural cell repair processes make the cut end meet again. However, the repair process is prone to errors, and often inserts or eliminates a letter from the base pair. It has multiple potential applications to genetically enhance crop seed genomes, insects, and genetic models. Also, in medicine to develop experimental therapies for humans. If you can cut out a gene from a (target) cell and create a rupture at the site of interest, then you can change that gene. It is a useful tool that allows us to change our relationship with nature. And, it allows us to change human evolution if we really wanted to. That is just how profound this is.

Base editing

It only corrects mutations at one point where the toxic version is different in a single letter only. Disorder is the result of a single incorrect base letter in a gene. It is a new second-generation genetic editing technology based on CRISPR-Cas9—a completely new way of gene editing—a more precise form fresh out of the laboratory in 2016. It makes it possible to use a base editor to correct a single disease-causing mutation provided that the correction involves a change from C to T (cytosine base editor) or from A to G (adenine base editor).

It has been a tremendous breakthrough in the field of precision gene editing. It allows the substitution of a single DNA base pair in the genome for a different base pair making the double-strand break unnecessary, which prevents it from causing unwanted mutations associated with the cut. A total of 30% of all known genetic problems are due to specific mutations

DNA

Deoxyribonucleic acid is the master blueprint for life. The mechanism of heredity that passes genetic information from generation to generation. It is the chemical molecule that carries the genetic instructions in living beings written in 4 letters designated by the first letter of their chemical names, A T G C. It consists of two strands that twist around each other making up a double helix. Every living being has its own unique DNA that determines what that being will be, a plant, an animal, a man or a rat. Specific sequences code specific genes that, in turn, give instructions to assemble specific proteins. However, if a mutation mixes up the letters, the instructions can be confusing and produce a different version of the protein causing a disease.

RNA

Ribonucleic Acid. It often carries genetic information from the DNA to ribosomes, the cellular factories that assemble proteins. It is a chemical cousin of DNA. Like DNA, it has four letters (known as bases) and can create pairs with matching letters in the DNA. Unlike DNA it has a single strand. RAN letters make it possible for Cas9 to find a unique sequence in DNA. Human Genome it is like a book where each chromosome is a different chapter, and every gene is like a sentence. If we compare the genome with a thick encyclopedia, CRISPR would be the tool to find a specific word in that encyclopedia capable of deleting or changing it. Every human cell has a collection of 46 large DNA molecules known as chromosomes included inside the cell nucleus. Genetic information is distributed among the 46 different chromosomes, a total of approximately 6400 million base pairs of the DNA sequence, which together make up the human genome.

These chromosomes are 23 pairs of chromosomes. (Diploid). These chromosomes are numbered from 1 to 22, ordered by decreasing size (chromosome 1 is the largest of them all). The 23rd pair of chromosomes determines whether a person will biologically be a male or a female and comes in 2 versions: a larger X chromosome and a smaller Y chromosome that have different genes. With some exceptions, females have two X chromosomes in every cell while males have one X and one Y chromosome. Chromosomes within each pair are mostly identical (except for X and Y chromosomes). However, occasional, they have imbalances in base pairs of DNA sequence across the strands.

These imbalances—also known as variants—are responsible for making each person unique. One of the chromosomes of each pair is inherited from the person's mother, and the other chromosome from the father. The variants coming from the mother are the ones that make a person look like the mother in all kinds of traits like physical appearance, health, and risk of disease. Similarly, the variants inherited from the father create similarities with the father. This mixture of variants from the mother and the father makes the person a true hybrid of both patents. Due to this chromosome pairing, most genes in the genome are present in two versions, two copies, one from the mother, and one from the father.

Mutation

It is a particular error in a gene that makes its coded protein change an amino acid in one position for another one eventually altering its function.

Genetic Code

Instructions contained in a gene that tell the cell how to make a specific protein.

Human Genome Project

It is an international effort led by the U.S. National Health Institutes. Its objectives were to determine complete base pairs of DNA sequences in the 23 chromosome pairs and identify and map accurately the location of all the genes. Launched back in 1990, it was declared completed in 2003. A total of 20 000 protein-coding genes were identified in the human genome. The cost of the project was $3 billion. Dr. J. Craig Venter founded the company Celera Genomics in 1998 with the intention of sequencing the human genome as a private effort parallel to the Human Genome Project.

The commercial model of this alternative source was to sell access to the patented Celera sequence database to all those researchers willing to pay thousands of U.S. dollars in fees every year. Celera's competition with the U.S. federal government with the intent of making money was controversial. However, since sequence data was so useful, researchers used this system provided by Celera to track data and find exactly what they needed.

Technological Revolutions in Biology

- In the 1980s: 1985 (K. Mullis) Polymerase Chain Reaction, known as PCR.
- In the 1990s: High-performance DNA Sequencing.
- In the 2000s: Gene Editing Technology.

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The emergence of coronary intravascular lithotripsy

El auge de la litotricia intravascular coronaria

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ABSTRACT

The presence of coronary artery calcification is an independent predictor of poor procedural outcomes. Several techniques, such as cutting or scoring balloons, rotational and orbital atherectomy devices, and excimer laser, are available for plaque modification in the modern catheterization laboratories; however, their use has been associated with increased risk of complications such as vessel dissection, slow or no flow, perforation, or occlusion. Lately, intravascular lithotripsy (IVL) has emerged as a safe and effective tool for the treatment of severely calcified coronary lesions. IVL utilizes spark-gap technology to transform electrical energy to mechanical energy, generating acoustic shock waves that travel transmurally and circumferentially, inducing a therapeutic field effect, and selectively causing fracture of superficial and deep vascular calcium, which is essential for optimal stent expansion. The purpose of this article is to review the mechanism of this novel technology and summarize the pertinent studies leading to its regulatory approvals.

Keywords: *intravascular lithotripsy, coronary calcification, atherectomy.*

RESUMEN

La presencia de calcificación en las arterias coronarias es un predictor independiente de malos resultados operatorios. En la actualidad, en las modernas salas de hemodinamia, existen diferentes técnicas de modificación de la placa tales como balones de corte o *scoring balloon*, dispositivos de aterectomía orbital y rotacional y el láser Excímer. No obstante, su uso se asocia a un mayor riesgo de complicaciones tales como disecciones del vaso, flujos lentos o fenómenos de *no-reflow*, perforaciones u oclusiones. Últimamente ha aparecido la litotricia intravascular (LIV) como una herramienta segura y efectiva para el tratamiento de lesiones coronarias fuertemente calcificadas. La LIV emplea una tecnología basada en la producción de una chispa eléctrica que transforma la energía eléctrica en energía mecánica generando ondas de choques que viajan transmural y circunferencialmente induciendo un efecto de campo terapéutico que provoca, a nivel selectivo, la fractura del calcio vascular superficial y profundo, algo clave para una expansión óptima del stent. El propósito de este artículo es revisar el mecanismo de esta nueva tecnología y resumir los estudios pertinentes que han hecho que esta tecnología haya sido aprobada por diferentes agencias reguladoras.

Palabras clave: *litotricia intravascular, calcificación coronaria, aterectomía.*

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INTRODUCTION

The management of coronary artery calcium has been challenging since the inception of percutaneous coronary intervention (PCI). It is one of the strongest markers for the presence of coronary artery disease (CAD) and has been extensively studied since the 1990s.[1,2] It is encountered in about one-third of cases and is often underdiagnosed with routine coronary angiography.[3] Further, moderate to severe coronary calcification is an independent predictor of poor procedural outcomes and increased ischemic target lesion revascularization (TLR) at 1 year.[4] It not only impedes stent delivery and expansion but could damage the polymer or drug coating resulting in increased risk of stent thrombosis.[5] Stent underexpansion is considered a strong predictor of future adverse events such as stent thrombosis and restenosis.[6] Thus, proper lesion preparation with the use of ablative techniques is strongly recommended for plaque modification and optimal stent implantation.[7,8] However, the use of these techniques comes at the expense of increased risk of complications such as vessel dissection, slow or no flow, perforation, or occlusion.[9,10] While cutting or scoring balloons lack robust trial data and may be biased toward noncalcified segments of the artery leading to dissection, rotational and orbital atherectomy-mediated calcium modification may be limited by guidewire bias.[11,12] Lately, intravascular lithotripsy (IVL; Shockwave Medical Inc., Santa Clara, California, USA) has emerged as a promising technique for the treatment of severely calcified coronary lesions. It works on the principle of generating shock waves (acoustic or pressure waves) that traverse through a medium with peak positive and negative pressure phases, causing tensile stress, shear forces, and cavitation, which modifies calcified plaque.[13] It is a novel technique derived from established extracorporeal shockwave lithotripsy (ESWL) treatment for nephrolithiasis. The technique has been streamlined for the coronaries by arranging multiple emitters in a series along the shaft of the coronary balloon to deliver adequate compressive force for calcium modification while mitigating vascular parenchymal injury.[14] It offers unique advantages, including no requirement for specific training in comparison to conventional atherectomy devices. Also, IVL eliminates guidewire bias as seen with other ablative techniques.

INTRAVASCULAR LITHOTRIPSY SYSTEM

The IVL system consists of a rechargeable and portable generator, a connector cable with a push button for activation, and a catheter available in both over-the-wi-

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re and rapid exchange systems that is advanced over a 0.014-inch wire. The sterile, disposable, single-use catheter is available in 2.5- to 4.0-mm range diameters (0.5-mm increments) and is 12 mm in length. The device is default preset to deliver approximately 10 pulses in a sequence, at a frequency of 1 pulse per second for a maximum of 80 pulses per catheter.[15] The distal end of the catheter system has a novel semi-compliant balloon containing a 50:50 mixture of contrast and fluid and incorporates multiple arrayed lithotripsy emitters in a longitudinal manner. The balloon is sized in a 1:1 ratio to the reference coronary vessel, often guided with the use of intracoronary imaging. Once electrically stimulated, the emitters vaporize the fluid within the balloon, creating shock waves in a circumferential fashion, generating a therapeutic field effect, which selectively fractures superficial and deep vascular calcium.[15] The balloon inflation is restricted to 4 atm to limit the barotrauma while the fluid within the balloon mitigates the thermal injury, keeping the underlying vessel architecture unperturbed. After the delivery of therapy, the balloon is inflated to 6 atm prior to deflation. As the energy is delivered in a circumferential and unfocused manner, the pressure effect reduces with the distance traveled. The pulse duration of these waves is 0.6 - 1.2 μs, delivered at frequency of 1 pulse/s (1 Hz), and produces low amounts of energy (8 - 10 μJ) without introducing electrical components into the localized tissue.[14]

Figure 1 represents a case example of calcium modification by the use of IVL. The severely calcified lesion in the left anterior descending artery was identified on angiography and confirmed via optical coherence tomography (OCT) imaging (luminal area 1.18 mm^2). There was a significant luminal gain post IVL (4.29 mm^2) with multiple calcium fractures and optimal stent expansion (luminal area 5.60 mm^2).

THE USE OF IVL IN CAD

Disrupt CAD I (Shockwave Coronary Rx Lithoplasty® Study) was the initial study testing the feasibility of IVL in CAD patients.[15] It was a prospective, multicenter, single-arm pilot study of 60 patients with ≥1 heavily calcified lesion on both sides of the vessel wall. The primary outcome was major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI), or target vessel revascularization (TVR). The study reported a procedural success rate of 95% facilitating the delivery of stents in all patients. The primary endpoint was observed in 8.3% at 30 days, and there was no unresolved dissection, slow/no flow, embolization, or perforations.[15] The OCT substudy identified intraplaque calcium fracture in 43% of lesions; mean acute area gain was 2.1 mm2 and minimal stent area was 5.94 ± 1.98 mm^2.[16] It also revealed the distinct mechanism of IVL causing circumferential calcium modification independent of calcium thickness in contrast to the guidewire-dependent course of rotational and orbital atherectomy devices.[16] Also, the number of calcium fractures was proportional to the severity of vascular calcification. On the basis of this study, IVL was granted CE mark approval for the treatment of severely calcified coronary lesions.

Following this, Disrupt CAD II (Shockwave Coronary Lithoplasty® Study) was conducted on 120 patients to evaluate safety and efficacy of IVL. The primary endpoint of MACE (cardiac death, MI. or TVR) was observed in 5.8% of patients, including 7 non-Q-wave MIs.[17] The post-IVL acute lumen gain was 0.83 ± 0.47 mm, and residual stenosis of 7.8 ± 7.1% after stent deployment confirmed the effectiveness of IVL in optimal stent expansion.[17] The OCT substudy identified calcium fracture in 78.7% of lesions, with multiple fracture in more than half of lesions and approximately 3.4 ± 2.6 fractures per lesion, results consistent with the Disrupt CAD I. Disrupt CAD II showed successful delivery of IVL across all the lesions with no concerns of slow or no reflow, abrupt closure, or perforations during the procedure.

Disrupt CAD III (Disrupt CAD III With the Shockwave Coronary IVL System) was a US Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study designed for possible regulatory approval of coronary IVL. It was comparatively a larger study that enrolled 384 patients who had severely calcified de-novo coronary artery lesions and used an intention-to-treat analysis. The primary safety endpoint of freedom from MACE (a composite of cardiac death, MI, and TVR) occurred in 92.2% patients, and the primary effectiveness endpoint of procedural success (successful stent deployment with <50% residual stenosis without in-hospital MACE) was achieved in 92.4% patients.[18] The OCT substudy included 100 patients and confirmed severe calcification of vascular lesions, with calcium angle of 292.5 ± 76.5 degrees and calcium thickness of 0.96 ± 0.25 mm at the site of maximum calcification. Calcium fractures were observed circumferentially and longitudinally in 67.4% patients, with multiple fractures in 67.7% of patients with fractures. Minimal stent area, area stenosis, and stent expansion were comparable via OCT irrespective of presence or absence of calcium fractures. Overall, the study successfully achieved safety and effectiveness endpoints with low rates of peri-procedural and angiographic complications, leading to FDA approval on February 12, 2021.

Disrupt CAD IV (Disrupt CAD IV With the Shockwave Coronary IVL System) was a prospective, multicenter study that enrolled 64 patients with similar eligibility criteria to Disrupt CAD III and was designed to assess the safety and effectiveness of coronary IVL for Japanese regulatory approval. These patients were compared to a propensity-score-matched subgroup of Disrupt CAD III patients for primary endpoints, which served as the control group (IVL control) for Disrupt CAD IV. The primary endpoint of freedom from 30-day MACE (cardiac death, MI, or TLR) was accomplished in 93.8% of IVL patients vs. 91.2% of control (p=0.008), and the primary effectiveness endpoint of procedural success was achieved in 93.8% of IVL patients vs. 91.6% of control (p=0.007). Consistent with prior studies, no perforations, abrupt closures, or slow or no-reflow phenomena occurred during the procedures.[19] An OCT analysis showed that calcium fractures were observed in 53.5%, with multiple fractures in 60.5% of patients with fractures. The mean acute gain was 1.42 ± 0.42 mm and minimal stent area was 5.65±1.45 mm^2.

Recently, a patient-level pooled analysis of all 4 trials (n=628) reported that the primary safety outcome

TABLE 1. Coronary intravascular lithotripsy study details.

Studies	Disrupt CAD I	Disrupt CAD II	Disrupt CAD III	Disrupt CAD IV
Study Aim	Feasibility testing	Safety and effectiveness	Regulatory approval	Japanese regulatory approval
Identifier	NCT02650128	NCT03328949	NCT03595176	NCT04151628
Number of patients enrolled (n)	60	120	384	64
Number of sites	7	15	47	8
Primary endpoint	MACE as a composite of cardiac death, MI, or TVR.	MACE as a composite of cardiac death, MI, or TVR.	MACE as a composite of cardiac death, MI, or TVR.	MACE as a composite of cardiac death, MI, or TVR
Criterios de inclusión	• Patients with moderate to severely calcified de novo coronary artery disease presenting with stable or unstable angina and silent ischemia with: • ≥50% stenosis • Lesion length ≤32 mm • RVD 2.5-4.0 mm	• Patients with moderate to severely calcified de novo coronary artery disease presenting with stable or unstable angina and silent ischemia with: • ≥50% stenosis • Lesion length ≤32 mm • RVD 2.5-4.0 mm	Patients with moderate to severely calcified de novo coronary artery disease presenting with stable or unstable angina and silent ischemia with: ≥70% to <100% stenosis or Visually assessed ≥50% to 70% stenosis with evidence of positive stress test, or FFR ≤0.80, or iFR <0.90 or IVUS or OCT MLA ≤4.0 mm^2 Lesion length ≤32 mm RVD 2.5-4.0 mm	Patients with moderate to severely calcified de novo coronary artery disease presenting with stable or unstable angina and silent ischemia with: ≥70% to <100% stenosis or visually assessed ≥50% to 70% stenosis with evidence of positive stress test, or FFR ≤0.80, or iFR <0.90 or IVUS or OCT MLA ≤4.0 mm^2 Lesion length ≤32 mm RVD 2.5-4.0 mm
Key exclusion criteria	Concomitant use of atherectomy, special balloons LVEF <40% BP>180/110 mmHg Acute MI Cardiogenic shock NYHA class III and IV Target vessel diameter <2.4 mm Target lesion length >32 mm Unprotected LM >50% stenosis CTO	Concomitant use of atherectomy, special balloons LVEF <40% BP>180/110 mmHg Acute MI Cardiogenic shock NYHA class III and IV Target vessel diameter <2.4 mm Target lesion length >32 mm Unprotected LM >50% stenosis CTO	Concomitant use of atherectomy, special balloons LVEF <25% BP>180/110 mmHg Acute MI Cardiogenic shock NYHA class III and IV Target vessel diameter <2.4 mm Target lesion length >32 mm Unprotected LM >30% stenosis CTO	Concomitant use of atherectomy, special balloons LVEF <25% BP>180/110 mmHg Acute MI Cardiogenic shock NYHA class III and IV Target vessel diameter <2.4 mm Target lesion length >32 mm Unprotected LM >30% stenosis CTO
Target vessels	LM: 2% LAD: 47% LCx: 13% RCA: 38%	LM: 0,8% LAD: 62,5% LCx: 11,7% RCA: 25%	LM: 1,6% LAD: 56,5% LCx: 12,8% RCA: 29,2%	LM: 1,6% LAD: 75% LCx: 6,3% RCA: 17,2%
MACE at 30 dayss	5%	7,6%	7,8%	6,2%
Acute gain (mean)	1,7 ± 0,4 mm	1,6 ± 0,49 mm	1,7 ± 0,48 mm	1,42 ± 0,42 mm
Dissection	0%	1,7%	0,3%	0%
Perforation	0%	0%	0,3%	0%
Abrupt closure	0%	0%	0,3%	0%
No flow or slow flow	0%	0%	0%	0%
Stent delivery	100%	100%	99,2%	100%

FFR: fractional flow reserve, iFR: instantaneous wave free ratio, IVUS: intravascular ultrasound, OCT: optical coherence tomography, MLA: minimum lumen area, MACE: major adverse cardiac events, LM: left main, LAD: left anterior descending artery, LCx: left circumflex artery, RCA: right coronary artery, RVD: reference vessel diameter, CTO: chronic total occlusion, MI: myocardial infarction, TVR: target vessel revascularization, BP: blood pressure, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, IVL: intravascular lithotripsy. .

was accomplished in 92.7% of patients, and the primary effectiveness outcome was achieved in 92.4% of patients.[20] The target lesion failure rate was 7.2%, cardiac death was 0.5%, and stent thrombosis was 0.8% at 30 days. There were lower rates of angiographic complications with no perforation, abrupt closure, or no reflow.[20] Although all the studies (summarized in **Table 1**) were prospective and multicentered, still the major concerns were the absence of a control arm and possibility of proceduralist preferences for the selective cases suited for IVL. Also, long term data would provide more insight into later procedural complications, such as in-stent restenosis. Further, we do not know whether some of these lesions were compatible with high-pressure balloons to begin with. It would be reasonable to conduct further studies with a control arm (preferably rotational or orbital atherectomy) and the use of intracoronary imaging to better define calcium lesions better suited for IVL compared to other ablative techniques, especially given the higher cost associated with it.

Moreover, the data regarding the effect of IVL on nodular and eccentric calcium remain limited. A patient-level pooled analysis of the Disrupt CAD I and II trials (n=180) with 47 eccentric lesions (26%) showed comparable angiographic outcomes and complications between the eccentric and concentric lesion groups(21). While the preliminary data appear promising, it would be interesting to see whether further studies provide consistent results regarding the role of IVL in the treatment of nodular calcification. Further, randomized clinical trials are warranted to validate the superiority or non-inferiority of IVL against other atherectomy devices or high non-compliant pressure balloon angioplasty.

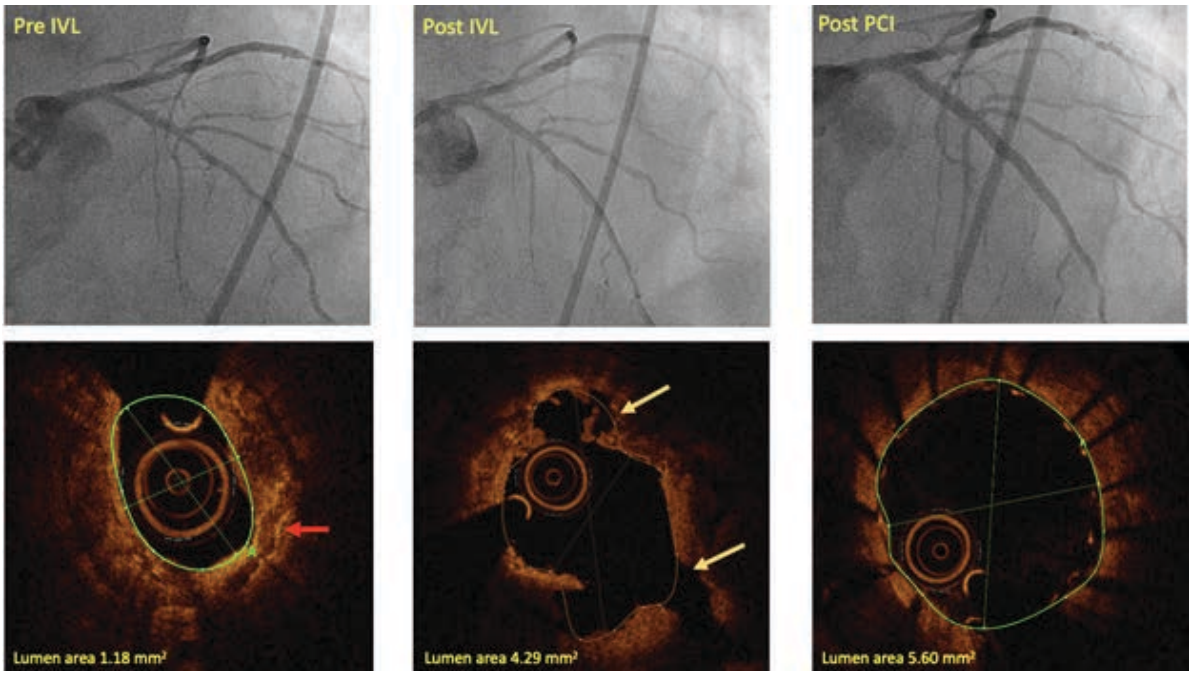

Figure 1. *A case example with angiographic images (pre-IVL, post-IVL, and post-PCI) and corresponding OCT images showing severe calcification (red arrow, pre IVL), fractured calcium at 1 and 4 o'clock post-IVL therapy (yellow arrows), and post-PCI images showing optimal stent expansion. OCT: optical coherence tomography; IVL: intravascular lithotripsy; PCI: percutaneous coronary intervention.*

IVL EFFECT ON CARDIAC ELECTRICAL ACTIVITY

One major concern regarding coronary IVL is its effect on cardiac rhythm, as was already evident in the past, even with ESWL(22). IVL's pulsatile shock waves of can cause localized myocardial depolarization, resulting in an isolated ventricular ectopic ("shocktopics") or asynchronous cardiac pacing (≥2 successive beats)(23). A retrospective study of 54 patients found a higher incidence (77.8%) of ventricular capture, with heart rate being an independent predictor and 16-fold increased likelihood of IVL-induced myocardial capture with heart rate <65 beats per min(23). It was further evaluated systematically in Disrupt CAD III, and the use of IVL was found to be safe, without increased risk of sustained ventricular arrhythmias. The study found the incidence of IVL-induced capture was 41.1% and male sex, total number of IVL pulses delivered, and heart rate ≤60 beats per min were independent predictors(18). The drop in systolic blood pressure was comparable between the IVL-capture versus no-IVL-capture groups. Taken together, although there is a theoretical risk of potential arrhythmias with IVL, no malignant arrhythmias have been reported so far, further solidifying its safety.

CONCLUSION

Coronary IVL is a novel technique, emerging as a safe and effective alternative for the treatment of moderate to severely calcified coronary lesions. However, further studies, preferably with a control group, are warranted to better define the calcified lesions best suited for IVL compared to other techniques.

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Endovascular resolution of complicated pulmonary pseudoaneurysm after right heart catheterization

Resolución endovascular de pseudoaneurisma pulmonar como complicación del cateterismo derecho

Macarena Matus de la Parra[1], José María Milanesi[1], Agustín Hauqui[2], Raúl Solernó[3], Ricardo Aquiles Sarmiento[4]

ABSTRACT

Right heart catheterization with a Swan-Ganz catheter is a commonly used method for the hemodynamic assessment of hospitalized patients in critical care units or else as part of the evaluation of pulmonary circulation in many different diseases. It is often considered a safe procedure with a low rate of complications. Pulmonary pseudoaneurysm is a rare complication although it is associated with a high mortality rate. This is the case of a pulmonary pseudoaneurysm that occurred as a complication associated with the use of a Swan-Ganz catheter and its resolution through percutaneous endovascular treatment.

Keywords: *pseudoaneurysm, therapeutic embolization, Swan Ganz catheterization.*

RESUMEN

El cateterismo cardíaco derecho con catéter de Swan-Ganz es un procedimiento utilizado para el monitoreo hemodinámico de los pacientes internados en unidades de cuidados críticos o como parte de la evaluación del circuito pulmonar en diversas patologías. Generalmente es una intervención segura y con baja tasa de complicaciones. El pseudoaneurisma pulmonar es una complicación rara, pero de elevada mortalidad. Presentamos un caso de pseudoaneurisma pulmonar como complicación del uso de catéter de Swan-Ganz y su resolución mediante tratamiento percutáneo endovascular.

Palabras clave: *pseudoaneurisma, embolización, cateterismo derecho.*

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INTRODUCTION

Swan-Ganz (SG) catheter has facilitated the hemodynamic management of patients hospitalized in intensive care units, as well as the intra- and postoperative management of severe patients treated with high-complexity surgeries. Although its routine used has decreased, it is occasionally used for hemodynamic monitoring purposes in intensive therapies, assessment of medically unexplained dyspnea or suspected pulmonary hypertension. It is often a safe procedure. However, the placement and use of the SG catheter is associated with potential risks. One rare complication with a high mortality rate is the formation of pulmonary pseudoaneurysms, which is associated with its rupture or dissection. This is the case of a woman who developed a pulmonary pseudoaneurysm after right heart catheterization in an effort to portray this entity as a complication following the use of the SG catheter and its resolution through endovascular percutaneous treatment.

CASE REPORT

This is the case of a 55-year-old woman with a past medical history of smoking on oral anticoagulant drugs due to internal jugular vein thrombosis. The patient was in her postoperative period after liver transplant due to primary biliary cirrhosis and on immunosuppressive drugs with mycophenolate, tracrolimus, and corticoid therapy. During transplantation a SG catheter was used for intraoperative hemodynamic management. **The catheter was inserted "in the blind", that is, without radioscopic or echocardiographic guidance. Also, no guidewires were required or catheter exchange for its placement.** Fifteen days after surgery, the patient started having episodes of persistent cough without hemoptysis or episodes of desaturation in the blood gas analysis. The physical examination confirmed the presence of right pulmonary baseline hyperventilation without other clinically significant findings. The multislice helical computed tomography (CT) coronary angiography revealed the presence of a 20 mm nodular image with homogeneous enhancement after the administration of contrast at right lower pulmonary lobe level (**Figure 1**). Also, laminar right pleural effusion was revealed, which had already been found in different studies prior to transplantation. Considering the patient's recent history of pulmonary catheterization, a pulmonary arteriography was performed to confirm or discard the presence of a possible vascular lesion as the complication associated with the placement of the SC catheter. A 6-Fr RadiofocusR introducer sheath (Terumo Corporation, Tokyo, Japan) was inserted via right common femoral vein. One 5-Fr pigtail catheter mounted on a 0.035-in J-tip guidewire was advanced until it reached the right pulmonary artery infe-

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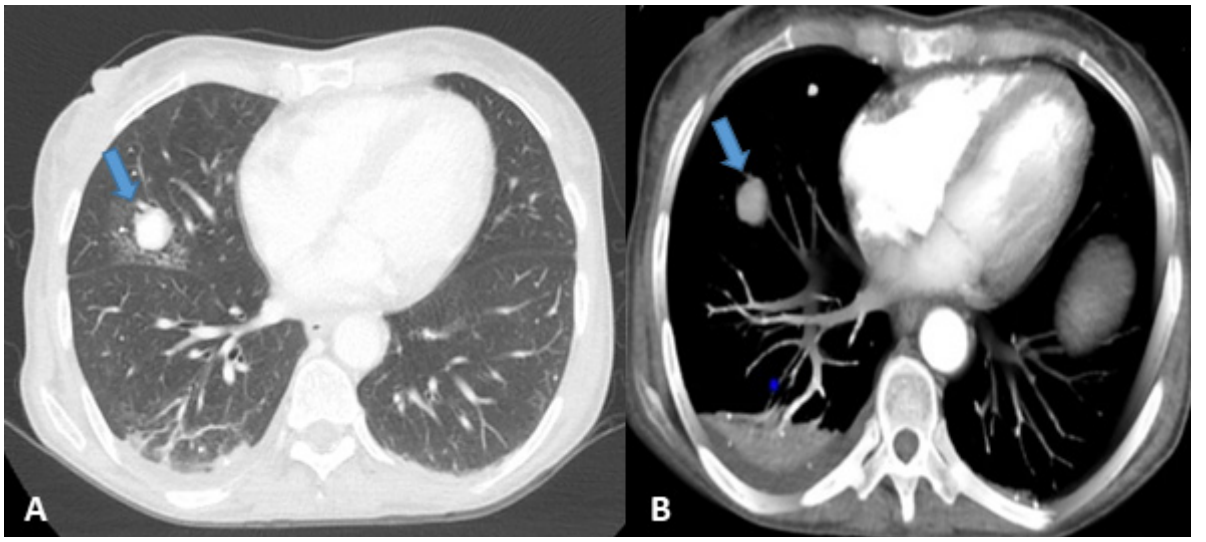

Figure 1. *Axial view (A) and 3D reconstruction (B) of thoracic multislice computed tomography images showing a 20 mm nodular image with homogeneous enhancement after the administration of contrast located at right pulmonary inferior lobe level (blue arrow).*

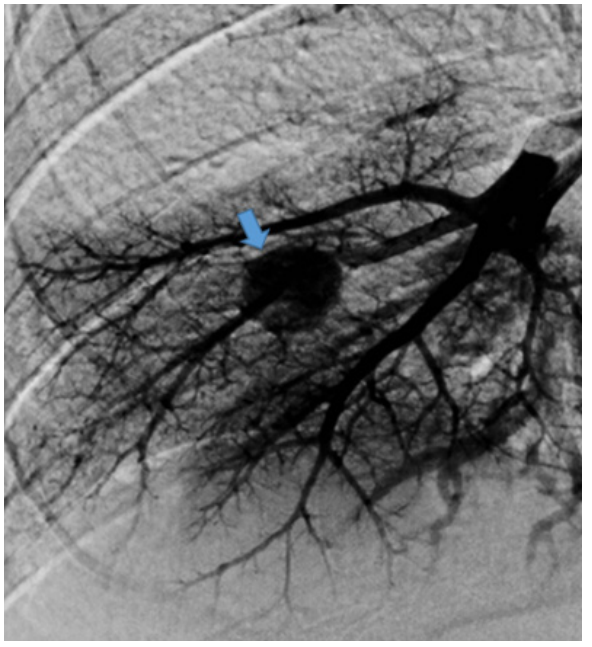

Figure 2. *Anteroposterior right pulmonary angiography showing a pseudoaneurysm in right lateral segmental branch (inferior lobe).*

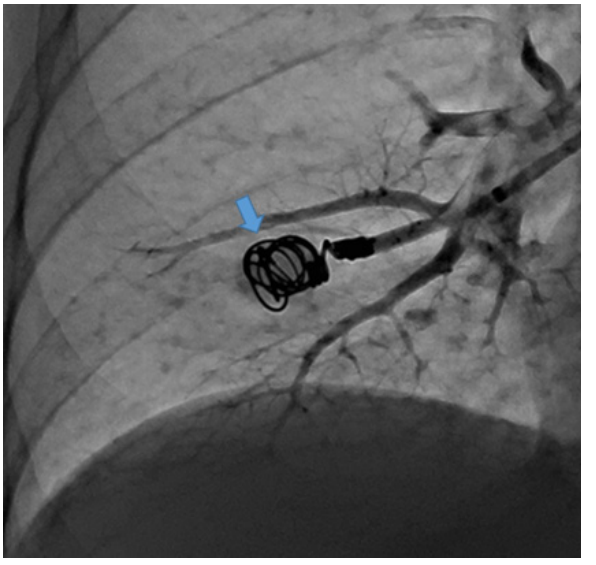

Figure 3. *Anteroposterior pulmonary angiography showing micro-coil migration inside the pseudoaneurysm that successfully excludes the pseudoaneurysm from pulmonary circulation (blue arrow).*

rior lobar branch. Afterwards, an arteriography identified the presence of a pseudoaneurysm at right anterior segmental branch level (segment 8b) **(Figure 2)**. Afterwards, the femoral introducer sheath was exchanged for a 6-Fr DestinationR sheath (Terumo Corporation, Tokyo, Japan) via femoral vein. Then, a 5-Fr MPA 1 Impulse™ multipurpose catheter (Boston Scientific, MA, United States) was used for selective catheterization. The branch was embolized using four 9 mm × 2.7 mm 2D Helical-35 micro-coils (Boston Scientific, MA, United States). After releasing the micro-coils, the exclusion of the pseudoaneurysm was confirmed **(Figure 3)**. Patient's progression was good and without postoperative complications. The patient was released from the hospital 11 days later. The control coronary computed tomography angiography performed at 30 days confirmed the absence of opacification in the target lesion **(Figure 4)**.

DISCUSSION

The SG catheter was designed thanks to the ingenuity of two doctors, Dr. Jeremy Swan, a cardiologist born in Ireland (1922-2005), and Dr. Willam Ganz, a cardiologist born in Czechoslovakia (1919-2009). The SG catheter is a tool that has facilitated the hemodynamic management of patients hospitalized in intensive care units (ICU).[1] This device consists of a multiple branch catheter capable of measuring cardiac intracavitary pressures (right atrium, pulmonary pressures, pulmonary capillary pressure), estimating cardiac output, and obtaining "indirect" parameters like pulmonary and systemic vascular resistances, cardiac index, etc.[2] Although it has not been confirmed yet that it reduces mortality rate or the length of stay of critically ill patients, it is still a valuable tool to determine the patient's hemodynamic status and prescribe the proper therapy.

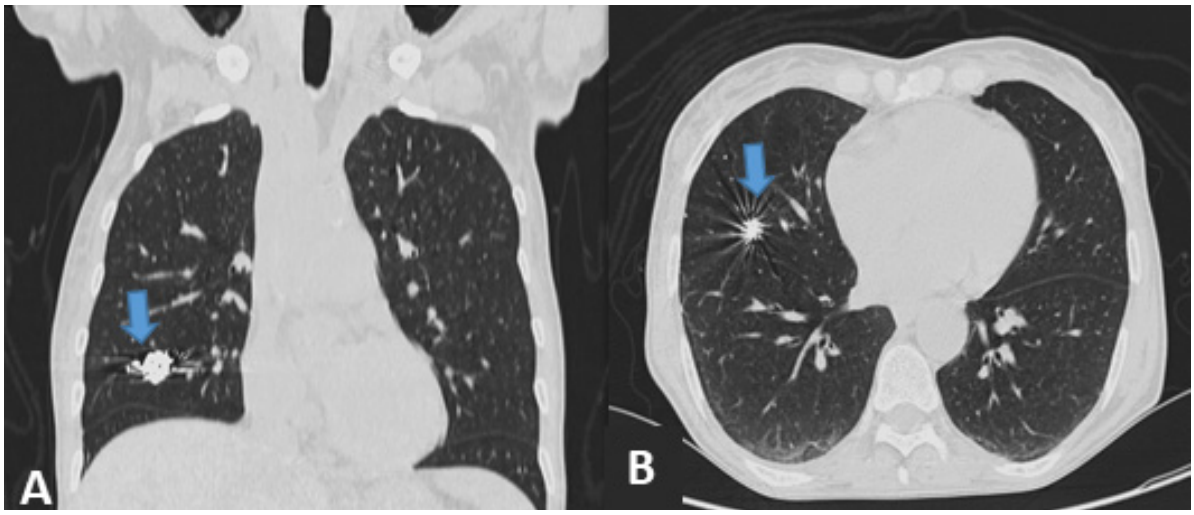

Figure 4. *Coronal (A) and axial (B) views of thoracic multislice computed tomography images of pulmonary window showing the presence of coils and lack of aneurysmal sac opacification (blue arrow).*

Pulmonary artery catheterization is an invasive procedure that is often performed without fluoroscopic control. At times, its use has been associated with different complications .[3] A systematic case review informed that the main complications associated with SG catheter insertion occur in 3% to 17% of the cases.[4] Atrial and ventricular arrhythmias, and intracardiac rolling have been among the most common complications reported. Pneumothorax, carotid or subclavian artery puncture, and balloon tears have also been reported, but to a lesser extent.[4] Episodes of coronary embolisms, pulmonary hemorrhages, and pulmonary artery ruptures with formation of pseudoaneurysms have been reported as the least common complications with the highest possible risk.[4] The latter has been described in 0.05% to 0.2% of the cases being the mortality rate reported due to massive hemoptysis of up to 50%.[4] There is a series of risk factor predisposing to vascular ruptures like anticoagulation, pulmonary hypertension, long courses of corticoids, hypothermia during surgery, intraoperative cardiac manipulation, age > 60 years, and feminine sex.[4,5] However, the exact mechanism of damage to the arterial wall is still unknown, but it could be associated with balloon hyperinflation and/or vascular perforation directly induced by the tip of the catheter on the vascular wall. On the other hand, pulmonary arterial hypertension would create a pressure gradient through the balloon towards the periphery where arterioles are smaller and more fragile, thus increasing the chances of vascular damage. Although anticoagulant therapy does not increase the risk of injury *per se*, it can inhibit the capacity of the anticoagulation system to seal the defect.[5]

Although pulmonary artery pseudoaneurysms have been reported more frequently after vascular trauma, and in patients with tuberculosis (Rasmussen aneurysms), these can be associated with pulmonary abscesses, septal embolisms, systemic vasculitis, bronchiectasis, and pulmonary neoplasms.[6]

Regarding clinical signs, these patients often present with hemoptysis, and the appearance of an infiltrate of poor demarcated borders on the thoracic x-ray being the infiltrate undistinguishable from a pulmonary infarction at the beginning of the examination. A persistent denser central region is often seen as associated with the pseudoaneurysm itself. Presentation often occurs within the first 24 hours after cardiac catheterization. However, it has been reported up to 14 days later. The right pulmonary artery location is the most common of all, and it occurs in 93% of the cases, often in mid and inferior lobes.[4,5] Not so frequently though, patients remain asymptomatic and no cases of cough signs like our case have been described in the medical literature.

The diagnostic method of choice is thoracic coronary computed tomography angiography with opacification protocol of pulmonary arteries. It not only allows us to recognize this vascular lesion, but also to rule out other possible causes.[7] In addition, pulmonary angiography is the method of reference to diagnose pseudoaneurysm and facilitates the embolization of the aneurysmal sac excluding it from the circulation. Catheter-directed embolization has become the treatment of choice as it is a fast, and safe procedure associated with low morbidity and mortality rates in these patients displacing pulmonary resection (lobectomy) that has become a second therapeutic option.[7,8]

CONCLUSION

Ruptured pulmonary arteries and the formation of pseudoaneurysms are among the most serious complications associated with the use of the SG catheter. Patients with this complication can remain asymptomatic or develop hemoptysis right after the procedure or a few days later. The reference diagnostic test here is pulmonary angiography and the treatment of choice is transcatheter embolization. Proper training to learn how to place the SG catheter and knowing the balloon inflation pressure both reduce the rate of vascular complications.

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Intracoronary lithotripsy for stent underexpansion resolution: utility of enhanced stent visualization or StentViz™

Litotricia intracoronaria para la resolución de la subexpansión del stent: utilidad del uso de realce de la visualización del stent o StentViz™

Juan Mieres[1], Carlos Fernández-Pererira[1], Diego Ascarrunz[1], Matías Rodríguez-Granillo[1], Alfredo E. Rodríguez[1]

ABSTRACT

Percutaneous coronary intervention is always supported by elements of innovative technologyto create solutions to everyday problems that are complex like the management of severely calcified plaques, and a complication that is sometimes unexpected, which is stent underexpansion that can be truly challenging. We present three cases of stent underexpansion throughout different time periods, the first one presented in an acute form, and was solved within the first 24 hours. The second case was chronic stent underexpansion of several-month evolution that worsened due to the presence of acute coronary syndrome and that was solved in the same hospitalization. The last case was extremely challenging and involved the left main coronary artery that presented a slight stent underexpansion that, within a few months, became symptomatic and was successfully solved. All these cases were solved using intracoronary lithotripsy, a novel device that through ultrasound probes transmitted by a rapid exchange catheter breaks down coronary calcium. These were tested in de novo calcified plaques. We present patients who already had a previous stent and were guided by the stent enhancement technique, General Electric angiography systemStentViz™.It uses an algorithm to visualize the stent struts and allow detailed monitoring to achieve the proper stent expansion, which is associated with fewer cardiovascular events at follow-up.

Keywords: *underexpansion of the stent, IVL, intracoronary lithotripsy, StentViz™, ESV, enhanced stent visualization.*

RESUMEN

La intervención percutánea siempre está apoyada en elementos de tecnología innovadora tratando de crear soluciones a problemas cotidianos que son complejos como el tratamiento de placas severamente calcificadas y una complicación a veces inesperada que es la subexpansión del stent, que puede ser un gran desafío. Presentamos tres casos de subexpansión en diferentes períodos de tiempo, el primero en forma aguda que pudo resolverse dentro de las primeras 24 horas, el segundo una subexpansión crónica de varios meses que se reagudizó por un síndrome coronario agudo y que se resolvió en la misma internación, y el tercero, muy desafiante, del tronco de coronaria izquierda que presentó una subexpansión leve que en pocos meses se volvió sintomática y fue resuelta exitosamente. Todos estos casos fueron resueltos con litotricia intracoronaria, novel dispositivo que a través de sondas ecográficas transmitidas por un catéter de rápido intercambio permite fracturar el calcio, estos fueron probados en placas de novo, presentamos pacientes que ya tenían un stent previo y guiados por la técnica del realce de la visualización del stent en los angiógrafos General Electric, llamado StentViz™, técnica que a través de un algoritmo permite claramente la visualización de los struts del stent y posibilita un seguimiento detallado para alcanzar una correcta expansión, que está asociada a disminución de los eventos cardiovasculares en el seguimiento.

Palabras clave: *subexpansión del stent, IVL, litotricia intracoronaria, StentViz™, RVS, realce de la visualización del stent.*

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INTRODUCTION

Complex angioplasties associated with heavily calcified plaques have always been challenging regarding percutaneous coronary interventions (PCI) in the routine clinical practice.[1] There are 2 different devices available that we use daily in our cath labs to perform these PCIs: enhanced stent visualization (ESV), which is a technology provided by an angiographic system built by General Electric (GE, Boston, MA, United States), the so-called StentViz™.[2] It allows us to view the stent struts very rapidly (**Figure 1**). Secondly, all devices capable of treating these plaques, among them, rotational ablation,[3] high and very-high pressure balloons that can reach up to 40 atmospheres,[4,5] and finally intracoronary lithotripsy (ICL) (Shockwave Medical, Fremont, CA, United States)[6] used to treat de novo plaques before stenting. However, there are times when the stent has already been implanted and stent underexpansion becomes a serious problem. We should mention that proper stent expansion is associated with fewer cardiovascular adverse events in the long term.[7]

We will be describing three different cases of stent underexpansion solved with StentViz™-guided ICL.

CASE PRESENTATION

Case #1

The patient was a 65-year-old man with type 2 diabetes and a severe lesion at the origin of the right coronary artery, another lesion in the proximal third, another in the middle third, and yet another moderate-to-severe lesion in the distal third. Also, the presence of severe calcification in the entire arterial trajectory was confirmed. PCI was started with predilatation of the ostial, proximal, and middle plaques using compliant and non-compliant balloons. Afterwards, a 3.0 mm x 23 mm stent (Waltz™, Microport, Shanghai, China) was implanted in the proximal third. The StentViz™ visualization tool confirmed the presence of severe stent underexpansion. Several attempts were made to expand the stent with different 3.0 mm, 3.5 mm, and 4.0 mm non-compliant balloons (Firefighter™ NC, Microport, Shanghai, China) for extended periods of time. Then, we rapidly thought of the different options available and decided to go with ICL.

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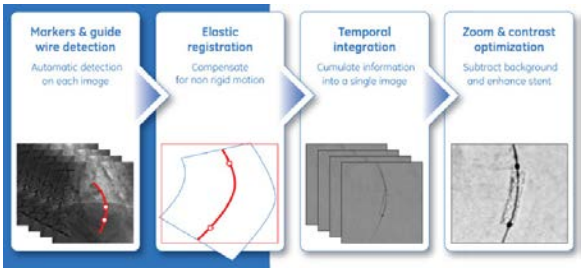

Figure 1. *Unlike other technologies available, StentVizTM detects automatically detects both the guidewire and balloon markers to perform an elastic registry to compensate for the stent rigid deformity. Also, it detects and eliminates radiopaque objects for optimal stent visibility and solid performance. StentViz Enhanced Stent Visualization Dr. Morice, Dr. Lefèvre, Dr. Hovasse, Dr. Chevalier, Dr. Louvard Institut Cardiovasculaire Paris Sud, Massy, France. January 25, 2018.*

Then, we used one 2.5 mm x 15 mm Shockwave balloon at 4 atm and 6 atm (8 cycles, 10 pulses each) until completing 80 pulses. The entire procedure was closely monitored with the StentViz™ visualization tool. Balloon started expanding and the ICL was completed with a 3.0 mm non-compliant balloon (Firefighter™ NC, Microport, Shanghai, China) that was inflated at high atmospheres. We did not think it was necessary to implant another stent. In the lesion located at the middle third we performed a de novo ICL and a 3.0 mm x 23 mm stent (Waltz™, Microport, Shanghai, China) was implanted. A different 4.0 mm x 18 mm stent (Waltz™, Microport, Shanghai, China) was implanted into the ostium and the whole vessel showed a uniform appearance. The patient was discharged 48 hours later with clopidogrel, apixaban, and aspirin for 1 month plus colchicine for 3 months. The patient was on anticoagulation therapy due to AF **(Figure 2)**.
The patient remained asymptomatic at 6-month follow-up.

Case #2

It is a 60-year-old man with a past medical history of heavy smoking and COVID-19-related ARDS 2 months before hospitalization with coronary artery disease and several previous angioplasties due to multivessel disease with known chronic stent underexpansion in the middle third of the left anterior descending coronary artery. While hospitalized the patient developed an acutely occluded left anterior descending coronary artery that was partially solved with the use of non-compliant balloons that were inflated at high atmospheres and extended inflations. A few months later, the patient is readmitted to our center with a STEMI at left anterior descending coronary artery level with an acute occlusion of the proximal-middle third. Occlusion is solved implanting a 3.0 mm x 18 mm stent (Firehawk, Microport, Shanghai, China) into the proximal-to-middle third resulting in flow restoration. An attempt is made to fully expand this plaque using several non-compliant balloons. However, due to the presence of persistent chronic exacerbated stent underexpansion, it is decided to complete the expansion with using ICL with a 3.0 mm x 12 mm balloon. A total of 80 pulses were delivered at 4 to 6 atmospheres at the location of stent underexpansion. Full expansion was achieved with a 3.5 mm x 20 mm non-compliant balloon (Firefighter™ NC, Microport, Shanghai, China) with excellent angiographic results. The patient was discharged on prasugrel and aspirin at 48 hours.
The patient remained asymptomatic at 4-month follow-up.

Case #3

It is a 63-year-old woman with a past medical history of smoking and dyslipidemia with previous coronary artery disease and multiple previous angioplasties since 2004, among them, 1 with acute myocardial infarction with cardiogenic shock that required the use of intra-aortic balloon pump. This year in January the last angioplasty was performed on the left main coronary artery due to mild stent underexpansion. Patient is discharged, but since her condition progresses into dyspnea, she is readmitted for reassessment at 2 months. The presence of severe restenosis due to stent underexpansion at left main coronary artery level is confirmed. Restenosis is thoroughly observed using the StentViz™ visualization tool (General Electric, Boston, MA, United States). Predilatation was decided using a 3.0 mm x 12 mm non-compliant balloon and inserting a Shockwave balloon-catheter system from left main coronary artery to left anterior descending coronary artery delivering 80 pulses. This results in the gradual expansion of the stent. Aferwards, complete expansion is attempted with a 4.0 mm x 15 mm non-compliant balloon (Firefighter™ NC, Microport, Shanghai, China). Then, an angioplasty is performed on the left circumflex artery proximal third and the procedure is completed with a kissing balloon with optimal results as confirmed on the StentViz™ visualization tool. The patient remains on prasugrel, aspirin, rosuvastatin, carvedilol, and fenofibric acid **(Figure 3)**.
The patient remained asymptomatic at 3-month follow-up.

DISCUSSION

We presented 3 complex cases of stent underexpansion, the first one an acute case, the second a chronically underexpanded stent, and the third one a subacute underexpansion. In the first case, despite predilatation and stent impaction the proper expansion was not achieved. In the second case, the underexpansion was exacerbated by STEMI. The third one was a case of stent underexpansion at left main coronary artery level. All these cases were directly guided by the ESV visualization tool manufactured by GE, StentViz™.
There is no doubt that coronary artery calcification (CAC) has always been challenging because it prevents devices from navigating easily. Most important of all is that stent expansion cannot be fully achieved, which is associated with the occurrence of more cardiovascular events. CACs were solved with compliant balloons, non-compliant balloons, and very high-pressure balloons plus a series of different atherectomy techniques. However, these techniques are also associated with certain complications and even have the potential to be lethal.[1,3-5].
The arrival of ICL has revolutionized the expansion of heavily calcified plaques easy and fast with a rapid exchange catheter giving the PCI an innovative tool. The first presentation of this device was made by Brinton et al. in TCT back in 2016 where the DISRUPT CAD trial was introduced for the first time. This multicenter study conducted in 5 countries included heavily calcified plaques treated primarily with OCT-guided ICL. Favorable results were seen in a significant number of patients.[6,7] Afterwards, the results from the DISRUPT CAD II, DISRUPT CAD III, and DISRUPT CAD IV clinical trials were reported.[8-10]
In previous issues of our journal, we have already reported on 4 cases of primary ICL in heavily calcified plaques or that

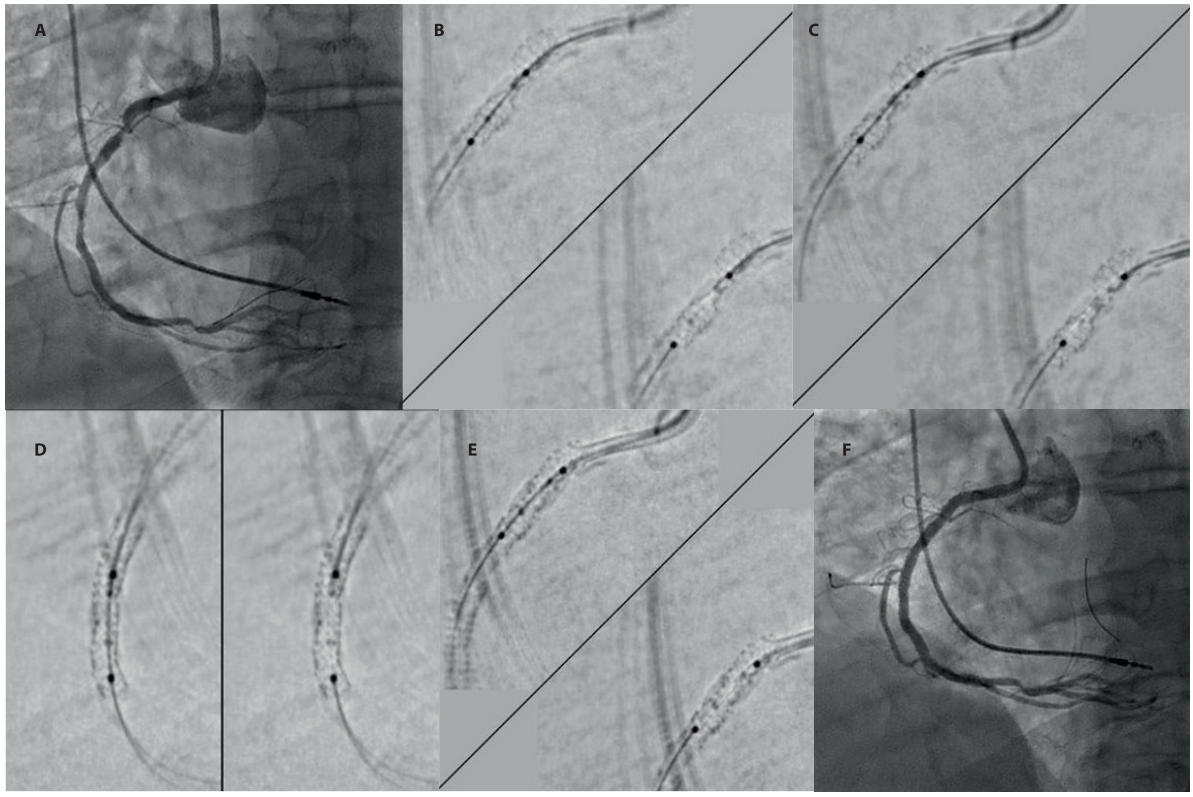

Figure 2. *2A. Angiographic presence of proximal severe stent underexpansion and severe lesion to the heavily calcified middle third. 2B. Early StentVizTM showing severe stent underexpansion. 2C. After the first few pulses of the StentVizTM-guided ICL, the gradual dilatation of the lesion becomes obvious. 2D. StentVizTM in the artery middle third with complete dilatation. 2E. StentVizTM-guided complete dilatation of both plaques. 2F. Angiographic control with optimal outcomes.*

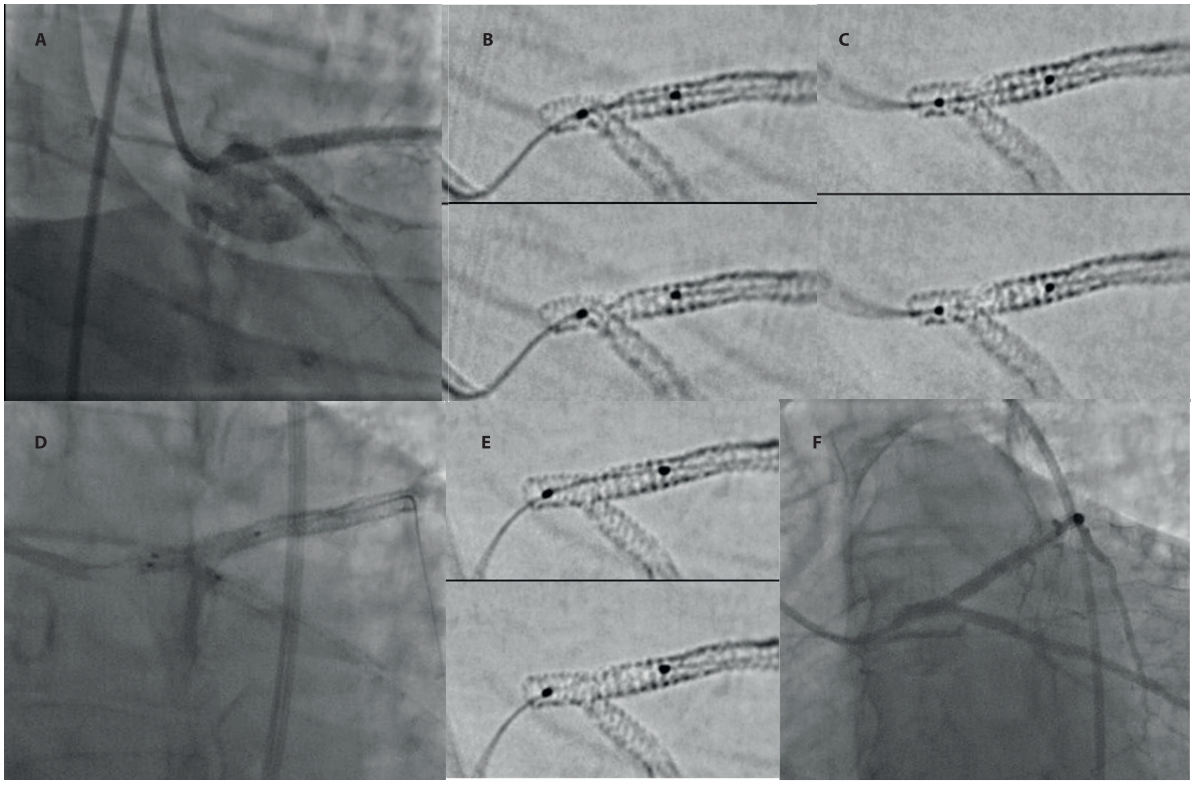

Figure 3. *3A. Presence of severe left main coronary artery stenosis. 3B. StentViz™ confirms the presence of stent underexpansion. 3C. After the pulses delivered by Shockwave ICL system the almost complete expansion of the stent can be seen. 3D. Kissing balloon is used due to the presence of a bifurcation lesion on the LMCA. 3E. The StentViz™ control performed confirms the complete expansion of the stent. 3F Angiographic control with optimal outcomes.*

could not be dilated with non-compliant balloons as our first experience in our region[11] with very good short-term results. Now we are reporting 3 cases of stent underexpansion treated with ICL and guided by the ESV visualization tool manufactured by GE, StentViz™.

After the early use of ICL in calcified plaques the first report on the management of stent underexpansion came out as a case report[12]. It was later followed by the publication of a 13-patient registry from 6 different centers that used OCT-guided ICL to treat stent underexpansion without MACCE at 30-day follow-up.[13]

These days the European-Canadian CRUNCH registry is being published including 70 patients with stent underexpansion and a rate of device success of 92.3%. The in-stent minimal lumen diameter increased from 149 mm ± 0.73 mm to 2.41 mm ± 0.67 mm (P < .001) while stent expansion went all the way up to 124.93% ± 138.19% (P = .016). No in-hospital complications or MACCE were reported .[14]

In conclusion, the ESV visualization tool manufactured by GE—StentViz™—is a new imaging modality to visualize coronary stents.[15] This technology consists of a software that improves the image quality of stent struts by acquiring cine cardiac imaging using the markers of a deflated balloon to compensate for cardiac movement. The result is an improved image of the stent that allows detailed assessments of the expansion, architecture, and position of the stent in relation to other stents. StentViz™ is a new ESV platform that uses a non-linear registry process based on balloon and intracoronary guidewire markers to compensate for the non-linear deformity of coronary artery. Theoretically, this feature can generate a more precise representation of the stent compared to algorithms that are based on a linear technique targeted at balloon markers only. Also, the StentViz™ visualization tool is unique because it facilitates guidewire removal.[16,17]

The ESV algorithm is divided into 4 big aspects that are image acquisition, imaging direction, image combination, and image processing on screen.

With simple tools like the ESV technology plus a rapidly exchangeable balloon catheter that generates intracoronary lithotripsy we can solve very complex cases like the ones described herein even for the lack of intravascular images.

CONCLUSIONS

The use of intracoronary lithotripsy (ICL) and enhanced stent visualization (ESV) to guide angioplasty can be an affordable, highly effective tool to treat stent underexpansion in the routine clinical practice.

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Critical limb ischemia: case presentation of retrograde endovascular approach

Tratamiento de isquemia crítica en miembros inferiores: presentación de un caso con resolución endovascular por vía retrógrada

Deysi Vanessa Cuadros Morales[1]

ABSTRACT

Critical lower limb ischemia is a serious medical condition with a high risk of major amputation, disability, and death. Treatment of choice is percutaneous due to its low rate of complications. However, it poses a challenge when performing antegrade (femoral) revascularization in chronic total coronary occlusions with technical failure rates between 10% and 40%. For this reason, the retrograde approach ofinfrapopliteal vessels arises as an alternative with successful results, and a low risk associated with the puncture site.

This is the case of a patient with critical ischemia who required unconventional access to achieve revascularization.

Keywords: *critical ischemia, lower limbs, occlusive lesions, angioplasty retrograde.*

RESUMEN

La isquemia crítica de miembros inferiores genera una condición médica grave con alto riesgo de amputación mayor, incapacidad y muerte. El tratamiento percutáneo es de elección por su baja tasa de complicaciones. Sin embargo, presenta un reto cuando se realiza revascularización por vía anterógrada (femoral) en oclusiones crónicas, con fracaso técnico entre un 10 y un 40%. Por ello surge como alternativa el abordaje retrógrado sobre los vasos infrapoplíteos, con resultado exitoso y bajo riesgo asociado al sitio de punción.

Reportamos un caso de paciente con isquemia crítica que requirió de acceso no convencional para lograr la revascularización.

Palabras clave: *isquemia crítica, miembros inferiores, lesiones oclusivas, angioplastia retrógrada.*

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INTRODUCTION

Lower limb critical ischemia is a serious manifestation of lower limb peripheral arterial disease. It poses a high risk of amputation or complications associated with tissue loss, gangrene, sepsis or multiple organ failure.[1] This ischemia is characterized by the coexistence of pain at rest or foot or toes ulceration or gangrene. It often presents as a chronic total coronary occlusion (CTO) in the femoropopliteal segment (FP).[2]

Endovascular treatment is the therapy of choice to revascularize patients with critical limb ischemia thanks to its results and low morbidity and mortality rates reported.[3] Technical success is defined as the arrival of direct flow towards the foot through, at least, 1 patent infrapopliteal blood vessel.

Access via femoral approach—antegrade—is the common access route to perform an angioplasty of lower limb arteries. The rate of technical failure regarding revascularization is somewhere between 10% and 40%. Retrograde approach techniques via the accesses opened in anterior and posterior tibial, feet, fibular, and metatarsal arteries respond to the goal of reducing the rate of technical failure.

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CASE REPORT

This is the case of a 92-year-old woman with a positive cardiovascular risk factor for arterial hypertension. Her past medical history included non-anticoagulated atrial fibrillation, and peripheral arteriopathy with intermittent claudication at 54 yards. Also, the patient's medical history included hip fracture with metal prosthesis in right lower limb. She is referred from a different center with lower limb critical ischemia of 20-day evolution with necrotic ulcer of right hallux up to the third ipsilateral phalange (Rutherford V).[4]

The physical examination confirmed the presence of palpable femoral pulse grade 2/2 with reduced popliteal pulse and absence of anterior tibial artery with slightly reduced temperature, paleness, delayed capillary pulse, and right foot hyperalgesia. The ankle-brachial index (ABI) before treatment was 0.5.

Other additional tests:

- Laboratory tests: RBC, 39%: WBC, 9.7 million/mm^3; platelets, 200 million/mm^3 creatinine levels, 1.4 mg/dL; urea levels, 57 mg/dL.
- Arterial Doppler ultrasound: occlusion of right superficial femoral artery.

Procedure is performed under sedoanalgesia and systemic heparinization through antegrade puncture and insertion of a 6-Fr introducer sheath (Avanti Plus; Cordis Corporation, Miami Likes, FL, United States) into the right common femoral artery. The diagnostic arteriography performed reveals a total chronic coronary occlusion at superficial femoral artery (SFA) level from the ostium towards the distal third with recanalization at popliteal level due to collateral circulation (**Figures 1 A-B**). An occlusion of the anterior tibial artery is revealed at infrapopliteal level with distal recanalization. Afterwards, a 5-Fr diagnostic

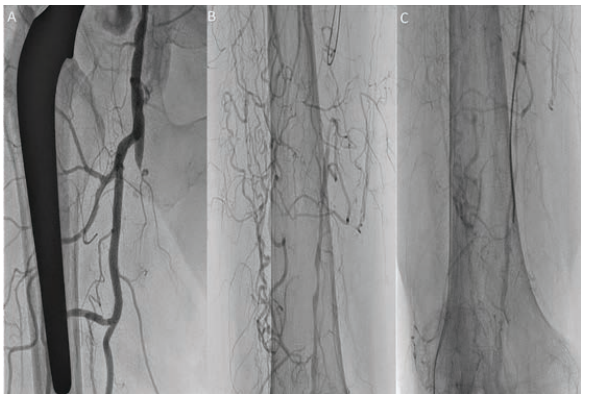

Figure 1. *A. and B. Angiography reveals the occlusion of the superficial femoral artery from the ostium towards the distal third. C. Failed angioplasty via antegrade access of SFA.*

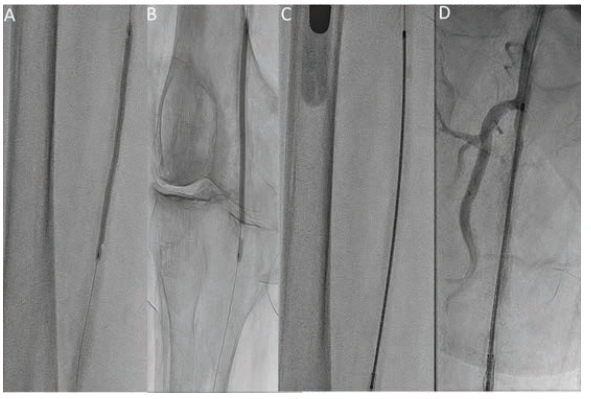

Figure 3. *A. and B. Balloon angioplasty of SFA and popliteal artery. C. and D. Positioning and implantation of self-expanding stents into the SFA.*

catheter (Impulse™ MPA2, Boston Scientific, MA, United States) is mounted on a 150 cm 0.035 in J-tip hydrophilic guidewire (Radiofocus™ Guide Wire M, Terumo Corporation, Tokyo, Japan) that is advanced towards the mid third of the SFA. Then, it is exchanged for a 4-Fr hydrophilic vertebral catheter (Radiofocus™ Glidecath™, Terumo Corporation, Tokyo, Japan) in an attempt to recanalize the crossing. Procedure is difficult due to the presence of severe calcification with failing antegrade revascularization **(Figure 1C).**

The posterior tibial artery is treated with retrograde puncture at distal third level with a 21G needle (Cook Medical Inc. Bloomington, IN, United States) with fluoroscopy guidance. Afterwards, a 5-Fr radial introducer sheath is inserted (Terumo Corporation, Tokyo, Japan) followed by a 0.014 in guidewire (Cross-IT 300 XT, Abbott Vascular, Santa Clara, CA, United States) mounted over a 2.0 mm x 20 mm OTW balloon (Ryujin Plus, Terumo Corporation, Tokyo, Japan) until reaching the inside of the vertebral catheter placed via antegrade access at the SFA mid third level to eventually connect the retrograde and antegrade accesses (SAFARI technique)[5] **(Figures 2 A-C)**. Afterwards, access is reversed and angioplasty is completed with a 3 mm x 80 mm balloon (RapidCross, Medtronic, Minneapolis, MN, United States), a 5 mm x 120 mm OTW balloon (Admiral Xtreme, Medtronic, Minneapolis, MN, United States) **(Figures 3 A-B)**, and implantation of three 6 mm x 120 mm self-expanding stents (Everflex™, Medtronic, Minneapolis, MN, United States) covering the ostium until the distal third of the right SFA **(Figures 3 C-D)**.

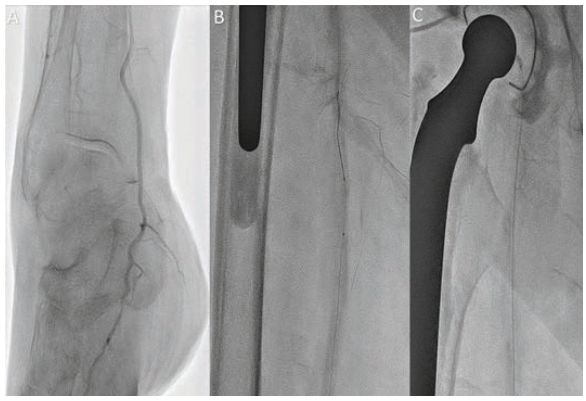

Figure 2. *A. Scarce blood supply at foot dorsal level where the patent posterior tibial artery can be seen. B. and C. Using the posterior tibial access, insertion of the guidewire into the catheter inserted via femoral access and use of the SAFARI technique.*

Control angiography shows patency in the entire territory of the right superficial femoral artery, and in the popliteal and right posterior tibial arteries with increased infrapatellar flow. These arteries had been hypoperfused before the procedure **(Figures 4 A-F)**. Homeostasis was performed with compressive bandage at the posterior tibial puncture site without further complications.

Technical success facilitated the revascularization of the previously occluded superficial femoral artery that had caused the problem, and increased flow while keeping patent, at least, 1 infrapopliteal vessel. In the immediate postoperative period, the foot artery recovered pulse with an ABI (angle-brachial index) of 1 with better color, capillary refill, and with normal temperature.

At the outpatient follow-up, a control Doppler echocardiography was performed at 6 months with preserved right posterior femoral and tibial flow that progressed into the healing of the lesion and no pain at rest while on ASA, clopidogrel, cilostazol, and statins.

DISCUSSION

The presence of critical ischemia (pain at rest or trophic lesions) requires early revascularization treatment due to the high risk of losing the limb in an elevated number of patients causing functional disability, and social and economic losses. The rate or primary amputation at 1 year is 25%.[1]

Over the last decade, the arrival and perfectioning of new percutaneous technologies has turned into a significant growth of endovascular strategies.[6] However, in complex cases of extensive occlusions, the rate of failure is somewhere between 10% and 40% when performed via antegrade femoral access. Even in reference centers, the rate of technical failure associated with long chronic total coronary occlusions can be up to 17.8%.[7] When this happens, an option that should be taken into consideration is retrograde access[8] that is associated with higher chances of technical success (of up to 85%) in cases with failing conventional antegrade access.[9] This approach should be performed with extreme caution and, on many occasions, it is the only patent infrapatellar vessel responsible for keeping the limb viable.

Good angiographic results were reported when proper flow was reestablished in the ulcer region, which facilitated the healing of the lesion, and prevented amputations.

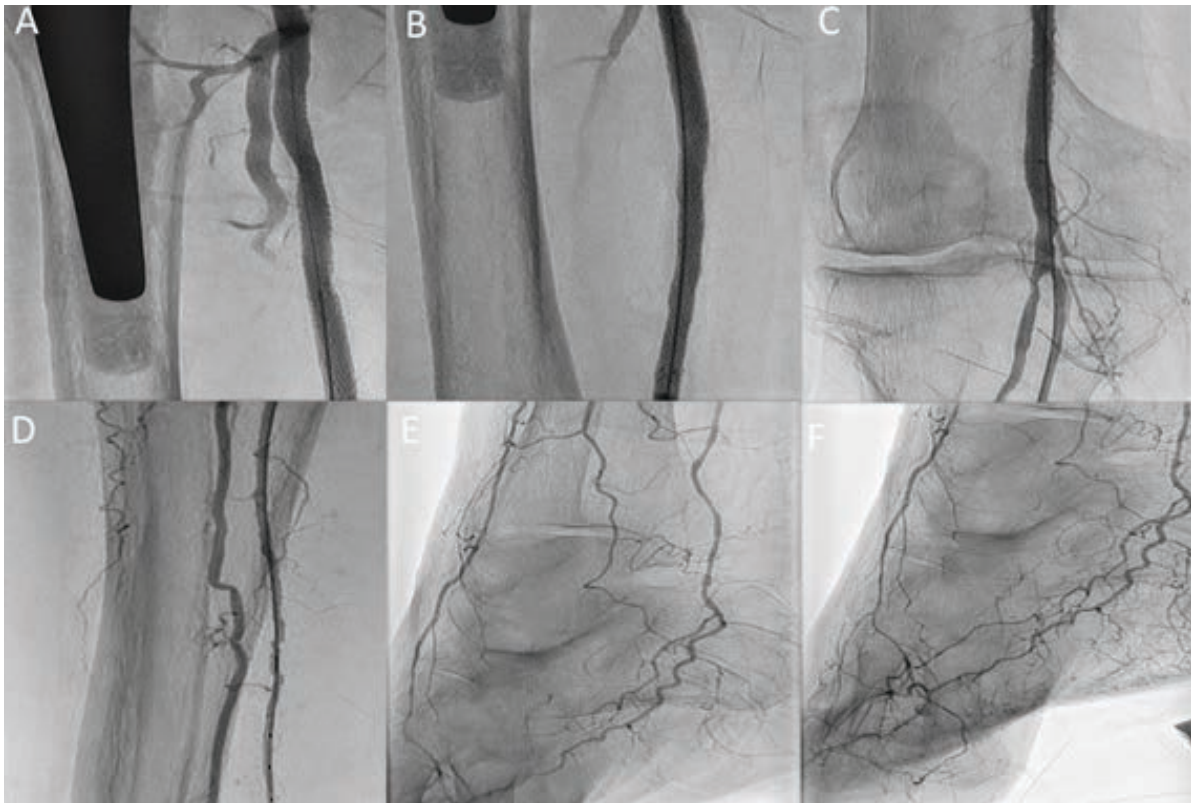

Figure 4. *A-C. Angiography after treatment showing patency from the ostium until the distal third of the previously occluded SFA. D-F. Patency of posterior tibial and plantar arteries with significant flow improvement in the fibular and foot arteries, both of which were hypoperfused before treatment.*

CONCLUSION

Peripheral angioplasty via retrograde access in long occlusive lesions is a viable therapeutic option.This new therapeutic strategy allows the endovascular revascularization of most patients with successful results, which improves the viability of the limb with lower rates of amputation, morbidity, and mortality associated with this condition.

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Transcatheter aortic valve replacement for failing homograft

Reemplazo valvular aórtico transcatéter en fallo de homoinjerto

José María Milanesi[1], Martín Oscos[2], Diego Grinfeld[2], Raúl Solernó[3], Ricardo Aquiles Sarmiento[4]

ABSTRACT

Aortic valve replacement with homograft is a rarely used option due to the risk of late degeneration involved. Reoperation in patients with aortic valve replacement with homograft represents a high risk. Transcatheter aortic valve replacement is an established therapy for patients with severe aortic stenosis. However, its use in aortic homograft failure has been reported in very few publications. This is the case of transcatheter aortic valve replacement for failing homograft.

Keywords: *aortic valve stenosis, transcatheter aortic valve replacement, homograft, allograft.*

RESUMEN

El reemplazo valvular aórtico con homoinjerto es una opción poco utilizada debido al riesgo de degeneración tardía. La reintervención quirúrgica en pacientes con reemplazo valvular aórtico con homoinjerto representa un riesgo elevado. El reemplazo valvular aórtico transcatéter es un tratamiento reconocido para pacientes con estenosis aórtica severa, pero su uso en fallo de homoinjerto en posición aórtica ha sido reportado en escasas publicaciones. Presentamos un caso de reemplazo valvular aórtico transcatéter en fallo de homoinjerto.

Palabras clave: *estenosis valvular aórtica, reemplazo valvular aórtico transcatéter, homoinjerto, aloinjerto.*

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INTRODUCTION

Surgical aortic valve replacement (SAVR) with homograft is prone to late degeneration as it is associated with severe calcification and vascular dysfunction. Surgical reintervention in patients treated with SAVR with homograft can be associated with a significantly high risk.[2] Transcatheter aortic valve implantation (TAVI) has become a known therapy for patients with severe aortic stenosis (AoS) with high risk for conventional surgery. This is the case of a failing aortic homograft on which TAVI was performed.

CASE REPORT

This is the case of a 65-year-old man, former smoker, and with a past medical history of high digestive bleeding due to duodenal ulcer treated with endoscopic therapy. He showed severe aortic valvular disease that was treated with SAVR back in 2003 with homograft placement, chronic atrial fibrillation on anticoagulant therapy, recent transient ischemic attack, and VVI pacemaker implantation due to sinus node disease. The patient presented with NYHA functional class (FC) II-IV progressive dyspnea of 14-day evolution.

The transthoracic echocardiography performed revealed the presence of a homograft with sclerocalcification in the aortic position conditioning a moderate-to-severe restriction in its opening. Mean gradient was 41 mmHg, the continuity equation area, 1.02 cm^2, and the patient showed moderate aortic regurgitation with an eccentric jet. The presence of mild tricuspid regurgitation allowed us to estimate pulmonary systolic pressure in 64 mmHg. The left ventricle was slightly dilated with preserved systolic function, same as the right ventricle. The cine coronary arteriography performed found no coronary lesions. The cardiac examination was completed with a coronary computed tomography angiography that confirmed the presence of severe calcification of the aortic homograft and ascending aorta. Size of the valvular annulus was 29.3 mm, the left main coronary artery-valvular plane distance was estimated at 15 mm, and the right coronary artery-valvular plane distance at 14.7 mm.

Following the findings made in the additional methods used, the clinical signs were interpreted as failing homograft after 17 years. EuroScore II risk score was 11.33%, and the STS risk score, 5.1%. The case was brought to the heart team to assess the therapeutic strategy that should be followed and, considering the risks associated with reinterventions, it was decided to go with TAVI.

Procedure was performed by puncturing the right femoral artery using a minimally invasive technique.[6] An Avanti+® 7-Fr femoral introducer sheath was used (Cordis, CA, United States). Valvular plane was crossed using a 0.035 in straight Starter™ guidewire (Boston Scientific, MA, United States) and a 6-Fr Impulse™ AL2 catheter (Boston Scientific, MA, United States). The system was changed for a Confida™ guidewire (Medtronic, Minneapolis, MN, United States), and a no. 29 CoreValve™ Evolut R™ system was advanced

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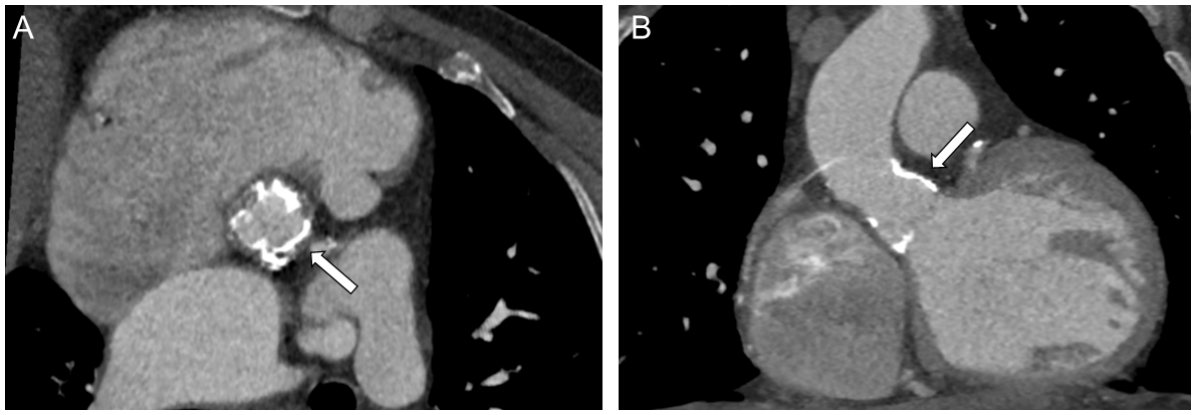

Figure 1. *Axial view (A), and long axis of left ventricle (B) on cardiac computed tomography scan. Severe calcification of aortic homograft (white arrows).*

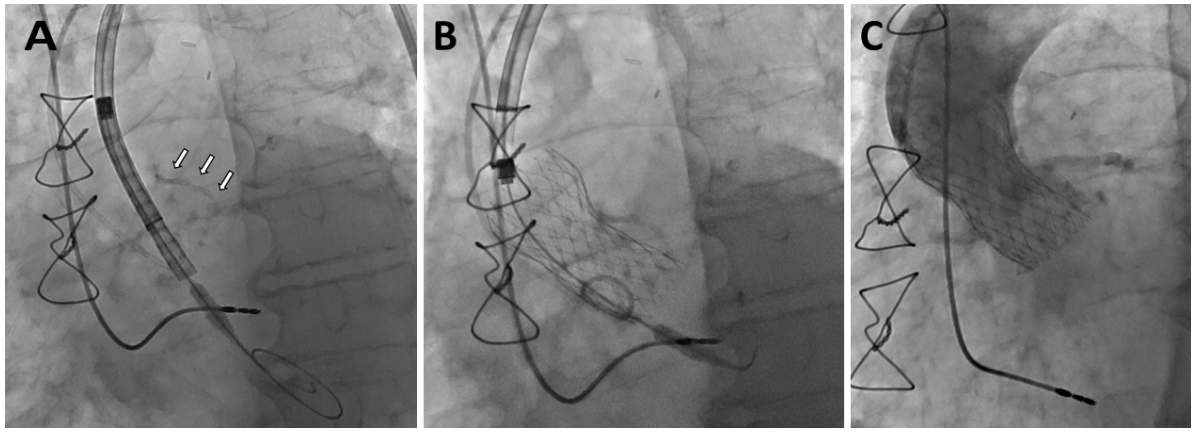

Figure 2. *Fluoroscopic images in LAO and caudal angulation (CAU) projection angles (A and B) and cranial LAO view (C) during transcatheter aortic valve implantation. Image A shows the severe calcification of the aortic homograft (white arrows). Image B shows the CoreValve™ Evolut R™ system successfully implanted. Image C corresponds to the thoracic aortogram after TAVI with no paravalvular leaks or residual AR findings.*

(Medtronic, Minneapolis, MN, United States) that was placed in the valvular plane and released successfully. Angiographic and echocardiographic control confirmed the right position of the system without paravalvular regurgitation. Peak-to-peak aortic gradient was estimated at 5 mmHg. Femoral percutaneous closure was performed using a Proglide™ device (Abbott Laboratories, IL, United States). The patient was discharged from the hospital 72 hours after the procedure and once in a normal range of anticoagulation.

DISCUSSION

This is the case of a patient with a severe aortic valvular homograft dysfunction considered of high surgical risk for reintervention. Although the medical literature available does not establish any specific recommendations on how to treat this type of patients we decided to go with TAVI with favorable hemodynamic, echocardiographic, and clinical outcomes.

Aortic root homografts are rarely used for SAVR. They are often spared for very complex repairs where a tissue engineered valve is required, as well as for cases when the bioprosthetic valve is not good enough due to infections or other factors.[1] The advantages of valvular replacement with homograft are its excellent hemodynamic profile and good homeostasis, as well as the low risk of thromboembolism and infection of the prosthetic valve. The setback is its durability due to the destruction and degeneration of the valve. Also, because it is not available everywhere.[2] However, several studies suggest that homografts rarely deteriorate after 5 years, and that the need for reintervention appears, on average, after 12 years (RI, 8 to 13 years).[2,3]

Conventional surgical reintervention is technically challenging because it requires coronary artery reimplantation, often in elderly patients with comorbidities and worsening ventricular function.[2] High surgical risk determines whether reintervention will be an alternative or not. The experience published in the medical literature comparing therapeutic options regarding failing homografts in the aortic position is scarce. Sedeek et al. compared conventional surgical reintervention vs TAVI only to find a higher rate of bleeding in the surgical option (58% vs 0% $P = < .001$), and more vascular access complications in the percutaneous option (36% vs 15% $P = .193$). Morbidity and mortality risk was high regardless of the replacement technique used. Avoiding vascular complications may lead to better results in the TAVI group.[3]

When considering percutaneous treatment in this type of cases there are different questions that should be studied prior to the procedure and that are often complex issues. The anatomy of the aortic root is often distorted, which complicates the measurement of the annulus and the placement of the prosthetic valve. Multislice computed tomography provides clear images of the anatomy and geometry of the aortic root, the distribution of coronary calcium, and most important of all, accurate measurements of annular size.[2] Although there is a higher risk of paravalvular leak due to the

stent asymmetrical dilatation and patient-prosthesis mismatch, overinflating balloons of balloon-expandable valves or postdilatation can tear both the root and the annulus of the heavily calcified aortic homograft.[4] Another variable that should be taken into consideration is the possibility of coronary ostia obstruction as it is the case with valve-in-valve procedures. Precise measurements of valvular annulus and coronary ostia are essential to prevent this potential complication.[4,5]

CONCLUSION

In our case, SAVR with TAVI turned out to be a safe option to treat a failing homograft in the aortic position. We should mention the importance of planning and taking previous measurements of the anatomy of valvular apparatus and ascending aorta through computed tomography scans since the usual geometry is often distorted. The minimally invasive technique promotes early hospital discharges.

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Venous thoracic outlet syndrome, angiographic diagnosis

Síndrome del opérculo torácico venoso, diagnóstico angiográfico

Jorge Cortez[1], Derwin Plazas Álvarez[1], Patricio Rattagan[1], Andrés E. Dini[1], Miguel Osvaldo Villegas[1]

ABSTRACT

The thoracic outlet syndrome is an extremely rare entity. It is characterized by the compression of neurovascular structures(brachial plexus, subclavian artery and vein) being venous compression the second most common of all. Although diagnosis is suspected based on the patient's past medical history and physical examination, imaging studies are required to confirm the diagnosis. The most widely used imaging modalities are the ultrasound, the magnetic resonance imaging, and the computed tomography scan. This is the case of a patient with a past medical history of recurrent deep venousthrombosis (DVT) of right upper limb.Diagnostic certainty was achievedthrough dynamic venous angiography.

Keywords: *thoracic outlet syndrome, venous occlusion, venous syndrome, operculum.*

RESUMEN

El síndrome del opérculo torácico es una entidad poco frecuente. Se caracteriza por la compresión de las estructuras neurovasculares (plexo braquial, arteria y vena subclavia), siendo la compresión venosa la segunda en frecuencia. Si bien el diagnóstico se sospecha en base a la historia clínica y el examen físico, se requieren estudios de imagen para confirmar su diagnóstico. Los métodos más utilizados son la ecografía, la resonancia magnética y la tomografía computarizada. Se presenta el caso de una paciente con historia de trombosis venosa profunda (TVP) recurrente sobre el miembro superior derecho, cuyo diagnóstico de certeza se obtuvo por angiografía venosa dinámica.

Palabras clave: *síndrome del opérculo, obstrucción venosa, síndrome venoso, opérculo.*

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INTRODUCTION

The axillary vein is a continuation of the brachial vein that ascends towards the thorax. Then, it turns into the subclavian vein as it passes above the first rib underneath the clavicle. Then, it meets with the internal jugular vein to become the brachiocephalic vein. The term *axillosubclavian* is used to refer to the axillary and subclavian segments of the vein. To reach the internal jugular vein, the subclavian vein needs to run through the thoracic outlet. Tunnel roof is the clavicle, the floor is the first rib. Medially, the sides are made up by the subclavian and costoclavicular ligaments; laterally, by the anterior scalene muscle. Both the clavicle and the first rib meet in a support site that allows exerting maximum strength between the two in the region where the vein resides. The subclavian muscle is another significant structure of the thoracic outlet. This muscle, as its name indicates, is found underneath the clavicle, and can compress the subclavian vein **(Figure 1)**.[1] Thoracic outlet syndrome (TOS) is a rare disease that mostly affects young patients. It is due to the compression of neurovascular structures. Depending on what structure is compromised it can be categorized into neurogenic (due to brachial plexus compromise), venous, and arterial (due to subclavian compromise). Although the main cornerstones of diagnosis are the past medical history and physical examination **(Table 1)**,[1-3] imaging modalities are useful to confirm diagnosis or the site of the lesion, outline abnormal anatomies, assess other possible causes for the symptoms, and categorize the situation of the patient properly **(Table 2)**.[1,3-6] This is the case of a female patient treated with phlebography with an image suggestive of recanalized thrombus. Dynamic angiography confirmed the diagnosis of venous thoracic outlet syndrome (VTOS) with compressed subclavian vein in the proximal third. The objective of this case is to know the pathophysiology and most convenient hemodynamic study to achieve diagnosis.

CASE REPORT

This is the case of a 28-year-old woman with a past medical history of 2 episodes of deep venous thrombosis (DVP) of right upper limb at right subclavian vein level confirmed on the venous Doppler echocardiography with favorable response to anticoagulant therapy. Due to suspected VTOS, the patient was referred to our unit

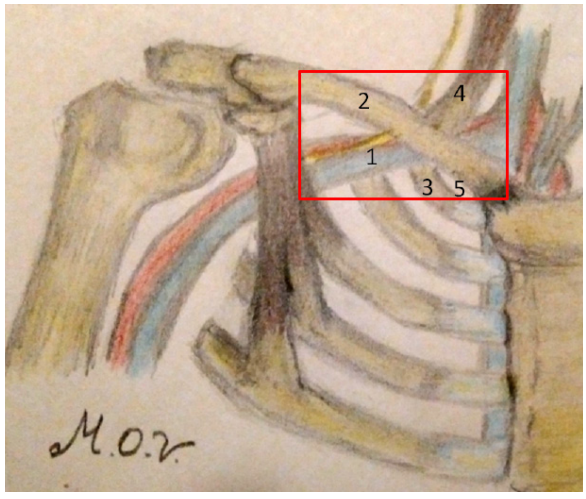

Figure 1. *Limits of thoracic outlet syndrome and its association with the subclavian vein: 1) Subclavian vein, 2) Clavicle (upper limit), 3) First rib (lower limit), 4) Anterior scalene muscle (lateral limit), 5) Costoclavicular ligament (medial limit).*

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TABLE 1. Different diagnostic maneuvers.

Maneuvers	Definition	Results	Sensitivity	Specificity
Adson's test	The radial pulse of the limb under study is palpated. Patient is asked to take a deep breath by rising his chin and leaning his head backwards, rotating it towards his shoulder in such a way that the ear contacts the shoulder without stopping breathing.	If radial pulse decreases the test is considered positive.	79%	76%
Wright's test	Arm adduction is performed > 90º with external rotation while radial pulse is palpated at wrist level.	If radial pulse decreases the test is considered positive.	70%	53%
Roos' test	The patient is asked to open and shut his hands for 3 minutes while keepinghisupper limbs in 90º of adduction, external rotation, and maximum horizontal adduction.	The test is considered positive when the patient is unable to take the test during this period due to hand claudication and symptom worsening.	84%	30%

TABLE 2. Diagnostic imaging modalities.

Imaging modality	Sensitivity	Specificity	Advantage	Disadvantage
Thoracic x-ray	60%	50%	• Accesible • Low cost • Identifies osseous anatomy anomalies.	• Low sensitivity is used with detection purposes • Use of radiation.
Doppler echocardiography (thrombus detection)	78% 82%	100% 100%	• Accesible. • Non-invasive. • Non-use of radiation • Dynamic assessment of blood vessels even in an upright body position • Additional technique to computed tomography or magnetic resonance imaging.	• Operator-dependent • Challenging in muscular patients and with large adipose tissue.
CT scan	70%	60%	• Proper imaging quality (bone tissue). • Non-invasive.	• Use of contrast • Use of radiation • Dynamic movements are limited by the size of the CT scan tunnel • Supine position.
Magnetic resonance imaging	75%	60%	• Proper imaging quality (soft tissue). • Non-invasive, non-ionizing.	• Cannot identify the anomaly of osseous anatomy • Dynamic movements are limited by the size of the CT scan tunnel • Supine position • Possibility of false negatives.
Angiography	82%	90%	• Precise assessment of the anatomy, characteristics of thrombus, occlusion time, and degree of collateralization • Dynamic assessment of blood vessels • Additional technique to computed tomography or magnetic resonance imaging.	• Invasive. • Use of contrast. • Use of radiation.

to confirm the diagnosis. At the questioning, she complains of right upper limb pain, swelling, functional disability, and color changes during movement. Angiography of central veins is performed with hyperabduction maneuver and right upper limb stretch. It reveals the presence of a dynamic obstruction at right subclavian vein level with abundant collateral circulation with flow and caliber recovery during adduction and flexion (**Figure 2**). The patient is then referred to the vascular surgery unit for treatment.

DISCUSSION

TOS describes the possible compression of neurovascular structures: by order of frequency, brachial plexus (90% to 95%), subclavian vein (5%) and artery (1%). Patients show specific signs and symptoms of the compromised anatomic structure. VTOS or the Paget-Schroetter syndrome is a rare entity with an incidence rate of 1/100 000 inhabitants/year. The population with more chances of being affected are active young men in their thirties with a 2:1 ratio compared to women being right arm the most commonly affected limb. Overall, the cause is associated with an intense physical activity or anomalous position of the arms (elevation) that causes the compression of the subclavian vein. Other structures like cervical ribs and anomalous ligament bands also promote compression. It has been suggested that the continuous compression of the vein would generate an inflammatory reaction at endothelial level that, added to venous stasis, would promote thrombosis.[7] Clinically, it presents with edema, cyanosis, and color in the damaged upper limb. In chronic disease progressions, dilated superficial veins on the upper side of the arm, neck, and thorax are visible. Diagnosis is achieved through non-invasive images like the ultrasound. One limited acoustic window can complicate the acquisition of direct images of the costoclavicular interval. Also, it is operator-dependent and can be a technical challenge in muscular patients or with large adipose tissue. Magnetic resonance imaging is the non-invasive imaging modality of choice since assessing position narrowing requires image acquisition in multiple positions. This gives an inherent advantage over the computed tomography scan due to its lack of ionizing radiation being particularly beneficial in the population of often young patients. Last but not least, computed tomography scan is performed when magnetic resonance imaging is not a possibility due to dialysis-dependent chronic kidney disease, claustrophobia or incompatibility with the device implanted. However, venous angiography is still the key to diagnose vascular lesions. In case of DVP, treatment is based on the administration of thrombolytic drugs depending on the severity of the patient's symptoms with further surgical decompression. In certain

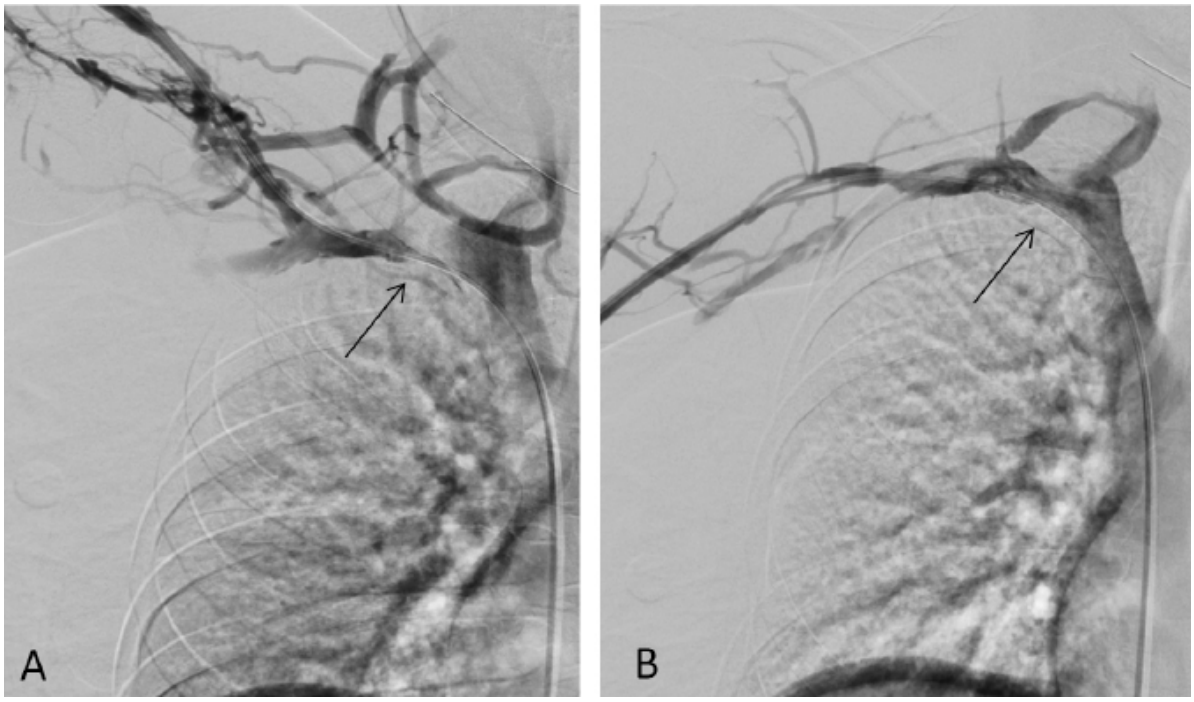

Figure 2. *A: The compression of the vein can be seen with the arm stretched out and hyperabduction with abundant colateral circulation too (arrow). B: Vein with normal flow when the arm is flexion (arrow).*

cases, anticoagulation for 2 up to 4 weeks followed by surgical decompression would be enough. The latter is recommended even if the vein remains occluded after thrombolysis since, over time, more than 90% of these patients will recanalize properly. The use of stents is ill-advised as first-line therapy due to the risk of fracture with the corresponding vascular occlusion and difficulty involved in the reconstruction of surgical anatomy.[1-4]

CONCLUSION

Our case emphasizes the importance of knowing pathophysiology, provocation maneuvers, and the performance of a dynamic angiographic study to achieve diagnostic certainty. The development of new devices with properties that appeal to flexuosity and compression can be future effective alternatives for endovascular treatment.

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Letter from the President of CACI

Carta del Presidente de CACI

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Dear colleagues,

Our journal successful path is on the rise, and the highly scientific content published truly makes us proud. In addition, over the last few months numerous comments have been posted on our social media (Facebook, Instagram, and Twitter). I wish to thank Dr. Alfredo Rodríguez, and Dr. Carlos Fernández Pereira, his collaborator, for their uplifting spirit to keep making our journal grow.
As always, we ask all our colleagues to keep submitting their manuscripts for assessment and publication.
The greatness of our college is everyone's accomplishment thanks to the participation of different collaboration and working and groups.

Sincerely,

Dr. Martín Cisneros
President of CACI

Publication Guidelines of the *Revista Argentina de Cardioangiología Intervencionista*

Reglamento de Publicaciones de la *Revista Argentina de Cardioangiología Intervencionista*

The *Revista Argentina de Cardioangiología Intervencionista (RACI)* is a quarterly journal published by the Argentinian College of Interventional Cardiologists (CACI). Its goal is to spread scientific and educational material on this medical specialty. Distribution is nation wide and open-access and is targeted at interventional cardiologists, clinical and pediatric cardiologists, radiologists, neurologists, operators, and other specialists. The publication is both digital (www.caci.org.ar) and in print.

The editorial principles of the journal are based on the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals and have been written by the International Committee of Medical Journal Editors - ICMJE in its most recent iteration available online at www.icmje.org.

For editorial reasons starting with issue #2, volume 9, year 2018 the graphic elements of the journal (figures, tables, and pictures) will be published in two colors only (blue and black). Readers who wish the full-color edition will need to pay an additional US$200.

The articles submitted to the journal shall be originals. The Editorial Committee will study the papers submitted and confirm whether they follow the Publication Guidelines established by the journal. The Director, and/or Associate Directors will be responsible for submitting these papers for the external blind peer review process. This means that the authors do not know the reviewers' name and the reviewers do not know the name of other reviewers. This policy established by RACI follows the same criteria implemented by the Review and Editorial Committee of the *Journal of the American College of Cardiology* (JACC), the highest impact factor cardiology journal. The Editorial Committee will make the final publication decision in accordance with the conclusions drawn by blind peer reviewers. Similarly, the Editorial Committee can introduce grammar related editorial changes according to the publication needs of the journal always after obtaining prior consent from the authors. Review articles and editorials will be subject to the same review process. Editorials are often required by the Editorial Committee as well.

After the first review, the articles can be accepted in the same form they were initially submitted; minor reviews are those pertaining to articles with significant contributions that still have some minor limitations that need to be corrected or proof read before its eventual publication; major reviews are those pertaining to articles that are unfit for publication as originally submitted to the journal. In any case, the Editorial Committee can consider new submissions called de novo submissions as long as the article is modified substantially; the rejection of the article occurs when both the reviewers and the Editorial Committee deem the article unfit for publication in the RACI journal.

In special cases of diagnostic and/or treatment consensus achieved by CACI and related scientific societies combined, such consensus will be supervised by the latter and being the Editorial Committee fully aware. Only then this consensus can be published exceptionally by the official journals of both societies simultaneously.

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Each article shall be presented with a first page that should include: (a) title (both informative and precise); (b) the complete names of the authors and centers involved in the writing of the manuscript; (c) a short version of the title for the runner head; (d) the total amount of words contained in the paper excluding the references; (e) the name and full address, fax, and e-mail address of the corresponding author. The second page will include the abstract in Spanish and English with 3-6 keywords at the end of both abstracts with terms from the Index Medicus term list (Medical Subject Headings - MeSH). The third page will carry the content of the manuscript (see Preparation of the manuscript) including a new page per section. All pages will be numbered from the title page.

The paper (text, tables, and figures) will be submitted electronically to the following e-mail address *revista@caci.org.ar* with a note signed by all authors (see model in website)with the name of the section the manuscript belongs to, and a clear statement that the contents of the manuscript have never been published before.

Those appearing as authors of the article need to have contributed to the study or writing of the manuscript and will be liable for the content published.

A maximum of eight (8) authors shall be allowed in each paper and they must follow the authorship standards established by the IMCJE. Each manuscript received is examined by the Editorial Committee and one or two external reviewers. Afterwards, the lead author will be notified on the acceptance (with or without corrections and changes) or rejection of the manuscript. After the article has been approved for publication, RACI has the copyright for its total or partial reproduction.

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These are scientific or educational papers of original basic or

clinical studies. Requisites: a) general text, up to 5000 words including references; b) abstract, up to 250 words; c) tables + figures, up to 8; d) authors, up to 10.

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The studies published under this section follow the same criteria established for original articles, but do not have enough patients to be considered as such.

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These are articles on the rational and protocolized management of the different circumstances that can occur in the routine clinical practice. They are reviewed and agreed previously with subject matter experts and include a flow charton the diagnostic and therapeutic management of the disease. The following requisites have been established by the Editorial Committee. Requisites: a) general text, up to 2500 words excluding the references; b) abstract, up to 150 words; c) tables + figures,up to 6; d) references, up to 20; e) authors, up to 4.

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This is the description of a clinical case of unusual characteristics with its diagnostic and therapeutic management, and final resolution. It needs to include a brief reference search. Requisites: a) general text, up 1200 words; b) abstract, up to 100 words; c) tables + figures, up to 4; d) references, up to 10; e) authors, up to 5.

How did I approach it?
Under the title "How did I approach it?" the authors will be presenting a challenging case and a description of their management. The title needs to be included at the beginning of the text, for instance, "How did I treat an aneurysm in the left anterior descending coronary artery?" Then the authors' names, last names, specialties, and working centers should be included as well. Corresponding author, address, and e-mailwill be included as well. All authors need to declare their conflicts of interest. If they do not have any they need to say so. Text, figures, and references will follow the same criteria established for the clinical case.

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The publication of images describing exceptional cases that the Editorial Committee and external reviewers consider significant for the journal will be accepted for publication. They will need to be followed by an explanatory text and a brief summary of the clinical history. Requisites: a) general text, up to 300 words; b) 2 original figures only; c) references, up to 3; d) authors, up to 5.

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The publication of research protocols—preferably multicenter—will be accepted and published by the journal as special articles as long as these protocols do not include the study partial or total results.

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They are analyses and/or comments on relevant issues on the specialty or general cardiology field in relation with our specialty and always upon request by the Editorial Committee to a subject matter expert. Similarly, comments on issues unrelated to an article in particular can be requested by the Editorial Committee. Requisites: a) general text, up to 2000 words; b) references, up to 40.

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This is an opinion on an article published in the last issue of the journal that requires the arbitrage of the members of the Editorial Committee. Requisites: a) text, up to 250 words; b) one table and/or figure can be published; c) references, up to 5. Only letters submitted within a month following the print edition of the issue of the journal where the original article was published will be accepted.

PREPARATION OF THE MANUSCRIPT

The article will be written in Spanish language using a Microsoft® Word text processor and saved under the *.doc file extension. The size of the page will be A4 or letter with double-spacing, 25 mm margins, fully justified text, and 12-point Times New Roman or Arial font. Pages will be numbered consecutively starting with the cover. The manuscript (original article) needs to follow the so-called IMRAD structure: Introduction, Material and method, Results, and Discussion (see the ICMJE Publication Guidelines). Also, it will include Title, Abstract, Conflicts of Interest, and References. At the end of each original article, before the references, it should be done as a Table of the relevant points of the work that will be called Summary of Highlights. In 4 or 5 sentences authors should introduce the purpose of the study presented. The previous data published and the additional information provided by authors in their work, highlighting major contributions and final statements. At the end of references a acknowledgements for others people involved in the study together with a supplementary appendix when necessary should be added.

The metric system will be the standard system of measurement used with comas to write the decimals. All clinical, hematologic, and chemical parameters will be expressed in units of measure from the metric system and/or IU. Only common abbreviations will be used except for the title and the abstract. The first time these abbreviations are used they will be preceded by the whole term except for the use of standard units of measure.

Tables must be presented in individual sheets and they need to be numbered consecutively with Arabic numbers (0, 1, 2, etc.) according to the order in which they were quoted in the text with a short title for each and every one of them. All of the non-standardized abbreviations of the table need to be explained and developed. Explanatory notes will be placed at the foot of the table using the following symbols in this sequence: *, †, ǂ, §, ¶, **, ††, ǂǂ, etc.

Figures need to be submitted in TIFF, PSD or JPEG format and each figure will be submitted in a separate file with a resolution of 300 dpi in its final format. Each of them will be numbered consecutively together with the explanatory legend in a separate file. The normal size of the photographs will be 127 mm x 173 mm. Titles and detailed explanations will be included in the text of the legend, not the illustration.

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1. *Registro de Procedimientos Diagnósticos y Terapéuticos efectuados durante el período 2006-2007. Colegio Argentino de Cardioangiólogos Intervencionistas (CACI). Disponible en http://www.caci.org.ar/addons/3/158.pdf. consultado el 01/01/2009.(Página Web.)*
2. *Magid DJ, Wang Y, McNamara RL, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. JAMA 2005;294:803-812. (Revistas en inglés.)*
3. *Aros F, Cuñat J, Marrugat J, et al. Tratamiento del infarto agudo de miocardio en España en el año 2000. El estudio PRIAMHO II. Rev Esp Cardiol 2003;62:1165-1173. (Revistas en español).*

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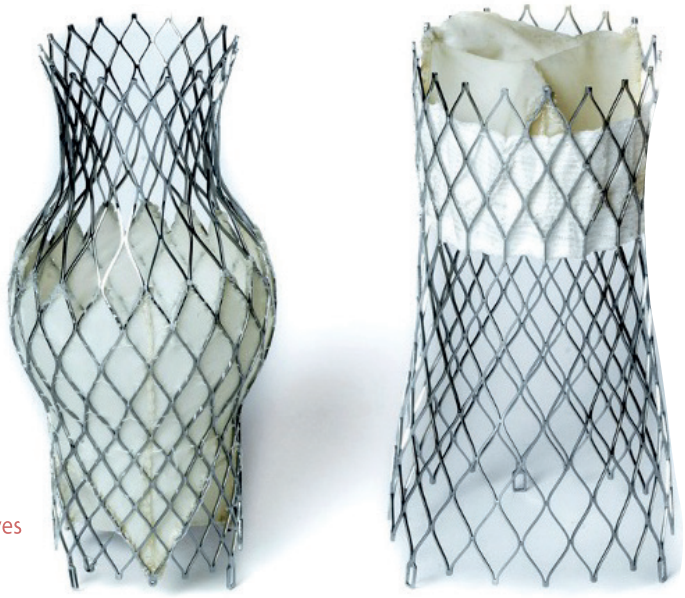

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1 Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. Valgimigli M et al. N Engl J Med. 2021;385:1643-1655

* MASTER DAPT included patients at high bleeding risk who had undergone implantation of Ultimaster™ family stent; results may not extend to patients who are not at high bleeding risk or who receive other stent types.

HBR: high bleeding risk; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; DES: drug-eluting stent

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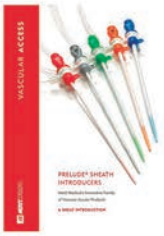

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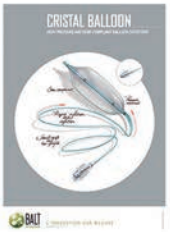

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Catheter/ Sheath Size	7.5Fr.	7.5Fr.	7.5Fr.	7.5Fr.	8Fr.	7.5Fr.
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