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- Efficacy of treatment with evolocumab in ischemic heart disease
- Characterization of patients undergoing cardiac implantable electronic device
- Major cardiovascular events in coronary revascularization
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Vol. 32 No. 2
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Contents / Contenido

Editorial

Translational medicine/research: who receive the benefits? 64
Guillermo Ceballos, Miguel Ortiz-Flores, Nayelli Nájera

Original Research

Efficacy of treatment with evolocumab in patients with ischemic heart disease 66
Juan Carlos Ramos-Martínez, Marco Antonio Hernández-Mercado, Laura Pérez-Campos Mayoral, Edgar Gustavo Ramos-Martínez

Characterization of patients undergoing cardiac implantable electronic device implantation in a Tertiary Center: emphasis on complications 72
Andrés Ramiro Gómez-Valencia, Julián Aristizábal-Aristizábal, David Ocampo-Moreno, María José Fernández-Turizo, María Camila Galindo-Quintero, Elsa María Vásquez-Trespalacios, Laura Lopera-Mejía, Mauricio Duque-Ramírez

Major cardiovascular events in failed versus successful coronary revascularization in patients with chronic total occlusion 82
Andrea Janet López Valencia, Enrique Alfredo Bernal Ruiz, Germán Ramón Bautista López, Adolfo Asahel Hernández Padilla, Martha Alicia Hernández González

Coronary arteriography with radial access in coronary acute disease and its relation with handgrip strength and radial artery permeability (CARHANG) 94
Simón Gaviria, Mateo Alzate, Andrés Ramírez, Jessica Villegas, Amalia Restrepo, Juan José Ospina, Nicolás Jaramillo, Sara Moreno-Bedoya, Heidy Contreras

Clinical Cases

Transthyretin cardiac amyloidosis with an unusual clinical presentation: dilated cardiomyopathy 101
Alain García-Olea, Javier Gregorio Rekondo, Mikel Maeztu, Iria Fernández

Isolated congenital left ventricular diverticulum in adult: an unusual finding in a cocaine-associated myocardial infarction 105
Rafael Pedraza-Jiménez, José Martín Alanís-Naranjo, Martha Morelos-Guzmán

Editorial

Medicina/investigación translacional: ¿quién recibe los beneficios? *64*
Guillermo Ceballos, Miguel Ortiz-Flores, Nayelli Nájera

Trabajos de Investigación

Eficacia del tratamiento con evolocumab en pacientes con cardiopatía isquémica *66*
Juan Carlos Ramos-Martínez, Marco Antonio Hernández-Mercado, Laura Pérez-Campos Mayoral, Edgar Gustavo Ramos-Martínez

Caracterización de los pacientes llevados a implante de dispositivos de estimulación cardíaca en un Centro de Tercer Nivel: énfasis en complicaciones *72*
Andrés Ramiro Gómez-Valencia, Julián Aristizábal-Aristizábal, David Ocampo-Moreno, María José Fernández-Turizo, María Camila Galindo-Quintero, Elsa María Vásquez-Trespalacios, Laura Lopera-Mejía, Mauricio Duque-Ramírez

Eventos cardiovasculares mayores en revascularización coronaria fallida versus exitosa en pacientes con oclusión total crónica *82*
Andrea Janet López Valencia, Enrique Alfredo Bernal Ruiz, Germán Ramón Bautista López, Adolfo Asahel Hernández Padilla, Martha Alicia Hernández González

Arteriografía coronaria con acceso radial en la enfermedad coronaria aguda y su relación con la fuerza de agarre y la permeabilidad de la arteria radial (CARHANG) *94*
Simón Gaviria, Mateo Alzate, Andrés Ramírez, Jessica Villegas, Amalia Restrepo, Juan José Ospina, Nicolás Jaramillo, Sara Moreno-Bedoya, Heidy Contreras

Casos Clínicos

Amiloidosis cardiaca por transtiretina con una presentación clínica atípica: miocardiopatía dilatada *101*
Alain García-Olea, Javier Gregorio Rekondo, Mikel Maeztu, Iria Fernández

Divertículo ventricular congénito izquierdo aislado en adulto: un hallazgo inusual en infarto de miocardio asociado a cocaína *105*
Rafael Pedraza-Jiménez, José Martín Alanís-Naranjo, Martha Morelos-Guzmán

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Editorial

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Translational medicine/research: who receive the benefits?

Medicina/investigación translacional: ¿quién recibe los beneficios?

Guillermo Ceballos,* Miguel Ortiz-Flores,* Nayelli Nájera*

Translational medicine/research in the cardiovascular area has as main objective the integration of basic and clinical knowledge to improve human health. This must be a bidirectional concept/effort, i.e., laboratory bench results are translated to bedside efforts and bedside knowledge is reciprocally translated to bench analysis. A good example of these interactions is the testing of new therapies developed in basic research laboratories and latter tested clinically, providing a feedback to improve novel therapeutic approaches.

The term translational medicine reflects several, not excluding, points of view: physicians use the term to refer to the need to accelerate the incorporation of basic research into clinical medicine, and to close the gap between knowledge and practice. Researchers interpret translational medicine as the testing of novel concepts obtained in basic research in clinical situations, which in turn provide the opportunity for the identification of new paradigms. On the other hand, pharmaceutical companies could use the concept as a process to speed up the development and commercialization of therapies. These points of view reflect only different priorities for achieving as a common goal the prevention or control of human diseases. So, translational medicine, by enhancing the efficiency of biomedical discovery and its application, has become a unifying concept between the complex, specialized and sometimes fragmented field of biomedical research and physicians' expertise.

However, even when translational medicine is a highly desirable conjunction of efforts and perhaps, the best approach to improve human health and quality of life in the short term, there are several problems associated to the translation of biomedical discoveries into clinical practice. Preclinical studies are necessary not only to understand basic mechanisms, but also to obtain information about the safety and efficacy of new molecules. Animal studies provide information without the risk of harming humans. However, studies in animals are simplified models that do not completely reflect clinical situations. There are not «exact/accurate» animal models for each human pathology, but only good approximations, fact that limits the extrapolation results directly into clinical practice. Other associated problem is the cost of producing new molecules, their preclinical testing, and human clinical trials to obtain regulatory agencies' approvals, can be very high, sometimes tens of millions of dollars. To solve these limitations, we need to improve translational medicine, with more accurate preclinical testing and developing creative cost-effective solutions to clinical testing. In consequence, there is a need for clinical scientists who can serve as facilitators of the translational process with a strong basic background and excellent clinical qualities. The training of such scientists is lengthy and expensive, we need to find the best and short way to find/form them or to implement strong and wide connections among basic and clinical researchers specially those working already in similar fields.

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On regard to these efforts, as it happens in all medical fields, translational medicine/research similarity in the cardiovascular area is relevant. It must be taken into account that, even when vast advances in the development of molecules for the treatment of cardiovascular diseases (CVD) (i.e., statins, antihypertensives, etc.) have been recently implemented and approved for their use in humans, the morbidity and mortality of CVD is still high. The only way to bring down these outcomes, is to implement approaches to develop translational medicine/research to unify efforts and decrease time and costs associated with its development. Several efforts have been implemented in this regard, as example, the International Society for Cardiovascular Translational Research (www.isctr.org) coordinate basic and clinical researchers, regulatory authorities and medical industry with the goal of improve the transfer of new evidence into clinical applications. We need to follow them and increase the interaction between basic and clinical research, particularly in developing countries where the support to any type of research is null or scarce.

At the end, basic researchers, clinical physicians and most importantly, patients will receive the benefits of these interactions.

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Original Research

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Efficacy of treatment with evolocumab in patients with ischemic heart disease

Eficacia del tratamiento con evolocumab en pacientes con cardiopatía isquémica

Juan Carlos Ramos-Martínez,* Marco Antonio Hernández-Mercado,*
Laura Pérez-Campos Mayoral,‡ Edgar Gustavo Ramos-Martínez‡

Keywords:
Low density lipoprotein, PCSK9 inhibitor, evolocumab, ischemic heart disease, cholesterol.

Palabras clave:
Lipoproteína de baja densidad, inhibidor PCSK9, evolocumab, cardiopatía isquémica, colesterol.

ABSTRACT

Introduction: A new target level for low-density lipoprotein cholesterol (LDL-C) has been established in patients at very high cardiovascular risk. However, treatment with evolocumab combined with atorvastatin to attain this target level has not been evaluated. **Objective:** To evaluate the efficacy of evolocumab to achieve the target LDL-C levels in patients with ischemic heart disease at very high cardiovascular risk. **Material and methods:** Twenty patients with ischemic heart disease at very high cardiovascular risk were treated with evolocumab and atorvastatin for 24 weeks. Levels of serum LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides were determined before and after treatment. **Results:** After 24 weeks of treatment, an average percentage reduction of 55% for LDL-C was obtained, and 11 of the 20 patients reached the target levels for LDL-C. No differences were found in the levels of HDL-C or triglycerides. **Conclusions:** evolocumab treatment was safe, effective, and reduced the concentration of LDL-C in all patients. However, the target level for LDL-C was only reached in half of the patients.

RESUMEN

Introducción: *Se ha establecido un nuevo nivel objetivo de lipoproteína de baja densidad (C-LDL) en pacientes con muy alto riesgo cardiovascular. Sin embargo, no se ha evaluado si el tratamiento con evolocumab en combinación con atorvastatina permite alcanzar estos niveles.* ***Objetivo:*** *Evaluar la eficacia de evolocumab para lograr los niveles objetivo de C-LDL en pacientes con cardiopatía isquémica y muy alto riesgo cardiovascular.* ***Material y métodos:*** *Veinte pacientes con cardiopatía isquémica y muy alto riesgo cardiovascular fueron tratados con evolocumab más atorvastatina durante 24 semanas. Se determinaron los niveles de C-LDL, C-HDL, colesterol total y triglicéridos en suero antes y después del tratamiento.* ***Resultados:*** *Después de las 24 semanas de tratamiento, se obtuvo un promedio del porcentaje de reducción de C-LDL de 55% y 11 de los 20 pacientes alcanzaron los niveles objetivos de C-LDL. No se encontraron diferencias en los niveles de (lipoproteínas de alta densidad) HDL ni de triglicéridos.* ***Conclusiones:*** *El tratamiento con evolocumab fue seguro y eficaz, ya que redujo la concentración de C-LDL en todos los pacientes; sin embargo, sólo se alcanzó el nivel objetivo de C-LDL en la mitad de los pacientes.*

INTRODUCTION

PCSK9 (proprotein convert subtilisin/kexin type 9) is a plasma enzyme that binds the low-density lipoprotein receptor on hepatocytes' surface, thus promoting their metabolism and subsequent degradation in lysosomes.[1] The use of monoclonal antibodies against PCSK9 increases the half-life of the low-density lipoprotein receptor, leading to a reduction in the plasma concentration of low-density lipoprotein cholesterol (LDL-C) and a lower long term cardiovascular risk.[2,3]

Evolocumab was the first monoclonal antibody against PCSK9 to be authorized as a lipid-lowering drug. It is indicated for adult patients with familial heterozygous hypercholesterolemia, familial homozygous hypercholesterolemia, non-familial hypercholesterolemia and primary mixed dyslipidemia. Additionally, it has been used for treatment in patients with myocardial

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infarction that does not respond to statin therapy.[2,3]

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, treatment with evolocumab for 48 weeks reduced LDL-C levels from an average of 92 to 30 mg/dL, with an average percentage reduction of 59% (95% CI, 58-60). Also, evolocumab reduced the risk of cardiovascular events, non-HDL-C and apolipoprotein B levels.[4]

In the YUKAWA-2 (Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients with Advanced Cardiovascular Risk) trial, performed in Japanese individuals at high risk of cardiovascular disease, evolocumab in combination with atorvastatin was found to reduce LDL-C concentration by 60-70%. The increased reduction in LDL-C concentration of this trial, compared to the FOURIER[4] and LAPLACE-2 (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy)[5] trials, is due to intrinsic differences in the Japanese population at high cardiovascular risk and not to complementary treatments or the baseline levels of LDL-C or PCSK9.[6] Other phase III clinical trials have been consistent in showing a reduction of LDL-C with evolocumab treatment.[7,8]

Table 1: Clinical characteristics of the patients studied.

Patient characteristics	Number of patients
Total patients	20
Age	58 ± 9.9 years
Females	6
Diabetes mellitus 2	10
Systemic arterial hypertension	18
Smoking	11
Dyslipidemia	20
Ischemic heart disease	20
Previous cardiovascular complications	20
Pre-treatment	
Statin	17
Fibrates	4
Ezetimibe	4
Statin intolerance	1

Recently, the European Society of Cardiology (ESC) has set new targets in managing of patients at very high cardiovascular risk. A target concentration of LDL-C ≤ of 55 mg/dL with a reduction of more than 50% has been established.[9] These targets are more ambitious than recommendations outlined in 2016.[10] Therefore, therapies that combine a PCSK9 inhibitor and statins are a treatment option to achieve the new target LDL-C concentrations in patients at very high cardiovascular risk.

Despite the benefits of evolocumab shown in previous studies, this drug's general use is uncommon due to its relatively high cost compared to statins.[11] Thus, a cost-benefit assessment of treatment with evolocumab should first be considered.[12] As shown in previous studies, the benefit of this treatment depends on the intrinsic characteristics of the population to be treated.[6] Therefore, it is necessary to evaluate the efficacy and safety of evolocumab treatment and to establish whether the new objectives set by the ESC for patients at very high cardiovascular risk can be achieved. In the present study, we evaluated levels of LDL-C, HDL-C, total cholesterol, and triglycerides, before and after treatment with evolocumab in combination with atorvastatin.

Objective: To evaluate the efficacy of evolocumab to achieve the target LDL-C levels in patients with ischemic heart disease at very high cardiovascular risk.

MATERIAL AND METHODS

A pre-experimental study was conducted and approved by the Committee of Health Research and Ethics Research with registration number 043/18. The procedures followed were per relevant clinical research ethics committee regulations and with those of the Code of Ethics of the World Medical Association (declaration of Helsinki). Twenty patients with a diagnosis of ischemic heart disease diagnosed by coronary angiography were included in the study. The patients were treated at the Cardiology Department of the *Instituto de Seguridad Social del Estado de México y Municipios*. The inclusion criteria for this study were males and females 18 years or older, diagnosis of ischemic cardiopathy, and failure to reach

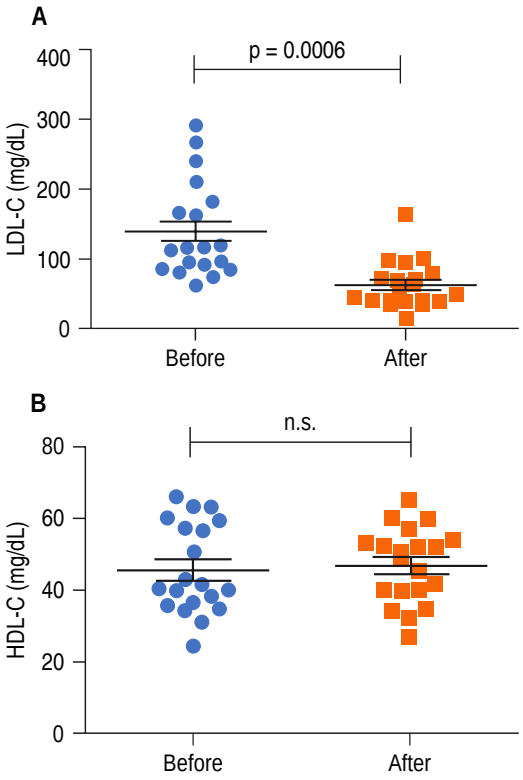

Figure 1:

Treatment with evolocumab decreases the concentration of LDL-C but not HDL-C in plasma. The graph shows the concentration in mg/dL of LDL-C **(A)** and HDL-C **(B)** of 20 patients before and after treatment with evolocumab. The horizontal lines indicate the mean and standard error. The data were compared with the Wilcoxon matched-pairs test.

a concentration ≤ 55 mg/dL of LDL-C after treatment with statins at the maximum dosage for three months or longer. All patients were classified to be at very high cardiovascular risk based on ESC criteria, by a cardiologist.[9]

Patients were treated with evolocumab (140 mg, subcutaneous dose) every two weeks. Additionally, 80 mg of atorvastatin was administered every 24 hours as an adjunct therapy, except for one patient who was only treated with evolocumab due to an intolerance to atorvastatin. Both treatments were administered for 24 weeks. At the end of this period, total cholesterol, triglycerides, LDL-C, and HDL-C concentrations were determined by commercial methods (Beckman). Neurocognitive impairment was determined by applying the mini-mental state examination (MMSE) test, adapted to the Mexican population,[13] before and after treatment. The MMSE test addresses the following five cognitive domains: temporospatial orientation, deferred memory, attention and computation, language, and visuoconstructive drawing ability.[14]

Statistical analysis

The results are reported as a mean ± S.E.M. Data were checked for normality with the Kolmogorov-Smirnov test, and the Wilcoxon matched-pairs test was performed. All statistical analyses were performed with the GraphPad Prism software version 5.

RESULTS

The patients treated included six women and 14 men of mixed race, with an average age of 58 ± 9.9 years. All patients presented previous cardiovascular complications, 20 patients had acute coronary ischemic syndrome, a patient had ventricular tachycardia, and another had a third-degree atrioventricular block. All patients were classified at very high risk according to ESC criteria.[9] Intolerance to statins was considered to be any adverse event secondary to the drug administration that led to the impossibility of its use. During the study, one patient presented intolerance to atorvastatin by referring to muscle pain, which led to atorvastatin's withdrawal. No biochemical or functional alteration was observed in the laboratory exams or cabinet studies. The clinical data of the patients are shown in *Table 1*.

The average LDL-C concentration before treatment with evolocumab was 138.3 ± 15 mg/dL. After 24 weeks of treatment, a significant reduction was found ($p < 0.001$) in LDL-C concentration with a final average of 62.2 ± 7.5 mg/dL *(Figure 1A)*. The average percentage reduction in LDL-C was 55% (95% CI, 45 to 65). Conversely, the average HDL-C concentration before treatment (45.8 ± 2.8 mg/dL) and after treatment (47 ± 2.3 mg/dL) was not significantly different *(Figure 1B)*.

Treatment with evolocumab reduced plasma cholesterol concentration *(Figure 2A)* but not triglyceride concentration *(Figure 2B)*. The average total cholesterol concentration before treatment (203.0 ± 15.2 mg/dL) and after treatment (147.4 ± 12.1 mg/dL) was significantly different ($p < 0.001$). Triglyceride concentration was 224.2 ± 41.7 mg/dL before treatment and 206.1 ± 23.4 mg/dL after treatment. One patient had severe heel pain after the administration of the antibody,

although not attributed as a side effect. No neurocognitive adverse events were observed either.

DISCUSSION

In our study, patients at very high cardiovascular risk were treated with 140 mg of evolocumab every two weeks, combined with atorvastatin. Clinical trials of evolocumab, alone or in combination with statins, have shown that treatment with 140 mg every two weeks or with 420 mg once a month are of equal efficacy.[4,6,8]

Patients had previously been treated with ezetimibe in combination with high-intensity statins, yet LDL-C levels were not achieved. For this reason, it was decided to add evolocumab to the therapy, in combination with a high-intensity statin. Dual therapy was maintained in our study, but in a Mexican population, as in the YUKAWA-2 and LAPLACE-2 studies, since in these studies a significant reduction of LDL-C was achieved and the target levels of LDL-C were reached.[6,15] Therefore, the objective of the present study was to evaluate if the target level of LDL-C could be achieved in the Mexican population without having to use an additional drug. Using two drugs is advantageous because it allows for greater adherence to treatment. Administration of more than two drugs correlates with poor treatment adherence, a key factor in lipid-lowering therapies.[16]

The average percentage reduction of LDL-C concentration in this work was 55% (95% CI, 45-65). This percentage of reduction was similar to the one obtained in the FOURIER trial, where an average percentage reduction for LDL-C of 59% (95% CI, 58-60) was obtained.[4] The significant variability in our results can be attributed to the sample size. In the YUKAWA-2 trial, a 75.9% reduction in LDL-C concentration was found in Japanese patients at very high cardiovascular risk treated with 140 mg of evolocumab every two weeks combined with 20 mg/day of atorvastatin.[6] This percentage reduction was higher than that reported in our study, although the atorvastatin dose in our study was four times higher. This more significant reduction in LDL-C concentration was not due to the differences at the baseline level since the YUKAWA-2 trial baseline was 109 ± 35 mg/dL, and in our study, the baseline was 138 ± 67 mg/dL, which are not statistically different. Although the reduction in LDL-C in our study was not as pronounced as that observed in the YUKAWA-2 trial, 11 of 20 patients managed to achieve an LDL-C concentration ≤ 55 mg/dL, the recommended level by the ESC.

In our work, we did not find an increase in HDL-C concentration after treatment with Evolocumab. However, other studies have reported an increase in HDL-C levels. For example, in the YUKAWA-2 trial, evolocumab increased HDL-C by 10-17%.[6,17] A direct mechanism can be attributed to this increase in HDL-C concentration has not been evaluated yet. However, a possible indirect mechanism may act through the decrease in the concentration of LDL-C, which would affect the enzymatic activity of cholesteryl ester transfer protein, an enzyme that transfers cholesterol from HDL to LDL.[6]

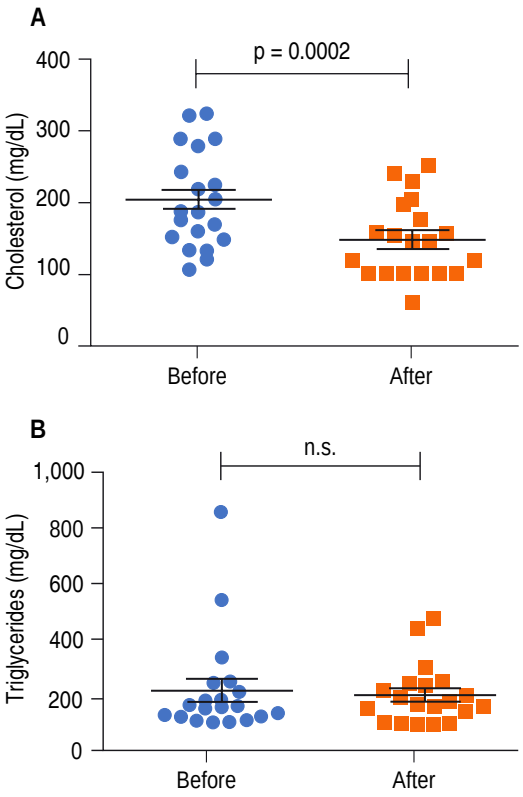

Figure 2: Treatment with evolocumab reduces the concentration of total cholesterol in plasma but not triglyceride concentration. The graph shows the concentration in mg/dL of total cholesterol **(A)** and triglycerides **(B)** of 20 patients before and after treatment with evolocumab. The horizontal lines indicate the mean and standard error. Total cholesterol and triglyceride concentrations were compared with the Wilcoxon matched-pairs test.

In previous reports, there has been a low rate of complications inherent to treatment with evolocumab. In the FOURIER study, only 0.1% of patients stopped treatment due to reactions at the puncture site.[4] In our study, there were no complications related to medications, and all patients finished the entire treatment. No cases of neurocognitive adverse events were reported after 24 weeks of treatment. Long-term studies such as EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects) study did not find differences in cognitive function between patients treated with evolocumab and the placebo group, as well.[18]

A limitation of the present study is the lack of ezetimibe as a complementary treatment. Possibly, the combined use of the three therapies (evolocumab, atorvastatin, and ezetimibe) will allow a greater number of patients to achieve target C-LDL levels. Although this study has its limitations such as the length of time for treatment and sample size, results showed that treatment with evolocumab combined with atorvastatin reduces LDL-C concentration to the recommended levels. However, not all the patients achieved the LDL-C target level, and given the high cost of the drug, cost-benefit analyses are required to assess therapy with evolocumab.

CONCLUSIONS

A 55% reduction in LDL-C concentration was observed in patients treated with evolocumab in combination with atorvastatin. The LDL-C level recommended by the ESC was reached in 11 of the 20 patients treated. Given the high cost of treatment with evolocumab, additional strategies are required to achieve the target LDL-C level in a greater patients population.

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Characterization of patients undergoing cardiac implantable electronic device implantation in a Tertiary Center: emphasis on complications

Caracterización de los pacientes llevados a implante de dispositivos de estimulación cardíaca en un Centro de Tercer Nivel: énfasis en complicaciones

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Keywords:
Heart block, postoperative complications, pacemaker, electrodes.

Palabras clave:
Bloqueo cardiaco, complicaciones posoperatorias, marcapasos, electrodos.

ABSTRACT

Introduction and objectives: Currently, there are scarce data about follow-up and complications in patients taken to implantation of cardiac implantable electronic devices. We sought to describe the incidence of complications and characteristics of 997 patients, taken to the implant of cardiac implantable electronic devices in a tertiary center in Colombia. **Material and methods:** An observational, descriptive study, with the follow-up of a retrospective cohort, was performed. Based on the systematic revision of medical histories from patients taken to cardiac electronic device implant during 2017 and 2018 in Las Americas clinic, located in Medellin, Colombia. **Results:** 997 patients were included. All of them counted with available medical profiles and histories, with an average age of 74 years old. 55.6% of the patients were males. The most commonly implanted cardiac electronic devices were, dual-chamber pacemakers and the predominant indications for implantation were AV block (47%) and sinus node dysfunction (25.6%). The most frequent complications were the displacement of one of the cardiac electrodes (2.2%), followed by pocket hematoma (1.5%). There were no deaths related to the implantation of the cardiac electronic devices. **Conclusions:** The majority of patients had an advanced age and a high burden of comorbid conditions. However, the procedures related to the implantation of electronic cardiac devices had a low frequency of complications. The population under study had a similar frequency of complications derived from the procedures, to the ones reported through literature. This demonstrates these procedures are also safe and successful in our environment.

RESUMEN

Introducción y objetivos: *En la actualidad, existen escasos datos sobre el seguimiento y las complicaciones en pacientes llevados a la implantación de dispositivos electrónicos cardíacos. Se buscó describir la incidencia de complicaciones y las características de 997 pacientes, llevados al implante de dispositivos electrónicos cardíacos en un centro terciario de Colombia.* ***Material y métodos:*** *Se realizó un estudio observacional, descriptivo, con el seguimiento de una cohorte retrospectiva. Basado en la revisión sistemática de historias clínicas de pacientes llevados a implante de dispostivos electrónicos cardíacos durante 2017 y 2018 en la clínica Las Américas, ubicada en Medellín, Colombia.* ***Resultados:*** *Se incluyeron 997 pacientes. Todos ellos contaban con perfiles e historiales médicos disponibles, con una edad media de 74 años. El 55.6% de los pacientes eran varones. La mayoría de los dispositivos electrónicos cardíacos implantados fueron los marcapasos bicamerales y las indicaciones predominantes para su implantación fueron el bloqueo AV (47%) y la disfunción del nodo sinusal (25.6%). Las complicaciones más frecuentes fueron el desplazamiento de uno de los electrodos cardíacos (2.2%), seguido del hematoma de bolsillo (1.5%). No hubo muertes relacionadas con la implantación de los dispositivos electrónicos cardíacos.* ***Conclusiones:*** *La mayoría de los pacientes tenían una edad avanzada y una alta carga de condiciones comórbidas. Sin embargo, los procedimientos relacionados con la implantación de dispositivos cardíacos electrónicos tuvieron una baja frecuencia de complicaciones. La población estudiada tuvo una frecuencia de complicaciones derivadas de los procedimientos similar a la reportada por la literatura. Esto demuestra que estos procedimientos también son seguros y exitosos en nuestro medio.*

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INTRODUCTION

A considerable increase in the age of general population and the rapid development of technology during the last decades have led to an increase in the detection and management of heart diseases, specifically rhythm disorders, coronary heart disease and heart failure. Different types of cardiac implantable electronic devices (CIEDs) are part of the management of such conditions, whether it be conventional pacemakers for bradycardia, implantable cardioverter-defibrillators (ICDs) for the prevention of sudden cardiac death due to malignant ventricular arrhythmias, or cardiac resynchronization therapy devices (CRT) for the relief of heart failure symptoms, with or without the use of defibrillators.

With the increasing number of implants and procedure complexity, there may be an increment in the incidence of complications directly associated with the intervention. Despite this, its rate is usually low. International literature reports describe a general risk of complications after pacemaker implant of up to 5-6%, with an approximate risk of major complications of 3-4%.[1] In the case of ICDs and CRT, which involve more complex implant procedures, the overall risk of complications is approximately 3-8%,[2] CRT defibrillators (4.1% in-hospital adverse events), and unicameral or bicameral ICDs (2.9% and 1.9%, respectively) with a death incidence of 0.4%.[3]

The most frequent complications are electrode displacement (1%), pocket hematoma (0.9%) and pneumothorax (0.4%); regarding inpatient treatment they are: infection, hematoma, bleeding and mechanical complications, which are directly related to factors such as the center and operator experience, the type of vascular access (puncture or dissection), antibiotic prophylaxis, procedure time, and underlying diseases and comorbidities.[3]

The present study sought to describe the incidence of complications in patients undergoing procedures for CIEDs implants in a tertiary center, as well as the characteristics which could be associated with the development of complications in this population.

MATERIAL AND METHODS

This is an observational, descriptive, follow-up study to a retrospective cohort, based on the review of clinical history records of patients who underwent CIEDs implant during 2017 and 2018 at Las Americas Clinic in Medellin, Colombia. Comparisons were made between the group of patients who underwent complex CIEDs implant (ICDs, CRT or CRT defibrillators) and those who underwent non-complex CIEDs implant (conventional unicameral or bicameral pacemakers and implantable loop recorders (ILR)). The data were collected in an electronic database with all the relevant variables related to implant history and follow-ups.

The confidentiality and anonymity of patients whose records were consulted were guaranteed at all times.

For the analyses, the quantitative variables were presented in the form of averages with their respective dispersion measures according to the distribution. Qualitative variables were summarized by percentages, and mean comparisons were made using the student's t-test for independent samples or Mann-Withney's U test as applied. For the comparison of groups, the chi-square tests and the Fisher test were used for the categorical variables and the ANOVA and Kruskal-Wallis tests to compare continuous variables. Statistical analyses were performed with SSPS software, version 21.

RESULTS

A total of 1,006 CIEDs procedures were performed during the study period, of which 997, with available records of clinical history, were included.

The patient's age was mainly in the eighth decade of life, with a range from 16 to 102 years and an average of 74.4 ± 14 years. There were 554 male patients (55.56%) and 443 female patients (44.44%).

In terms of comorbidities, the most frequently documented were hypertension, followed by dyslipidemia, coronary artery disease, diabetes and hypothyroidism. Other comorbidities recorded that are important from a cardiovascular standpoint, were renal insufficiency, chronic obstructive pulmonary

disease (COPD) and cerebrovascular events, which were found in a percentage equal to or less than 15%. The data on comorbidities in patients who were implanted with complex and non-complex devices are summarized in *Table 1*.

Devices

In terms of implanted devices, the pacemakers were the most common, corresponding to 74% of all devices, followed by ICDs and CRT. For the two initially mentioned, bicameral devices were chosen in most cases, *Table 2*.

Table 1: Clinical characteristics.

Characteristic	Non-complex (N = 794) n (%)	Complex (N = 203) n (%)	p
Age (years)	76.84 ± 13.26	65.31 ± 13.25	0.000*
Gender			0.002
Male	423 (76.4)	131 (23.6)	
Female	371 (83.7)	72 (16.3)	
Comorbidities			
Arterial hypertension	642 (80.5)	156 (19.5)	0.120
Dyslipidemia	370 (76.6)	113 (23.4)	0.013
Diabetes mellitus	199 (79.0)	53 (21.0)	
Hypothyroidism	181 (80.0)	45 (19.9)	0.863
Obesity	131 (84.5)	24 (15.5)	0.129
COPD	108 (78.3)	30 (21.7)	0.709
Stroke	63 (88.7)	8 (11.3)	0.217
TIA			
OSA	21 (80.8)	5 (19.2)	0.559
Medication used			
Beta blockers	343 (65.4)	181 (34.6)	0.000
ACE inhibitors	135 (64.6)	74 (35.4)	0.000
ARBs	379 (81.7)	85 (18.3)	0.112
MRAs	81 (38.8)	128 (61.2)	0.000
Statins	390 (72.2)	149 (27.6)	0.000‡
Furosemide	189 (65.4)	100 (34.6)	0.000
Anticoagulants	323 (72.9)	120 (27.1)	0.000
Antiplatelet agents	44 (56.4)	34 (43.6)	0.000

COPD = chronic obstructive pulmonary disease, TIA = transient ischemic attack, OSA = obstructive sleep apnea, ACE = angiotensin-converting enzyme, ARBs = angiotensin receptor blockers, MRAs = mineralocorticoid receptor antagonists. *Student's t-test. ‡ Fisher's exact test.

In general, 2.70% of patients got a CRT alone, while 5% a CRT defibrillator for the additional prevention of sudden death.

Indications

Conduction disorders such as atrioventricular block and impaired cardiac impulse generation, such as sinus dysfunction, were the most common device implant indications, with unicameral or bicameral pacemakers being the most frequently implanted devices. On the other hand, ICDs and CRT defibrillators were implanted for primary prevention of sudden death in patients with ischemic cardiomyopathy, being almost twice the number of implanted devices for secondary prevention. In the case of nonischemic cardiomyopathy, the number of implanted defibrillation devices was very similar for primary and secondary prevention of sudden death. 2% of indications corresponded to the implant of CRT alone for the management of heart failure symptoms.

A total of 6% ILR were implanted in similar proportions to search for syncope causes of unknown origin and possible atrial fibrillation in embolic events without documented cause *(Table 3)*.

Hospitalization and follow-up

In terms of in-hospital stay, the implant of cardiovascular devices is a procedure that did not require prolonged hospitalization in most cases. Analysis of the data showed that the most frequent number of hospitalization days was zero (less than 24 hours), indicating that after the procedure was performed, the patient was discharged after a short observation period in the recovery room without being hospitalized. 65.3% of procedures required hospitalization for less than 48 hours 9.3% of patients had an in-hospital stay of more than seven days, 7.5% of these cases were due to complications related to device implant; in the remaining cases, prolonged hospital stays were due to associated comorbidities of each patient, unrelated to the procedure. In the latter group of patients, 77.8% were aged 60 or older, being those with longer hospitalizations generally elderly patients.

Table 2: Type of cardiac device implanted.

Devices	n (%)	Relative (%)
Pacemaker	738 (74.0)	
Bicameral	621 (62.2)	84.1
Unicameral	117 (11.7)	15.8
ICD	126 (12.6)	
Bicameral	78 (7.8)	61.9
Unicameral	13 (1.3)	10.3
Not specified	35 (3.5)	27.7
CRT-D	50 (5.0)	–
ILR	56 (5.6)	–
CRT	27 (2.7)	–
Total devices	997	

ICD = implantable cardioverter defibrillator, CRT-D = cardiac resynchronization therapy-defibrillators, ILR = implantable loop recorder, CRT = cardiac resynchronization therapy.

89% of patients had at least one follow-up appointment from the procedure to the end of the investigation, 59% had two follow-ups. The average for follow-up days was 256, with a range between 90 and 738 days from implant day to the end of the research.

Complications

A total of 76 events that were compatible with those previously defined as complications were recorded during follow-up. It was corresponding to 7.7% complications. In two cases, it was impossible to define whether there had been any complication due to the absence of clinical data.

The most frequent complications were the displacement of one of the electrodes and pocket hematoma. During the observation period there were no cases of death associated with the procedure, complications requiring cardiovascular surgery management, or hemothorax presence *(Table 4)*.

Some specific aspects of each type of complication are described below.

Electrode displacement: it was the most frequently found complication with a total of twenty-two cases. In eleven cases the ventricular electrode was displaced, four of them in conventional pacemakers, four were high-energy electrodes, and three were left ventricular electrodes. In the remaining six cases, the displaced electrode was the one in the atrium. No information was obtained regarding the displaced electrode in five cases.

Pocket Hematoma: it was the second most frequent complication and all the cases detected in the first two weeks after the procedure, without any drainage required in any case whatsoever. Out of the fifteen patients who developed a pocket hematoma, eight of them were in direct oral anticoagulants (DOACs) therapy. Of these, four patients were receiving antiplatelet therapy simultaneously with Acetylsalicylic acid (ASA). One patient received dual antiplatelet therapy, and two patients received ASA alone.

Infection: a total of six infection events occurred, two cases corresponded to soft tissues infection circumscribing the implant site, in one case there was a pocket abscess which required drainage, and two events of

Table 3: Indications for device implant.

Indications	n (%)
Atrioventricular block	465 (47.0)
Sinus disfunction	255 (25.6)
Sinus disfunction and atrioventricular block	18 (1.8)
Heart failure	23 (2.3)
Primary prevention for SCD, ischemic cardiomyopathy	74 (7.4)
Secondary prevention for SCD, ischemic cardiomyopathy	38 (3.8)
Primary prevention for SCD, nonischemic cardiomyopathy	38 (3.8)
Secondary prevention for SCD, nonischemic cardiomyopathy	31 (3.1)
Syncope	30 (3.0)
Suspected atrial fibrillation	22 (2.2)
Other	3 (0.3)
Total	997 (100.0)

SCD = sudden cardiac death.

bacterial endocarditis requiring complete device explant were reported, which were diagnosed at 172 and 540 days after the procedure respectively; methicillin-resistant *Staphylococcus aureus* was the responsible bacteria in both cases. The last case corresponded to the development of an early granuloma at the implant site with pocket remodelling because of a previous explant, that subsequently presented infection and the need for device explant.

Extracardiac and diaphragmatic stimulation: two cases were reported, both of them with left endocardial ventricular electrode, explant and re-implant of the left electrode was needed in one of them.

Table 4: Presence of complications according to device type and patient comorbidities.

Characteristic	Complication, n (%)		p
	Yes (n = 78)	No (n = 917)	
Gender			
Male	35 (6.3)	519 (93.7)	0.030
Female	43 (9.8)	398 (90.2)	
Comorbidities			
Arterial hypertension	67 (8.4)	730 (91.3)	0.115*
Diabetes mellitus	22 (8.8)	229 (91.2)	0.307*
Obesity	13 (8.4)	142 (91.6)	0.449*
Device type			
Pacemaker	51 (7.0)	682 (93.0)	
ICD	14 (10.4)	121 (89.6)	
CRT-D	9 (19.1)	38 (80.9)	0.008
ILR	1 (1.8)	54 (98.2)	
CRT	3 (12.0)	22 (88.0)	
Procedure			
Implant	55 (7.7)	660 (92.3)	
Explant/implant	18 (7.2)	232 (92.8)	
Upgrade	2 (20.0)	8 (80.0)	
Electrode repositioning	0 (0.0)	4 (100.0)	0.301
Explant	1 (12.5)	7 (87.5)	
Explant/implant and electrode repositioning	2 (25.0)	6 (75.0)	

ICD = implantable cardioverter defibrillator, CRT-D = cardiac resynchronization therapy-defibrillators, ILR = implantable loop recorder, CRT = cardiac resynchronization therapy.
* Fisher's exact test.

Venous thrombosis: two cases of venous thrombosis of the upper left limb at the subclavian level were detected in follow-up, both cases recognized after 60 days of the implant. They were managed with chronic oral anticoagulation, without any complication reported.

Pneumothorax: a total of seven cases were reported, three of which required thoracotomy. Detection was performed during or immediately after the procedure in all cases, except in one in which the diagnosis was made after 12 hours of the implant.

Pericardial effusion and heart tamponade: there were four cases of pericardial effusion documented after the procedure, all requiring percutaneous drainage by pericardiocentesis. All were associated with manipulation of the right ventricular electrode.

Other complications: during the follow-up period, a pacemaker explant and re-implant were performed on a patient with chronic pocket pain without other documented causes, and another case of intermittent edema of the upper left limb secondary to proximal subclavian slow flow without documented thrombosis, which received conservative management.

There were neither complications that required cardiovascular surgical management nor death cases associated with the device implant during the study period. The three cases of death documented corresponded to heart failure worsening in one patient and to non-cardiovascular causes on the two other cases.

Bivariate analyses did not find a statistically significant difference in any comorbidities, nor in the relationship of the type of procedure with or without the development of complications, or at least with the most frequently presented. It was documented that complications occurred more frequently in females and patients receiving statins, both with statistically significance ($p = 0.03$ and $p = 0.04$, respectively). In respect to the type of devices, CRT-D showed the highest frequency of complications and ILR showed the lowest frequency of them; this difference in complications related to the type of device is considered statistical significance ($p = 0.008$) *(Tables 4 and 5)*.

Table 5: Bivariate and multivariate analysis.

	Bivariate		Multivariate	
Characteristic	OR (CI 95%)	p	OR (CI 95%)	p
Age				
16-45	Ref.			
46-75	0.26 (0.035-1.95)	0.191		
≥ 76	0.40 (0.05-3.02)	0.376		
Female gender	1.03 (1.00-1.07)	0.030	1.71 (1.06-2.74)	0.026
Arterial hypertension	1.56 (0.80-3.01)	0.115		
Diabetes mellitus	1.17 (0.70-1.97)	0.307		
Hypothyroidism	1.37 (0.81-2.30)	0.144		
Device type				
Pacemaker	Ref.		Ref.	
ICD	0.65 (0.35-1.21)	0.179	0.58 (0.31-1.10)	0.10
ILR	0.34 (0.15-0.77)	0.012	0.35 (0.15-0.79)	0.012
CRT-D	0.43 (0.14-1.30)	0.180	4.0 (0.54-29.78)	0.172
CRT	0.434 (0.14-1.30)	0.137	0.40 (0.13-1.22)	0.109
Statins	1,56 (1.0-2.53)	0.041		
Beta blockers	1,26 (0.79-2.01)	0.194		

ICD = implantable cardioverter defibrillator, ILR = implantable loop rec order, CRT-D = cardiac resynchronization therapy-defibrillators, CRT = cardiac resynchronization therapy.

In the multivariate analyses, the statistical significance was preserved for the difference in female patient's complications and those who were taken to ILR implant.

The patient's age was not significantly associated with the presentation of complications. p = 0.334 (Mann-Whitney U test).

DISCUSSION

CIEDs implant is an increasingly common procedure in high-complexity centers. The current work was carried out in a center with a high implant volume (> 400/year). This high volume could be explained by the high complexity of the center in which the study was performed, which receives a large population of patients from multiple insurers, health care providers and electrophysiology service with multiple specialists (six electrophysiologists plus training specialists). We analyzed 997 clinical history records, finding a predominance of men in the group analyzed, who had a more significant burden of cardiovascular diseases and comorbidities. In general, the patients evaluated had a significant burden of comorbidities. The population's age could explain this; also, the attention took place in a fourth-level complexity center where complex cases that cannot be solved in other hospitals are referred. We also found a high burden of cardiovascular risk factors, with a higher prevalence of arterial hypertension, dyslipidemia and diabetes mellitus, which predispose to ischemic and nonischemic cardiovascular disease, therefore, eventually relating directly and indirectly to cardiac electrical problems and the need for CIEDs implant. Almost a third part of the patients had coronary artery disease, most of which had been actively managed, especially percutaneously.

The use of cardiovascular medication was also frequently found, highlighting statins, beta-blockers and ASA, which are typically used to manage coronary artery disease, thus supporting the common finding of this

condition and/or its associated risk factors like dyslipidemia.

These data suggest an elderly and comorbid population in general, with active management of its comorbidities, especially coronary artery disease.

Another striking fact was the high prevalence of anticoagulated patients corresponding to 26% of the total. All patients with mechanical valve prostheses were anticoagulated with Warfarin. In most cases, the predominant anticoagulants used were DOACs, principally factor X inhibitors; this allows us to infer that the pharmacological management of patients was adjusted to guidelines and recommendations of optimal pharmacological therapy.

17% of patients had flutter or atrial fibrillation, and all of them were considered a high embolic risk with a CHA2DS2VASC score of 4 in most cases. This information is closely related to anticoagulation data. It suggests an adequate frequency of anticoagulation in patients with high embolic risk atrial fibrillation, because the percentage of anticoagulated patients is higher than that of patients with atrial fibrillation.

The most commonly implanted devices were bicameral pacemakers, being atrioventricular block and sinus dysfunction its more frequent indications. The available literature also shows a higher proportion of bicameral pacemaker implants than unicameral pacemakers for the management of these disorders, which ensures a more synchronous type of pacing and lowers the incidence of atrial arrhythmias and pacemaker syndrome.[4] In the population studied, despite the high average of age, bicameral pacemakers were frequently implanted, demonstrating that priority is given to physiological heart stimulation and that the implant of a second electrode in the right cavities does not generally represent a step that makes this procedure more complex or that increases complications significantly.

ICDs were the second most implanted type of device, also predominantly bicameral. There are no data on the need for bradycardia stimulation in these patients, which would have allowed us to infer if its indication was the aim of atrioventricular synchrony during stimulation or the improvement in discrimination of cardiac arrhythmias.

Regarding cardiac resynchronization therapy devices, the CRT-D was the most commonly implanted, highlighting the importance of the prevention of sudden cardiac death in patients with symptomatic heart failure who were candidates for resynchronization therapy.

Regarding the general short in-hospital stay, it can be inferred that although these are high complexity technological devices, the implant procedure usually requires short periods of hospitalization. In the cases of prolonged in-hospital stays, the cause of the hospitalization was not directly related to the device implant.

The events referred to as «complications» occurred in 7.7% of all implanted electronic devices. In general, the literature describes the presence of complications in a 3-5% after device implants, being a little higher (5-8%) for complex devices such as ICDs, CRT or CRT-D.

There is no homogeneous definition of «complication», and this introduces a wide variability in the frequency and type of complications reported, making comparisons difficult. Despite this, some universally reported complications such as infection, hematoma, electrode displacement and surgery requirement (by perforation, hemothorax or pneumothorax).[5,6]

The ideal time for discharge has been a matter of discussion considering the safety and the presentation time of complications. The Emotion trial showed no difference in terms of complications, including electrode displacement, in patients taken to CIEDs implant who were early mobilized compared to those mobilized up to 24 hours after the procedure.[7] Similarly, a recent German study mentions that most of the potentially fatal complications occur between the initial 24-72 hours after device implant and that a safe discharge implies to discard them.[8]

In our study, severe pneumothorax and pericardial effusion complications were detected immediately, and only in one case during the first 6-12 hours post-procedure. On the other hand, none of the patients discharged within the first 24 hours presented any severe complications that would have been detected after discharge.

Potentially fatal complications such as hemothorax, pneumothorax, and cardiac tamponade are related to vascular access. The standard vascular approach in our group was cephalic vein dissection, which may reduce some risks, especially for pneumothorax or hemothorax.

In the population studied, most of the complications reported were not severe complications. The most common of these was electrode displacement followed by pocket hematomas, device threshold increase, and infections.

When discriminating between complications of conventional pacemakers and «complex» devices (ICDs, CRT and CRT-D), 4.8% of the complications were found in pacemakers and 2.8% in complex devices, being the most common complications after pacemaker implant pocket hematoma followed by electrode displacement, and after complex device implant the contrary: displacement of the electrodes (usually high energy or left ventricular), followed by pocket hematomas. These discriminated data are compatible with what is reported in the international literature, even with a lower percentage of complications.[3,9]

Surgical management was not required in any case, nor deaths directly associated with the procedure presented. No hematoma required drainage. Although electrode displacement is not the most frequently reported complication, in the case of our population, several circumstances can contribute to this finding, first of all, patients have multiple comorbidities. They are treated in a teaching center by a group with training specialists, in which, despite adequate supervision, the skill acquisition curve in the implant process may play an important role in this regard.[10] Besides, with respect to comorbidities, the fact of being more ill can also mean greater structural heart disease, which in turn increases the technical difficulty of the implant and the possibility of electrodes displacement. The largest number of displaced electrodes were ventricular electrodes, and a significant percentage were high-energy defibrillator electrodes.

It is also a center in which multiple commercial house devices are implanted, thus introducing certain variability related to the elements and the implant for each specific brand. Despite being the same type of devices, the different materials between commercial houses may contribute to this finding.

Finally, it exists the possibility that more frequent events like hematomas have been mild enough in several cases to not to be reported in the history after implant or in follow-ups, thus, making electrode displacement the most frequent event in our study, without necessarily being so.

Women presented more complications in a statistically significant way. This difference was mainly explained by infection events, since other frequent complications such as hematomas and electrodes displacement were presented in a similar pattern for both genders. A large cohort of patients from Australia and New Zealand who were taken for CIEDs implants also found a higher risk of complications in women, which could be explained by anatomical differences.[11]

Concerning the more severe complications found in the study, pericardial effusion and cardiac tamponade occurred in a deficient number of cases. All of them could be managed percutaneously, being a less morbid treatment in relation to the need for open surgical management.[12]

A recently published study carried out in another center in the country, analyzed the rate of complications in a slightly smaller number of patients who underwent the CIEDs implant during the years 2012 to 2015.[13] In general, their population characteristics in terms of the average age of implant, gender distribution, and percentage of pacemakers implanted are similar to our findings. Similarly, the most frequent complications were electrode displacement and pocket hematoma.

It should be noted that in our population, approximately 0.9% of the implants corresponded to cardiac resynchronization left electrodes, being this procedure usually technically more laborious and bound to anatomical variations of the venous tree. On the other hand, in the previous work, the frequency of pocket hematoma, infection and other significant complications were higher than those found in the present investigation.

Some factors could influence this difference; first, these implants were performed between 2012 and 2015, that is up to six years before our study, and some tools and elements for the implants may have been optimized in this period; second, by the time this work was done, bridge therapy with low molecular weight heparins in anticoagulated patients was still common, which is now known to increase the risk of bleeding and implant associated hematoma possibly. Therefore, it is not generally used nowadays and was not used in the implants reported in our work.[14]

Finally, in the present study, the percentage of patients under antiplatelet therapy was between 43 and 56%, and under anticoagulants of 21 and 72%, for patients with complex and non-complex devices, respectively.

It has been observed that the presence of antiplatelet therapy and the basal count of platelets in patients with CIEDs implants are independent risk factors for the development of hematomas.[15] In our case, the presence of antiplatelet therapy or anticoagulation in patients taken to implant more complex devices was not so high, which may also influence the fact that hematoma was not the most frequent complication found.

CONCLUSIONS

The implant of cardiac electronic stimulation devices is a frequent procedure which is part of the active management of the patients' different diseases and comorbidities included in our study. Despite the advanced age and significant disease burden, these patients had low complication rate procedures, similar to the ones reported on the national and international literature, thus suggesting that these procedures, even in the case of high complexity devices, are successful and safe in our environment.

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Major cardiovascular events in failed versus successful coronary revascularization in patients with chronic total occlusion

Eventos cardiovasculares mayores en revascularización coronaria fallida versus exitosa en pacientes con oclusión total crónica

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Keywords:
Chronic total occlusion, stable angina, percutaneous coronary intervention, failed revascularization, major cardiovascular events.

Palabras clave:
Oclusión total crónica, angina estable, intervención coronaria percutánea, revascularización fallida, eventos cardiovasculares mayores.

ABSTRACT

Introduction: Chronic coronary occlusions are associated with a negative impact on long-term prognosis. **Objectives:** To know if there is a difference in major cardiovascular events in patients undergoing successful revascularization versus failed revascularization of chronic total occlusion lesions instable angina. **Material and methods:** Cross-sectional, correlational study with two independent groups. **Results:** 71 patients were evaluated, in a context of stable chronic angina, in the High Specialty Medical Unit of Bajio, from January 2013 to February 2020; 41 patients with successful revascularization (RE) and 30 with revascularization was failed (RF). The revascularization success rate was 57.7%. The rate of major cardiovascular events found among patients with RE vs RF in this study were: unstable angina events post-revascularization in 12.5% of the RE group and in 13.3% of the RF group (p = 0.918). AMI (acute myocardial infarction) occurred in 0% of the RE group and in 3.3% of the RF group (p = 0.245). Death of cardiac origin occurred in 0% of the RE group and in 3.3% of the RF group (p = 0.245). In contrast 0% of the RE group and 6.7% of the RF group patients needed new vascularization. The survival rate in RF patients was 96.7%, and in RE patients, it was 100%. **Conclusions:** Successful versus failed revascularization did not show statistically significant differences in the rate of major cardiovascular events.

RESUMEN

Introducción: *Las oclusiones coronarias crónicas se asocian con un impacto negativo en el pronóstico a largo plazo.* ***Objetivos:*** *Conocer si existe diferencia en los eventos cardiovasculares mayores en pacientes sometidos a revascularización exitosa vs revascularización fallida de lesiones de oclusión total crónica en angina estable.* ***Material y métodos:*** *Estudio correlacional, transversal, con dos grupos independientes.* ***Resultados:*** *Se evaluaron 71 pacientes, en un contexto de angina crónica estable, en la Unidad Médica de Alta Especialidad del Bajío, del periodo de enero de 2013 a febrero de 2020, se obtuvieron 41 pacientes con revascularización exitosa (RE) y 30 con revascularización fallida (RF). La tasa de éxito de revascularización fue de 57.7%. La tasa de eventos cardiovasculares mayores encontrados entre pacientes con RE vs RF en este estudio fueron: eventos de angina inestable postrevascularización en 12.5% del grupo RE y en 13.3% del grupo RF (p = 0.918). El grupo de revascularización exitosa tuvo ausencia de infartos agudos al miocardio y en 3.3% del grupo RF (p = 0.245) sí hubo. Ocurrió muerte de origen cardiaco en 0% del grupo RE y en 3.3% del grupo RF (p = 0.245). Mientras que tuvieron necesidad de nueva vascularización el 0% del grupo RE y el 6.7% de los pacientes del grupo RF. La tasa de supervivencia de pacientes con RF fue de 96.7% y en pacientes con RE fue de 100%.* ***Conclusiones:*** *La revascularización exitosa vs fallida no demostró diferencias estadísticamente significativas en la tasa de eventos cardiovasculares mayores*

INTRODUCTION

Chronic total occlusions (CTO) can be considered the end-stage of obstructive coronary disease (CAD) and are associated with a negative impact on long-term prognosis. A CTO is defined as a complete luminal obstruction of a native coronary artery for

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a duration of equal to or greater than three months. CTOs are classified according to the TIMI flow grade, as a scale that evaluates epicardial coronary blood flow, thus being a «true» CTO with a TIMI 0 flow grade and a «functional» CTO with invasive coronary angiography. TIMI 1 flow grade. In large clinical records, CTO was diagnosed in 16-18.4% of CAD patients.[1,2] These large registries showed that the current mainstay in treating patients with CTO is optimal medical therapy (OMT), and only a minority of these individuals receive additional surgical (22-26%) or percutaneous (10-22%) revascularization.[3]

The true prevalence of CTO lesions is difficult to confirm because many patients with CTO have no symptoms and are not referred for medical evaluation. In some registry studies,[2,4] the prevalence of CTO among patients undergoing coronary angiography was approximately 18.4 to 52%. Unfortunately, most patients lacked obvious symptoms and signs[2] contributed to a delay in the diagnosis and treatment of CTO. Mortality at one year in patients with CTO was higher than in patients without CTO, and the prognosis was even worse when more than one CTO lesion was found.[5]

In general, patients with CTO are seen more frequently in men and have a relatively unfavourable cardiac risk factor profile than patients with non-occlusive CAD. A higher prevalence of diabetes mellitus (34 vs 26%), hypertension (75 vs 68%), hyperlipidemia (82 vs 78%), current smoking (33 vs 24%), peripheral vascular disease (8 vs 4%) and a previous myocardial infarction (MI) is observed (40 vs 23%) in patients with CTO compared to patients with non-occlusive CAD.[1]

An undiagnosed or untreated acute thrombotic event is the origin CTO development, which is supported by the electrocardiographic evidence of pathological Q waves corresponding to the terminal myocardium subtended by an occluded artery in a quarter of patients.[4] However, most patients (60%) with a CTO did not have a previous MI. In these patients, the occlusion appears to result from a long-term gradual luminal narrowing that allows the recruitment of fibroblasts, calcium, cholesterol, and inflammatory infiltrate into the occluded vessel. Collateral recruitment has a protective role by supplying myocardial blood flow to the CTO territory, thus preventing acute myocardial ischemia. Therefore, the preserved viable myocardium subtended by the occluded artery, and the absence of cardiac symptoms are therefore common observations.[2]

The development of a CTO, either after a thrombotic event or by a long-term gradual luminal narrowing, is not reserved only to the natural vascular wall and can occur in a stent previously implanted in patients treated with early PCI, going beyond three months as the definition indicates, however, approximately one in four CTO patients experience no symptoms. Chest pain is a fairly late expression in the ischemic cascade, and symptoms may even be absent in the presence of moderate to severe intermittent ischemia. The lack of symptoms may be amplified due to autonomic neuropathy in diabetic patients, strongly represented in the OCD patient population.[6]

In symptomatic patients with CTO, typical cardiac chest pain may be less prominent than shortness of breath or atypical symptoms including physical activity limitation, extensive fatigue, or palpitations due to ventricular arrhythmias. Patients with a CTO and an implantable cardioverter-defibrillator for the primary or secondary prevention of sudden cardiac death have a higher incidence of appropriately administered shocks and therapies compared to patients with ischemic cardiomyopathy without a CTO.[6]

Objectives: Main goal: Know if there is a difference in major cardiovascular events in patients undergoing successful vs failed revascularization of chronic total occlusion lesions in stable angina.

Secondary objectives: Establish the success rate of successful revascularization in patients with stable angina and chronic total occlusion lesions in our hospital. Know the rate of immediate complications during the procedure and hospitalization related to successful or failed revascularization of patients with stable angina and injuries with chronic total occlusion.

MATERIAL AND METHODS

This study that was carried out through a cross-sectional, correlational study of patients with

lesions with chronic total occlusion, which required management with percutaneous coronary intervention to manage the symptoms, observing the result of the findings found in cardiac catheterization and focusing on the management Invasive treatment of all coronary arteries with significant lesions, and depending on the findings of the coronariography / angioplasty, they were classified as successful or failed.

The database of patients with chronic total occlusions, treated by percutaneous coronary intervention, of the hemodynamic service of the UMAE Bajío T1 was analyzed. Being the universe of study, the patients captured in the database of the hemodynamic service of the UMAE Bajio T1. With the following selection criteria:

Inclusion criteria: comply with the definition of chronic total occlusion type lesions, over 18 years of age and intervened by percutaneous coronary intervention in the hemodynamics service at UMAE Bajio T1.

Non-inclusion criteria: loss of follow-up by the institution.

Elimination criteria: desire not to participate in the study.

The following variables were evaluated, such as major cardiovascular events: Unstable Angina, Acute Myocardial Infarction (according to the 4 definition of Infarction), death from cardiac causes, and need for new revascularization as qualitative variables.

Quality of life was assessed through angina's functional class using the Stable Angina Classification of the Canadian Cardiovascular Society.

Coronary intervention technique used: anterograde and retrograde in a single patient. Materials used: right and left guide catheter 3.5, size 6 French. Angioplasty Guides, size 0.014. Various angioplasty balloons and drug-eluting stents.

The sample size was obtained from the results published in the article Explore, which found a proportion of patients with chronic total occlusions and percutaneous coronary intervention of 26.4% and patients with chronic total occlusions and medical treatment of 13%, in relationship with major cardiovascular events-Giving a sample size of 30 patients to have an Alpha error of 0.5, a Confidence of 95%, a Beta error of 0.2, and a Power of 80%.

The sampling was obtained by the data by appointments and / or by telephone of the patients intervened for chronic total occlusions that are registered in the database of the Hemodynamics service of the UMAE Bajio T1.

The variables that were used are defined below.

Operative definitions: chronic total occlusion: complete luminal obstruction of a native coronary artery for a duration of greater than or equal to three months. MACE (major cardiovascular events): time to cardiovascular death, myocardial infarction, cerebral infarction, hospitalization for unstable angina, or coronary revascularization. Percutaneous coronary intervention: invasive, the interventional procedure of a coronary artery with a significant stenosis > 70%, in which it is possible to improve coronary blood flow, decrease myocardial ischemia, using a balloon catheter (coronary angioplasty) or by placing a stent. Successful percutaneous coronary intervention: referring to a percutaneous coronary intervention, which is achieved by revascularization. Failed percutaneous coronary intervention: referring to a percutaneous coronary intervention, which cannot be revascularized. Acute myocardial infarction: acute myocardial damage with clinical evidence of acute myocardial ischemia and detection of an increase or decrease in high sensitivity troponin values, with at least 1 value above the upper limit of the 99th percentile and at least 1 of the following conditions: symptoms of myocardial ischemia, new ischemic changes on the electrocardiogram, appearance of pathological Q waves, imaging evidence of loss of viable myocardium, or new regional wall motility abnormalities following a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography or autopsy (not in MI types 2 or 3), The post mortem demonstration of acute atherothrombosis in the culprit artery of the infarcted myocardium meets the criteria of MI (myocardial Infarction) type 1, evidence of an imbalance myocardial oxygen supply and demand not related to acute

atherothrombosis meets criteria for MI type 2, cardiac death in patients with symptoms compatible with myocardial ischemia and presumed new ischemic changes on the ECG (electrocardiogram) before troponin values are available or they are altered meets the criteria for type 3 MI. Unstable angina: anginal pain prolonged (> 20 min) at rest or new-onset (de novo) angina (Canadian Cardiovascular Society class II or III) or recent destabilization of previously stable angina with at least class characteristics of angina III (angina in crescendo) of the Canadian Cardiovascular Society or acute post-MI angina. Classification of the Canadian Cardiovascular Society: it is the most commonly used classification to measure the severity of angina, in patients with stable angina, distinguishing four classes based on the limitation that this supposes in the daily activity of the patient. Coronary perforation: the adverse effect caused by of the coronary vessel wall caused by the instrumentation in the interventional procedure by permuting coronary artery. Ventricular arrhythmias: arrhythmias that originate in the ventricular myocardium or the His-Purkinje system include premature ventricular beats, ventricular tachycardias that can be sustained or nonsustained, and ventricular fibrillation.

DA: anterior descending coronary artery. CD: right coronary artery. CX: circumflex coronary artery. PL: Posterolateral coronary artery. OM: obtuse marginal coronary artery. The non-reflow phenomenon: it is defined as the persistence of inadequate flow lower than TIMI 3 during coronary angioplasty in the absence of a macroscopic obstruction in the epicardial coronary arteries. Cardiovascular death: cause of death that causes any heart condition that manifests itself through diseased blood vessels, structural problems, and blood clots. Need for new revascularization: the patient who is reoperated for percutaneous coronary revascularization. SYNTAX-II: score derived from clinical trials of the same name, which classifies coronary lesions based on the anatomical characteristics of coronary disease, is recommended by practice guidelines to decide between drug-eluting stent angioplasty or revascularization surgery. Collateral arteries: arteries that derive from the main vessel.

Using, for statistical management, the SPSS statistical computer program, with JAVA platform, analyzing, with the different variables searched, for which in turn, the following statistical methods were used: χ^2 for qualitative independent variables, t Student for quantitative independent variables, Kaplan-Meier curves to assess prognosis and morbidity and mortality, a difference of two proportions to calculate the sample of qualitative variables between the two groups. Moreover, the difference of two means to calculate the sample of the qualitative variables of the two groups.

RESULTS

Success of revascularization

We found a success of revascularization was 57% and failed revascularization 42%.

Demographic characteristics and comorbidities of the patients

When comparing the patient's demographic characteristics in both groups, the mean age in patients undergoing successful revascularization was 63.0 ± 9.4 years and in patients with failed revascularization 63.3 ± 8.8 years (p = 0.908). There were significant differences in sex between groups, but no significant differences were found in comorbidities between groups *(Table 1)*.

Coronary arteries affected

The most commonly affected coronary arteries were the right coronary artery in both groups (34.1% in the RE group and 36.7% in the RF group), followed by the anterior descending (31.7% and 30.0%, respectively) and the circumflex (9.8%) and 10.0%, respectively *(Figure 1)*.

Characteristics of the surgical procedure

The surgical technique used for revascularization was antegrade in 97.6% of the patients who underwent successful revascularization, and 100% failed revascularization. Retrograde revascularization was performed only in one patient in the RE group. However, no significant

Table 1: Comparison of demographic characteristics and comorbidities between patients undergoing successful and failed revascularization.

Characteristic	Group RE n = 41 (%)	Group RF n = 30 (%)	p
Age	63.0 ± 9.4	63.3 ± 8.8	0.908
Sex			
Female	11 (26.8)	20 (6.7)	0.030
Male	30 (73.2)	15 (50.0)	
Comorbidities			
Previous AMI	18 (43.9)	18 (60.0)	0.742
Mellitus diabetes	24 (58.5)	14 (46.7)	0.322
Hypertension	33 (80.5)	23 (76.7)	0.697
Dyslipidemia	26 (63.4)	19 (63.3)	0.994
Current smoking	27 (65.9)	18 (60.0)	0.613
Chronic kidney disease	0 (0.0)	0 (0.0)	1.000

RE = successful revascularization, RF = revascularization failed, AMI = acute myocardial infarction.

differences were found in the number of collaterals found in the right, circumflex, and anterior descending coronary arteries between groups *(Table 2)*.

SYNTAX-II score between patients in both groups

The mean SYNTAX-II score in the RE group was 26.2 ± 12.1, and in the RF group, it was 29.0 ± 8.9 (p = 0.375).

Comparison of immediate complications between patients with successful and failed revascularization

When comparing the immediate complications between patients with successful and failed revascularization, it was found that 97.6% did not present complications in the RE group. The only complication was the vagal reflex, which occurred in only one patient (2.4%). While, in the RF group, complications occurred in five patients (16.7%; p = 0.242). The complications that occurred in the RF group were: non-reflow phenomenon (3.3%, n = 1), ventricular arrhythmias (3.3%, n = 1), coronary perforation (9%, n = 3) *(Figure 2)*.

Comparison of the rate of major cardiovascular events between patients with successful and failed revascularization

Next, the rate of major cardiovascular events was compared between patients with successful and failed revascularization, finding that post-revascularization unstable angina events occurred in 12.5% of the patients in the RE group and in 13.3% of the patients in the RF group (p = 0.918). AMI (acute myocardial infarction) occurred in 0% of the RE group patients and in 3.3% in the RF group (p = 0.245). Death of cardiac origin occurred in 0% of the patients in the RE group and in 3.3% of the patients in the RF group (p = 0.245). In contrast 0% of the RE group patients and 6.7% of the patients in the RF group needed new vascularization *(Table 3)*.

Subanalysis of Comparison of the rate of major cardiovascular events between patients with successful and failed revascularization with the involvement of only the anterior descending coronary artery

A subanalysis of major cardiovascular events was performed in patients only affected by total occlusions in the anterior descending artery. Finding 15 patients with chronic total occlusions in the RE group and 11 patients with chronic total occlusions in the RF group, of whom they presented 2 patients with angina in the RE group and two patients with angina in the RF group (p = 1), 0 patients with infarction in the RE group and 0 patients with infarction in the RF group (p = 0), 0 patients in need of new revascularization in the RE group and 1 patient in need of new revascularization in the RF group (p = 0.34), 0 deceased patients in the RE group and 0 deceased patients in the RF group (p = 0) *(Table 4)*.

Factors associated with failed revascularization

Next, it was determined which clinical characteristics were associated with failed revascularization by calculating the Odds Ratio (OR), finding that the male sex was associated with a greater probability of

failed revascularization OR = 5.1 (95% CI 1.04-25.22, p = 0.030). No other factors were significantly associated with failed revascularization, including age, affected coronary artery, surgical technique, history of AMI, hypertensive diabetes, dyslipidemia, smoking, chronic kidney disease, chronic kidney disease, or SYNTAX-II score.

Comparison of survival in patients with failed and successful revascularization

The survival rate between patients with failed and successful revascularization was compared, finding that in patients with failed revascularization it was 96.7% and in patients with successful revascularization it was 100%. The Kaplan-Meier curve is presented in *(Figure 3)*.

Classification of the severity of angina by the Canadian Cardiovascular Society

Through the classification of the severity of symptoms in patients with stable chronic angina, according to the Canadian Cardiovascular Society, the level of symptoms of the patients was assessed, finding 36 patients (87.5%) of the group of RE with class I symptoms, 26 patients (86.7%) of the RF group with class I symptoms, 5 patients (12.5%) of the RE group with class II symptoms, 2 patients (6.6%) of the RF group with class II symptoms and 2 patients (6.6%) of the RF group with class III symptoms (p = 0.918) *(Figure 4)*.

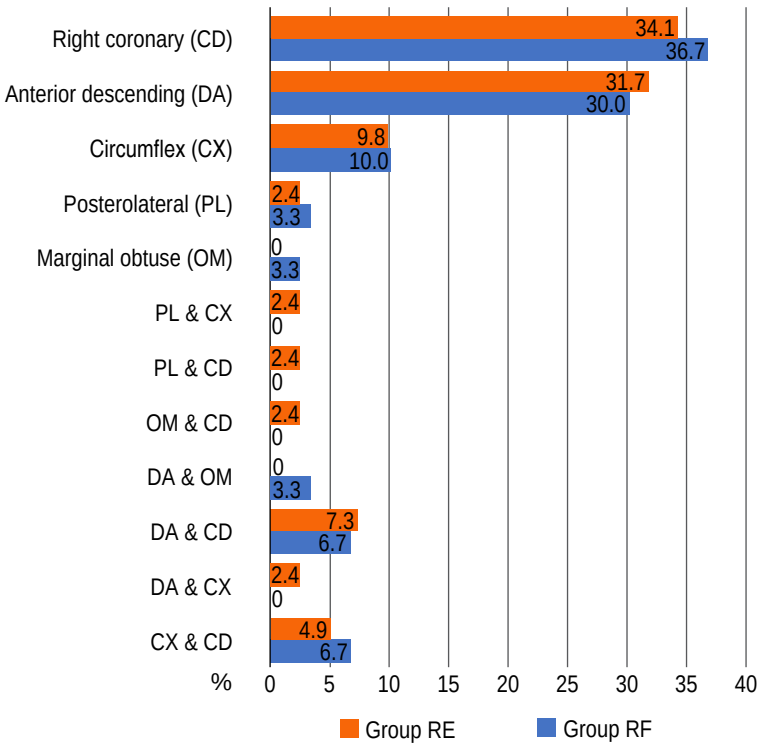

Figure 1: Affected coronary arteries.

DISCUSSION

71 patients were evaluated, in a context of stable chronic angina, in the Bajio High Specialty Medical Unit, from January 2013 to February 2020, which demonstrated chronic total occlusion in coronary angiography, proceeding to perform an intervention percutaneous coronary artery, of these, 41 patients achieved successful revascularization, and in 30 cases the revascularization was failed. With a revascularization success rate of 57.7%.

When comparing the patient's demographic characteristics in both groups, the mean age in patients undergoing successful revascularization was 63.1 ± 9.4 years and in patients with failed revascularization 63.3 ± 8.8 years (p = 0.908) in this study. There were significant differences to have a failed revascularization of a chronic total occlusion being a man, also, of having a chronic total occlusion (p = 0.03). No significant differences were found in comorbidities between groups.

In general, patients with CTO are more frequently identified in men, having a relatively unfavourable cardiac risk factor profile than patients with non-occlusive CAD. A higher prevalence of diabetes mellitus (34 vs 26%), hypertension (75 vs 68%), hyperlipidemia (82 vs 78%), current smoking (33 vs 24%), peripheral vascular disease (8 vs 4%) and a previous myocardial infarction (MI) is observed (40 vs 23%) in patients with CTO compared to patients with non-occlusive CAD.[3]

In this study, the most commonly affected coronary arteries were the right coronary artery in both groups (34.1% in the RE group and 36.7% in the RF group), followed by the anterior descending (31.7 and 30.0%, respectively) and circumflex (9.8 and 10.0%, respectively). The

Table 2: Comparison of surgical characteristics between patients undergoing successful and failed revascularization.

Surgical characteristic	Group RE n = 41 (%)	Group RF n = 30 (%)	p
Surgical technique			0.389
Antegrade	40 (97.6)	30 (100.0)	
Retrograde	1 (2.4)	0 (0.0)	
Number of stents placed	2.0 ± 0.9	0.1 ± 0.4	< 0.001
0	0 (0.0)	30 (100.0)	
1	15 (36.6)	0 (0.0)	
2	14 (34.1)	0 (0.0)	
3	10 (24.4)	0 (0.0)	
4	2 (4.9)	0 (0.0)	
Number of CD collaterals	0.3 ± 0.5	0.5 ± 0.5	0.069
0	28 (68.3)	14 (46.7)	0.067
1	13 (31.7)	16 (53.5)	
Number of CX collaterals	0.3 ± 0.5	0.3 ± 0.5	0.944
0	27 (65.9)	20 (66.7)	0.943
1	14 (34.1)	10 (33.3)	
Number of DA collaterals	0.4 ± 0.5	0.2 ± 0.4	0.134
0	26 (63.4)	24 (80.0)	0.130
1	15 (36.6)	6 (20.0)	

RE = successful revascularization, RF = failed revascularization, CD = right coronary artery, CX = circumflex, DA = anterior descending.

surgical technique used for revascularization was antegrade in 97.6% of the patients who underwent successful revascularization, and 100% of failed revascularization. Retrograde revascularization was performed only in one patient in the RE group.

No significant differences were found in the number of collaterals found in the right, circumflex or anterior descending coronary arteries between groups. The mean SYNTAX-II score in the RE group was 26.2 ± 12.1, and in the RF group, it was 29.0 ± 8.9 (p = 0.375).

Angiographically well-developed collaterals to the occluded artery are often assumed to be sufficient to prevent ischemia. Non-invasive and invasive studies have clearly demonstrated the limited functional capacity of collaterals to provide sufficient myocardial perfusion in the vast majority of patients. Therefore, the existence of well-developed collateral should not guide the indication for revascularization.[1,2,5]

When comparing the immediate complications between patients with successful and failed revascularization, it was found that 97.6% in the RE group did not present complications. The only complication that was evidenced in the RE group was a vagal reflex that occurred in only 1 patient (2.4%). While, in the RF group, complications occurred in 5 patients (16.7%; p = 0.242). The complications that occurred in the RF group were: non-reflow phenomenon (3.3%, n = 1), ventricular arrhythmias (3.3%, n = 1) and coronary perforation (9.9%, n = 3). The rate of major cardiovascular events found among patients with successful and failed revascularization in this study was: unstable angina events post-revascularization in 12.5% of the RE group patients and in 13.3% of the patients in the RF group (p = 0.918). AMI occurred in 0% of the RE group patients and in 3.3% in the RF group (p = 0.245). Death of cardiac origin occurred in 0% of the patients in the RE group and in 3.3% of the patients in the RF group (p = 0.245). In comparision 0% of the patients in the RE group and 6.7% of the patients in the RF group needed new vascularization.

In addition, a subanalysis of major cardiovascular events was performed in patients only affected by total occlusions in the anterior descending artery, finding 15 patients with chronic total occlusions in the RE group and 11 patients with chronic total occlusions in the RF group, of which presented 2 patients with angina in the RE group and two patients with angina in the RF group (p = 1), 0 patients with infarction in the RE group and 0 patients with infarction in the RF group (p = 0), 0 patients in need of new revascularization in the RE group and 1 patient in need of new revacularization in the RF group (p = 0.34), 0 deceased patients in the RE group and 0 deceased patients in the RF group (p = 0).

While CTOs are diagnosed in 16-18.4% of patients with CAD (coronary artery disease), one report stated that PCI (percutaneous coronary intervention), in patients with CTO represented only 4.8% of the total volume of PCI in 2013 in the United States.[4,7,8] In our hospital, Bajio High Specialty Medical Unit, of Mexican Social Security Institute, 780 angioplasties are performed annually, of

which CTO angioplasties account for 2% of the total. Because the specific material used for the management of CTO angioplasties is not routinely found in the hemodynamic service, which leads the interventional cardiologist not to attempt the procedure.

The SYNTAX II study demonstrated the incremental value of developing new strategies in the field of complex PCI where CTO is included, in patients with triple vessel disease, leading to improved clinical results compared to PCI performed in similar patients. In the original SYNTAX-I trial in 2012, a hybrid percutaneous treatment algorithm was introduced that focuses on retrovascularization of percutaneous CTO in the safest, most effective and efficient way.[9-11] Our center showed a success rate of 57%, which is lower than that described in the literature because, as previously mentioned, the specific material is not routinely available.

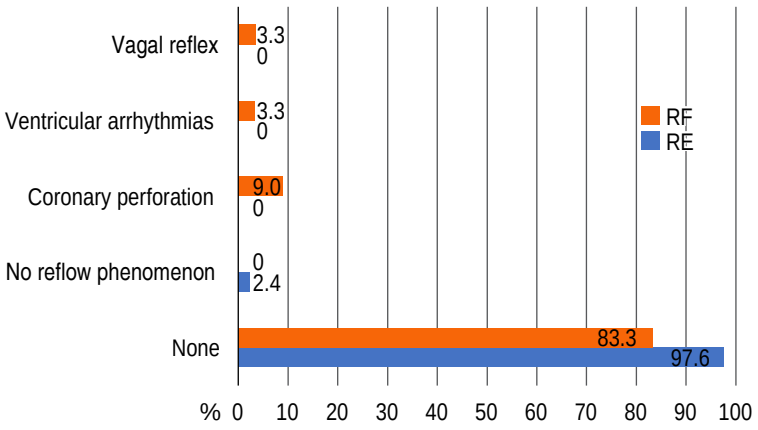

Figure 2: Comparison of complications between groups.

Table 3: Comparison of the rate of major cardiovascular events between patients with successful and failed revascularization.

Event	Group RE n = 41 (%)	Group RF n = 30 (%)	p
Unstable angina	5 (12.5)	4 (13.3)	0.918
Acute myocardial infarction	0 (0.0)	1 (3.3)	0.245
Need for new revascularization	0 (0.0)	2 (6.7)	0.098
Death from cardiac cause	0 (0.0)	1 (3.3)	0.245

RE = successful revascularization, RF = failed revascularization.

Retrograde approaches are complementary techniques to AWE (antegrade wire escalation) and have allowed a significant increase in technical success rates. However, they are often used for CTO lesions of greater anatomical complexity and are regularly the key to successful CTO crossover after a failed antegrade approach.[6,12]

The hybrid algorithm (antegrade and retrograde technique) provides a consistent and reproducible format that allows flexible switching to other techniques when one fails. The PROGRESS CTO score and the RECHARGE score are easy-to-use predictive tools to assess the risk of technical failure in ICP in CTO.[13-15] Both scores are based on the presence or absence of various angiographic features related to CTO and are validated in a cohort of CTO PCI based on the hybrid approach.[16-18] In our center, only 1 retrograde approach has been performed, and it was performed after a failed anterior approach, which was successful.

In this study, determined which clinical characteristics were associated with failed revascularization by calculating the Odds Ratio (OR), finding that the male sex was associated with a greater probability of failed revascularization OR = 5.1 (95% CI 1.04-25.22, p = 0.030). No other factors were significantly associated with failed revascularization, including age, affected coronary artery, surgical technique, history of AMI, hypertensive diabetes, dyslipidemia, smoking, chronic kidney disease, chronic kidney disease, or SYNTAX-II score. In addition, the survival rate between patients with failed and successful revascularization was compared, finding that in patients with failed revascularization was 96.7% and in patients with successful revascularization was 100%.

CURRENT PERSPECTIVES

CTOs are commonly diagnosed in CAD patients and have a negative impact on the quality of life and long-term prognosis. Observational studies point to additional benefits of ICP in OTC over OMT (optimal medical therapy) alone.[19-22] In the SYNTAX-I trial, a SYNTAX residual score greater than eight was associated with higher all-cause mortality at five years compared with

Table 4: Comparison of the rate of major cardiovascular events between patients with successful and failed revascularization with involvement of the anterior descending artery.

Event	Group RE n = 15 (%)	Group RF n = 11 (%)	p
Unstable angina	2 (13.3)	2 (18.1)	1.000
Acute myocardial infarction	0 (0.0)	0 (0.0)	0.000
Need for new revascularization	0 (0.0)	1 (9.09)	0.340
Death from cardiac cause	0 (0.0)	0 (0.0)	0.000

RE = successful revascularization, RF = failed revascularization.

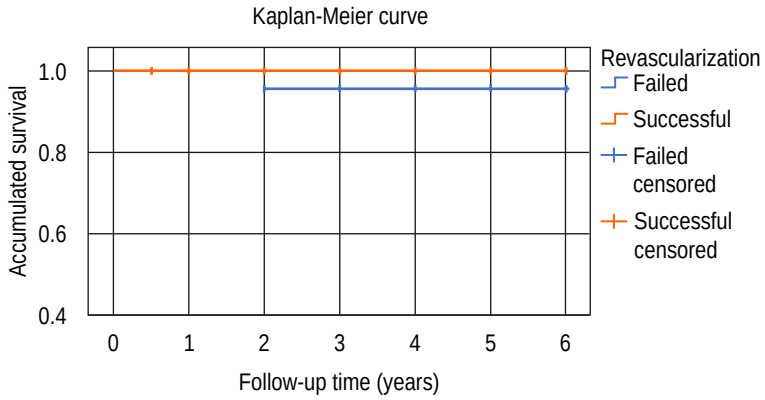

Figure 3: Kaplan-Meier survival curve of patients with successful and failed revascularization.

a SYNTAX-I residual score less than 8.9, despite the enormous evolution of the catheter-based intervention tools and techniques for CTO-PCI, the presence of a CTO itself represents the most frequent cause of incomplete coronary revascularization in general.[23-25]

The EXPLORE trial,[26,27] the only published randomized controlled trial to assess the impact of PCI in patients with OTC, found negative results and demonstrated that PCI could not improve left ventricular ejection fraction (LVEF) or reduce the risk of adverse heart failure or major cardiovascular events compared to OMT.[28-30] Most surprisingly, the proportion of patients who accepted repeat PCI in the percutaneous intervention group was higher than in the OMT group (26.4 vs 13.0%, p = 0.004) after a follow-up of four months. However, some cohort studies[28-30] indicated that PCI was associated with better long-term survival and a better prognosis relative to OMT.

We did not find significant differences in the MACE, which agrees with the EXPLORE study's findings. We may also contribute that 50% of the treated coronary arteries correspond to the CD and CX, which irrigate a territory smaller than the DA, explaining the absence of difference, although clinically the functional class of patients with complete revascularization improved compared to patients with incomplete revascularization.[31,32]

To assess symptoms in patients with stable angina was used the criteria scale of the Canadian Cardiovascular Society, described in 1976, is the most commonly used classification to measure the severity of angina, distinguishing 4 classes (I, II, III and IV) depending on the limitation that this supposes in the daily activity of the patient. Of which: class I is in which patients have no limitation of normal life. Angina only appears with strenuous exertion. class II is one in which patients have a slight limitation of physical activity. Angina appears when walking fast or climbing stairs or hills. The patient can walk more than 1 or 2 blocks or go up one floor of stairs. class III is one in which there is a marked limitation of physical activity. Angina appears when walking one or two blocks or when climbing a floor of stairs and finally class IV, where there is an inability to perform any activity, since angina occurs, which can appear at rest.[31-33]

It was obtained by classifying the severity of symptoms in patients with stable chronic angina, according to the Canadian Cardiovascular Society, the level of symptoms of the patients, finding 36 patients (87.5%) of the group of RE with class I symptoms, 26 patients (86.7%) of the RF group with class I symptoms, five patients (12.5%) of the RE group with class II symptoms, two patients (6.6%) of the RF group with class II symptoms and two patients (6.6%) of the RF group with class III symptoms (p = 0.918), thus demonstrating a better functional class of patients with success revascularization compared to patients with failed revascularization.

The most recent study that comparing OMT and PCI in patients with stable angina

is the ISCHEMIA presented on 16 November 2019 at the American Congress of Cardiology, carried out in 320 centers in 37 countries and included 5,179 patients with the disease. Stable coronary artery, preserved ejection fraction and moderate or severe ischemia in imaging studies or exercise tolerance marks an important watershed in patients with stable chronic angina, the primary end point at six months was 5.3% in the invasive strategy vs. 3.4% in the conservative and at five years the cumulative event rate was 16.4 vs 18.2%, respectively (95% CI 4.7 to 1.0). All-cause mortality was low and similar in both groups. At a mean of 3.3 years (2.2 to 4.4 years), the primary end point rate was 13.3 for the invasive group vs 15.5% for those with medical treatment only (HR 0.83; 95% CI 0.8 to 1.08). The event curves up to five years showed that the conservative strategy had fewer events in the first five years, while the invasive strategy was better between three and five years. The absolute difference between the two groups was almost identical, and it is planned to follow the patients for a further five years.[32,33] For the combined end point of death and infarction, the event curves follow a similar pattern, crossing around two years, but without differences at four years (13.9% for conservative treatment vs 11.7% for invasive treatment).[32,33]

Analyzing the rest of the study' objectives. It can be affirmed that a strategy with OMT carries a lower risk of presenting periprocedural myocardial infarction or hospitalization for heart failure. In comparison an initial strategy with PCI carries a lower risk of suffering from spontaneous myocardial infarction or unstable angina hospitalization. It is associated with an undeniable symptomatic benefit and an improvement in the quality of life in patients with anginal symptoms, for which ISCHEMIA re-establishes the importance of aggressive medical management in patients with stable coronary disease. However, it shows that revascularization improves the quality of life and has symptomatic benefit in patients.[32,33]

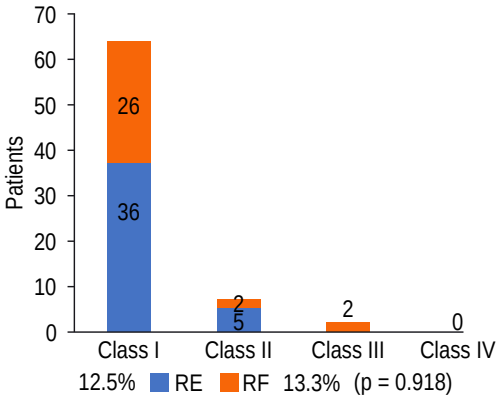

Figure 4: Classification of the severity of angina by the Canadian Cardiovascular Society in patients with successful and failed revascularization.

In the 2019 European guidelines for cardiology, the use of revascularization is discussed in the context of relieving symptoms in patients with angina and/or improving the prognosis of ischemic heart disease. The decision to revascularize for percutaneous coronary intervention or coronary bypass surgery is based on the clinical presentation (presence or absence of symptoms) and/or previous ischemia documentation (present or absent). In the absence of prior documentation of ischemia, indications for revascularization depend on an invasive evaluation of the severity of the stenosis or indications for prognosis. However, these could change if further studies were carried out demonstrating the usefulness of percutaneous coronary intervention in patients with stable chronic angina.[32,33]

Therefore, this study opens a panorama to be able to delve into patients with chronic total occlusions in the context of stable angina and assess the usefulness of complete coronary intervention in major cardiovascular events and the long-term benefit in patients.

CONCLUSIONS

The success rate of revascularization of CTO lesions in our unit is 57%, and successful vs failed revascularization did not show statistically significant differences in the rate of major cardiovascular events between patients; however, it did in the functional class of the patients.

Knowledge of our center's experience is very useful since it will allow us to guide the treatment of CTO lesions in patients with stable angina treated in our hospital.

LIMITATIONS OF THE STUDY

The main limitations present in the following study correspond to the lack of specific material to revascularize CTO lesions, which leads hemodynamists not to treat these lesions, decreasing our rate of revascularization successes and the number of patients treated.

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Original Research

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Coronary arteriography with radial access in coronary acute disease and its relation with handgrip strength and radial artery permeability (CARHANG)

Arteriografía coronaria con acceso radial en la enfermedad coronaria aguda y su relación con la fuerza de agarre y la permeabilidad de la arteria radial (CARHANG)

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Keywords:
Handgrip, acute coronary syndrome, vascular, coronary angiography, radial artery, vascular access, vascular complications.

Palabras clave:
Fuerza de agarre, síndrome coronario agudo, vascular, angiografía coronaria, arteria radial, acceso vascular, complicaciones vasculares.

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ABSTRACT

Introduction: Little research has been conducted on some complications secondary to radial access for coronary arteriography in patients with ACS, such as loss of handgrip strength and radial flow alteration. These are not routinely evaluated, unaware that they may compromise the performance of trades that require fine skills or activities in daily life. **Material and methods:** Prospective observational longitudinal cohort study, a sample of 77 patients diagnosed with ACS, undergoing radial access to coronary arteriography. For data analysis, we used the IBM SPSS® V.21 statistical package. We used a Sahean Corporation® brand hydraulic dynamometer for the force measurement, and we performed a comparative analysis of related samples; t-Student test and binary logistic regression. **Results:** Proportion according to gender was 48.1% women and 51.9% men, the median age of 66 years (58-72). In the handgrip strength of patients with radial access, we found a statistically significant difference between the initial and final measurement $p < 0.001$ (IC 95%: 1.59-4.07). **Conclusions:** We found a significant loss of handgrip strength in both genders, with lower than optimal force values for IADL, findings so far explained by the type of intervention that requires future studies.

RESUMEN

Introducción: *Se han realizado pocas investigaciones sobre algunas complicaciones secundarias al acceso radial para la arteriografía coronaria en pacientes con SCA, como la pérdida de fuerza de prensión y la alteración del flujo radial. Estos no se evalúan de forma rutinaria, sin saber que pueden comprometer el desempeño de los oficios que requieren habilidades finas o actividades en la vida diaria.* ***Material y métodos:*** *Estudio prospectivo observacional de cohorte longitudinal, con una muestra de 77 pacientes con diagnóstico de SCA, sometidos a coronariografía de acceso radial. Para el análisis de los datos, se utilizó el paquete estadístico IBM SPSS® V.21. Para la medición de la fuerza se utilizó un dinamómetro hidráulico de la marca Sahean Corporation® y se realizó un análisis comparativo de muestras relacionadas; prueba t-Student y regresión logística binaria.* ***Resultados:*** *La proporción por sexo fue de 48.1% mujeres y 51.9% hombres, la mediana de edad fue 66 años (58-72). En la fuerza de agarre de los pacientes con acceso radial, encontramos una diferencia estadísticamente significativa entre la medición inicial y final $p < 0.001$ (IC del 95%: 1.59-4.07). Teniendo en cuenta los criterios de discapacidad para las actividades instrumentales de la vida diaria (IADL), realizamos un análisis estratificado, encontrando diferencias significativas por género ($p < 0.05$).* ***Conclusiones:*** *Se encontró una pérdida significativa de fuerza de agarre en ambos sexos, con valores de fuerza menores al óptimo para IADL, hallazgos hasta ahora explicados por el tipo de intervención que requiere estudios futuros.*

INTRODUCTION

Currently, cardiovascular diseases are the leading cause of morbidity and mortality in the world. In 2012, 17.5 million deaths were recorded.[1-3] In Latin America, it is the leading cause of death, and it has been found that the mortality of patients with ACS is higher than in

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developed countries.[4] Coronary arteriography is the cornerstone of invasive treatment in patients with acute coronary syndrome.[5-7] This procedure has different techniques to reach vascular access, such as radial, femoral, brachial, and ulnar. Radial and femoral accesses are the most recognized and the ones with the most significant academic support at present.[8]

Femoral access is a procedure that is widely accepted due to its history, operator training, and extensive knowledge in the recognition and management of its complications, the most frequent being: major bleeding,[9,10] localized hematoma,[11] local bleeding, pseudoaneurysm, among others.[11,12] However, in the last decade, radial access has been implemented as the best alternative over femoral access, since a lower incidence of complications has been described with the same clinical results.[13] However, different studies have shown a higher than expected incidence of radial artery obstruction (RAO), and although this has been considered a benign complication, some reports raise doubts about it.[14,15]

Taking into account those as mentioned above, an exhaustive bibliographic review was performed where little information was found describing some vascular complications related to radial access for coronary arteriography, specifically the loss of handgrip strength in the corresponding upper limb of the access, which, if affected, can generate a significant negative impact in patients who have traded, where a subtle use of the upper limb is required, for example, pianists, painters, goldsmiths, artisans, surgeons, etcetera; moreover, in daily activities such as washing, ironing, managing finances, etcetera.

Some studies have suggested no significant compromise of handgrip strength after coronary arteriography with radial access.[14,16] Still, the need for more data is so prevalent that large-scale studies such as ARCUS have already begun to be proposed to answer this question.[17] Also, there are doubts about RAO's benignity and a sub-diagnosis of it,[15,17] and other studies even question whether radial access is better than ulnar in all clinical scenarios.[17] All these reasons make it mandatory to conduct more studies that explore the incidence of complications with the use of radial access after coronary arteriography. With a particular emphasis on the handgrip strength and its relationship with the radial flow to establish theoretical bases that can help modify protocols and standards currently used for coronary arteriography.

MATERIAL AND METHODS

It is a prospective observational longitudinal cohort study. We included 77 patients with a diagnosis of ACS confirmed by clinical and laboratory. The patients underwent coronary angiography with a radial access route using the classic Seldinger technique using nitroglycerin bolus diluted in 10 ccs of saline solution.[18] All the patients were treated at the Las Americas Clinic's hemodynamic service between February 2018 and January 2020. We performed a follow-up one month after discharge to evaluate the intervened radial artery's permeability, evaluation of handgrip strength in hand on the same access site, and clinical evaluation of possible complications. To evaluate permeability, we used ultrasound accompanied by the Doppler-color signal made with a 5 MHZ transducer, using General Electric and Toshiba equipment, both equipped with software for interpretation in the field peripheral vascular. Then, an internist with a peripheral vascular subspecialty read the results. We used a comparative hydraulic dynamometer to measure handgrip strength just before and one month after coronary arteriography. We used a Saehan corporation® brand hydraulic dynamometer and handled personnel with prior training and standardization from the American Society of Hand Therapists (ASHT). For this procedure, the patient must be seated with adduction of the shoulder and neutrally rotated, elbow flexed at 90º, the back of the hand and wrist in a neutral position. We made three prehensile force taps, and the average of the results obtained was used for analysis. We obtained Informed consent from all patients.

This research was carried out following international ethical principles for medical research in human beings outlined in the Declaration of Helsinki of the World Medical Association. In the same way, the study was approved by the institutional review board of the hospital.

Sample

Patients over 18 years of age, diagnosed with ACS, who met the inclusion and exclusion criteria. The sample was taken by convenience.

Inclusion

Patients diagnosed with ACS with ST-segment elevation by electrocardiography or without ST-segment elevation with an elevation of cardiac enzymes, over 18 years of age, informed consent signature, presence of a radial pulse, and available access defined by the interventionist, patients with availability contact.

Exclusion

Patients under 18 years of age, with a history of neurodegenerative disease, requiring percutaneous coronary intervention for reasons other than suspicion or diagnosis of the acute coronary syndrome, women with a clinical or laboratory diagnosis of pregnancy, and patients with a history of catheterization due to the same pathway, patients with sequelae of stroke were excluded from the study.

Data collection

The electronic health records with the questioning of each patient was the source of the following data: socioeconomic, personal history such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD), smoking, stroke (CVA), antiplatelet therapy, and anticoagulation, type of coronary angiography intervention and in-hospital complications.

Statistical analysis

For the analysis of the data, we used the statistical package IBM SPSS® V.21 licensed from CES University; a p-value less than 0.05 was defined as significant. The population's sociodemographic and clinical characteristics *(Table 1)* are represented using descriptive statistics, describing the prevalence of personal medical history in the study population. For bivariate analysis, we performed a comparison of related samples using the t-Student test for related samples. Also, We carried out a stratified analysis by gender, since the dependent variable defined as an Optimal Force for Instrumental Activities of Daily Living (OFIADL), taken from the disability criteria of the Instrumental Activities of Daily Living (IADL),[19] establishes different reference values between men and women as follows: for women, the optimal grip strength of the hand > 16 kg, and for men > 28.7 kg. Measures below this value: the patients present a functional impairment to daily living activities such as cooking, cleaning, laundry, transportation, and financial management.[19]

RESULTS

We included 77 patients, 48.1% women, and 51.9% men; the patients' median age was 66 years (58-72). In total, 14.3% of the patients undergoing coronary arteriography via radial access had a history of cardiac catheterization due to coronary disease performed via femoral access. Other sociodemographic characteristics and background are described in *(Table 1)*.

For the analysis of handgrip strength, we included all the patients, where a loss of handgrip strength was found in the hand of the access after catheterization. The average of strength before and after the procedure was 24.16 ± 7.57, 21.32 ± 7.90, respectively. We performed the follow-up for handgrip strength at least 30 days after the procedure (95% CI 1.59-4.07, $p < 0.05$).

Table 1: Sociodemographic and clinical characteristics N = 77.

Characteristics	Radial access, n (%)
Male	40 (51.9)
Female	37 (48.1)
History	
Hypertension	54 (70.1)
Diabetes mellitus	18 (23.4)
Dyslipidemia	45 (58.4)
Chronic kidney disease	5 (6.5)
Smoking	15 (19.5)
Stroke	2 (2.6)

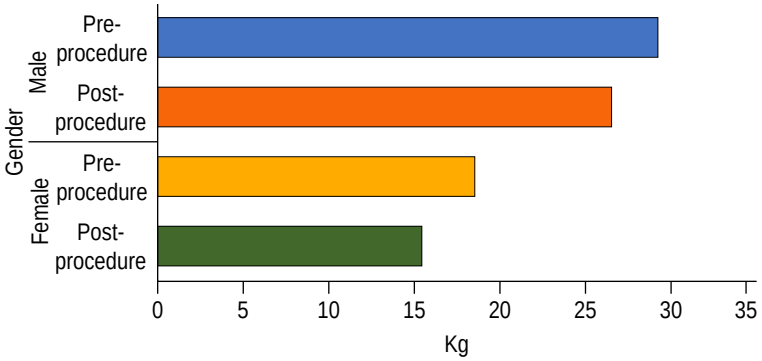

Figure 1: Loss of handgrip strength stratified by gender before the procedure, and after one-month follow-up. Results are expressed as mean ± standard error mean.

In the analysis stratified by gender, the mean handgrip strength before catheterization was higher than the optimal value for IADL compared to the post-coronary angiography handgrip strength for both genders *(Figure 1)*.

We defined the radial flow variable as permeable (presence of flow without any alteration) and flow alteration (no arterial flow, non-triphasic flow, intermittent flow). When distributed by gender, female patients had 83.8% arterial permeability after the procedure and men 77.5%.

We constructed the dependent variable optimal handgrip strength for the bivariate analysis considering the IADL criteria that establish cut-points of 16 kg for women and 28.7 kg for men.[19] We compared this variable with the radial flow, personal medical history, and type of intervention. We observed an interesting finding, where having a history of hypertension is the only statistically significant variable related to the loss of handgrip strength after radial access *(Table 2)*.

Regarding vascular complications other than loss of handgrip strength and alteration of arterial flow, we found one patient with perioperative stroke, one patient with unsuccessful angioplasty, and one patient with an immediate complication of arrhythmia (ventricular fibrillation). However, 74% did not report any type of vascular complication ($p > 0.05$).

DISCUSSION

The most critical finding in the study was the loss of handgrip strength after one month of follow-up, in patients undergoing coronary arteriography via radial access with ACS diagnosis. This compromise was only related to the procedure's performance since neither the past medical history nor the compromise of vascular flow impacted. The only remarkable variable was hypertension suggesting that it could play a role in optimal handgrip strength. It could be related to the use of arterial vasodilators in hypertensive patients.[18,20] However, studies with higher statistical power are required to confirm this finding. The loss of handgrip strength after an angiography is relevant, given that there is currently limited information, and after a search in databases such as PubMed and Ovid, no publication was found that has studied this phenomenon in the long term, specifically in patients with ACS.

Studies such as ARCUS and HANGAR are the most relevant in measuring the loss of handgrip strength; however, both studies were performed in populations undergoing coronary arteriography, not necessarily with ACS diagnosis, unlike our study.[14,21] An interim ARCUS report, with a sample of 191 patients, showed upper limb dysfunction. However, the methodology used in this study differs from ours since they are based on questionnaire-type scales.[21] On the other hand, when measuring the handgrip strength with a dynamometer, no loss of this was demonstrated, since they used percentages instead of absolute values of the scales proposed by the ASTH. Contrary to what we did in our study, absolute values were used and showed a decrease of handgrip strength in the general population and the same way in the distribution by gender. Additionally, the HANGAR study showed a loss of handgrip strength the day after coronary arteriography. However, in the 30-day follow-up, the handgrip strength returned to its baseline state, unlike our study, where the loss was evident 30 days after the procedure. However, the HANGAR study population was limited only to elective patients with chronic unstable angina.

When analyzing the clinical importance of handgrip strength loss, there was no clear consensus for the objective measurement in the post-procedure setting. Moreover, the scales available for evaluating upper limb dysfunction have little sensitivity and are highly

dependent on subjective standards, making it challenging to apply them in other studies.[21,22] Additionally, even though there are tools such as the hydraulic dynamometer to standardized guidelines for an objective measurement of handgrip strength loss,[22,23] the definitions are inconclusive about a clinically significant loss of strength is. The scales used for strength classification are not satisfactory for different patients (including category or specification by gender, age, and profession) in the clinical setting after coronary arteriography with radial access.[21,22] After a literature review, we decided to use the disability criteria for IADL,[19] which was initially used to assess handgrip strength loss in patients with sarcopenia. Based on these criteria, we found that the loss of handgrip strength in the analyzed patients translates into a compromise to perform daily living activities in both men and women, representing an essential adverse event since it negatively impacts performance and the fine motor capacity of the upper limb. Thus, leading to an alteration in the performance of specific activities that require this function, such as painting, playing the piano, sculpting, and daily living activities such as cooking, driving, dressing, among others.[24]

Table 2: Optimal handgrip strength.

Variables	Optimal handgrip strength, n (%)		
	Yes	No	p
Gender			
Female	17 (45.9)	20 (54.1)	0.934
Male	18 (45.0)	22 (55.0)	
Cardiac catheterization history			
Yes	3 (27.27)	8 (72.73)	0.191
No	32 (48.48)	34 (51.52)	
Hypertension history			
Yes	19 (35.19)	35 (64.81)	0.006
No	16 (69.57)	7 (30.43)	
Diabetes mellitus history			
Yes	8 (44.44)	10 (55.56)	0.922
No	27 (45.76)	32 (54.24)	
Dyslipidemia history			
Yes	20 (44.44)	25 (55.56)	0.833
No	15 (46.88)	17 (53.13)	
CKD history			
Yes	2 (40.00)	3 (60.00)	0.800
No	33 (45.83)	39 (54.17)	
CAD history			
Yes	4 (33.33)	8 (66.67)	0.359
No	31 (47.69)	34 (52.31)	
Smoking history			
Yes	19 (46.34)	22 (53.66)	0.868
No	16 (44.44)	20 (55.56)	
Type of intervention			
Conventional stent	0 (0)	0 (0)	
Drug eluding stent	15 (50)	15 (50)	
Balloon angioplasty without stent	0 (0)	2 (100)	0.380
None	20 (44.44)	25 (55.56)	
Radial flow permeability (by echography)			
Permeable	26 (41.94)	36 (58.06)	0.207
Flow alteration	9 (60.00)	6 (40.00)	

CKD = chronic kidney disease, CAD = coronary acute disease.

Handgrip strength must always be related to different sociodemographic characteristics. Some of these significantly impact their measures, such as age with an indirect relationship, gender differentiation where women have lower values than men, as we demonstrated in the results, which is consistent with other studies,[23,25] and evidences a pattern of behavior that is always maintained.[26]

Although radial flow obstruction has been described as one of the leading vascular complications after coronary arteriography through the radial route with incidences of up to 30%,[26,27] in our study, this was not evidenced as one of the main complications (2.6%) and nor did it show a statistically significant relationship with loss of handgrip strength, which is consistent with important studies such as HANGAR.

Loss of handgrip strength has a significant impact at the systemic level since it is a simple but powerful predictor of future disability, morbidity, and mortality. This was demonstrated in the PURE study, where they found that loss of handgrip strength was related to cardiovascular and non-cardiovascular mortality and the occurrence of cardio-metabolic diseases.[28,29] It is essential to begin identifying which patients may be at increased risk of developing clinically significant loss of handgrip strength following radial coronary arteriography. A consistent

approach might be to try targeting patients with low baseline handgrip strength, patients with neuromuscular diseases, those older than 65 years,[25] and racial groups such as Latinos and Asians could fall into this category.[23]

It is of great importance to recognize this type of complication at an early stage since people with limited mobility and impaired strength can benefit from preventive programs.[27,30] Also, this generates the need to create scales with scores that assess the risks before and after treatment, impact patients' lifestyle, and the performance of their work activities and daily life.

CONCLUSIONS

For this study, loss of grip strength as a measure of functionality and with an optimal strength cut-off point for IADL, there was a significant loss in both genders, with lower values that can even affect daily living activities. According to the study, loss of grip strength is inherent to the procedure and is not dependent on history or related to post-procedure radial flow. Further studies are required to assess the consequences of this loss of grip strength in patients undergoing coronary arteriography and to assess whether patients who require fine upper limb skills for work activities benefit from other vascular access.

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Transthyretin cardiac amyloidosis with an unusual clinical presentation: dilated cardiomyopathy

Amiloidosis cardiaca por transtiretina con una presentación clínica atípica: miocardiopatía dilatada

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Keywords:
Cardiomyopathy, dilated, amyloidosis, transthyretin, case report, heart failure.

Palabras clave:
Miocardiopatía, dilatada, amiloidosis, transtiretina, reporte de caso, insuficiencia cardiaca.

ABSTRACT

Transthyretin amyloid (ATTR) cardiomyopathy is an underdiagnosed clinical entity. The low awareness of the disease prevalence, the variability of its clinical presentation and the tissue biopsy histopathological-based diagnosis are the main reasons for its underdiagnosis. The recent development of specific therapies makes the celerity in the diagnosis and its characterization especially important in order to initiate an early treatment in selected variants. In most cases, its clinical manifestation is as congestive heart failure (HF), and echocardiographic studies show a hypertrophic, restrictive, non-compliant, non-dilated left ventricle. In this clinical case, we report an 85-year-old patient who had a first HF episode and whose echocardiogram revealed a dilated cardiomyopathy (DCM). After the study with MRI, bone scintigraphy and catheterization, the diagnosis of ATTR amyloidosis was achieved. ATTR should be included in the differential diagnosis of idiopathic DCM, especially in the elderly.

RESUMEN

La amiloidosis cardiaca por transtiretina (ATTR) es una entidad subdiagnosticada. Los principales motivos del infradiagnóstico son la baja percepción de la prevalencia de la enfermedad, la variabilidad de las formas de presentación clínica y la indicación de diagnóstico histopatológico basado en biopsia tisular. Ante los nuevos tratamientos dirigidos contra esta patología es de especial relevancia la rapidez en el diagnóstico y la caracterización del mismo para iniciar tratamientos precoces en algunas variantes. En la mayoría de casos la presentación inicial es con datos de insuficiencia cardiaca (IC) y el estudio ecocardiográfico muestra un ventrículo izquierdo hipertrófico, restrictivo, no distensible y no dilatado. En este caso clínico se describe un paciente de 85 años con datos de IC como manifestación inicial y cuyo ecocardiograma pone en evidencia una miocardiopatía dilatada (MCD). Tras el estudio con resonancia magnética, gammagrafía ósea, cateterismo cardiaco y estudios laboratoriales se llega al diagnóstico de miocardiopatía por ATTR. La amiloidosis cardiaca por ATTR debería ser incluida en el diagnóstico diferencial de la MCD, especialmente en pacientes ancianos.

INTRODUCTION

Dilated cardiomyopathy (DCM) etiological diagnosis is usually characterized as ischaemic and non-ischaemic. The non-ischaemic group requires a wide differential diagnosis based on echocardiography, gadolinium enhanced CMR, nuclear medicine techniques and even histological analysis to accomplish a definitive aetiologic diagnosis. Non-ischaemic DCM can be caused by genetic mutations, myocarditis/other systemic infections, hormonal or electrolyte disturbances and syndromic, neuromuscular or auto-inmune diseases.[1] Infiltrative diseases are not a common cause of DCM, although some end-stage disorders can manifest as this phenotype. Cardiac amyloidosis is probably one of the most common causes of infiltrative heart disease. Necropsy studies show myocardium amyloid deposits in 25% of octogenarians. In fact, ATTR is the main amyloid found in cardiac senile amyloidosis. Classically, cardiac amyloid disease clinical expression is a congestive heart failure

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with preserved ejection fraction with imaging studies disclosing a non-dilated, hypertrophic, restrictive, non-compliant left ventricle.[2] However, several publications refer to different, less common morphological patterns that this disease may show.[3] In this case report, we describe DCM as an initial presentation of cardiac senile amyloidosis.

CASE PRESENTATION

We report the case of an 85-year-old man who attended the emergency department due to dyspnea. His personal history included systemic hypertension treated with enalapril, a non-producing adrenal angiomyolipoma and a very active lifestyle.

The patient reported eight days of progressive dyspnea and the appearance of lower extremities edema. He denied chest pain, syncope or palpitations.

Upon arrival, his blood pressure was 106/62 mmHg, pulse rate 110 bpm and SaO_2 96%. No neck vein distension was observed, on physical examination, the precordial area with a rhythmic heartbeat at 110 bpm, no murmurs, clicks or gallop sounds. He had crackled in both lung bases. Abdomen without ascites or congestive hepatomegaly, he had bilateral perimaleolar edema. An electrocardiogram showed an atrial flutter with 2:1 AV conduction and the ventricular rate at 110 bpm without QRS-ST-T wave abnormalities. The blood analysis showed a NT-proBNP at 2,513 pg/mL, the remaining routine blood chemistry, serum electrolytes, and blood cell count were in the normal range. Chest X-ray disclosed cardiomegaly, increased vascular markings related to blood flow redistribution and pleural fluid related blunting of the costophrenic angles.

Congestive HF was diagnosed, and he began with intravenous loop diuretics, heart rate control with beta blocker, and anticoagulation with apixaban.

During his hospitalization congestive signs decreased, atrial flutter persisted with a well-controlled heart rate with low doses of bisoprolol and a mean ventricular rate around 60-75 bpm.

A transthoracic echocardiogram revealed a dilated left ventricle with end-diastolic diameter 60 mm, mild to moderate septal hypertrophy and severely depressed systolic function (20% LVEF by Simpson) due to global hypokinesia. He also had biatrial dilatation, a severely dilated right ventricle with depressed systolic function, mild regurgitation of the four heart valves, mild pulmonary hypertension and dilated inferior cava vein. A cardiovascular magnetic resonance (CMR) showed biventricular dilatation and systolic dysfunction *(Figure 1A)*. High native T1 values (1304 milliseconds) and an increase in extracellular volume (40 with a 43.2% hematocryte) were reported and T1 PSIR sequences disclosed epicardic mid inferolateral, inferoseptal, subendocardial anterior and anterolateral late gadolinium enhancement *(Figure 1B)*. These findings were

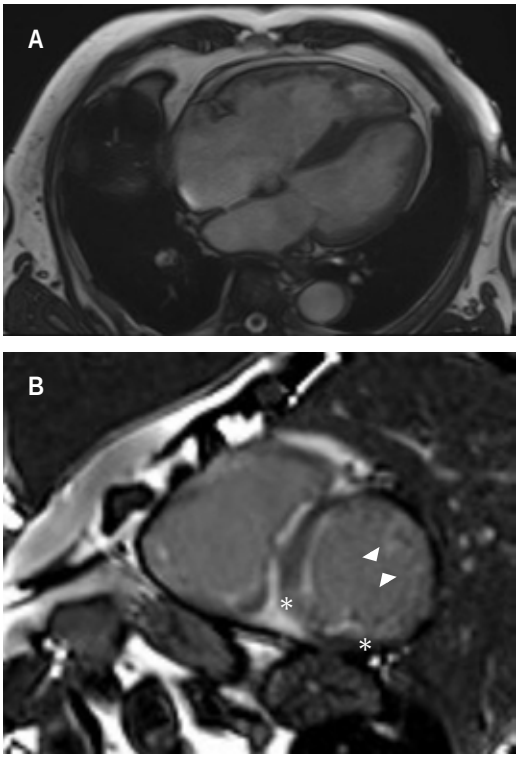

Figure 1: Cardio magnetic resonance. **A)** Four chamber view in a cine sequence frame with biventricular dilatation (telediastolic left ventricle normalized volume 151mL/m^2, right ventricle 110 mL/m^2) and septal moderate to severe hypertrophy. **B)** Short axis view in a late gadolinium enhancement T1 PSIR sequence. Epicardic mid inferolateral and inferoseptal (*) and subendocardial anterior and anterolateral (tips of the arrows) late gadolinium enhancement.

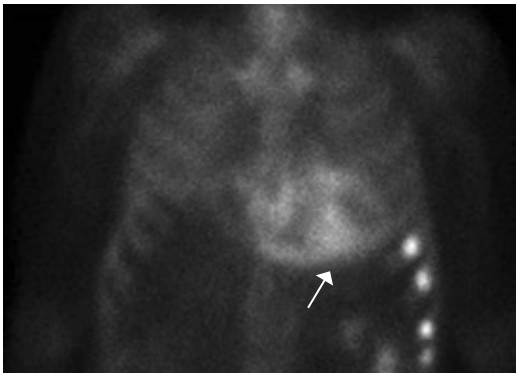

Figure 2: 99mTc-DPD scintigraphy: intense cardiac uptake (arrow) of the radiotracer is observed in both ventricles (Perugini score 3), with mild diffuse bone uptake that is higher in the broken left ribs.

compatible with infiltrative cardiomyopathy and suggestive of cardiac amyloidosis. At this point, a 99mTc-DPD bone scintigraphy, a blood and urine analysis to evaluate a possible monoclonal component -according to the latest recommendations on the diagnosis of cardiac amyloidosis[4] and cardiac catheterization were requested. ATTR cardiomyopathy compatible images were reported in the scintigraphy with a significant Perugini grade 3 heart uptake of the radiotracer *(Figure 2)*. The coronary angiography showed only mild irregularities in the left anterior descending and circumflex coronary arteries without significant obstructive lesions. The search for light chain immunoglobulin monoclonal gammopathy was negative, AL amyloid heart disease was ruled out, so ATTR cardiomyopathy was diagnosed.

A genetic study for ATTR gene variant mutation was negative, so he was diagnosed as wild type ATTR amyloid heart disease. The heart failure unit evaluated him for education on nutritional measures. After introducing low beta-blocker doses, he maintained good blood pressure control. ACEI was discontinued, and he was discharged without congestive signs, with appropriate heart rate control, diuretics and anticoagulant treatment.

DISCUSSION

Complementary tests are essential in the characterization of a congestive heart failure episode. Echocardiography is the most available tool, and it usually guides the diagnosis. In this particular case, echocardiographic images led to a DCM working diagnosis. In patients with a new onset of heart failure and DCM European guidelines suggest CMR with late gadolinium enhancement is a valuable test.[5] It can provide information about potential ischaemic or non-ischaemic etiology and guide the differential diagnosis of non-ischaemic causes. In this case report, the CMR gave important clues toward the correct diagnosis of infiltrative amyloid cardiac disease (hypertrophy, compatible enhancement, high extracellular volume and native T1 values). Besides, the absence of monoclonal light chain immunoglobulin and the evident Perugini grade 3 radiotracer uptake in the scintigraphy provided the ATTR cardiomyopathy definitive diagnosis without endomyocardial biopsy.[4]

Classical ATTR cardiomyopathy usually has clinical manifestations hypotension with systemic venous hypertension, low voltage QRS and pseudoinfarction pattern on the electrocardiogram, and discordance between low ECG QRS/severe left ventricle hypertrophy in echocardiogram, with a normal or small restrictive LV with preserved ejection fraction.

However, the heterogeneity in the presentation of this heart disease is widely described in the literature. In 2017, the European Society of Cardiology published a document that was focused on this clinical morphological and phenotypic presentation variability of cardiac amyloid disease.[3] In its supplementary data, values such as left ventricle end-diastolic diameters showed statistically significant differences between subgroups of the different countries involved in the study. We should recognize that non-dilatation is not such an indispensable morphological feature of this not so infrequent infiltrative heart disease with the data mentioned above.

CONCLUSIONS

In this clinical case a diagnosis of cardiac ATTR amyloidosis is established in a patient who is affected by a DCM. It is not the only case in the literature,[6] but because of its atypical presentation, its recognition is

infrequent. We consider this case report is important for several reasons. (a) Because it underlines that the proactive search of the non-ischaemic DCM aetiology with late gadolinium enhancement CMR, nuclear medicine techniques and special blood test to rule out systemic diseases are essential and entail prognostic and therapeutic value. (b) Because it shows the heterogeneity of cardiac amyloidosis morphologic expression. It can appear even with left ventricular dilatation and contractile dysfunction, which is very different and quite the opposite of the typical-classical echocardiographic presentation. Although some infiltrative diseases such as hemochromatosis might show ventricle dilatation in end-stages in the elderly, it is particularly uncommon to find this phenotype of DCM as the first manifestation in amyloid cardiomyopathy. (c) Cardiac ATTR amyloidosis is not included in the differential diagnosis of idiopathic DCM in the latest consensus documents.[1] Perhaps, in view of the recently new disease-modifying therapies for ATTR amyloidosis in early-stage disease, and the relatively common finding of cardiac amyloid in necropsy studies in octogenarians, the propagation of cases with this atypical clinical phenotype supports it should be included in subsequent reviews or consensus documents.

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Isolated congenital left ventricular diverticulum in adult: an unusual finding in a cocaine-associated myocardial infarction

Divertículo ventricular congénito izquierdo aislado en adulto: un hallazgo inusual en infarto de miocardio asociado a cocaína

Rafael Pedraza-Jiménez,* José Martín Alanís-Naranjo,‡ Martha Morelos-Guzmán§

Keywords:
Left ventricular diverticulum, isolated ventricular diverticulum, myocardial infarction, adult, coronary computed tomography angiography, cocaine use.

Palabras clave:
Divertículo ventricular izquierdo, divertículo ventricular aislado, infarto al miocardio, adulto, angiografía coronaria por tomografía computarizada, consumo de cocaína.

ABSTRACT

Congenital left ventricular diverticulum (CLVD) consists of an out-pouching of endocardium, myocardium, and pericardium, which often presents as a projection from the ventricular free wall, with a narrow neck connecting the cavity to the ventricle proper. Although it is often associated with other cardiac and extracardiac congenital anomalies, it may also present alone, as an incidental finding in adult patients. Due to its low overall prevalence and variability in presentation, a standardized treatment has yet to be delineated. We present the case of an adult patient with cocaine-associated myocardial infarction (MI), in which a septal CLVD was revealed by coronary computed tomography (CT) angiography. Other cardiac anomalies were ruled out and, the patient responded well to medical treatment after cardiac catheterization; thus, medical follow-up was preferred and did not surgery.

RESUMEN

El divertículo ventricular congénito izquierdo (DVCI) consiste en una bolsa de salida de endocardio, miocardio y pericardio, que a menudo se presenta como una proyección de la pared libre del ventrículo, con un cuello estrecho que conecta la cavidad con el ventrículo propiamente dicho. Aunque a menudo se asocia con otras anomalías congénitas cardiacas y extracardiacas, también puede presentarse solo, como un hallazgo incidental en pacientes adultos. Debido a su baja prevalencia general y variabilidad en la presentación, aún no se ha definido un tratamiento estandarizado. Presentamos el caso de un paciente adulto con infarto de miocardio (IM) asociado a cocaína, en el que se evidenció un DVCI septal mediante angio-TC coronaria. Se descartaron otras anomalías cardiacas y el paciente respondió bien al tratamiento médico tras el cateterismo cardiaco; por lo que se prefirió el seguimiento médico y no la cirugía.

INTRODUCTION

Congenital left ventricular diverticulum (CLVD) consists of an out-pouching of endocardium, myocardium, and pericardium, which often presents as a projection from the ventricular free wall, with a narrow neck connecting the cavity to the ventricle proper.[1] Although it is often associated with other cardiac and extracardiac congenital anomalies, it may also present alone, as an incidental finding in adult patients.[2] Due to its composition of normal cardiac tissue, as compared to a congenital left ventricular aneurysm (CLVA), the diverticulum contracts synchronously with the ventricle's remainder. Thromboembolic events, ventricular arrhythmias, heart failure, and free wall rupture have been documented to occur. Due to its low overall prevalence between 0.02% and 0.76%, and variability in presentation, a standardized treatment has yet to be delineated.[3] We present the case of an adult patient with cocaine-associated myocardial infarction (MI), in which a septal CLVD was revealed by coronary computed tomography (CT) angiography.

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CASE PRESENTATION

A 42-year-old male with a history of cocaine use presented to the hospital with progressive retrosternal chest pain, diaphoresis, and nausea. He associated symptoms after «snorting» approximately 3 grams of cocaine over the last two days.

On examination, his heart rate was 115 bpm. There was no respiratory distress with normal heart and respiratory sounds. The initial 12-lead electrocardiogram (ECG) showed an inversion of T wave in leads V2-V5 with an elevation of ST-segment of 2 mm in leads V2-V4 *(Figure 1)*. Blood tests were notable for elevated troponin of 16,000 ng/L. A transthoracic echocardiogram revealed akinesia in the apical segments, a left ventricular ejection fraction of 35%, and a pericardial effusion of 3 mm.

A coronary CT angiography with dipyridamole stress test produced a calcium score of 0 Agatston Units; however, it revealed a 10 mm length non-calcified occlusive plaque at the proximal portion of the left anterior descending artery and pericardial effusion at right cavities *(Figure 2)*.

Also, CT revealed a left ventricular out-pouching of 1.8 × 2 cm (longitudinal and transverse diameter, respectively). A neck diameter of 6 mm, arising from the septal wall, adjacent to the occlusive plaque with contraction relative to the left chamber *(Figure 3)*.

Based on these findings, he was diagnosed as having a cocaine-associated MI and CLVD. The patient underwent cardiac catheterization, with the left anterior descending artery's immediate blood flow after balloon dilation *(Figure 4)*. Medical treatment controlled his symptoms, and he was discharged symptom-free. He continued follow-up at cardiology and cardiothoracic surgery units.

At the one and two-year follow-up, the patient continued asymptomatic. Follow-up echocardiograms showed a left ventricular ejection fraction of 65% with no pericardial effusion and CT with no changes in the size of the CLVD.

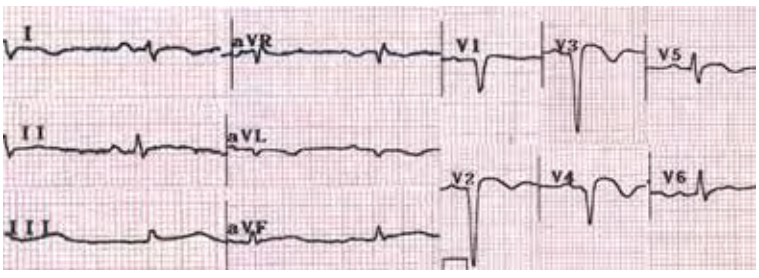

Figure 1: Initial 12-lead electrocardiogram: inversion of T wave in leads V2-V5 with an elevation of ST-segment of 2 mm in leads V2-V4 (anteroseptal necrosis).

DISCUSSION

CLVD is a rare and usually asymptomatic cardiac malformation. It frequently accompanies other cardiac abnormalities, and it is most commonly diagnosed during early childhood. About 30% of all cases are not associated with a congenital malformation, and they are defined as isolated CLVD. It is frequently challenging to diagnose CLVD because of its asymptomaticity.[4]

The differential diagnosis of left ventricular out-pouchings includes aneurysm, pseudoaneurysm, and diverticulum. According to Marijon et al., CLVD and aneurysm represent two distinct entities with different histological and morphologic characteristics and outcomes. The diverticulum is characterized by synchronal contractility and three myocardial layers on histological examination. There are two subtypes of CLVD: apical type cases are always associated with other cardiac anomalies or midline thoracoabdominal defects, whereas non apical type cases occur in isolation.[5]

According to structural characteristics of the wall, CLVD can be classified as muscular or fibrous. Fibrous CLVD consists mainly of fibrous tissue with few or no muscle fibers. The muscular type of CLVD must be distinguished from LV noncompaction, characterized by a prominent trabecular meshwork with a distinctly spongy appearance and deep intertrabecular recesses believed to be caused by an arrest in normal embryogenesis. When the CLVD is associated with congenital anomalies of the thoracic and abdominal midline, diaphragmatic and sternal defects, and partial absence of the inferoapical pericardium, this scenario is called syndrome or pentalogy of Cantrell.[4] CLVA represents the other end of the spectrum, whereby the out-pouching is dyskinetic or altogether akinetic

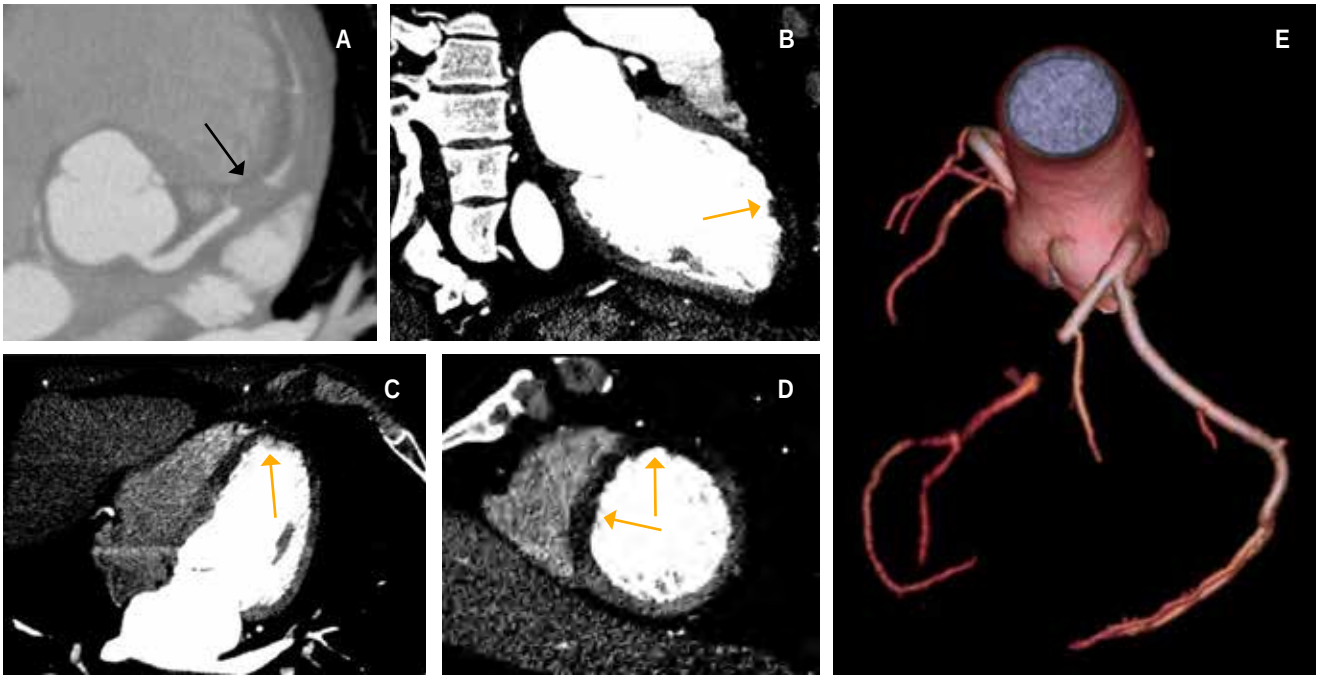

Figure 2: Coronary computed tomography angiography. **A)** Non-calcified occlusive plaque in the proximal third of the left anterior descending artery (arrow). **B)** Two-chamber view: perfusion defect in the anterior wall during the stress test (arrow). **C)** Four-chamber view: perfusion defect in the septal and lateral wall at middle and apical segments (arrow). **D)** Two-chamber view: perfusion defect in the anterior, anteroseptal and inferoseptal surfaces at the mid-segment (arrow). **E)** 3D reconstruction of coronary arteries: Total occlusion of the left anterior descending artery.

and histologically composed of fibrous tissue, dissimilar to that of the ventricular wall.[6]

CLVD is often clinically silent but may be associated with systemic embolism, arrhythmias, heart failure, myocardial ischemia, and cardiac rupture.[7] There are few reports in the literature of an isolated CLVD presenting as myocardial ischemia. However, this patient was asymptomatic for many years and presented to the hospital with chest pain due to cocaine-associated MI.

Mechanisms of acute MI resulting from cocaine use are multifactorial. At low doses, cocaine-induced sympathetic effects increase heart rate, blood pressure, and myocardial contractibility, leading to increased myocardial oxygen demand. Cocaine also enhances coronary spasm/vasoconstriction and platelet adherence/thrombosis, leading to the reduced myocardial oxygen supply. Thus, an imbalance between oxygen supply and demand results in MI. At high doses, cocaine-induced local anesthesia results in decreased left ventricular contractibility and prolonged QRS and QT intervals in electrocardiograms by blocking sodium transport and norepinephrine uptake in the myocardium. In vessels, cocaine contributes to MI by increasing endothelin-1 and reducing nitric oxide production in endothelial cells. When vessels are stressed, acute damages/ruptures can occur, promoting thrombosis by increasing platelet activity/aggregation and elevating fibrinogen levels and plasminogen activator inhibitor activity. These cellular and molecular cascades result in reduced cardiac blood flow, leading to acute MI and possibly atherosclerosis and coronary thrombosis in the long term. As such, cocaine induces acute MI by directly affecting myocardial tissues in the heart and indirectly enhancing thrombosis in vessels.[8] In this patient, the abnormal distribution of vessels due to septal CLVD and the effects of cocaine use could be the triggers of the myocardial infarction.

Diagnosis of CLVD can be made by echocardiography, computed tomography

angiography, magnetic resonance imaging, and cineangiography.[7] Ventriculography (95.5%), CT (88.9%), CMR (84.2%), and echocardiography (78.2%) are all sensitive tools for diagnosing CLVD.[9] Because of the patient´s clinical features, ECG, and enzyme changes, it was felt at first that this represented a cocaine-associated MI. For further evaluation, transthoracic echocardiography, coronary CT angiography, and cardiac catheterization were performed. Transthoracic echocardiography showed no ventricular pouch. Coronary CT angiography revealed abnormal coronary arteries with a left ventricular out-pouching arising from the septal wall. The pouch showed contraction relative to the main chamber, as the findings reported in ventricular diverticulum cases.

The incidence of adverse events in symptomatic patients with CLVD is increased during long-term follow-up.[7] In a review of 809 patients published since 1816 with either CLVD or CLVA, 4.5% of patients with CLVD were found to have an episode of rupture, and a 5% reported cardiac death rate. Other significant complications included ventricular tachycardia/fibrillation in 13.1%, embolic events 3.6%, and syncope 5.1%.[10]

Because of the inadequate data for universal guidance, management of CLVD remains unclear, and treatment options include close observation and surgery. Surgical removal should be considered based on the localization of the lesion and associated symptoms. Unfavorable anatomy of the diverticulum and patient's reluctance to undergo surgery adjudicated in favor of conservative management.[11]

Despite a concise review of the cases reported to date, there is little in the way of a detailed surgical approach. Some authors reported closure of the diverticulum neck with a patch, surgical glue closure, and plication with aneurysmorrhaphy. Other authors have described their technique as suture reapproximation in a double-layered fashion with the use of felt. In contrast, some describe the removal of the out-pouching cavity and closure with an *in-situ* patch. In 2020, Mejia J et al. reported a successful repair of a CLVD in an adult using a two-patch technique.[3]

Poor prognoses, including high mortality and morbidity, have been reported in infants and children with comorbid defects, and serious complications associated with CLVD include arrhythmias, embolism, cardiac failure, and rupture. In contrast, more favorable clinical outcomes have been demonstrated, most notably in asymptomatic adult patients, which may depend on no significant comorbidity.[12] In this case, other cardiac anomalies were ruled out, and the patient responded well to medical treatment after cardiac catheterization; thus, medical follow-up was preferred and did not surgery.

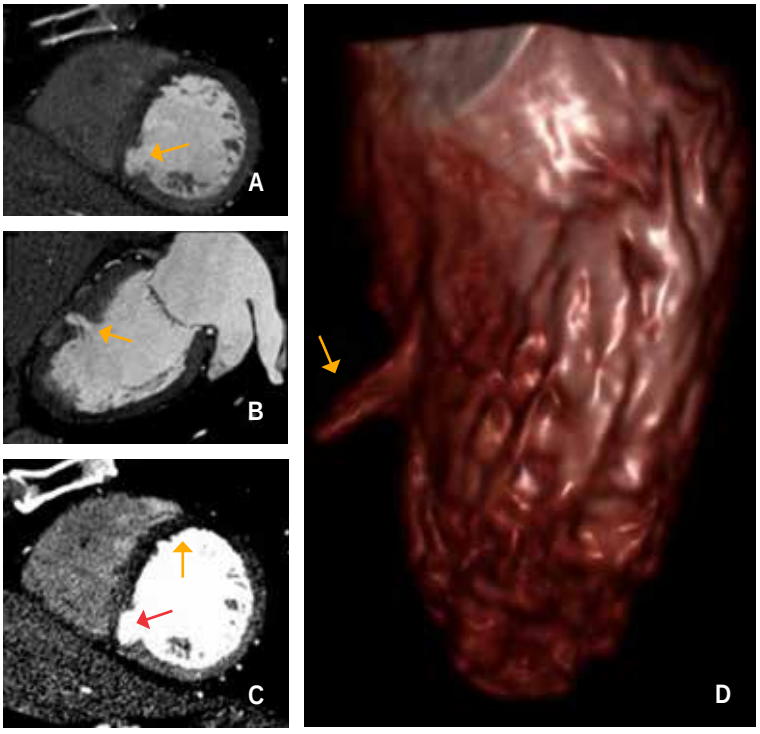

Figure 3: Coronary computed tomography angiography revealing a left ventricular diverticulum. **A & B)** Two-chamber view (arrow). **C)** Two-chamber view: Perfusion defect in the anterior and anteroseptal wall at the mid-segment (arrow). Ventricular diverticulum adjacent to ischemic myocardial tissue (red arrow). **D)** 3D reconstruction of left ventricular volume (arrow).

CONCLUSIONS

We present a patient with a rare cardiac malformation, with few cases documented in the literature. CLVD can simulate various heart diseases, and early diagnosis would be difficult due to a nonspecific clinical presentation.

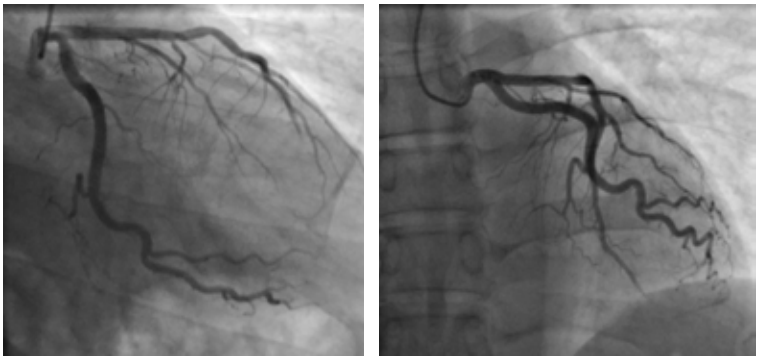

Figure 4: Cardiac catheterization showing blood flow of the left anterior descending artery after balloon dilation.

There are few reports in the literature of an isolated CLVD presenting as myocardial ischemia. The abnormal distribution of the coronary vessels due to septal CLVD and the effects of cocaine use could be the triggers of myocardial infarction in this patient. This case showed the importance of the cardiovascular imaging approach for the diagnosis of CLVD. Management remains unclear, and treatment options include close observation and surgery. Surgery in adults with isolated CLVD could be considered in symptomatic patients. The risks and prognosis of this malformation are challenging to assess due to its extremely low incidence. More studies are needed to determine the appropriate treatment.

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PERIODICA (Índice de Revistas Latinoamericanas en Ciencias) UNAM
http://periodica.unam.mx

Google Académico
http://scholar.google.com.mx/

Wissenschaftszentrum Berlin für Sozialforschung, Berlin WZB
http://rzblx1.uni-regensburg.de/ezeit/detail.phtml?bibid=WZB&colors=3&lang=de

Virtuelle Bibliothek Universität des Saarlandes, German
http://rzblx1.uni-regensburg.de/ezeit/search.phtml?bibid=SULB&colors=7&lang=de

University of South Australia. Library Catalogue
http://search.library.unisa.edu.au/az/a

Biblioteca electrónica de la Universidad de Heidelberg, Alemania
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Department of Library Services, Christian Medical College - Vellore
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TEPIC

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Segundo Curso :

"Riesgo Cardiovascular y Aterosclerosis: Actualización en el diagnóstico y tratamiento de las dislipidemias"

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Avales en trámite:
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Simposio Internacional ANCAM-SIAC:

"Manejo integral del paciente en prevención secundaria cardiovascular: un nuevo enfoque terapéutico"

20 de mayo de 2021

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Avales en trámite:
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2° Foro Nacional de Hipertensión ANCAM/GREHTA

28 y 29 de mayo de 2021

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13° Conferencia Científica Anual sobre Síndrome Metabólico

"Cardiometabolismo y Síndrome Metabólico"

CDMX

6 y 7 de agosto de 2021

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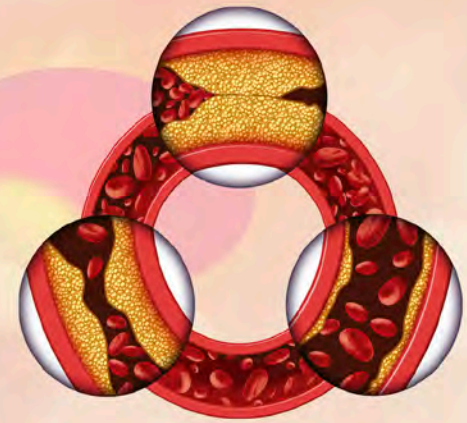

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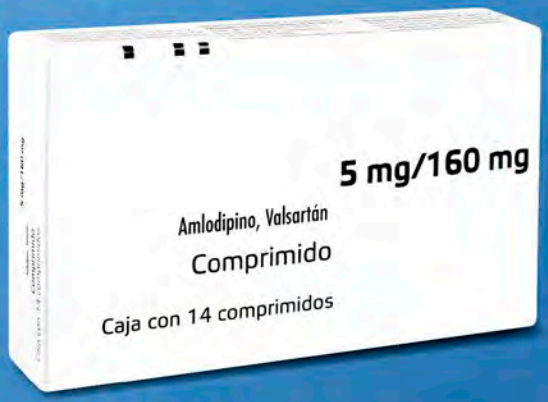

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