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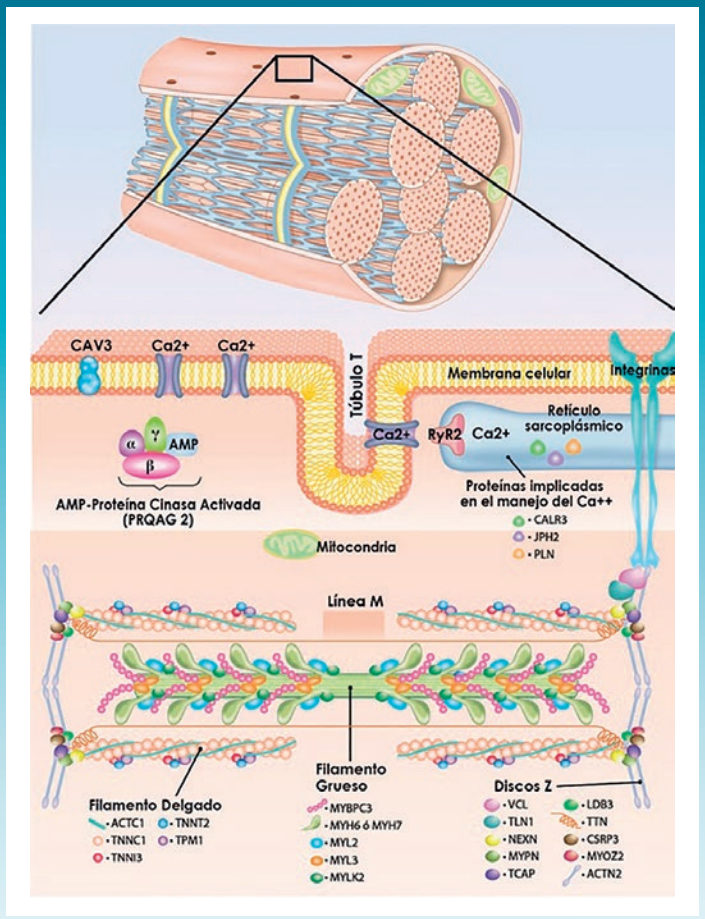

Figura 1. Sarcómero del músculo esquelético cardíaco. Se muestran las proteínas ubicadas en el sarcómero del músculo cardíaco y cuyas variantes patogénicas se relacionan con miocardiopatía hipertrófica primaria.

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Imagen portada: Figure 1. Congenital heart disease in adults. A: Chest X-ray showing snowman-shaped heart. B: Transthoracic echocardiogram from the suprasternal window showing vertical vein draining into the innominate vein. PA: posterioanterior projection; R: right side. Pp. 401.

Archivos de Cardiología de México

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SUMARIO

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EDITORIAL

Inauguración del XXXI Congreso Mexicano de Cardiología

Santiago de Querétaro, México, 2019

Inauguration of the XXXI Mexican Congress of Cardiology

*Dr. Pedro Iturralde Torres**

Presidente de la Sociedad Mexicana de Cardiología

Distinguida Ministra Secretaria de Gobernación Olga Sánchez Cordero, miembros de la Mesa de Honor, colegas cardiólogos, especialistas, enfermeras, invitados especiales, señoras y señores.

En nombre de la Junta de Gobierno de la Sociedad Mexicana de Cardiología 2018-2020, expreso cordialmente a todos los presentes la más afectuosa bienvenida a nuestro trigésimo primer Congreso Mexicano de Cardiología.

La Sociedad Mexicana de Cardiología cumplió 84 años de existencia y desde su nacimiento cada dos años congrega a sus miembros en sus congresos nacionales con el objetivo de difundir los conocimientos de los temas actuales de la Cardiología.

Cumplo gustosamente con el deber de recordar y rendir homenaje a nuestro fundador y presidente honorario, el maestro Ignacio Chávez, figura emblemática de la medicina, educación, cultura y humanismo en el siglo XX.

Nuestro reconocimiento a los expresidentes por su compromiso y dedicación para lograr el avance de nuestra Sociedad. Todos, en su momento, construyeron y consolidaron con su trabajo una plataforma académica muy sólida y de vanguardia científica.

«Los logros de una sociedad científica son la suma de las contribuciones de sus socios. Su proyección y alcance se fundamentan en el esfuerzo conjunto, en la unidad de miras y en la conjunción de voluntades.» Es así como la Sociedad continúa con su constante labor académica en beneficio de los cardiólogos mexicanos.

En México y en el mundo las enfermedades cardiovasculares representan la primera causa de muerte. El año pasado se reportaron 130,000 casos en el país, de las cuales 100,000 fueron por síndrome coronario agudo. Por lo tanto, causan más muertes que el cáncer.

Los factores de riesgo cardiovasculares más importantes son la obesidad y el sobrepeso, especialmente en niños, por lo que México ocupa el primer lugar en el mundo. La diabetes y la hipertensión arterial que sufren más de 30 millones de mexicanos, así como el aumento del colesterol, el tabaquismo y la vida sedentaria, han contribuido a que la tasa de mortalidad por infarto agudo de miocardio sea tres veces más alta que el promedio de los países de la Organización para la Cooperación y el Desarrollo Económico en pacientes mayores de 45 años, por lo que es imprescindible tomar medidas de prevención primaria para evitar que en la próximas décadas uno de cada dos mexicanos muera por enfermedades del corazón.

Esto implica un reto mundial y de ahí la importancia de la iniciativa «25 x 25» de la Federación Mundial del Corazón y la Organización Mundial de la Salud, que consiste en el compromiso de reducir en un 25% la mortalidad por enfermedades cardiovasculares para el año 2025. Aquí la importancia de las sociedades cardiológicas para que este proyecto tenga éxito.

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Durante el XXXI Congreso Mexicano de Cardiología contaremos con la participación de más de 400 prominentes profesores nacionales, todos ellos certificados por el consejo de especialidad correspondiente, y más de 100 excelentes profesores internacionales.

En conjunto con el congreso mexicano, se desarrollará simultáneamente el II Congreso Interamericano de Falla Cardiaca, con temas importantes y relevantes en las áreas de hipertensión pulmonar e insuficiencia cardiaca. Y también el III Congreso Mexicano de Rehabilitación Cardiovascular, Prevención y Cardiología del Deporte, que incluirá valiosos conceptos y destrezas que en la práctica diaria acompañarán al enfermo cardiópata durante su convalecencia hasta su reincorporación pronta e integral.

El programa académico consta de 426 horas, que conforman un total de 208 módulos con 537 sesiones, donde se incluyen todas las altas especialidades de la cardiología y enfermería distribuidas en sesiones plenarias, conferencias magistrales, simposias, mesas redondas, casos clínicos, debates y más de 80 horas de cursos precongreso, talleres y actividades sociales, culturales y deportivas.

Se desarrollarán más de 20 sesiones conjuntas con sociedades hermanas, como la Sociedad Interamericana de Cardiología, la Sociedad Española, la Sociedad Brasileña, la Sociedad y Federación Argentina, la Sociedad Paraguaya, el *American College of Cardiology*, la *American Heart Association* y la Sociedad Europea de Cardiología.

La conferencia de apertura del congreso lleva el título «Las estrategias de regeneración miocárdica», y será presentada por el Dr. Victor Dzau, Presidente de la Academia de Medicina de los Estados Unidos de América, quien nos honra con su presencia.

Diversas técnicas de intervencionismo coronario, estructural, de cardiopatías congénitas, cirugía cardiaca, electrofisiología e insuficiencia cardiaca, así como múltiples técnicas de imagen cardiovascular y enfermería cardiológica serán tratadas durante estos cuatro días por expertos que presentarán sus experiencias y las actualidades internacionales en dichos temas.

Constituye para todos nosotros un orgullo y un estímulo la presencia de 400 jóvenes médicos y residentes en cardiología que presentarán sus propios trabajos de investigación, con 389 presentaciones orales y 282 carteles electrónicos.

Todo ello en el marco de la emblemática ciudad de Santiago de Querétaro, que nos brinda su sede. El Estado de Querétaro está dotado de una riqueza natural y cultural que permite conocer nuestras raíces. Conserva cuatro patrimonios mundiales y seis «pueblos mágicos», y por su zona de monumentos en el centro histórico fue declarado en 1996 patrimonio cultural de la humanidad por la Organización de las Naciones Unidas para la Educación, la Ciencia y la Cultura.

Querétaro representa también el valioso pasado y el presente pujante. Valioso pasado porque ha sido protagonista en la historia de México en acontecimientos trascendentales, fue estratégica para las tropas durante la Guerra de Independencia y la Revolución Mexicana; y fue en el Gran Teatro de Iturbide, hoy Teatro de la República, un 5 de febrero, donde se firmó la Constitución de 1917.

Su presente es pujante porque se trata de una ciudad moderna y una de las ciudades con mayor crecimiento industrial de México. Hoy nos recibe con la hospitalidad que caracteriza a su gente y nos da la más cordial bienvenida.

«Los grupos de congresistas cambian, al igual que cambian las ciudades que nos brindan su sede. Pero el mensaje en su esencia sigue siendo el mismo. En la medida que refleja la verdad, su valor sigue inmutable. Por eso no importa que, en una forma o en otra, el mensaje se repita, si conserva la misma fuerza de realidad y de verdad.»

En palabras del maestro Chávez, «Un congreso científico cobra valor si asistimos a él dispuestos a someter nuestras ideas y nuestros hallazgos a la crítica de los demás, para beneficiarnos de ella. Un congreso debe ser un diálogo entre investigadores que buscan la verdad, una tribuna de discusiones con espíritu de honrada confrontación de ideas y con el ánimo abierto para admitir nuevas verdades.»

«La obligación primera de todo médico es saber cada día más para servir cada día mejor. De nada sirve que la medicina avance si los enfermos no pueden alcanzar sus beneficios. Las altas disciplinas científicas y el aprovechamiento de los grandes avances son para los enfermos su verdadera tabla de salvación y son además como el oxígeno del alma para los hombres que se consagran al cultivo de su conocimiento.»

El lema *(plus est en toi, plus est en vous)* «Hay más en ti» fue adoptado por el voto unánime de los miembros de la Sociedad Mexicana de Cardiología en 1979 por ser el lema de su fundador. Al adoptar su lema, los miembros de la Sociedad no solo afirman que tienen fe en el hombre y que creen en su destino. Se señala también una meta, se marca un ideal: la excelencia, que implica seguir la meta sin importar obstáculos y hacer caminos cuando no existan. Así pues, el ideal

de nuestra Sociedad es la excelencia en la ciencia y el humanismo.

La necesidad de enseñar, el deseo de compartir conocimientos y su experiencia, la pasión por aprender medicina y trasmitir lo aprendido fue lo que impulsó al Dr. Ignacio Chávez a ser un pedagogo ilustre, un forjador de programas de enseñanza, un director revolucionario en la facultad de medicina y un rector excepcional. Pero más que ello, lo convirtió en un guía, un ejemplo de la juventud, y le permitió labrar, pulir y formar personas superiores que son su mejor obra y la garantía plena de su trascendencia.

Ser médico, como lo enseñó el maestro, es el resultado de una vocación indeclinable, de un llamado interno que se acepta sin restricciones, de una manera total, absoluta y permanente.

En la conmemoración del cuadragésimo aniversario luctuoso del maestro Ignacio Chávez, que su memoria nos acompañe en nuestros congresos y que su espíritu viva siempre entre nosotros.

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ARTÍCULO DE INVESTIGACIÓN

Magnesium versus poly-L-lactic acid bioresorbable scaffolds: *in vivo* optical coherence tomography comparison of mechanical performance

Andamiajes bioresorbibles de magnesio versus poliméricos: comparación in vivo de su comportamiento mecánico por OCT

Rosa A. Abellás-Sequeiros[1,2], Raymundo Ocaranza-Sanchez[2], Carlos Galvaõ-Braga[3], Jorge Marques[3] y Carlos Gonzalez-Juanatey[2]*

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Abstract

Background: *Different mechanical properties have been suggested for metallic bioresorbable vascular scaffolds (BVS) in comparison to polymeric BVS. We aim to evaluate the acute mechanical performance of Magmaris® scaffold in comparison to Absorb®.* **Materials and Methods:** *Two groups of 10 coronary lesions treated with Magmaris® and Absorb® 1.1 (20584 vs. 21016 struts) were compared. In all cases, optical coherence tomographic (OCT) images were acquired after scaffold deployment. Baseline clinical, angiographic, and procedural characteristics were compared, including OCT evaluations.* **Results:** *No baseline clinical or angiographic significant differences were found between groups. The most common indication for revascularization was effort angina (60% vs. 70% p = 0.45) with no ST-elevation myocardial infarction (MI) cases. Main target artery was left anterior descending, with a mean vessel diameter of 3.46 ± 0.23 in Absorb® and 3.52 ± 0.19mm in Magmaris® groups (p = 0.56). All cases underwent pre- and post-dilatation with a procedural success rate of 100%. OCT analyses showed larger scaffold and vessel diameters in Magmaris® group: 3.11 ± 0.38 mm versus 3.07 ± 0.36 mm, p = 0.03 and 4.12 ± 0.51 mm versus 4.04 ± 0.46 mm, p = 0.04. Despite the application of slightly higher postdilatation pressures to Magmaris® devices (18.01 ± 2.15 vs. 17.20 ± 3.80 atm, p = 0.05), significantly lower percentages of disrupted and malapposed struts were identified within Magmaris® scaffolds (0.15% vs. 0.27%, p = 0.03 and 1.06% vs. 1.46% p = 0.01). No cardiac death, target vessel-related MI, or clinically driven target lesion revascularization was reported in a 30-day follow-up.* **Conclusion:** *Mechanical properties of Magmaris® scaffold allow achieving larger vessel and scaffold diameters in a safe manner, with lower rates of malapposition and scaffold disruption.*

Key words: *Bioresorbable scaffolds. Optical coherence tomography. Percutaneous coronary intervention. Magnesium scaffold.*

Resumen

Introducción: *Se ha sugerido la presencia de un distinto comportamiento mecánico entre los dos grupos principales de dispositivos bioresorbibles: metálicos y poliméricos. En este estudio evaluamos el comportamiento mecánico agudo del*

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andamiaje bioresorbible metálico Magmaris® frente al del polimérico Absorb®. **Métodos:** *Se compararon dos grupos de 10 lesiones coronarias tratadas con Magmaris® y Absorb® 1.1 (20584 vs. 21016 struts). En todos los casos se realizó estudio postimplante del dispositivo mediante tomografia de coherencia óptica (OCT). Se compararon las características basales clínicas y angiográficas, así como aspectos del procedimiento (incluídos los estudios de OCT) entre ambos grupos.* **Resultados:** *No se encontraron diferencias clínicas o angiográficas estadísticamente significativas entre ambos grupos. La indicación más frecuente de revascularización coronaria fué la presencia de angina de esfuerzo (60% vs. 70% p = 0.45), sin incluirse casos de IAMCEST. La arteria descendente anterior fué el principal vaso diana, con un diámetro medio de 3.46 ± 0.23 mm en el grupo de Absorb® y de 3.52 ± 0.19mm en el grupo de Magmaris® (p = 0.56). En todos los casos se realizó pre y postdilatación, con una tasa de éxito del procedimiento del 100%. Los estudios mediante OCT demostraron un mayor diámetro de stent y del vaso en el grupo de Magmaris®: 3.11 ± 0.38mm versus 3.07 ± 0.36 mm, p = 0.03 y 4.12 ± 0.51mm versus 4.04 ± 0.46mm, p = 0.04. A pesar de someter a los dispositivos Magmaris® a presiones de postdilatación ligeramente superiores (18.01 ± 2.15 vs. 17.20 ± 3.80 atm, p = 0.05), se identificó un menor porcentaje estadísticamente significativo de struts rotos o malapuestos en dicho grupo (0.15% vs. 0.27 %, p = 0.03 y 1.06 % vs. 1.46% p = 0.01). En un seguimiento a 30 días no se registraron eventos mayores: muerte cardíaca, IM relacionado con vaso diana o TLR.* **Conclusión:** *Las propiedades mecánicas del scaffold metálico bioresorbible Magmaris® permiten alcanzar mayores diámetros de stent y vaso de forma segura tras su implante, con una baja tasa de malaposición y disrupción.*

Palabras clave: *Andamiajes bioresorbibles. OCT. PCI. Scaffold de magnesio.*

Introduction and objective

Second-generation metallic drug-eluting stents (DESs) have become the first-line devices in percutaneous coronary intervention (PCI) thanks to lower rates of target lesion revascularization (TLR), stent thrombosis (ST), and major adverse cardiac events (MACE) when compared to simple angioplasty and bare metal stents[1]. Nevertheless, permanent caging of the vessel represents their main drawback. Bioresorbable vascular scaffolds (BVSs) appeared more than 10 years ago to avoid this problem. The first approved BVS was the Absorb® bioresorbable scaffolds (BRS) (Abbot Vascular, Santa Clara, California, USA) with an expected time to backbone resorption between 2 and 3 years due to PPLA hydrolysis[2]. To reduce this resorption process, Magmaris® scaffold (Biotronik AG, Bulach, Switzerland) was designed as the first non-polymeric scaffold, with a magnesium alloy backbone that can be completely degraded by 9-12 months after PCI[3]. Optimal expansion and apposition, with no significant scaffold disruption, have been demonstrated for Absorb® BVS immediately after PCI[4]; however, there is few evidence regarding Magmaris® acute performance after PCI.

Materials and methods

Study design and patient population

This study wants to evaluate the mechanical properties and performance of Magmaris® scaffold at baseline (immediately after PCI) in comparison to the most studied BVS: the Absorb 1.1® (Abbot Vascular, Santa Clara, California, USA). Within the global pool of patients admitted to PCI in our cath lab between November 2016 and October 2017, we looked for those who could benefit the most from metallic BRS[5]. According to this, 10 coronary lesions were treated with Magmaris® device in 10 different patients. Lesions considered as suitable for Magmaris® deployment included: *de novo* coronary lesions with a diameter between 2.5 and 3.5 mm and with none/mild calcification. Bifurcation lesions were also admitted, and there were no restrictions regarding PCI indication: stable angina and acute coronary syndrome were admitted. Left main disease (left main coronary artery disease [LMCD]) and ostial lesions were excluded, as well as chronic total occlusions or in-stent restenosis.

The clinical exclusion criteria included age > 75 years old, history or high risk of bleeding, heparin or antiplatelet treatments intolerance, and expected survival < 1 year.

On the other hand, 10 patients with 10 coronary lesions who had undergone PCI with at least one Absorb 1.1® BVS represented the control group. They were selected in a retrospective, blinded, non-randomized way from the total cohort of patients treated with Absorb® who had undergone intracoronary optical coherence tomography (OCT) evaluation at baseline. All indications for PCI had been admitted. The only angiographic exclusion criteria for this group had been: LMCD and lesions with diameters < 2.5 mm or > 4 mm. The aforementioned clinical exclusion criteria also applied to this group with the only exception of age.

Informed written consent was obtained in all cases.

Study devices

Ten coronary lesions were treated with Magmaris® scaffold and 10 lesions with Absorb 1.1® BVS. Even though Absorb® and Magmaris® are both of them BRS, important differences between their conformation and behavior must be highlighted. Magmaris® scaffold is the only available metallic BRS with CE approval. Its magnesium alloy backbone is completely coated by a bioresorbable polymeric layer of poly-L-lactic acid (PLLA) from which sirolimus antiproliferative drug is released[6]. The strut thickness is 150 μm[5]. On the contrary, Absorb® BVS is an everolimus-eluting polymeric BRS, with a PLLA backbone covered by a poy-D-lactic acid coating[2]. Absorb® strut thickness accounts to 156 μm[2]. Different mechanical properties have been described for these devices as, for example, higher tensile strength and elongation-to-break for Magmaris®[5]. Nevertheless, the main difference between them is the expected time to completely scaffold resorption: 9-12 months for Magmaris®[3,6] and 2-3 years for Absorb® BVS[2].

Procedure and OCT analyses

In our study, predilatation was mandatory for both groups. Semi-compliant balloons were used in a 1:1 balloon/artery relationship to warrant an optimal preparation of the lesion. Between all the different available diameters and lengths for each device, the operator decided the most appropriate size in each case according to visual and OCT assessment. Scaffold overlapping was allowed if necessary to warrant a completely coverage of the lesion. Per protocol, high-pressure postdilatation was mandatory after scaffold deployment in both Absorb® and Magmaris® groups. Non-compliant balloons were used in 1:1 balloon/scaffold relationship, with a minimum inflation pressure of 16 atmospheres (atm).

OCT intracoronary analyses were performed with the Lunawave Coronary console® and the Fastview Catheter® (Terumo Corp., Tokyo, Japan). In all cases, OCT evaluation was done after lesion predilatation and both after scaffold deployment and postdilatation to warrant: (a) the best evaluation of the lesion, (b) appropriate size of the device, and (c) optimal scaffold expansion and apposition. Images acquisition technique has been previously described[4].

Quantitative OCT analyses were done with the offline software provided by Terumo® (Terumo Corp., Tokyo, Japan). In both groups, we measured frame by frame all the scaffold segment of the vessel. Lumen, scaffold, and vessel diameters were measured, and malapposed and disrupted struts were also identified. Definitions and analysis methods have been previously published, and they were applied in both the Absorb® and Magmaris® groups[4,6].

All procedures were performed from a radial approach and under unfractionated heparin treatment. Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor was recommended according to current guidelines for a minimum of 12 months[7].

Study endpoints

Primary endpoint

Evaluation of acute effectiveness and safety of two different BVSs (Absorb 1.1® and Magmaris®) regarding OCT postprocedure evaluation of lumen, scaffold, and vessel diameters, as well as percentage of struts disruption and malapposition.

Secondary endpoints include

Procedural success rate (defined as the achievement of a residual stenosis < 20% in the absence of death, myocardial infarction [MI], or TLR during in-hospital stay), and MACE rate at 30-day follow-up (defined as the combination of cardiac death, target vessel-related MI, and clinically driven TLR).

Statistical analysis

Continuous variables with a normal distribution are presented as mean and standard deviations, while categorical variables are presented as percentages. Unpaired t-test (in case of parametric distribution) or Mann–Whitney U-test (in case of non-parametric distribution) was used to compare continuous variables between groups. Chi-square test or Fisher's exact test was used to assess significance associations for categorical variables. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21.

Results

A total of 20 patients (20 lesions) were included in this study. Eighteen Absorb® scaffolds were deployed for the treatment of 10 lesions between June and October 2015, and 10 lesions received 17 Magmaris® devices

Table 1. Baseline patients characteristics

	PLLA BVS group	Mg scaffold group	p value
	n: 10 (100%)	n: 10 (100%)	
Age (years)	56.79 ± 11.38	65.35 ± 9.75	0.45
Women Current smokers Ex-smokers Non-smokers	2 (20) 4 (40) 3 (30) 3 (30)	3 (30) 5 (50) 3 (30) 2 (20)	0.38 0.37 NA 0.38
Arterial hypertension	6 (60)	7 (70)	0.45
Dislypemia DM on AOD DM on insulin	9 (90) 3 (30) 1 (10)	7 (70) 4 (40) 0	> 0.45 Ø 0.45 0.09
Body mass index < 25 kg/m^2 25-29.9 kg/m^2 ≥ 30 kg/m^2	 0 5 (50) 5 (50)	 0 4 (40) 6 (60)	 NA 0.37 0.25
Previous stroke	0	0	NA
Peripheral artery disease	2 (20)	2 (20)	NA
Atrial fibrillation	0	0	NA
Previous coronary artery disease	1 (10)	1 (10)	NA
Previous target vessel revascularization	0	0	NA
Current indication for PCI Effort angina ACS without ST segment elevation STEMI	 7 (70) 3 (30) 0	 6 (60) 4 (40) 0	 > 0.45 0.45 NA
HbA1c (%)	6.05 ± 0.99	6.99 ± 0.78	0.28
Haemoglobine g/dL	14.72 ± 0.82	14.43 ± 0.35	0.54
Platelets × 10^3/µL	270.07 ± 93.4	253.52 ± 85.30	0.21
Creatinine mg/dl	0.77 ± 0.16	0.81 ± 0.21	0.24
Mean eGFR mL/min/1.73 m^2	112.31 ± 37.48	109.91 ± 41.3	0.17
Minimun eGFR	80.78	79.3	0.43

Values are n (%) or mean ± standard deviation; *NA: not applicable. ACS: acute coronary syndrome; AOD: antidiabetic oral drugs; DM: Diabetes Mellitus; ˣeGFR: estimated glomerular filtration rate; STEMI: ST-elevation myocardial infarction; HbA1c: hemoglobin A1C; BVS: bioresorbable vascular scaffolds; PLLA: poly-L-lactic acid.

between November 2016 and October 2017. Baseline clinical characteristics were well balanced between groups (Table 1). Most patients were men, with age ranged between 55 and 65 years and with a diagnosis of hypertension (60% vs. 70%, non-significant [NS]) and dyslipidemia (90% vs. 70% NS). No patients suffered from anemia or chronic kidney disease.

The most common indication for PCI was effort angina in both groups (70% vs. 60% NS) with no ST-elevation MI cases included. Main target vessel was left anterior descendent artery in both Absorb® (70%) and Magmaris® group (80%), with a mean vessel diameter of 3.46 ± 0.23 and 3.52 ± 0.19mm, p = 0.56, respectively. According to the American Heart Association classification, the most lesions were identified as moderate/high-risk lesions: 40% versus 60%, p = 0.37 were type B and 40% versus 30%, p = 0.45 were type C lesions in Absorb® and Magmaris® group, respectively. No statistically significant differences between groups were identified regarding to angiographic and procedural characteristics (Table 2) unless slightly higher post-dilatation pressures for Magmaris® devices (18.01 ± 2.15 vs. 17.20 ± 3.80 atm, p = 0.05). Procedural success rate was 100%. Postprocedural OCT findings are

Table 2. Angiographic lesion characteristics and procedural aspects

	PLLA BVS group	Mg scaffold group	p value
Angiographic lesion characteristic (%)	10 (100)	10 (100)	
Treated artery			
Left anterior descendent artery	7 (70)	8 (80)	0.39
Right coronary artery	3 (30)	2 (20)	0.38
AHA lesion classification			
A	2 (20)	1 (10)	0.39
B	4 (40)	6 (60)	0.37
C	4 (40)	3 (30)	0.45
Bifurcations	1 (10)	1 (10)	NA
Chronic total occlusions	0	0	NA
Thrombus	2 (20)	1 (10)	0.39
Mean vessel diameter mm	3.46 ± 0.23	3.52 ± 0.19	0.56
Procedural aspects			
Predilatation	10 (100)	10 (100)	NA
Mean predilatation balloon diameter mm	3.2 ± 0.36	3.39 ± 0.21	0.52
Mean predilatation balloon length mm	19.2 ± 4.37	19.4 ± 3.2	0.67
Mean predilation balloon pressure atm	12.4 ± 3.04	13.2 ± 2.9	0.49
Mean number of BVS deployed per lesion	1.79	1.63	0.23
Mean BVS diameter mm	3.22 ± 0.32	3.27 ± 0.28	0.21
Mean BVS length mm	22.5 ± 5.34	21.7 ± 6.16	0.41
Mean total length scaffold per lesion mm	35.21 ± 19.25	32.19 ± 15.38	0.09
Mean pressure used in BVS deployment atm	14.08 ± 2.73	14.98 ± 3.10	0.21
Postdilatation	10 (100)	10 (100)	NA
Mean postdilatation balloons diameter mm	3.5 ± 0.32	3.49 ± 0.39	0.23
Mean postdilatation balloons length mm	13.09 ± 3.55	13.78 ± 2.25	0.19
Mean postdilatation balloon pressure atm	17.20 ± 3.80	18.01 ± 2.15	0.05*
Maximum postdilatation balloon pressure atm	20.00 ± 3.80	21.00 ± 3.75	0.04*
Postdilatation balloon/scaffold diameter ratio	1.01	1.02	0.19
Pre-PCI TIMI flow			
0/I	0	0	NA
II	3 (30)	1 (10)	0.44
III	7 (70)	9 (90)	> 0.45
Post-PCI TIMI III flow	10 (100)	10 (100)	NA

Values are n (%) or mean ± standard deviation.
*NA: not applicable.
BVS: bioresorbable vascular scaffold; PCI: percutaneous coronary intervention; PLLA: poly-L-lactic acid; AHA: American Heart Association.

presented in Table 3. We analyzed 21,016 PLLA struts and 20,584 magnesium struts in each group. Both mean scaffold and vessel diameters were significantly larger in Magmaris® group: 3.11 ± 0.38 versus 3.07 ± 0.36 mm, p = 0.03 and 4.12 ± 0.51 versus 4.04 ± 0.46mm, p = 0.04; even in the presence of higher plaque burden (mean plaque area was 6.17 ± 1.79 mm^2 in Magmaris® group versus 6.07 ± 1.28 mm^2 in Absorb® group, p = 0.02). Low rates of malapposition and acute scaffold disruption were demonstrated for both devices after high pressure postdilatation; nevertheless, we identified significantly lower percentages of malapposed (1.06% vs. 1.46 %, p = 0.01) and disrupted struts (0.15% vs. 0.27 %, p = 0.03) in Magmaris® group. All patients completed 30-day follow-up with no cardiac death, target vessel-related MI, or clinically-driven TLR reported.

Discussion

In this study, we evaluated postprocedural performance of Magmaris® scaffold in comparison to the most studied to the date BVS: the Absorb 1.1® (Abbot Vascular, Santa Clara, California, USA). The chief findings are as follows: (a) there is no "class effect" regarding acute device performance between metallic and polymeric BRS, (b) higher scaffold and vessel diameters can be achieved with Magmaris® device in comparison to same size Absorb® BVS, (c) significantly higher percentage of

Table 3: Baseline optical coherence tomography findings. Lesion-level and strut-level analyses

	PLLA BVS	Mg scaffold	p value
	18 devices	17 devices	
Lesion-level analyses			
Mean lumen diameter mm	2.91 ± 0.38	2.99 ± 0.91	0.08
Minimal lumen diameter mm	2.70 ± 0.73	2.73 ± 0.76	0.07
Maximal lumen diameter mm	3.15 ± 0.41	3.22 ± 0.38	0.06
Mean vessel diameter mm	4.04 ± 0.46	4.12 ± 0.51	0.04
Minimal vessel diameter mm	3.87 ± 0.42	3.91 ± 0.48	0.05
Maximal vessel diameter mm	4.18 ± 0.47	4.23 ± 0.60	0.03
Mean scaffold diameter mm	3.07 ± 0.36	3.11 ± 0.38	0.03
Minimal scaffold diameter mm	2.86 ± 0.42	2.90 ± 0.70	0.02
Maximal scaffold diameter mm	3.30 ± 0.36	3.38 ± 0.46	0.03
Mean plaque area mm^2	6.07 ± 1.28	6.17 ± 1.79	0.02
Mean eccentricity index	0.13 ± 0.05	0.09 ± 0.01	0.02
Strut-level analyses			
Number of struts analyzed	21,016	20,584	0.29
% of malapposed struts	1.46	1.06	0.01
Total number of malapposed struts	308	219	
% of disrupted struts	0.27	0.15	0.03
Total number of disrupted struts	58	31	

Values are n (%) or mean ± standard deviation.
PLLA: poly-L-lactic acid; BVS: bioresorbable vascular scaffold.

elongation-to-break for Magmaris® device allows the operator to achieve higher scaffold and vessel diameters in a safe manner, with lower rates of acute scaffold disruption, and (d) for the same reason, high-pressure postdilatation has been demonstrated to be safe and useful as it reduces malapposition rates.

BVS "class effect" has been suggested due to their common resorbable nature and structural features, such as wide struts thickness (150 μm approximately)[2,5,8]. Absorb® and Desolve® are the polymeric scaffolds meanwhile Magmaris® is the only metallic BRS. Mattesini et al.[9] demonstrated comparable results in terms of mean lumen and scaffold area when analyzing postdeployment OCT evaluations for both polymeric devices, so similar acute mechanical properties have been suggested for both Absorb® and Desolve®. However, do these results also apply to metallic BRS? A time-dependent recoil phenomenon as well as higher rates of acute recoil has been demonstrated for polymeric BVS when compared to Magmaris® in preclinical studies[10]. We report the first *in vivo* comparison of acute mechanical performance between Magmaris® and Absorb® devices. Significantly, larger vessel and scaffold diameters were demonstrated in Magmaris® group when comparing to a well-balanced cohort of patients treated with Absorb® (4.12 ± 0.51 vs. 4.04 ± 0.46 mm, p = 0.04 and 3.11 ± 0.38 vs. 3.07 ± 0.36 mm, p = 0.03, respectively). As there were significant differences neither in lesion characteristics nor in procedural aspects between groups, these results suggest higher expansion and radial force for Magmaris®. Furthermore, lower eccentricity index (0.09 ± 0.01 vs. 0.13 ± 0.05, p = 0.02) supports the idea of a better geometrical adaptation to the vessel wall for magnesium BVS, which could be explained thanks to its lower bending stiffness and higher flexibility[10].

In addition to this, Magmaris® greater percentage of elongation-at-break had been hypothesized attending to mechanical properties of magnesium alloy[11]. Nevertheless, no clinical evidence was available. We evaluated for the first time *in vivo* acute scaffold disruption of Magmaris® device by OCT intracoronary imaging (Fig. 1). The percentage of disrupted struts in Magmaris® group was minimal and significantly lower than in the Absorb® group (0.15% vs. 0.27%, p = 0.03). These results confirm metallic BRS higher resistance to rupture, even when postdilatated at higher pressure levels (18.01 ± 2.15 vs. 17.20 ± 3.80 atm, p = 0.05).

Main concern about polymeric scaffolds comes from their original slightly higher rates of ST when comparing to second-generation DES[12,13]. Nevertheless, the application of the "PSP" strategy (including high-pressure postdilatation) has demonstrated a significant reduction in ST and MACE rates after BVS scaffolding with the Absorb® device[14,15], with no higher rates of acute scaffold disruption[4]. In line with this, we decided to perform and evaluate high-pressure postdilatation "per protocol" in all lesions treated with Magmaris® in

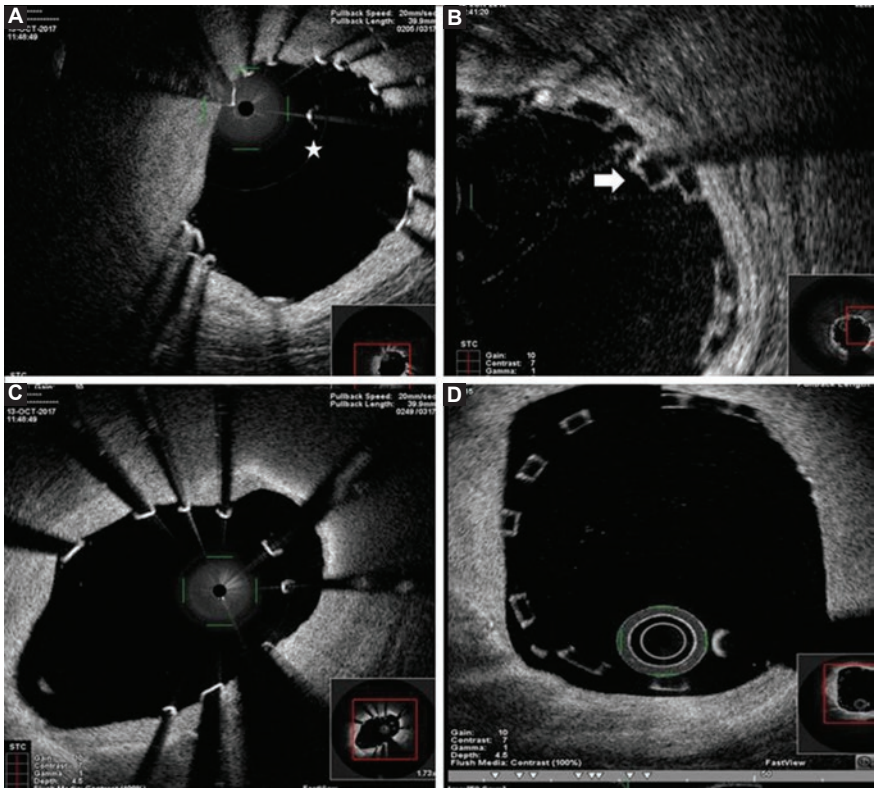

Figure 1. Optical coherence tomography (OCT) *in vivo* evaluation of Magmaris® and Absorb® scaffolds disruption and malapposition. **1A** and **1B**: show different OCT intracoronary images of disrupted struts: the star points to a magnesium isolated strut and the arrow a stacked polymeric disrupted strut. Meanwhile, images **1C** and **1D** show metallic (**1C**) and polymeric (**1D**) bioresorbable scaffolds malapposition.

our cath lab. We confirmed that a greater percentage of elongation-at-break allowed the operator to reduce Magmaris® malapposition rates in a safe manner (1.06% vs. 1.46 %, p = 0.01 of malapposed struts in Magmaris® and Absorb® groups, respectively). Even though Magmaris® device has been suggested to have lower acute thrombogenicity[16] with no reported cases of ST[6,17,18], it is well known that malapposition and infraexpansion significantly increase the risk of scaffold thrombosis and restenosis. According to this, we support the use of high-pressure postdilatation after magnesium-scaffold deployment to optimize angiographic and secondary clinical results, specially avoiding scaffold malapposition (Fig. 1).

In conclusion, this first comparative study between Absorb® and Magmaris® devices supports the use of a "PSP strategy" for both scaffolds deployment. Optimal preparation of the lesion joined to appropriate sizing of the scaffold and high-pressure postdilatation reduces scaffold infraexpansion and malapposition, without acute security concerns. However, slight differences in acute mechanical performance between both devices have also been demonstrated, refusing a common "class effect" for all BVS.

Limitations

Main limitation of our study comes from the small number of patients included. However, we want to highlight that this study is the one which includes the highest number of struts analyzed for Magmaris® device after deployment (20584 struts vs. only 195.67 struts in Biosolve II trial[6]). Moreover, the date is the only study which compares Absorb® versus Magmaris® scaffolds. We are also aware of limitations derived from the non-randomized, observational nature of the study, as well as the possible bias generated by patients' selection. Nevertheless, we would like to emphasize patients/lesions included represent the target population for these devices. More evidence is needed to confirm our findings in a larger population, as well as to complete short–long-term clinical follow-up.

Conclusion

Mechanical properties of Magmaris® scaffold allow the operator to achieve larger vessel and scaffold diameters in a safe manner, with lower rates of malapposition and scaffold disruption.

Conflicts of interest

The authors report no competing interests.

Funding

There are no grants for this study.

Ethical disclosures

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

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

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

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Unusual ventricular activation produced by temporary transvenous cardiac pacing: electrovectorcardiographic findings

Activación ventricular inusual producida por estimulación cardíaca transvenosa temporal: hallazgos electrovectorcardiográficos

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Abstract

Complete heart block (CHB) results from dysfunction of the cardiac conduction system, which results in complete electrical dissociation. The ventricular escape rhythm can have its origin anywhere from the atrioventricular node to the bundle branch-Purkinje system. CHB typically results in bradycardia, hypotension, fatigue, hemodynamic instability, syncope, or even Stokes-Adams syndrome. Escape rhythm originating above the bifurcation of the His bundle (HB) produces narrow QRSs with relatively rapid heart rate (HR) (except in cases of His system disease). We present a middle-aged man with an HR of 34 bpm, progressive fatigue, in whom a temporary pacemaker was implanted in the subtricuspid region. The post-intervention electrocardiogram had unusual features.

Key words: *Temporary transvenous cardiac pacing. Complete atrioventricular block. Left septal fascicular block.*

Resumen

El bloqueo cardíaco completo (BCC) resulta de la disfunción del sistema de conducción cardíaco, lo que ocasiona una disociación eléctrica completa entre aurículas y ventrículos. El ritmo de escape resultante puede tener su origen en cualquier lugar desde el nodo auriculoventricular hasta el sistema His Purkinje. El BCC generalmente produce bradicardia, hipotensión, fatiga, inestabilidad hemodinámica, síncope o incluso el síndrome de Stokes-Adams. El ritmo de escape que se origina por encima de la bifurcación del haz de His produce intervalos QRS estrechos con frecuencia cardíaca no muy lenta (excepto en casos de enfermedad del sistema Hisiano). Presentamos a un hombre de mediana edad con una frecuencia cardíaca de 34 lpm, fatiga progresiva, en el que se implantó un marcapasos temporario en la región subtricuspídea. El electrocardiograma resultante a la intervención presentó características inusuales.

Palabras clave: *Marcapaso temporario tranvenoso. Bloqueo cardiaco completo. Bloqueo de las fibras medio de rama izquierda.*

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Introduction

The left septal fascicular block (LSFB) was contested until recently, but in recent years has been confirmed by employing several methods, such as electro-vectorcardiogram, exercise stress testing, electrophysiological atrial extra stimuli and anatomical studies of ungulate and human hearts using contrast-enhanced micro-computed tomography associated with high-resolution three-dimensional imaging of the human cardiac conduction system. The main cause of LSFB is coronary artery disease with proximal obstruction of the left anterior descending coronary artery before its first perforator branch. The demonstration of its transient form is a compelling fact to rule out other causes responsible for prominent anterior QRS forces. In the present case, we describe for the first time in the literature to our knowledge, ventricular activation with the association of left anterior fascicular block (LAFB) + left septal fascicular block (LSFB) during temporary transvenous pacemaker implanted in the subtricuspid region.

Case report

Male 47 years old, Caucasian from Fortaleza city, Brazil, who complained of progressive fatigue for 3 months with worsening in the last month. No syncope, dizziness or palpitations.

Family history: nothing worthy of note. Physical: heart rate 35 bpm without murmurs, blood pressure: 110/70 mmHg. Normal laboratory tests. The electrocardiogram (ECG) is shown in Fig. 1. A temporary transvenous pacemaker was implanted through the left subclavian vein. The lead was placed in the subtricuspid area. ECG/vectorcardiography (VCG) performed immediately after this procedure showed an unusual pattern (Fig. 2).

Fig. 3 shows the ventricular activation pathway in the horizontal and right sagittal views.

Discussion

El-Sherif et al.,[1] in an experimental model, and Narula et al.,[2] in humans, showed that a lesion in the His bundle (HB) produced classical changes of bundle branch block (BBB). These researchers explained the finding on the basis of longitudinal dissociations. It meant that certain fibers within the HB are predestined to function in the same manner as fibers in the BBBs or fascicles. Pacing proximal to the lesion produced QRS morphology and axis identical with the baseline sinus rhythm, whereas pacing a few millimeters distally resulted in BBB. An explanation for these findings is anisotropic conduction. For example, anisotropic reentry results in greater conduction velocity in longitudinal direction of the fibers and slower conduction with transversal fiber orientation. This velocity difference favoring the longitudinal direction is a consequence of the greater density of the so-called “gap junctions” in the ends of the cells in comparison to the lateral area, which will provide sufficient delay to produce a BBB because the His-Purkinje system (HPS) impulse feed distal to the lesion may be delayed sufficiently and can be overcome by pacing distally.

Ever since Rosenbaum et al. described their findings, there has been an assumption that the left bundle branch (LBB) has only two fascicles. Many investigators before and subsequently have presented strong evidence to suggest that there are three divisions of the LBB, and therefore, the terms fascicular blocks have been preferred over the term hemiblocks. Trifascicular LBB should not be confused with trifascicular atrioventricular (AV) block. The latter term evolved when there was a combination of two fascicles showing block and additional first-degree AV block. This was thought to reflect the conduction delay in the third fascicle. This line of thinking did not pan out because in many cases, the PR prolongation was due to AV nodal delay and not additional HPS conduction block. Some aspects of the fascicles of the LBB need further discussion, especially with regard to the existence and physiologic/pathophysiologic role of the left septal fascicle (LSF).

A component of vertical orientation has been used in the definition of fascicular blocks because this diagnosis was made by the QRS orientation in the frontal plane. Hence, the left anterior fascicle (LAF) becomes anterosuperior, and the left posterior fascicle (LPF) has been termed posteroinferior.

The presence of an LSF as a separate division has been implied by several investigators; although pathologic specimens clearly show the LSF in humans[3], the clinical aspects of the left septal fascicular block (LSFB) have not been convincingly demonstrated until recently using ECG/VCG[4]. Demoulin and Kulbertus reinforced earlier studies of the trifascicular nature of the left conduction system, demonstrating a third branch in 11 of 20 hearts[5,6]. Kulbertus et al. showed that the majority of examined hearts had an LSF that was easily identifiable[7,8].

Ungulate hearts demonstrated the trifascicular nature of the LBB[9]. In addition, Stephenson et al.

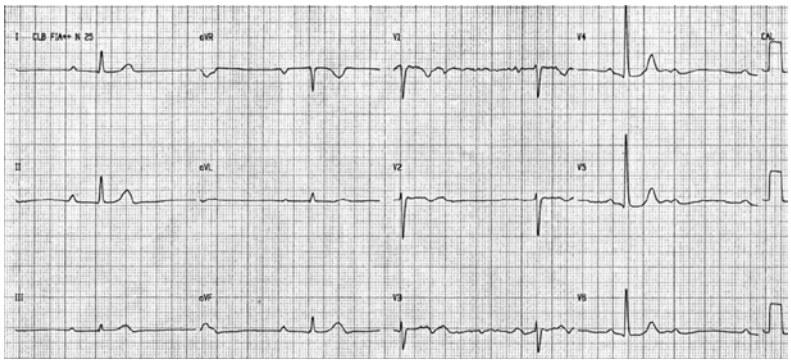

Figure 1. Electrocardiogram (ECG) at admission. 12-lead ECG-1: complete heart block, heart rate 34 bpm, narrow QRS complex with QRS axis at +40°.

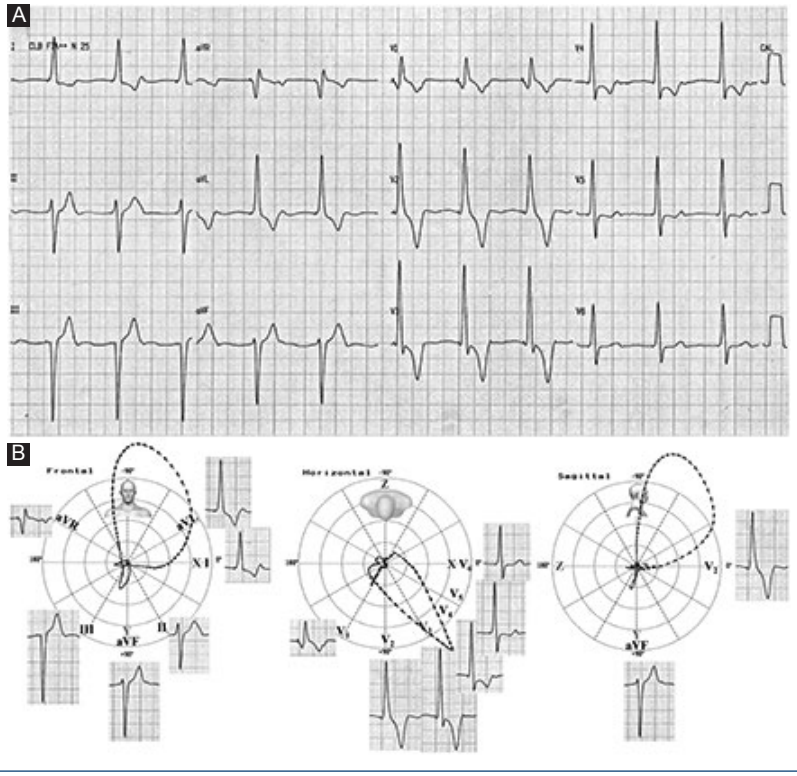

Figure 2. 12-lead electrocardiogram (ECG)/vectorcardiography (VCG) performed after temporary transvenous pacemaker implantation. **A:** ECG: pacemaker rhythm, QRS duration 160 ms, extreme left axis deviation (QRS axis at –55°), rS pattern in the inferior leads, SIII > SII, wide R-wave without initial q wave in I and aVL. This indicates atypical left anterior fascicular block (LAFB) by the absence of the first middle septal vector. In the precordial leads, prominent anterior QRS forces: qR pattern in the right precordial leads, R-wave voltage "in crescendo" from V_1 to V_3, and Rs-type QRS with decreasing R-wave amplitude from V_4 to V_6. The absence of initial q wave in V_5 to V_6 indicating lack of first mid-septal vector. These ECG findings are compatible with the left septal fascicular block (LSFB). **B:** VCG: frontal plane: initial 20 ms vector with slow inscription and directed from right to left, extreme left axis deviation (SÂQRS –50°). QRS loop predominantly located in the upper left quadrant and final vectors with slow inscription in the right superior quadrant. T-loop with clockwise rotation in the inferior right quadrant (≈+110°). Horizontal plane: visible spike of pacing (a), initial 20 ms vector of slow inscription and directed to the back and leftward signaling initial activation dependent on the LPF. QRS loop predominantly located in the left anterior quadrant, clockwise rotation, and final vectors of slow inscription located in the right quadrants. Right sagittal plane: initial vectors slowly inscribed and directed downward and leftward, QRS loop almost completely located in the upper anterior quadrant, and counterclockwise rotation. T-loop directed downward and slightly backward: positive T wave in aVF and negative in V2. Conclusion: pacing rhythm with LAFB + atypical LAFB.

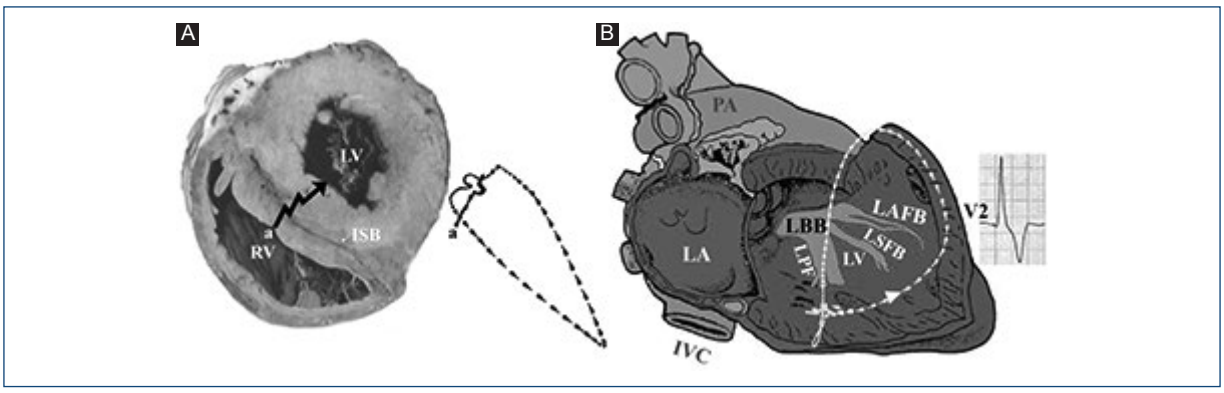

Figure 3. Ventricular activation route in the horizontal. **A:** and right sagittal. **B:** views. LPF: left posterior fascicle; LBB: left bundle branch; LSFB: left septal fascicular block; LAFB: left anterior fascicular block; LA: left atrium; LV: left ventricle; ISB: intraseptal barrier; a: subtricuspid region; PA: pulmonary artery; IVC: inferior vena cava; RV: right ventricle.

demonstrated the same using contrast-enhanced micro-computed tomography associated with high-resolution three-dimensional (3D) imaging of the human cardiac conduction system. This study was the first 3D representation of the cardiac conduction system within an *ex vivo* intact human heart in an attitudinally correct position.

There are several pieces of evidence that indicate an active role in the left ventricular (LV) activation pathway inside of the LV following three pathways[10-12].

The second ECG of our patient shows a rather unique combination of the left-sided conduction block in the setting of a temporary pacemaker lead (Fig. 2): in the extremity leads, there is atypical left anterior fascicular block (LAFB) (by the absence of the first middle septal vector), and in the precordial leads, there are prominent anterior QRS forces, and the ECG criteria of LSFB are fulfilled.

Sung et al. hypothesized that retrograde conduction over the LSF produces alternate fascicular patterns as well as narrow forms of ventricular tachycardia (VT). Ablation of the respective fascicle was successful in abolishing fascicular tachycardia but did not preclude the development of bundle branch reentrant VT, unless the LSF was targeted and ablated. This manuscript strongly supports the trifascicular nature of the LBB[13]. Akhtar et al.[10] found some evidence that more convincingly than before brought together the trifascicular nature of the LBB and active participation of the LSF in the LV activation.

Recently, Upadhyay et al. were able to delineate septal conduction in an LBBB case. These authors performed detailed intracardiac mapping of the left septal conduction system to assess for the presence and level of complete conduction block in the HPS. They studied patients with and without complete conduction block in the His conduction system. They observed heterogeneous septal conduction in patients with a surface LBBB pattern, ranging from no discrete block to complete conduction block. When block was present, they observed pathology localized within the left-sided His fibers, which was most amenable to corrective HB pacing by recruitment of latent Purkinje fibers. ECG criteria for LBBB incompletely predicted complete conduction block, and intracardiac data might be useful in refining patient selection for resynchronization therapy[14].

Conclusion

We have presented a patient case, where temporary pacemaker leads implantation in the subtricuspid region resulted in ECG findings compatible with the LAFB + LSFB. To the best of our knowledge, this is the first case ever published with these ECG features in this clinical setting. We think that this case adds to our understanding of the LSF in the human heart. Without detracting from the importance of the original Rosenbaum et al. contribution, some investigators have questioned various aspects of the basic hemiblock concept.

Conflicts of interest

None.

Funding

None.

Ethical disclosures

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

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

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

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ARTÍCULO DE INVESTIGACIÓN

Central blood pressure and vascular stiffness in Mexican population

Presión central aórtica y rigidez vascular en mexicanos

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Abstract

Introduction: *Central blood pressure (CBP) is considered a measure of prognostic value for cardiovascular risk. In turn, the aortic pulse wave velocity (PWVAo) and augmentation index (Aix) have been related to arterial stiffness and cardiovascular risk. Controversies exist regarding the reference values in different ethnic groups, ages, and anthropometrics. The objective of this study is to evaluate the CBP and arterial stiffness parameters in a Mexican population by age, gender, and anthropometry.* **Methods:** *Between 2015 and 2016, 1009 apparently healthy subjects were recruited in the Instituto Nacional de Cardiología Ignacio Chávez. Using the Arteriograph (TensioMed) equipment with an oscillometric technique, CBP, central pulse pressure (cPP), PWVAo, and Aix were acquired. All results were automatically obtained by computer software version 3.0.0.4.* **Results:** *Female sex was prevalent (72%), mean age was 47 ± 12 years; 26% had normal weight, 43% were overweight, and 30% had obesity. The reference values were higher than those reported in other populations. PWVAo and Aix were always found to be higher in females. A central-brachial pressure gradient was observed in < 40 years with lower CBP. Body mass index (BMI) presented a direct and positive correlation with CBP ($p < 0.001$); however, PWVAo and Aix were not modified.* **Conclusion:** *CBP, cPP, PWVAo, and Aix parameters should be considered based on age, gender, and BMI. In Mexican population, CBP and cPP values were higher compared with other previously reported values, especially in women, the elderly, and obese. PWVAo and Aix are higher in older women; however, they are not modified by BMI.*

Key words: *Central blood pressure. Aortic pulse wave velocity. Aix aortic. Hispanic. Hypertension.*

Resumen

Introducción: *La presión central aórtica (PCA) se considera una medida del valor pronóstico. A su vez, la velocidad de la onda del pulso aórtico (VOPA) y el índice de aumento (IA) se han relacionado con la rigidez arterial y riesgo cardiovascular. Existen controversias sobre los valores de referencia en diferentes grupos. El objetivo de este estudio es evaluar estos parámetros en una población mexicana por edad, género y antropometría.* **Métodos:** *Entre 2015 y 2016 se reclutaron 1,009 sujetos aparentemente sanos en el Instituto Nacional de Cardiología Ignacio Chávez. Usando el equipo de Arteriograph (TensioMed) con*

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técnica oscilométrica, se adquirieron: PCA, presión de pulso central, VOPA e IA. Todos los resultados fueron obtenidos automáticamente. **Resultados:** *El sexo femenino fue prevalente (72%), edad de 47 ± 12 años; 26% con peso normal, 43% con sobrepeso y 30% con obesidad. Todos los valores fueron superiores a los reportados en otras poblaciones. VOPA e IA siempre fueron más altos en mujeres. Se observó un gradiente de presión central-braquial en < 40 años, con menor PCA. El IMC presentó una correlación directa y positiva con la PCA (p < 0,001), sin embargo, VOPA e IA no se modificaron.* **Conclusión:** *Los parámetros de PCA, VOPA e IA deben considerarse en función de edad, género e IMC. En una población mexicana, los valores de PCA fueron más altos en comparación con informados previamente (Europa y Asia), especialmente en mujeres, ancianos y obesos. VOPA e IA son más altos en mujeres mayores; sin embargo, no son modificados por el IMC.*

Palabras clave: *Presión central aórtica. Velocidad de onda de pulso aórtico. Índice de aumentación aórtica. Hipertensión.*

Introduction

Central blood pressure (CBP) has been established as a strong predictor of cardiovascular risk. European guidelines for systemic arterial hypertension recognize CBP as a useful tool in the evaluation of treatment, risk stratification, and detection of target organ damage[1]. Likewise, surrogate markers of CBP that translate vascular stiffness, aortic pulse wave velocity (PWVAo), and aortic augmentation index (Aix) have been associated with cardiovascular risk[2].

However, the measurement of CBP is far from its use in daily clinical practice due to multiple factors including the lack of reference values between individuals of different races, gender, age, and body mass index (BMI).

The objective of this study was to evaluate the CBP, central pulse pressure (cPP), PWVAo, and Aix in a population of healthy Mexican subjects, to identify reference values, and to know their behavior according to gender, age, and BMI.

Methods

Design and population

Between 2015 and 2016, an observational cross-sectional study was conducted. The recruitment was done through open invitation to the people who were accompanying patients of the outpatient care department of our institution by convenience. These subjects were asked to fill out a survey and undergo an electrocardiogram to rule out any cardiovascular disease. Those with a history of hypertension, diabetes mellitus, smoking, alcoholism, ischemic heart disease, peripheral vascular disease, and electrocardiographic data of hypertensive heart disease were excluded from the study. A clinical questionnaire was applied and anthropometric measurements of weight in kilograms and height in meters were made to calculate the BMI. Subjects were classified according to their BMI values: underweight (< 18.5), normal (18.5-24.9), overweight (25-29.9), obesity Grade 1 (30-34.9), obesity Grade 2 (35-39.9), and obesity Grade 3 (≥ 40).

Measurement of CBP

An Arteriograph (TensioMed) device with oscillometric technique was used for its evaluation[3]; the CBP measurements of the subjects were carried out between 9:00 a.m. and 11:00 a.m., on a single occasion, all records were obtained in a quiet environment, after resting in supine position for 5 min and later analyzed with software (version 3.0.0.4.), which reported CBP, cPP, systolic brachial pressure (SBP), brachial pulse pressure (bPP), PWVAo, and Aix.

Statistical analysis

The numerical variables are summarized as mean and standard deviation or median and quartiles 25 and 75, according to their distribution. The categorical variables are summarized in frequency and percentage. We performed bivaried analysis of two independent groups with t-test or Mann–Whitney U-test for numerical variables and Chi-square test for categorical variables. When there are more than two groups to be compared, the ANOVA, Kruskal–Wallis, and Chi-square linear trend tests were used, depending on the case. Bivaried correlations were performed (Pearson or Spearman, according to distribution). Multivariate analysis was performed with logistic regression to predict CBP > 140 mmHg, PWVAo > 9 m/s, and Aix > 33% using the Statistical Package for the Social Sciences 22.0, a two-tailed $p < 0.05$ was considered statistically significant.

Results

We included 1009 participants, 72% were female, average age of 47 ± 12 years (minimum of 15, maximum of 89 years), 7% with active smoking, 26% with

Table 1. Central blood pressure and arterial stiffness parameter by sex

Parameter	Total (n = 1009)	Female (n = 727)	Male (n = 282)	p-value
Age in years	47 ± 12	48 ± 12	46 ± 13	NS
BMI (kg/m^2)	27 (24-30)	27 (24-31)	27 (24-30)	NS
SBP (mmHg)	126 (117-139)	126 (117-141)	129 (119-139)	NS
bPP (mmHg)	53 ± 10	54 ± 11	52 ± 9	0.001
CBP (mmHg)	126 (113-141)	127 (113-143)	124 (111-138)	0.03
cPP (mmHg)	53 ± 14	54 ± 14	47 ± 12	< 0.001
PWVAo (m/s)	7.8 (6.9-9.3)	7.9 (7-9.7)	7.6 (6.8-8.5)	< 0.001
Aix (%)	33 ± 13	36 ± 13	27 ± 13	< 0.001
Arterial age	40 ± 16	41 ± 16	38 ± 15	0.001

BMI: body mass index; SBP: systolic brachial blood pressure; bPP: brachial pulse pressure; CBP: central blood pressure; cPP: central pulse pressure; PWVAo: aortic pulse wave velocity; Aix: augmentation index. Variables are summarized as mean and standard deviation or median and quartiles 25 and 75, according to their distribution.

normal weight (BMI in the whole population: 28 ± 4.6 kg/m^2), 43% overweight, 22% obesity Grade 1, 6% obesity Grade 2, and 2% obesity Grade 3.

Analysis by sex

Table 1 shows the results divided by sex. There were no differences in age, BMI, or brachial systolic blood pressure. However, women had higher levels of CBP and cPP, with higher proportions with CBP above the expected limit, without statistical significance (> 140 mmHg, 29% vs. 23%, p = 0.056). At the same time, women had significantly higher values of PWVAo and Aix. Similarly, the calculated arterial age was higher for women, despite similar chronological ages. When taking the CBP cutoff points ≥ 140 mmHg and cPP ≥ 50 mmHg for the diagnosis of high blood pressure, a higher proportion of new diagnoses was observed in women, without observing important changes in men or when using brachial measurements (Fig. 1).

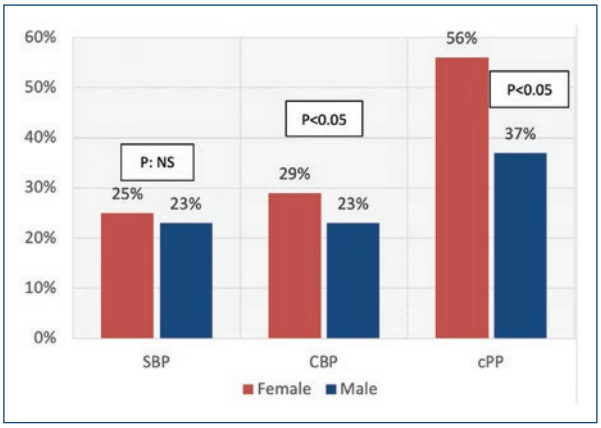

Figure 1. New diagnoses of high blood pressure. Red bar represents female. Blue bars represent male. With SBP, similar proportion of new high blood pressure diagnosis was made. With CBP, a higher proportion of high blood pressure new diagnosis in female was observed. The proportion is higher with cPP. SBP: systolic brachial blood pressure; CBP: central blood pressure; cPP: central pulse pressure.

Analysis by age

Table 2 shows the measurements obtained by age group. We observed a moderate direct association between age and SBP (rho = 0.34, p < 0.001), which improves for CBP (r = 0.47, p < 0.0001) and cPP (r = 0.49, p < 0.0001). Two other phenomena were observed: the first, in subjects younger than 40 years, a significant gradient between SBP and CBP is observed, after this age, the pressures are similar (Fig. 2). Second, women under 40 years have lower values of CBP; however, when this age is exceeded, CBP exceeds men (Fig. 3). Regarding the parameters of vascular rigidity, both have moderate direct association with age (r = 0.52, p < 0.001 for PWVAo and r = 0.57, p < 0.001 for Aix). Regardless of age, women have higher Aix values.

BMI analysis

Table 3 shows the measurements by weight category. Weak direct associations were observed between BMI,

Table 2. Central blood pressure and arterial stiffness parameter by age

Parameter	< 30a (n = 95)	30-39a (n = 156)	40-49a (n = 286)	50-59a (n = 285)	60-69a (n = 150)	> 70a (n = 37)	p-value
BMI (kg/m^2)	24 (25-28)	27 (25-31)	27 (25-31)	27 (25-31)	27 (24-30)	27 (26-29)	< 0.001
SBP (mmHg)	120 (112-126)	121 (115-130)	124 (117-137)	129 (120-144)	138 (124-152)	142 (130-165)	< 0.001
bPP (mmHg)	52 (45-59)	49 (44-56)	51 (44-57)	52 (46-59)	58 (50-56)	63 (52-74)	< 0.001
CBP (mmHg)	109 (103-118)	114 (107-128)	124 (113-137)	131 (120-149)	140 (127-156)	145 (135-168)	< 0.001
cPP (mmHg)	42 (38-45)	43 (38-50)	48 (42-58)	54 (45-63)	63 (52-71)	69 (57-79)	< 0.001
PWVAo (m/s)	6.3 (6-6.9)	7.1 (6.4-7.6)	7.6 (7-8.3)	8.4 (7.5-10)	9.7 (8.3-11)	10.5 (8.7-11)	< 0.001
Aix (%)	18 (11-24)	24 (15-32)	31 (23-39)	39 (31-46)	44 (35-52)	47 (37-53)	< 0.001
Arterial age	18 (15-27)	31 (18-38)	38 (30-46)	47 (38-60)	60 (46-60)	60 (51-60)	< 0.001

BMI: body mass index; SBP: systolic brachial blood pressure; bPP: brachial pulse pressure; CBP: central blood pressure; cPP: central pulse pressure; PWVAo: aortic pulse wave velocity; Aix: augmentation index. Variables are summarized as median and quartiles 25 and 75, according to their distribution.

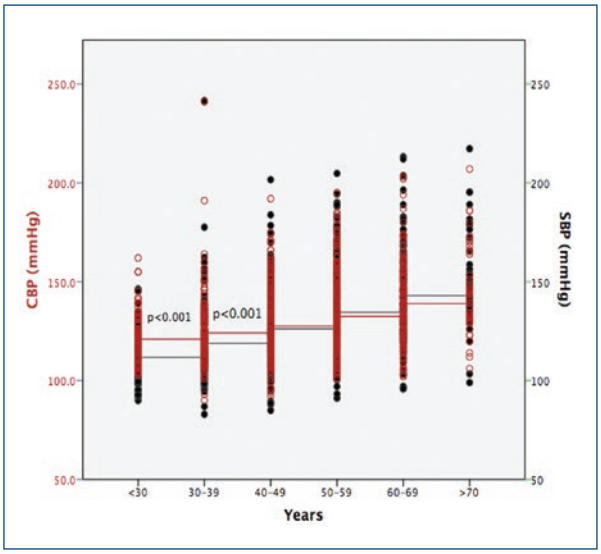

Figure 2. Gradient between CBP and SBP by age. Black circles represent SBP. Red circles represent CBP. There is a significant gradient CBP-SBP before 40 years. After this age, CBP and SBP are similar. SBP: systolic brachial blood pressure (black circles); CBP: central blood pressure (red circles).

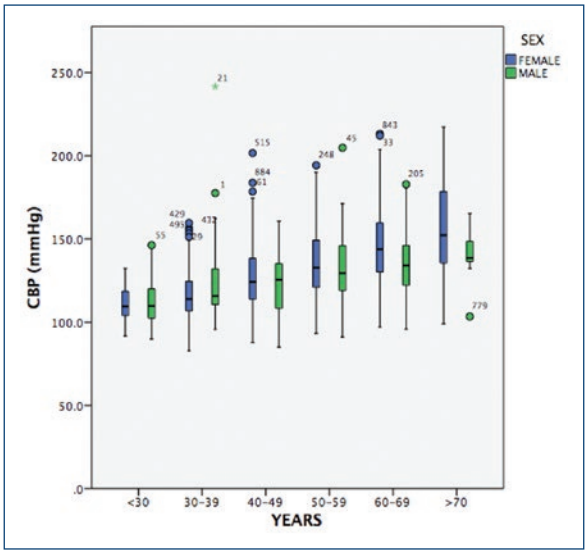

Figure 3. CBP by age and sex. The blue box plots represent CBP in females. The green box plots represent CBP in males. Notice similar values between females and males before 40 years. After 40 years, CBP is higher in female subjects. CBP: central blood pressure.

SBP (rho = 0.24, p < 0.001), and CBP (rho = 0.19, p < 0.001); however, the values of these last two increase to a greater degree of obesity in a significant way. When analyzing vascular rigidity parameters, no association with BMI is observed.

Logistic regressions

Table 4 shows logistic regressions. Independent predictors for CBP > 140 mmHg are age and BMI and for PWVAo > 9 m/s and Aix > 33% are age and sex, without showing effect by the BMI on these parameters related to vascular stiffness.

Discussion

Central aortic pressure has been established as a reliable measure for the stratification of prognosis and cardiovascular risk. Its elevation has been correlated with the thickness of the intima-media of the carotids[4], increase and regression of left ventricular mass in hypertensive patients[5], and with a better ability to predict

Table 3. Central blood pressure and arterial stiffness parameter by BMI

Parameter	Normal (n = 264)	Overweight (n = 441)	Obesity Grade 1 (n = 228)	Obesity Grade 2 (n = 57)	Obesity Grade 3 (n = 19)	p-value
Age by years	46 (33-57)	49 (41-57)	49 (40-57)	48 (42-55)	48 (43-56)	0.003
SBP (mmHg)	124 (114-133)	125 (117-138)	130 (12-144)	143 (124-154)	143 (129-159)	< 0.001
bPP (mmHg)	51 (44-57)	51 (45-58)	54 (48-61)	60 (53-65)	60 (52-73)	< 0.001
CBP (mmHg)	121 (109-136)	125 (112-141)	128 (115-145)	142 (124-155)	139 (132-162)	< 0.001
cPP (mmHg)	48 (41-60)	49 (42-60)	51 (43-63)	59 (51-69)	59 (50-69)	< 0.001
PWVAo (m/s)	7.7 (6.7-9.4)	7.8 (6.9-9.4)	7.9 (7-9.2)	8 (7.2-9.5)	8.2 (7.5-9.2)	0.42
Aix (%)	33 ± 14	33 ± 13	32 ± 13	34 ± 12	35 ± 13	0.79
Arterial age	39 (24-60)	41 (29-60)	42 (30-60)	43 (33-60)	45 (37-60)	0.27

BMI: body mass index; SBP: systolic brachial blood pressure; bPP: brachial pulse pressure; CBP: central blood pressure; cPP: central pulse pressure; PWVAo: aortic pulse wave velocity; Aix: augmentation index. Variables are summarized as mean and standard deviation or median and quartiles 25 and 75, according to their distribution.

Table 4. Logistic regressions

Parameter	OR (CI 95%)	p-value
To predicts CBP > 140 mmHg		
Age by years	1.08 (1.06, 1.1)	< 0.0001
BMI (K/m^2)	1.09 (1.05, 1.13)	0.001
Male sex	0.8 (0.5, 1.1)	NS
To predicts PWVAo > 9 m/s		
Age by years	1.12 (1.1, 1.14)	< 0.0001
BMI (k/m^2)	1 (0.9, 1.03)	NS
Male sex	0.36 (0.24, 0.54)	< 0.0001
To predicts Aix > 33%		
Age by years	1.11 (1.09, 1.13)	< 0.0001
BMI (k/m^2)	0.97 (0.94, 1)	NS
Male sex	0.25 (0.18, 0.36)	< 0.0001

BMI: body mass index; CBP: central blood pressure; PWVAo: aortic pulse wave velocity; Aix: augmentation index.

cardiovascular events compared to brachial blood pressure[2]. Similarly, the cPP ≥ 50 mmHg is associated with morbi-mortality[1].

However, the measurement of CBP in daily clinical practice is far from being a reality, for a variety of reasons. Among them, the multitude of equipment available for measurement, the lack of normal reference values for particular populations (such as Hispanics) and of reference tables in patients according to age, sex and body weight[6].

In addition, the evidence regarding CBP in relation to cardiovascular risk is not conclusive since it mostly comes from subanalysis, with sometimes contradictory results. Therefore, although it shows a promising role in the non-invasive stratification of risk, CBP has not succeeded in replacing brachial measurements in the diagnosis, follow-up, and prognosis of patients with systemic arterial hypertension.

The present study tries to solve, in part, the problem described above, delimiting the normal values of reference in healthy Hispanic population (which in itself presents a higher cardiovascular risk than other races) and with the use of equipment widely validated in the previous studies, with the objective of establishing a base in the area of research on central aortic pressure in Mexican population.

CBP and gender

Regarding the relationship between CBP and sex, a statistically significant difference was observed between men and women, however, with a delta of only 3 mmHg. Studies with a large number of patients in China and Europe showed similar results[7,8]. It is noteworthy that, after 40 years of age, the CBP is equal and even, when over 60 years old, the gradient is reversed and becomes greater for women than men.

Notably, the use of CBP and its measurements increased the proportion of women with a new diagnosis of hypertension, but not with the use of SBP. According to data from ENSANUT 2016, the prevalence in Mexico of hypertension is 25.5%, and 40% do not know its diagnosis[9]. The greater proportion of new diagnoses in women is due to the effect of the use of CBP, despite the fact that SBP values were similar.

When comparing the reference values of our population with European and Asian results, higher values were found[7,8]. These results are relevant because they may

be associated with a higher baseline cardiovascular risk in Hispanics, according to previously reported[10].

Regarding the cPP and Aix, women presented higher statistically significant values, however, directly influenced by the height, a finding already described previously[11]. However, the PWVAo (which is not modified by the height) is elevated in women, probably in relation to greater vascular rigidity. Although our results cannot be conclusive in this regard, we believe that they support the hypothesis that women may present different risk and pathophysiology, so they may also need special considerations in treatment.

CBP and age

The increase in age leads to an increase in CBP and vascular rigidity parameters. This association has been reproduced by various publications[7,8,12], which is reflected in the higher prevalence of hypertension as the age advances[13].

Of relevance, a statistically significant gradient of central-brachial pressure was observed in patients under 40 years of age. After this age, the significance is lost and both pressures present similar measurements. Our results show CBP values of 109 (103-118) and 114 (107-128) mmHg in < 30 and 30-40 years, respectively, and a central-brachial gradient of 11 and 7 mmHg was observed and may consider normal.

The significance of the loss of this gradient or the presence of higher CBP values in this age group and its relationship with an increased risk of arterial hypertension remains to be clarified. Saladini et al.[14] recruited 305 patients with an age of 37 ± 10 years and performed measurements of SBP and CBP, finding this central-brachial gradient; at follow-up, subjects with a lower gradient had a higher incidence of high blood pressure. Therefore, the measurement of CBP could have a potential impact on the early diagnosis of high blood pressure in subjects less than 40 years.

CBP and BMI

Regarding the BMI, it was found that the greater the degree of obesity, there is an increase in the CBP and the brachial measurements, data observed in previous publications[15,16]. However, the parameters of vascular rigidity did not show differences between the degrees of obesity. Other authors have reported this finding[15-17], suggesting that different physiopathological mechanisms are present in the patient with obesity. Messerli et al.[18] conducted a study to assess the hemodynamic differences associated with hypertension and obesity, reporting that the total blood volume is significantly increased in obese hypertensive patients and found no differences in peripheral resistance or plasma renin activity. The same author later published that obese subjects had lower values of circulating catecholamines when compared with subjects of normal weight[19]. These data suggest that, at least partially, a cause of arterial hypertension in obese patients is the increase in blood volume and not an effect of vascular rigidity or catecholamines so that treatments should possibly be aimed at this objective.

Conclusion

We observe significant differences in CBP, cPP, PWVAo, and Aix based on age, gender, and BMI. In a Mexican population, higher values of CBP and cPP were found in female, the elderly, and obese, with a central-brachial gradient in younger than 40 years. PWVAo and Aix are high in women and the elderly; however, they are not modified by BMI.

Limitations

The main limitations of our study are the sample size, although, to our current knowledge, it could be the largest Hispanic population included in this issue. On the other hand, the lack of follow-up and hard outcomes makes it difficult to relate our findings to risk, so additional studies are needed to clarify the role of CBP and the parameters of vascular rigidity in the stratification and diagnosis of hypertension in Hispanics. Our study included a greater proportion of female sex because socially in our environment is this gender the natural companion of patients to their medical consultations; this could have an impact on the generalization of the results, mainly in the differences by gender.

Conflicts of interest

None declared.

Funding

None.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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ARTÍCULO DE INVESTIGACIÓN

The Hospital Zambrano Hellion venous thromboembolism rapid response team (*PREVENTION-team*): Improving pulmonary embolism and deep venous thrombosis patient care

Equipo de respuesta rápida para tromboembolismo venoso del Hospital Zambrano Hellion (PREVENTION-Team): *Mejorando el manejo del tromboembolismo pulmonar y trombosis venosa profunda*

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Abstract

Background: *Fast-track worldwide reperfusion programs improve outcomes in ST-elevation myocardial infarction and stroke. Similar programs called Program Evaluation and Review Technique (PERT) focus on submassive and massive pulmonary embolism (PE) excluding deep venous thrombosis (DVT).* **Methods:** *PREVENTION-team (Hospital Zambrano Hellion Venous Thromboembolism [VTE] Rapid Response).* **Primary objective:** *Fast-track stratification, diagnostics, and treatment (60-90 min) to improve proximal DVT and submassive and massive PE patients care.* **Secondary objectives:** *Increase diagnosis rate of low-risk PE and distal DVT; exploration of cause; long-term anticoagulation; identify high-risk profile for chronic complications; community-based support groups and patient education to extend the concept of the thrombosis-free hospital to thrombosis-free home.* **Structure and organization:** *The team includes cardiologists, vascular medicine, angiologist, echocardiographer, cardiovascular imaging, and interventional cardiologists. The team will be accessible 24 h a day, 7 days a week, 365 days a year, and base on previous national experience. The cardiology fellow on call will be responsible for activation and evaluation. We will design several tools to accelerate these processes. Risk stratification and therapeutic approach will be based on clinical presentation, echocardiogram, and biomarkers findings. According to PERT stratification based on resources and medical specialties, Hospital Zambrano Hellion has level 1 PERT. PREVENTION-team links physicians with different expertise, provide fast, efficient, and time-saving treatment, potentially saving lives and reducing bleeding and chronic complications in VTE patients. Finally, establishing a network in our hospital and health system to improve VTE patients care. To the best of our knowledge, this is the first rapid response team focused on VTE in Mexico.*

Key words: *Venous thromboembolism. Pulmonary embolism. Deep vein thrombosis. Rapid response teams. Program evaluation and review technique. Mexico.*

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Resumen

Antecedentes: *Programas de reperfusión mejoraron la evolución en infarto con elevación del ST y accidente cerebrovascular embólico. Programas similares llamados PERT para TEP masiva o submasiva excluyen TVP.* **Métodos:** *Equipo PREVENTION (Hospital Zambrano Hellion Venous Thromboembolism Rapid Response).* **Objetivo primario:** *Estratificación, diagnóstico y tratamiento acelerado (60-90 minutos) para mejorar atención del TVP proximal y TEP masiva o submasiva.* **Objetivos secundarios:** *Incrementar diagnóstico de TEP de riesgo bajo y TVP distal; explorar causa; anticoagulación a largo plazo; perfil de riesgo alto para complicaciones crónicas; grupos de soporte en la comunidad y educación para pacientes, y extender el concepto de hospital libre de trombosis a hogar libre de trombosis.* **Estructura y organización:** *Incluye cardiólogos, medicina vascular, angiólogo, ecocardiografistas, imagen cardiovascular. Basado en experiencia nacional, el equipo estará accesible 24 horas del día, siete días de la semana, 365 días del año. El residente de cardiología realizará la activación y estratificación. Diseñamos herramientas para acelerar el proceso. La estratificación de riesgo y el abordaje terapéutico se basará en presentación clínica, hallazgos ecocardiograficos y biomarcadores. El Hospital Zambrano Hellion tiene nivel PERT 1 de acuerdo a la estratificación PERT basada en recursos y especialidades. Equipo-PREVENTION en TEV vincula médicos con diferentes capacidades, ofrece rápido y eficiente tratamiento para preservar vidas y reducir complicaciones hemorrágicas y crónicas. En nuestro hospital y sistema de salud establecer una sólida red de trabajo para mejorar la atención. Hasta nuestro conocimiento, en México este podría ser el primer equipo de respuesta rápida enfocado en TEV.*

Palabras clave: *Tromboembolismo venoso. Tromboembolia pulmonar. Trombosis venosa profunda. Equipos de respuesta rápida. PERT. México.*

Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a worldwide disease characterized by cardiovascular mortality, impaired quality of life and significant long-term complications such as recurrence, a chronic thromboembolic pulmonary disease with or without pulmonary hypertension, and post-thrombotic syndrome (PTS)[1]. PE – the most severe consequence – is the third cause of cardiovascular mortality after myocardial infarction and stroke, the leading preventable cause of death in hospitalized patients, the main cause of pregnancy-related maternal death in developed countries, and the second cause of mortality in cancer patients[1]. Furthermore, VTE is the third most common complication in trauma patients, and PE is the third most common cause of death in patients who survive the first 24 h after injury[2]. PE survivors commonly have persistent right ventricle dysfunction, impaired functional status (NYHA Class II–IV), diminished exercise capacity (6-min walk test), and reduced quality of life in the follow-up[3]. In addition, 3.8% are predicted to develop chronic thromboembolic pulmonary hypertension[4].

On the other hand, up to 70% of patients with PE have DVT, and up to 32% of patients with DVT have asymptomatic PE[5,6]. Furthermore, PTS can be observed in up to 25-50% of DVT cases, of which, 5-10% later have severe limitations and poor quality of life. In addition, PTS exponentially increases health-care costs in the United States and Canada[7]. Despite this evidence, advanced therapies to reduce PTS incidence are not carried out expeditiously. Recently, Heart Teams are launched to improve the management of complex cardiovascular diseases[8], including PE patients. In 2012, the Massachusetts General Hospital (MGH) created the first formal and successful multidisciplinary rapid-response team, called program evaluation and review technique (PERT), to assess and provide clinical recommendations for patients with submassive and massive PE in real time[9]. Worldwide institutions reproduced similar concepts, mobilizing multidisciplinary teams that coordinate and provide optimal therapeutic options, which in turn improve patient care[10]. However, PERTs does not include DVT – the source of PE – despite the negative impact it has in terms of quality of life and public health costs[11]. We designed to improve the quality of care[12] of the entire clinical spectrum of VTE, the first – to the best of our knowledge – rapid response team in Mexico, called Hospital Zambrano Hellion VTE Rapid Response Team (PREVENTION-team).

Materials and methods

PREVENTION-team objectives

Primary objective: to provide fast-track stratification and diagnostics (60-90 min) after protocol activation to initiate anticoagulation alone promptly or anticoagulation plus advanced therapy (systemic or mechanical thrombolysis) in submassive, massive, and proximal DVT. The decision-making between anticoagulation alone or

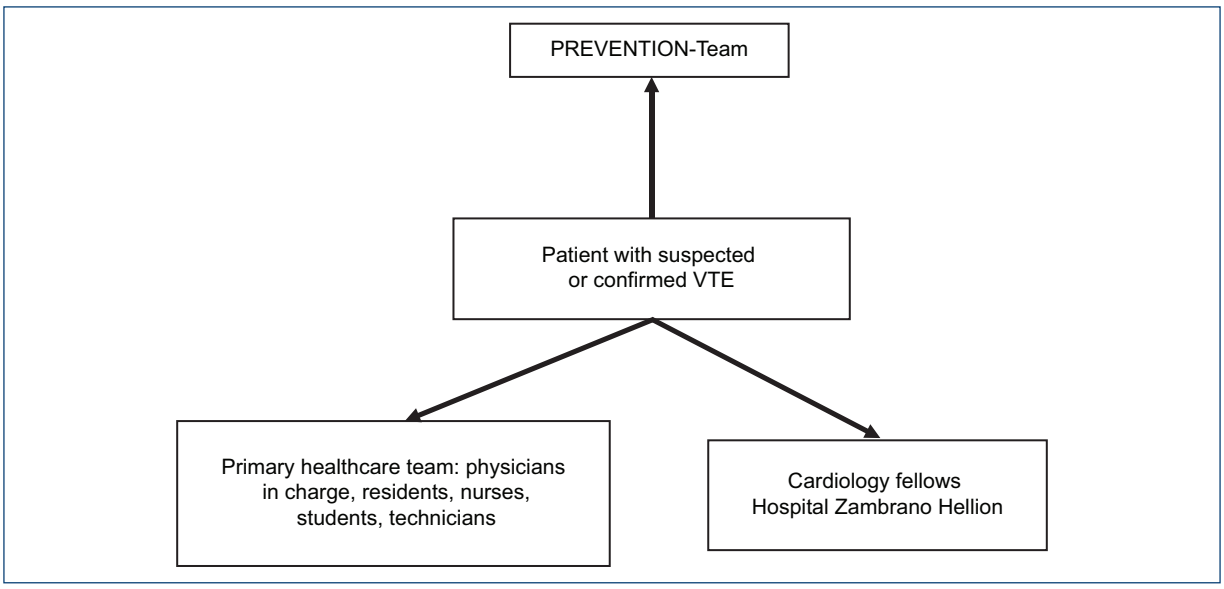

Figure 1. The PREVENTION-team is a patient-centered three-arm team where collaboration and effective communication is key for protocol success. VTE: venous thromboembolism.

advanced therapy will be by an experienced clinician and depends on the extension of the thrombus burden and right ventricular dysfunction severity. Secondary objectives: (1) in-hospital increased rate of low-risk PE and distal VTE patients; (2) exploration into the cause of PE as ensuring age-specific cancer-related screening, thrombophilia testing in patients <40 years with weak triggers, thrombus in unusual sites, or strong family history[10]; and (3) long-term anticoagulation management: election and length of anticoagulation, adherence, bleeding complications, and management. (4) To identify those with a high-risk profile for chronic thromboembolic disease, post-PE syndrome, chronic thromboembolic pulmonary hypertension, and PTS patients[10]. (5) To implement a prospective registry on Research Electronic Data Capture, an online platform high-quality surveys, and databases from Vanderbilt University supported by the National Institutes of Health (https://projectredcap.org/). (6) Organize community-based support groups, and patient education to improve adherence, to reduce recurrence, and bleeding complications, with de intention of extending the concept of the thrombosis-free hospital to thrombosis-free home.

PREVENTION-team: structure and organization

The multidisciplinary team includes physicians trained in cardiology, vascular medicine, angiology, echocardiography, cardiovascular imaging, and interventional cardiology. The team cornerstone will be the health-care team in charge (physician, nurses, residents, students, and technicians), cardiology fellows, and PREVENTION-team. Furthermore, effective coordination and communication will be mandatory for a successful program (Fig. 1). The team must be easily accessible and provide a consistent, rapid, and effective multidisciplinary response in the emergency room, intensive critical care unit, or in-hospital setting. The PREVENTION-team organization ensures a fast-track program to start specific treatment between 60 and 90 min after code activation, reproducing ST-elevation myocardial infarction, and ischemic stroke reperfusion programs.

PREVENTION-team: activation and execution

Table 1 shows the principal steps and the staff involved in the execution of the program. The first step of activation, which is based on clinical presentation (sudden dyspnea, near or syncope, chest pain such as angina, respiratory distress, and hypoxemia) suggests submassive or massive PE[13] or proximal DVT (leg pain and swelling). Therefore, the hospital staff must know the VTE risk factors and how to identify high-clinically suspicious patients. Before the official launch, we will conduct educational programs, round table discussions,

Table 1. Key steps, events, and personnel in the execution of the PREVENTION-team protocol

Phase	Key event (s)	Key members	
Pre-activation and activation	– VTE detection and/or suspicion by referring MD or member of the team in charge – A call placed to PREVENTION-team line	Referring MD Hospital residents	Nurses Medical students
Initial response	On-call cardiology fellow: – Calls back referring MD – Gathers case history – Notifies PREVENTION-team members of event and plans online meeting	On-call cardiology fellow Referring MD	
Response	– Online meeting – The case will be present by an on-call fellow with images and laboratory results – Consensus treatment will be mandatory – Treatment recommendation is given to the primary health-care team in written form	On-call cardiology fellow Referring MD PREVENTION-team	
Transfer	– Transfer patient to necessary department (ICU, OR, and catheterization laboratory)	On-call fellow Nurses and hospital staff	
Execution	– Carry out planned treatment – Immediate revascularization	Catheterization laboratory personnel OR personnel PREVENTION-team	

VTE: venous thromboembolism; ICU: intensive care unit; OR: operating room.

and case simulations geared toward hospital physicians, nurses, residents, students, and technicians. Furthermore, patient education will be mandatory to improve the outcome and reduce recurrence and bleeding complications in the follow-up.

An activation line will be available 24 h a day, 7 days a week, and 365 days a year. The cardiology fellow on call will be responsible for the protocol activation, immediate patient evaluation, and obtain imaging and laboratory studies to accelerate the diagnostic process and save time. This information will be present during an online meeting. The checklist called S_2HIELD_B (**S** signs and symptoms, **H** history, **I** image, **E** Electrocardiography, **L** laboratory, **D** demographics, and **B** bleeding risk) provides the team with the necessary information to establish a high-clinical suspicion, diagnosis, bleeding risk, and decision-making (Table 2). Risk stratification will be base on clinical presentation, echocardiogram, and biomarkers findings. Imaging techniques and or ultrasound will prove the final diagnosis.

After protocol activation, the on-call cardiology fellow will reach out to the PREVENTION-team through an electronic message. The team will be ready to hold an online conference as soon as possible (30 min), providing the on-call fellow enough time to assess the patient and obtain enough data to prove VTE accurately and PE diagnosis, quantify the venous thrombus burden and assess right ventricular dysfunction severity. Finally, within 60-90 min of the initial call, a treatment recommendation will be issued to the physician in charge. The program will follow-up on the clinical condition, treatment response, and in-hospital complications to consistently improve patient care. All information, including clinical data, risk factors, clinical presentation, electrocardiogram (ECG), chest X-ray, biomarkers, diagnosis studies, as well as, therapeutic approach, will be captured in an electronic database. On discharge, patients will have a follow-up in the outpatient clinic if the healthcare team deems it necessary.

We considered 60-90 min as a window based on (1) our previous experience[14-20], in which we perform stratification, diagnosis, and systemic thrombolysis in the first 90 min after PE patients arrive at the emergency room[15]; (2) thrombus resistance[21], right ventricular ischemia, and myocardial infarction[17] are all time-dependent; and finally, (3) evidence from mechanical and pharmacological reperfusion in ST-elevation myocardial infarction and ischemic stroke programs[11,22-24]. Furthermore, we will activate the cardiac catheter lab and transesophageal echocardiography units in specific cases. According to PERT MGH hospital stratification based on resources and medical specialties[9], Hospital Zambrano Hellion has Level 1 PERT; in other words, we have all the resources necessary to carry out a successful program. Recently,

Table 2. S_2HIELD_B: Mandatory data to collected after PREVENTION activation

Date:	**Time of activation/initial evaluation:/**		**Age and sex:**
Allergies: Yes/No	**Days in hospital: ____**	**Days symptomatic in hospital/at home: ____**	
Signs and symptoms		**History**	
Signs Systolic blood pressure: ____ Heart rate: ____ O_2 saturation: ____ **Symptoms** **Assess DVT:** Lower limb pain: Yes/No Swelling: Yes/No Erythema: Yes/No Homans sign: Yes/No Ollow sign: Yes/No	**Assess PE:** Dyspnea: Yes/No Ischemic like chest pain: Yes/No Near or syncope: Yes/No Cardiac arrest: Yes/No **Assess paradoxical embolism:** Headache: Yes/No Back pain: Yes/No Abdominal pain: Yes/No Paresthesia: Yes/No	VTE: Yes/No Obesity: Yes/No Recent infection: Yes/No Puerperium recent: Yes/No Pregnancy: Yes/No Major surgery recent: Yes/No Minor surgery recent: Yes/No Prolonged bed rest/trip: Yes/No Estrogen/OCP use: Yes/No Known active cancer: Yes/No	
Imaging			
Chest X-ray Westermark sign: Yes/No PA amputation: Yes/No	**Echocardiogram** RV dilation: Yes/No McConnell sign: Yes/No In-transit thrombus:Yes/No	**CT angiogram** Size: Location: Burden thrombus:	Lower limb **Doppler US** Thrombus: Yes/No Location: distal/ Proximal Burden Thrombus: Floating thrombus: Yes/No
	ECG	**Laboratory**	
Tachycardia: Yes/No Atrial fibrillation or flutter: Yes/No RBBB: Yes/No S1Q3T3: Yes/No	ST dynamic changes: Yes/No aVR ST elevation: Yes/No V1 qR and ST elevation: Yes/No RV strain overload: Yes/No	Hemoglobin: ____ Platelets: ____ BNP: ____ D-dimer: ____ High-sensitivity troponin I: ____ eGFR: ___	
Bleeding risk			
>65-75 years: Yes/No Female: Yes/No BMI < 24 kg/m^2: Yes/No Weight < 50-60 kgs: Yes/No Cancer: Yes/No INR > 2.5: Yes/No	Oral anticoagulation: Yes/No Recent major surgery: Yes/No Uncontrolled hypertension: Yes/No eGFR < 30 ml Liver/kidney disease: Yes/No	Bleeding predisposition: Yes/No Alcohol abuse: Yes/No Thrombocytopenia: Yes/No History of stroke: Yes/No	

DVT: deep venous thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; OCP: oral contraceptive pills; PA: pulmonary artery; RV: right ventricle; RBBB: right bundle branch block; BNP: B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; INR: international normalized ratio.

the impact of PERT MGH was demonstrated by a significant mortality reduction (25%) in massive PE compared with the previous registries[25]. This evidence suggests that a rapid response team can modify in-hospital outcomes in a group of patients with high mortality risk.

PREVENTION-team: therapeutic approach

Anticoagulation

The foundation of VTE treatment is anticoagulation, and advanced therapy is the option in impending or clinically unstable patients. Table 3[11,26,27] shows anticoagulation options in the acute phase, long-term, and extended phase. Unprovoked VTE, recurrence, active cancer, proved or strong suspicion of thrombophilia and a persistently abnormal D-dimer required long-term anticoagulation. In patients with DVT with or without PE, we suggest low-molecular-weight heparin, enoxaparin instead of unfractionated heparin. Furthermore, non-Vitamin K antagonist oral anticoagulants are effective and possess a safer profile compared to Vitamin K antagonists (Table 3). Anticoagulation alone is recommended in low-risk PE patients (clinical stability, no biomarkers expression, without severe right ventricular dysfunction, and moderate thrombus burden); the route

Table 3. Parenteral and oral anticoagulants[11,26,36]

Acute phase	**Weight-adjusted unfractionated heparin** 1. Unfractionated heparin 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U) **Standard unfractionated heparin regimen** 2. Unfractionated heparin 80 U/kg bolus followed by 18 U/kg/h infusion **Low-molecular-weight heparin** 3. Enoxaparin intravenous bolus 30 mg followed by subcutaneous injection (1 mg/kg BID or 1.5 mg/kg ONCE); in patients > 75 years no bolus and 0.75 mg/kg BID **Non-vitamin K antagonist oral anticoagulants (NOACs)** 4. Apixaban: 10 mg twice daily for 7 days, followed by 5 mg twice daily 5. Rivaroxaban: 15 mg twice daily for 3 weeks, followed by 20 mg daily
Long-term anticoagulation (3-6 months) and Extended treatment (> 6 months)	**Vitamin K antagonists** Warfarin 5 mg daily, overlapped with heparin for first 5 days until two consecutive INR in therapeutic ranges (2-3), and then dose-adjusted to maintain INR 2-3 **Low-molecular-weight heparin** In patients with active cancer: subcutaneous injection 40 mg ONCE **NOACs** Dabigatran: 150 mg BID Apixaban: 5 mg or 2.5 mg BID Rivaroxaban: 20 mg or 15 mg ONCE

NOACs: non-Vitamin K antagonist oral anticoagulants; INR: international normalized ratio.

of administration regimen and type will be up to the preference of the physicians in charge. In the extended phase, the low-molecular-weight heparin, enoxaparin, is indicated in active cancer patients. Unfractionated heparin is an option in severe kidney diseases, high-risk bleeding, >75 years, hypotension, impending clinical instability patients, and as adjunctive treatment[11]. We recommend enoxaparin in low-risk PE patients starting with an intravenous bolus, except in elderly patients in whom a dose reduction is mandatory (Table 3)[11]. Loading apixaban or rivaroxaban doses are an effective and safe option in low-risk PE patients. In intermediate-risk, also called submassive PE, we recommend weight-adjusted unfractionated heparin for the first 24-48 h, over enoxaparin to avoid heparin crossover if clinical status worsens. The use of unfractionated heparin as adjunctive treatment with a posterior switch to enoxaparin is a worldwide recommendation. This regimen was effective and safe, without intracranial hemorrhage in Mexican PE patients submitted to systemic thrombolysis[15].

Advanced therapy

DVT thrombolysis and percutaneous thrombectomy

Although there are not recommendations to systemic thrombolysis in iliofemoral DVT patients[26], we recommend catheter-directed thrombolysis with alteplase at a dose of 0.01 mg/kg/h (maximum 1 mg/h) for iliofemoral DVT (Table 4)[11]. This therapeutic approach could reduce thrombus burden and venous hypertension, restore venous permeability, rescue limb in case of ischemia, and decrease PE risk. We also recommend percutaneous mechanical or pharmacomechanical thrombolysis. Various percutaneous devices are available with different mechanical principles for the removal of clot or thrombolysis: suction, rotation, rheolytic thrombectomy, and ultrasound[28-31]. The pharmacoinvasive approach combines the mechanical method and pharmacologic therapy to achieve thrombolysis[32]. This approach has shown to be effective with a lower dose of the thrombolytic drug and shorter procedural time with no difference in major bleeding or recurrence[33]. As part of the thrombectomy procedure, we recommend the use of a prophylactic vena cava filter, as 17% of patients treated suffered asymptomatic PE demonstrated on computed tomography scans[34]. These filters should be removed as soon as possible[35]. When DVT occurs in the left iliac vein, we encourage the use of intravascular ultrasound to diagnose iliac compression (May-Thurner syndrome)[36]. If an iliac obstruction, residual thrombus or iliac stenosis is observed, angioplasty and dedicated vein stents use must be considered to improve patency[28].

PE thrombolysis

International and national guidelines[26,27-38] recommend unfractionated heparin as adjunctive treatment and systemic thrombolysis in a well-selected (Table 5)[11]

Table 4. Anticoagulation and advanced therapy in venous thromboembolism patients[11,26,36,37,38]

Distal deep venous thrombosis	**Anticoagulation** **Weight-adjusted unfractionated heparin** Unfractionated heparin 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U) **Standard unfractionated heparin regimen** Unfractionated heparin 80 U/kg bolus followed by 18 U/kg/h infusion **Low-molecular-weight heparin** Enoxaparin intravenous bolus 30 mg followed by subcutaneous injection (1 mg/kg BID or 1.5 mg/kg ONCE); in patients > 75 years no bolus and 0.75 mg/kg BID **Non-Vitamin K antagonist oral anticoagulants (NOACs)** Apixaban: 10 mg twice daily for 7 days, followed by 5 mg twice daily Rivaroxaban: 15 mg twice daily for 3 weeks, followed by 20 mg daily
Proximal deep venous thrombosis	**Adjunctive treatment** **Weight-adjusted unfractionated heparin** Unfractionated heparin 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U) **Standard unfractionated heparin regimen** Unfractionated heparin 80 U/kg bolus followed by 18 U/kg/h infusion **Catheter-directed thrombolysis** Alteplase, 0.01 mg/kg/h (maximum 1 mg/h) **Ultrasound-facilitated catheter-directed thrombolysis (USCDT)**
Low-risk PE	**Anticoagulation** **Weight-adjusted unfractionated heparin** 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U) **Low-molecular-weight heparin** Enoxaparin intravenous bolus 30 mg followed by subcutaneous injection (1 mg/kg BID or 1.5 mg/kg ONCE); in patients > 75 years no bolus and 0.75 mg/kg BID **Non-Vitamin K antagonist oral anticoagulants (NOACs)** Apixaban: 10 mg twice daily for 7 days, followed by 5 mg twice daily Rivaroxaban: 15 mg twice daily for 3 weeks, followed by 20 mg daily
Intermediate risk/ submassive PE with or without impending clinical instability	**Weight-adjusted unfractionated heparin** 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U) and close monitoring of blood pressure, oxygen saturation, heart and respiratory rate (consider thrombolysis in case of impending or hypotension or clinical instability) **Ultrasound-facilitated catheter-directed thrombolysis (USCDT)** USCDT × 2 h with alteplase infusion at 2 mg/h/catheter (range 4-8 mg; 1 vs. 2 lungs)
A high-risk or massive PE or submassive PE with impending clinical instability	**Adjunctive treatment** **Weight-adjusted unfractionated heparin** 60 U/kg bolus (maximum 4000 U) followed by 12 U/kg infusion (maximum 1000 U)/24 h or 48 h followed by enoxaparin 1 mg/kg BID or 1.5 mg/kg ONCE/5 days or apixaban or rivaroxaban **Systemic thrombolysis** 50 mg of alteplase in 1-2 h in > 60 years 100 mg of alteplase in 1-2 h in < 60 years Weight-adjusted tenecteplase bolus in < 60 years: 30 mg < 60 kg, 35 mg 60-70 kg, 40 mg 70-80 kg, 45 mg 80-90 kg, 50 mg > 90 kg **Catheter-directed thrombolysis** 30 ± 10 mg of alteplase **Pharmacoinvasive approach** Thrombus fragmentation with pigtail catheter, 20 mg alteplase infusion in the pulmonary artery and manual or percutaneous aspiration with aspiration device (Aspirex or Pronto) **Ultrasound-facilitated catheter-directed thrombolysis (USCDT)** USCDT × 2 h with alteplase infusion at 2 mg/h/catheter (range 4-8 mg; 1 vs. 2 lungs)
Absolute contraindication for anticoagulation or thrombolysis	**Venous cava filter** Removed temporary filters between day 24 and 54 after placement.

high-risk or massive PE patient (IIb). European and American College of Chest Physicians[27,37] recommendations are against thrombolysis in intermediate high-risk or submassive PE patients because of the increased rate of intracranial hemorrhage[39]. The PEITHO study[40] and additional previous evidence have shown in-hospital improvement outcome, with systemic thrombolysis[14,16,17,19] in this group. Considering current and previous evidence, we recommended weight-adjusted unfractionated heparin as adjunctive treatment and systemic thrombolysis (IIB) in a well-selected high-risk or massive PE patient. We recommend half dose

Table 5. Absolute contraindications for thrombolysis[11]

Previous intracranial hemorrhage Structural cerebrovascular disease Intracranial malignant neoplasm Active bleeding (especially gastrointestinal in last 30 day	Aortic dissection or suspicion of Recent cranial surgery or facial trauma with evidence of fracture or cerebral lesion INR > 2.5 Stroke in past 3 months

INR: international normalized ratio.

Table 6. Therapeutic alternatives in high-risk bleeding patients[11,42]

Low-dose catheter-directed thrombolysis (alteplase 20-40 mg) **OPTALYSE study:** treatment arm 1 (alteplase 2 mg/lung/2 h) and treatment arm 2 (alteplase 2 mg/lung/4 h)	Invasive pharmacological treatment with thrombi fragmentation and aspiration Surgical embolectomy Vena cava filters

short-term alteplase infusion (Table 4), instead tenecteplase in patients over 60 years considering the high incidence of intracranial hemorrhages, especially in female patients. At present, to the best of our knowledge, half dose short-term alteplase infusion has no evidence of intracranial hemorrhage in the elderly population[40]. Furthermore, we recommend 1 or 2 h 100 mg alteplase infusion or tenecteplase in a bolus in patients <60 years. Avoid unnecessary venous or arterial punctures to reduce major or minor bleeding complications. Systemic thrombolysis would be an important therapeutic option in intermediate-high-risk or submassive PE with impending clinical instability[11] defined with at least one: oxygen desaturation <90%, respiratory distress, blood pressure in lower limits, advanced degree right branch block, severe global right ventricular hypokinesis, tricuspid annular plane systolic excursion <13 mm, high measurements of cardiac I troponin high-sensitivity, and B-type natriuretic peptide.

We recommend pharmacoinvasive therapy in patients with intermediate- or high-risk bleeding complications since this therapeutic approach showed efficacy and safety in the Mexican population[41]. Recently, the OPTALYSE trial[42] significantly reduced alteplase dose and procedure time compared with previous ultrasound-facilitated catheter-directed thrombolysis studies[43,44] (Table 6). The OPTALYSE approach improves the inadmissible long-term infusions (~12 h) in cardiogenic shock or low cardiac output syndrome patients through a low-dose ultrasound-facilitated catheter-directed thrombolysis. Although alteplase 2 mg in 2-h short infusion had no major bleeding complications in a broad clinical PE spectrum, including submassive PE patients, we will recommend 4 mg to obtain a better reperfusion[42] (Table 4). Finally, we recommend temporary inferior vena cava filters in patients with absolute contraindications for anticoagulation and thrombolysis in probed proximal DVT with or without in-transit thrombus patients[11] (Table 4).

Patent foramen oval (PFO) and clinical or subclinical paradoxical cerebral or systemic emboli are frequent and an underestimated complication in submassive and massive PE patients[45]. Transesophageal echocardiogram identifies a high incidence of PFO (56%) and cerebral magnetic resonance a high incidence (17%) of subclinical ischemic stroke-related with a large shunt in submassive PE patients. Hemorrhagic transformation of subclinical ischemic stroke[45] could explain unexpected intracranial hemorrhages after anticoagulation alone or advanced therapy in PE patients. Transthoracic echocardiogram with peripheral intravenous agitated saline bubbles to screen for PFO is mandatory[45]. PREVENTION-team should look for symptoms or signs suggesting central or systemic embolism in the clinical evaluation of high-clinical suspicion PE patients (Table 2).

Research and educational activities

Members of the core team will be the steering committee for all PREVENTION-team activities. Secondary objectives include leading research protocols, creation of support groups, and expand our network. We will set into an online database that will store all information regarding demographics, clinical presentation, therapeutic and diagnosis approaches, as well as the overall outcome for further research and analysis. Expansion of the network will allow us to implement our system in another clinical setting, identify possible loopholes not evident at our hospital, and further improve awareness of VTE. The creation of support groups creates a feeling of identification among patients, improving their well-being and health care. The PREVENTION-team will hold monthly meetings to review protocol activations, assess the response of the team, and troubleshoot and address any system issues. Educational activities, such as clinical case presentations and discussions, teaching sessions, and case simulations, will be important to maintain program quality.

Although the main target of the program is an optimal fast-track treatment in VTE patients, primary or secondary prevention to reduce incidence or recurrence will be mandatory. We have had in-hospital strategies (thrombosis-free hospital), such as thrombosis risk stratification and pharmacologic and no-pharmacologic primary prevention to reduce VTE events for many years; however, these kinds of strategies lack at home. We identified that over 70% of PE patients come from a hospital outside. Thus, we propose patient and family education to stimulate early VTE recognition, identify trigger factors, and implement secondary no-pharmacologic prevention to extend the concept of a thrombosis-free hospital to a new concept: a thrombosis-free home.

Discussion

VTE is a major health problem, annually affecting 108 people per 100,000[46] and in the United States 300,000-600,000[47]. The chronic complications of VTE increase mortality, decrease functional class and quality of life, and increase health-care costs. Patients with PTS increase the cost (2-10 billion dollars annually)[47] in the United States (7000) and Canada (4527) compared with DVT patients[7]. PE is the cause of preventable in-hospital and home mortality through pharmacologic or non-pharmacologic primary or secondary prevention. Considering the link between DVT and PE[5,6], its high recurrence[48], and the high health systems costs[7], DVT should not be underestimated[48]. In the PREVENTION-team, we include the broad clinical spectrum of VTE to perform a fast-track risk stratification, multimodal diagnosis, and treatment to improve PE and DVT patient care. Another important objective will also be to increase the detection of in-hospital and in the emergency room of low-risk PE patients, whose impact and prevalence are not well defined.

At present, national and international guidelines lack the strong class of recommendation and level of evidence (IA) and do not yet consider new therapeutic approaches[11,26,27]. Furthermore, there is an underuse of systemic thrombolysis even in high-risk PE due to a fear of bleeding complications, and we do not have any evidence or recommendations in octogenarian and nonagenarian patients. Although systemic thrombolysis is a dark zone in intermediate high-risk or submassive PE patients, those with impending clinical instability should be eligible. In addition, treatment decision-making more often is based on personal medical experience[9] instead of consensus discussion among experts. We hope that PREVENTION-team unifies risk stratification, diagnosis, and therapeutic approach through a coordinated action among health system staff to improve the quality of VTE patient care in our hospital.

The first "Mexican PERT"

In 1993, we performed the first successful systemic thrombolysis in a massive PE patient in Mexico[17], following the lesson from the first national program on systemic fibrinolysis in ST-elevation myocardial infarction in the emergency room at Cardiology Hospital of the National Medical Center, IMSS. Shortly after that, we launched a successful open-label, randomized control trial proving that short-term streptokinase infusion by peripheral vein compared with unfractionated heparin reduces mortality in cardiogenic shock and massive PE patients[19]. The emergency, nuclear medicine, and echocardiography teams were activated quickly and efficiently, and systemic thrombolysis was delivered in the first 90 min after patient arrival at the emergency room department. The next challenge was to reproduce this approach 24 h a day, 365 days a year. All emergency physicians received training in echocardiography to improve patient care, and in the case of V/Q lung scan unavailability, in high clinical suspicion patients with clinical, ECG, and echocardiographic findings of severe pulmonary hypertension and right ventricular dysfunction with impending clinical instability or hypotension, an experienced physician administered thrombolysis by peripheral vein. Following this strategy, we perform successful systemic thrombolysis in 11 PE patients[16]. European Cardiology Society guidelines provide for this approach IC evidence level[27].

In another hand, the process was very slow and complicated in submassive PE patients. In this group, although echocardiogram aided in the evaluation of the right ventricular function, the support of the departments of echocardiography and nuclear medicine had delays of up to 24 h[16]. Hence, we launched a working group, including physicians of the emergency room department and heads of echocardiography and nuclear medicine departments. After several meetings, we were able to agree in a significant reduction (90 min) of the time needed to perform the studies. Eight years later, in 2009, we perform our second 24 h a day, 365 days a year fast-track program for thrombolysis in submassive, impending clinical instability, and massive PE patients[15]. In this period, we perform under high clinical suspicion, ECG, and echocardiography findings successful thrombolysis in 8 PE patients. The time to perform risk stratification, diagnosis, and systemic thrombolysis treatment were around 60 min in submassive and massive PE[15].

The need to improve PE patient care

Nineteen years after our fast-track programs for thrombolysis in massive[19] and submassive[16] PE patients, the first formal PERT[9] emerged as a priority need to deliver rapid assessment and treatment of patients whose clinical condition is deteriorating but are not yet in shock or cardiac arrest[49]. The PERT consortium was then officially inaugurated in 2015, to create a sense of community where the different PERT programs across the world could share their experiences and work together and improve patient care. The design of our program is based on the already existing protocols and in our 24 years of experience[14-20]. We add some characteristics obtained from our experience with the entire clinical spectrum of VTE in mind what increases the quality of the program. With the implementation of the PREVENTION-team program, we look to provide fast, efficient, and time-saving treatment, potentially preserving lives and reducing bleeding and chronic complications in VTE patients. Furthermore, we will try to increase detection of low-risk PE. The success of the program will be the rapid and efficient communication among paramedic staff, technicians, residents, fellows, medical students, and physicians. Furthermore, the proper layout, functioning, and usage of the resources will be determinant in protocol success.

Finally, the activation of the PREVENTION-team program will pave the way for research and educational activities, including grand rounds, innovation projects, teaching sessions, and case discussion. Furthermore, another objective is to inspire consciousness among the hospital community, creating a learning environment and experience for everyone, and increasing the quality program. At present, although we have strategies including risk questionnaires at admission, compression stockings, or primary pharmacologic prevention to prevent in-hospital VTE, preventive strategies are lacking at home for patients with the same VTE high-risk. Finally, considering these observations, it is mandatory to extend the concept of the thrombosis-free hospital to the thrombosis-free home.

VTE is a very common cardiovascular disease with high morbidity and mortality, increased health-care costs, and complex treatment. Current VTE treatment is not standardized and depends on individual decisions of several medical specialties related to patient care (pulmonologists, cardiologists, internal medicine, surgeons, etc.). In addition, to the best of our knowledge, there are no available fast-track advanced programs in Mexico. Furthermore, international and national guidelines for PE management[11,26,27] do not include a specific door-to needle timeframe to initiate advanced therapy, even though right ventricular ischemia and thrombus resistance are time dependent. Therefore, it is imperative to improve health care through an expert-conformed multidisciplinary team to fast-track stratification and optimal treatment to improve the outcome and long-term complications of VTE patients. PREVENTION-team links a group of physicians with different areas of expertise, guaranteeing collective, and synchronized medical care. We hope to create a strong network and inspire physicians, fellows, residents, nurses, medical students and staff of our hospital and health system not only to be aware of the problem but also enrich themselves with the necessary tools to diagnose and offer the best treatment possible.

Conflicts of interest

None.

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Ethical disclosures

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

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

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

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ARTÍCULO DE INVESTIGACIÓN

Implementación del tamizaje diagnóstico de cardiopatías congénitas en Hidalgo, México

Implementation of diagnostic screening for congenital heart disease in Hidalgo, Mexico

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Resumen

Objetivo: *Implementar el tamizaje mediante la oximetría de pulso (OP) y un modelo de gestión del conocimiento (MGC) para la detección oportuna de cardiopatías congénitas (CC) que amenazan la vida en el período neonatal.* **Material y métodos:** *Estudio piloto de implementación de OP apoyado en criterios clínicos, realizado en recién nacidos (RN) de dos hospitales públicos de Hidalgo. Los pacientes que resultaron positivos fueron objeto de ecocardiografía (EC) y los diagnosticados con cardiopatías congénitas críticas (CCC) se refirieron a tratamiento.* **Resultados:** *Se tamizó a 1,748 RN (29 positivos), CC en 62% y CCC en 13.8 %, 1 muerte y 3 programados para operación paliativa.* **Conclusiones:** *La OP ayuda en el diagnóstico de CC en combinación con criterios clínicos y EC. Un MGC favorece la innovación y la gestión de recursos.*

Palabras clave: *Oximetría. Gestión del conocimiento. Tamiz. Cardiopatía congénita.*

Abstract

Objective: *Implementing screening through pulse oximetry (PO) and a knowledge management model (KMM) for early detection of life-threatening congenital heart disease (CHD) in the neonatal period.* **Material and methods:** *Pilot study of PO implementation supported by clinical criteria performed in newborns at two public hospitals of Hidalgo State. Those who tested positive were referred for echocardiography and those diagnosed with critical CHD (CCHD) were referred to specialized hospitals for treatment.* **Results:** *1748 newborns were screened: 29 positive, 62% with CHD and 13.8% with CCHD, one death, three referrals to palliative treatment.* **Conclusion:** *PO as a method of screening helps in early diagnosis of CHD added to clinical and echocardiography studies. KMM fosters innovation and resource management.*

Key words: *Oximetry. Knowledge management. Screening. Congenital heart disease.*

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Introducción

Las anomalías congénitas graves más comunes que se presentan al nacimiento son las cardíacas (8 a 11 por cada 1,000 RNV)[1,2], con una mortalidad del 18 al 25% en el primer año de vida; algunas no pueden diagnosticarse antes o en el momento del fallecimiento[3,4]. Alrededor de una cuarta parte de estos niños tendrá una cardiopatía congénita crítica[5] potencialmente letal[6]. Los RN que egresan sin diagnóstico corren el riesgo de sufrir colapso cardiovascular y muerte, por lo que la detección temprana es crucial para cambiar el pronóstico[7]. En México se registraron 17,596 muertes por CC en menores de un año en un período de cinco años (2010 a 2014), 346 de las cuales ocurrieron en el estado de Hidalgo[8].

Medir la saturación de oxígeno (SO_2) mediante OP en RN para identificar hipoxemia aumenta la detección temprana de las CCC[9]. La OP es una prueba no invasiva con alta especificidad y sensibilidad moderada para reconocer CCC[10,11] y desde el 2011 se ha recomendado como parte de la detección en los RN[12]. En este trabajo se analiza la implementación de la OP para proponer un programa de tamizaje cardíaco neonatal (TCN) en el estado de Hidalgo.

Material y métodos

Se llevó a cabo un estudio piloto descriptivo observacional durante seis meses para analizar la utilidad de la OP como TCN. Con anterioridad se establecieron acuerdos de referencia para el tratamiento en hospitales especializados de la Ciudad de México. Este estudio recibió aprobación del comité de ética e investigación del Hospital del Niño DIF-Hidalgo (HND-H).

Población de estudio

Se incluyó a todos los RN del Hospital Obstétrico (HO) y Hospital General (HG) de Pachuca de los servicios de salud de Hidalgo (SSH). Las pruebas se realizaron en los RN en alojamiento conjunto en las primeras 24 a 72 horas de vida.

Procedimientos

Mediante el MGC se identificaron necesidades de fortalecimiento y se desarrollaron competencias en comunidades de práctica para generar, almacenar, distribuir y utilizar el conocimiento entre el personal operativo, mandos medios y directivos, así como para la gestión de recursos humanos, financieros y de equipamiento.

Tras estandarizar la técnica de tamizaje se registró información mediante formas de informe de caso y una máscara de captura en el software Microsoft Access.

Se efectuó OP en dos sitios: preductal (prd) en mano derecha y postductal (pod) en cualquier pie, colocando el sensor entre los dedos índice y medio de la mano y entre el segundo y tercer dedos del pie, en zonas translúcidas y con buen flujo sanguíneo.

Se utilizó el algoritmo de tamizaje para CCC recomendado por la American Academy *of Pediatrics* con tres resultados posibles[11]:

1. **Negativo (neg):** SO_2 de 95% o más en ambas lecturas (prd y pod) o cuando la diferencia entre éstas era $\leq$ 3%.
2. **Positivo inmediato (PI)**: SO_2 < 90% prd o pod en el primer registro.
3. **Positivo (P)**: Resultado de tres pruebas positivas. SO_2 entre 90 y 95% (prd y pod) o una diferencia de saturación > 3% entre ambos sitios en el primer registro; se realizó otra medición una hora después de la primera y se dio por terminada la prueba si resultaba negativa; cuando era positiva se repetía una hora después de la segunda.

Seguimiento de resultados anormales

Con los resultados PI o P hubo valoración clínica por el jefe de pediatría y, en su caso, envío para confirmación diagnóstica mediante evaluación clínica y EC en el Hospital del Niño DIF-Hidalgo (HND-H); los casos de CCC se enviaron al Hospital Infantil de México Federico Gómez (HIM-FG) para tratamiento quirúrgico y los de cardiopatía simple (CS) recibieron seguimiento en el HND-H.

Análisis estadístico

Descripción mediante tablas y gráficas de datos demográficos y, para la SO_2, distribución de frecuencias y medidas de tendencia central; se realizó análisis de calidad de la oximetría: sensibilidad, especificidad y valores predictivos positivo y negativo; además, se determinó la relación entre los resultados del tamiz y los de EC. Paquete estadístico SPSS para Windows, 2013.

Equipos

Oxímetros Radical-7®-Masimo para la OP en condiciones de movimiento y baja perfusión (Masimo-SET®),

Tabla 1. Características de la población de estudio

		n = 1748	SDG† $\bar{x}$ ± DE	VN‡		Peso en kg $\bar{x}$ ± DE	HT¶ $\bar{x}$ ± DE	SO2§ ± $\bar{x}$ DE
				V	A			
HGP*	H M	n = 517 (51.1%) n = 494 (48.9%)	39 (± 1) 38.91 (± 1.48)	218 (42.2%) 210 (42.5%)	299 (57.8%) 284 (57.5%)	3.02 (± 0.45) 2.94 (± 0.46)	29 (± 11) 30 (± 11)	
HO**	H M	n = 350 (47.5%) n = 387 (52.5%)	39.04 (± 0.96) 39.15 (± 0.97)	230 (65.7%) 252 (65.1%)	120 (34.3%) 135 (34.9%)	3.11 (± 0.43) 3.07 (± 0.39)	27 (± 10) 27 (± 10)	prd 96.18 % (± 2.45)
TOTAL	H M	n = 867 (49.59%) n = 881 (50.41%)	39 (± 1)	910 (52%)	838 (48%)	3.03 (± 0.44)	28 (± 11)	pod 96.59 % (± 2.29)

*Hospital General de Pachuca.
**Hospital Obstétrico.
†Semanas de gestación
‡Vía de nacimiento (V: vaginal; A: abdominal).
¶Hora de vida extrauterina en que se realizó el tamizaje.
§Saturación de oxígeno (prd: preductal; pod: postductal).
Fuente: Registro de Tamizaje Cardíaco Neonatal (TCN) por oximetría de pulso de la Dirección General de Proyectos Estratégicos de Salud – Secretaría de Salud de Hidalgo.

software especializado para el TCN (Eve™) y sensores Newborn desechables (Masimo-Rainbow®SET)[13].

Ecocardiógrafo Philips HD 11 XE para los EC, software Qlab, imagenología Doppler tisular y un intervalo de frecuencias de transductor de 1 a 15 MHz para aplicaciones neonatales[14].

Resultados

Durante seis meses se tamizó a 1,748 RN del HG (n = 1,011, 57.8%) y HO (n = 737, 42.2%), 49.59% hombres y 50.41% mujeres, con 39 ± 1 SDG; por vía vaginal nació 52% y por vía abdominal 48%; peso de 3.03 ± 0.44 kg; hora de tamizaje a las 28 ± 11 horas de vida extrauterina; la media de SO_2 prd fue de 96.18% y la de pod de 96.59% (Tabla 1).

En la primera medición, el 95.5% fue negativo, 0.7% positivo inmediato y el resto positivo (3.8%); una hora después sólo el 43 % de los positivos se mantuvo en ese estado y dos horas después el 72.41% de éstos se registró como positivo (Fig. 1). Se realizaron 29 EC, de los cuales se confirmaron 14 casos de cardiopatías simples y 3 de CCC (Fig. 2); se identificó una relación (χ^2 = 979, p > 0.05) entre los resultados del tamiz y la confirmación por EC (Fig. 1). Además se identificó una CCC por clínica que no requirió tamizaje.

Se diseñaron procedimientos operativos para la referencia de casos con tamiz P o PI y procesos de comunicación directa por vía telefónica del jefe de servicio de pediatría del HO y el HG con el cardiólogo para gestionar fecha y hora de evaluación clínica y EC en el HND-H. Otro procedimiento sirvió para la gestión de la adquisición y distribución de PgE_1 a través del REPSS para apoyar a los RN dependientes del conducto.

En RN dependientes del conducto, el cardiólogo inició tratamiento farmacológico en la Unidad de Cuidados Intensivos Neonatales del HG con uso de PgE_1 a dosis de 0.05 a 0.1 pg/kg/min de inicio, se valoró su efectividad con la SO_2 y se cuidaron las reacciones adversas conocidas. Asimismo, se redujeron los estímulos al mínimo para evitar estrés, se mantuvo la normotermia y se suministraron soluciones parenterales con dextrosa al 10% y bicarbonato de sodio.

El cardiólogo local envió al Servicio de Cardiología del HIM-FG a todos los casos de CCC y se consideraron como pacientes elegibles para operación a los RN mayores de 37 SDG, peso mayor de 2,850 g, sin dificultad respiratoria y sin datos de infección.

En el HIM-FG se establecieron dos opciones terapéuticas de acuerdo con las condiciones del neonato:

1. Si el caso podía atenderse en forma ambulatoria, se citó al paciente a consulta externa y se registró en lista de espera para operación paliativa.
2. Los casos graves ingresaron a la Unidad de Cuidados Intensivos para tratamiento médico-quirúrgico.

Una vez establecido el tratamiento quirúrgico paliativo, se realizó contrarreferencia al hospital de procedencia con tratamiento indicado de acuerdo con el tipo de cardiopatía y seguimiento en el HIM-FG hasta los 18 años de edad. De las cuatro CCC, tres requirieron intervención paliativa y sobrevinieron dos muertes (Tabla 2).

En este estudio se desarrollaron las competencias necesarias para implementar el tamiz cardíaco neonatal, procedimientos para el diagnóstico y sistema de vigilancia epidemiológica en dos hospitales públicos de los SSH, además de establecer el vínculo y la referencia para su tratamiento paliativo en hospitales de tercer

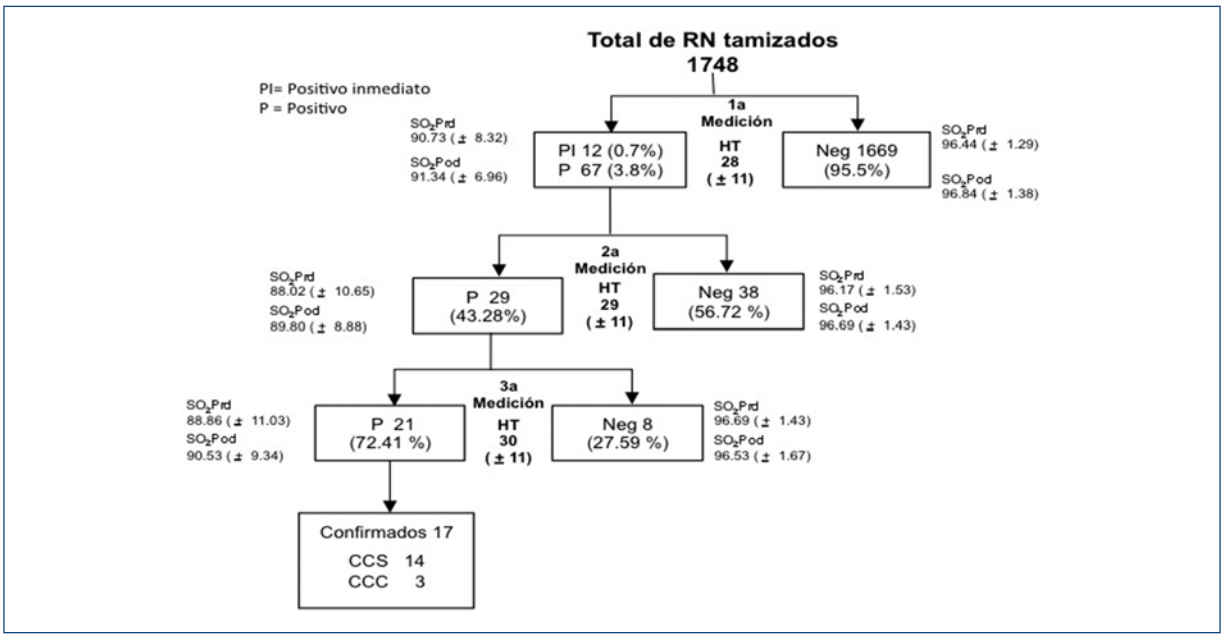

Figura 1. Resultados de la implementación del tamizaje cardíaco neonatal. Se muestran los resultados de la implementación de la prueba piloto del tamizaje cardíaco neonatal mediante oximetría de pulso. Los casos de tamiz P y PI se confirmaron con ecocardiografía.
SO_2: saturación de oxígeno; Prd: preductal; Pod: postductal; P: positivo; PI: positivo inmediato.
Fuente: Registro de Tamizaje Cardíaco Neonatal (TCN) por oximetría de pulso y Registro de Ecocardiogramas y Seguimiento de Recién Nacidos con Sospecha de Cardiopatía después del TCN de la Dirección General de Proyectos Estratégicos de Salud – Secretaría de Salud de Hidalgo.

nivel y el control farmacológico inicial de estas anomalías (Fig. 3).

También se destacó el desarrollo de competencias de gestión y se logró la adquisición de prostaglandinas E_1 (PgE_1) necesarias para el tratamiento inicial de cardiopatías dependientes del conducto. Para tal propósito se diseñó el algoritmo que establece la vía, adquisición y suministro de manera oportuna (Fig. 3).

El sistema de salud del estado de Hidalgo, y en general del país, no considera las cardiopatías congénitas en el registro formal de la morbilidad; sólo se tienen datos aislados de estas alteraciones y por lo general se utiliza la clasificación de la CIE-10 Q24[9] (malformación congénita cardíaca no especificada), por lo que no se cuenta con la incidencia de estos defectos al nacimiento.

Para iniciar el registro de las cardiopatías congénitas se diseñó el estudio epidemiológico de defectos cardiovasculares validado por la Subdirección de Epidemiología de los SSH. A partir de la confirmación por EC de estos casos, se inició el llenado del estudio y el registro en el Sistema Único de Información para la Vigilancia Epidemiológica (SUIVE) en el apartado "otras enfermedades de interés local o regional", por lo que es posible contar con el registro de la morbilidad de estas malformaciones al nacimiento (Fig. 3). El Servicio de Cardiología del HND-H mantiene en seguimiento a las CS.

Discusión

La NOM 034 SSA2 2013[15] establece que los defectos al nacimiento deben buscarse de manera intencionada durante la exploración de los RN mediante estudio clínico y, en caso de sospecha, hay que estabilizarlos y referirlos para diagnóstico, tratamiento y seguimiento. También establece que la cardiopatía fetal debe diagnosticarse por ultrasonido a partir de la semana 18° de gestación; éstas son las malformaciones más difíciles de diagnosticar antes del nacimiento, por lo que existe una proporción significativa de RN afectados sin diagnóstico[16,17], situación que se agrava por las tendencias al egreso temprano[18]. Para las unidades hospitalarias de los SSH no ha sido factible casi nunca tratar este tipo de padecimientos porque no cuentan con la infraestructura y recursos específicos y resulta complicado el traslado de estos pacientes a los centros de alta especialidad en la Ciudad de México, tal y como lo reflejan las 177 muertes por CC no especificadas y 17 CCC entre los años 2009 y 2013[19].

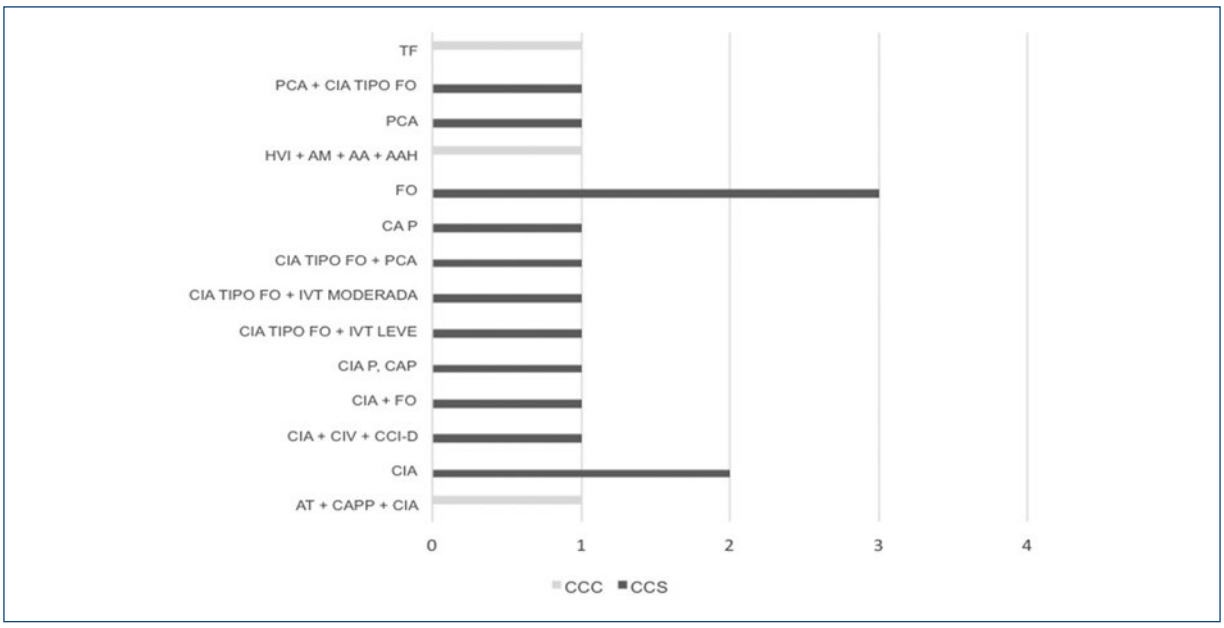

Figura 2. Número y tipos de cardiopatías identificadas mediante ecocardiograma después del tamiz. Se muestran las cardiopatías diagnosticadas.
TF: tetralogía de Fallot; PCA: persistencia del conducto arterioso; CIA: conducto interauricular; FO: foramen oval; HVI: hipoplasia ventricular izquierda; AM: atresia mitral; AA: atresia aórtica; AAH: arco aórtico hipoplásico; CAP: conducto arterioso permeable; IVT: insuficiencia valvular tricuspídea; CIA P: conducto interauricular pequeño; CIV: comunicación interventricular; CCI-D: cortocircuito izquierda-derecha; AT: atresia tricuspídea; CAPP: conducto arterioso pequeño permeable; CCC: cardiopatías congénitas complejas; CCS: cardiopatías congénitas simples.
Fuente: Registro de Ecocardiogramas y Seguimiento de Recién Nacidos con Sospecha de Cardiopatía después del TCN de la Dirección General de Proyectos Estratégicos de Salud – Secretaría de Salud de Hidalgo.

Tabla 2. Informe del tratamiento de los recién nacidos con cardiopatía congénita compleja

Diagnóstico	SO_2 (%) prd / pod	Seguimiento terapéutico
– HPVI, AM, AA, AOH, IVTG	78 / 86	Defunción
– AT, CIA	31.8 / 47.1	Operación paliativa
– AP, PCA, ITG	SD / SD	Operación paliativa / Defunción
– TF	78 / 82	Operación paliativa

HPVI: hipoplasia del ventrículo izquierdo; AM: atresia mitral; AA: atresia aórtica; AOH: arco aórtico hipoplásico; IVTG: insuficiencia valvular tricuspídea grave; AT: atresia tricuspídea; CIA: comunicación interauricular; AP: atresia pulmonar; PCA: persistencia del conducto arterioso; ITG: insuficiencia tricuspídea grave; SD: sin datos; TF: tetralogía de Fallot.
No se realizó tamiz porque el RN presentó datos clínicos graves de hipoxia en las primeras horas de vida y se envió de inmediato a valoración por el cardiólogo pediatra, que confirmó diagnóstico con EC.
Fuente: Registro de Ecocardiogramas y Seguimiento de Recién Nacidos con Sospecha de Cardiopatía después del TCN de la Dirección General de Proyectos Estratégicos de Salud – Secretaría de Salud de Hidalgo.

Hasta el inicio de este protocolo, los estudios clínico y radiológico por médicos experimentados en los SSH eran los únicos métodos comunes para identificar la enfermedad cardíaca antes del alta del RN y sólo de forma ocasional se disponía de EC confirmatoria. Las publicaciones médicas refieren que en presencia de un soplo se agudiza en particular la posibilidad de establecer un diagnóstico[20,21]; sin embargo, la presencia de soplos cardíacos en los recién nacidos en la primera semana de vida varía, ya que pueden estar ausentes o ser imprecisos debido a la anatomía subyacente, la disminución prolongada de la resistencia vascular pulmonar o la función ventricular reducida por los cambios circulatorios que ocurren después del nacimiento[22,23].

La importancia de detectar de manera oportuna las CCC radica en que la primera manifestación de la insuficiencia cardíaca aguda puede ser el colapso circulatorio, que puede llevar a la muerte si no se atiende con rapidez. El retraso en el diagnóstico se relaciona con una morbilidad significativa para todas las CC. En México no hay ecocardiografía sistemática y ello conduce a una baja tasa de detección de las CCC dependientes del conducto y a una menor oportunidad para su atención, lo que ha llevado a una alta mortalidad por cardiopatías no diagnosticadas en los últimos años[24,25].

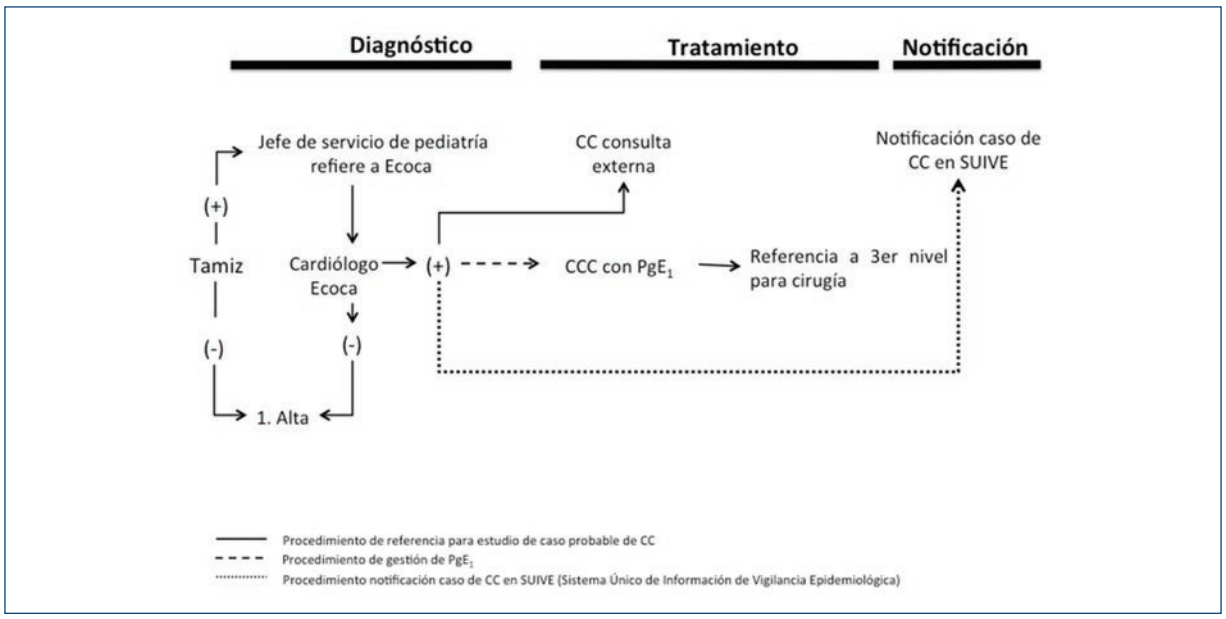

Figura 3. Diagnóstico, tratamiento y notificación de casos de cardiopatía congénita. Se muestran los procedimientos de operación para el diagnóstico, atención, referencia y notificación de casos de cardiopatía congénita.
Fuente: Esquema de elaboración propia. Dirección General de Proyectos Estratégicos de Salud – Secretaría de Salud de Hidalgo.

En este estudio se identificaron en promedio 3 CC por mes durante seis meses, con el diagnóstico y seguimiento oportuno en el 100% de los casos y sin muertes en el 50% de CCC en el primer año de vida. Se tamizó a 1,748 RN de los SSH de marzo a septiembre de 2015, 27 con tamiz positivo, y de éstos 17 tuvieron alguna cardiopatía detectada por EC, de las cuales tres fueron CCC. La prevalencia de todas las CC (10 por 1,000 RNV) fue similar a la de otras poblaciones en estudios de las mismas características que éste[23,26,27], mientras que la prevalencia de las CCC (1.5 por 1,000 RNV) es menor respecto de otras poblaciones[26,28], lo que resulta similar a la notificada por un estudio previo realizado en población mexicana (1.9 por 1,000 RNV)[23].

Con una sensibilidad de 88.2%, especificidad de 99.3% y una tasa de falsos positivos de 0.7% para todas las CC, la más frecuente fue el foramen oval, seguido de la comunicación interauricular (Fig. 2); la sensibilidad para las CCC fue de 100%, con especificidad de 99.3% y tasa de falsos positivos de 0.7%. Estos resultados confirman la alta especificidad y la baja tasa de falsos positivos de la oximetría de pulso registradas en estudios similares a éste y a otros realizados a gran escala[11,13,28-30].

En la entidad de los autores no se cuenta con un registro estadístico de las CC antes de esta prueba piloto, por lo que no es posible llevar a cabo un comparativo en forma retrospectiva, lo que hace necesario establecer el tamiz cardíaco dentro de la batería de estudios para el tamiz neonatal.

La institución del tamiz cardíaco como programa piloto en SSH introdujo como consecuencia cambios importantes en procedimientos sistemáticos de médicos y enfermeras en los servicios de pediatría. Se desarrollaron flujogramas que facilitan la pronta atención en todos los casos y el tratamiento farmacológico de las cardiopatías dependientes del conducto prioritario hasta que se aceptan en hospitales de tercer nivel en la Ciudad de México para el tratamiento quirúrgico paliativo. Estos resultados se pueden comparar con los informados en las publicaciones médicas respecto de la supervivencia de RN con CC dependientes del conducto.

Los principales puntos sólidos de este estudio son la aplicación por primera vez del tamiz cardíaco neonatal mediante un MGC en el país, y por consiguiente en esta entidad, así como el diseño de algoritmos para el seguimiento prospectivo que favorece el tratamiento de los RN diagnosticados con estos problemas.

La detección oportuna mediante OP y exploración física intencionada ha propiciado una oportunidad para la atención adecuada de estos pacientes. Con esta prueba piloto se ajustó la estancia del binomio madre-hijo más allá de 12 horas después de la resolución, según lo establece la NOM-007-SSA2-2016, y ello facilitó la realización de la OP.

Durante la institución del programa se observó una reducción de la estancia hospitalaria de los RN detectados con CCC gracias a que se establecieron diagnósticos específicos, lo que facilita su traslado a unidades de tercer nivel de atención en la Ciudad de México.

Para extender la prueba de tamizaje cardíaco a todos los hospitales y las unidades de primer nivel de atención de los SSH es necesario sensibilizar y concientizar al personal mediante comunidades de práctica, además de crear un área de oportunidad para lograr el trabajo colaborativo y establecerlo en forma sistemática como parte del tamiz neonatal.

El estudio de tamizaje cardíaco no dura más de 10 minutos y lo puede realizar cualquier personal de salud entrenado. Esta prueba es factible y conveniente, ya que agiliza el traslado del RN a hospitales de tercer nivel, lo cual reduce la estancia hospitalaria y los costos de atención. Si se desea mejorar la detección oportuna de las CCC, es recomendable realizar OP después de las primeras 24 horas de vida y antes de las 72 horas o en las primeras 24 horas de vida antes del egreso.

La OP es una técnica no invasiva que cuantifica la saturación de oxígeno (SO_2) como un reflejo de la hipoxemia. Se debe utilizar un oxímetro de pulso que tolere el movimiento y la baja perfusión de oxígeno[2], lo que hace posible detectar CCC que cursan con hipoxemia, entre ellas síndrome de hemicardio izquierdo hipoplásico, atresia de válvula pulmonar, tronco arterioso, conexión anómala total de las venas pulmonares, transposición completa de las grandes arterias, tetralogía de Fallot y atresia de la válvula tricúspide, como las que se registraron durante este estudio.

El tamiz cardíaco debe planificar todos los componentes, de modo inicial la capacitación del personal de salud que realice la prueba, la sensibilización de los padres y la disposición de un sistema eficiente para la pronta referencia a los centros hospitalarios especializados para establecer el tratamiento adecuado.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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ARTÍCULO DE REVISIÓN

Hemodynamic profiles related to circulatory shock in cardiac care units

Perfiles hemodinámicos relacionados con el choque circulatorio en unidades de cuidados cardiacos

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Abstract

One-third of the population in intensive care units is in a state of circulatory shock, whose rapid recognition and mechanism differentiation are of great importance. The clinical context and physical examination are of great value, but in complex situations as in cardiac care units, it is mandatory the use of advanced hemodynamic monitorization devices, both to determine the main mechanism of shock, as to decide management and guide response to treatment, these devices include pulmonary flotation catheter as the gold standard, as well as more recent techniques including echocardiography and pulmonary ultrasound, among others. This article emphasizes the different shock mechanisms observed in the cardiac care units, with a proposal for approach and treatment.

Key words: *Circulatory shock. Hemodynamic monitorization. Echocardiography. Pulmonary ultrasound.*

Resumen

Un tercio de la población de pacientes en unidades de cuidados intensivos se encuentran en choque circulatorio, el identificarlo y determinar su mecanismo de manera rápida y eficaz es de gran importancia. El contexto clínico y el examen físico son de gran utilidad, sin embargo existen situaciones de alta complejidad en las que se requiere del uso de las distintas modalidades de monitorización hemodinámica avanzada, tanto para determinar la causa, como para decidir el manejo y guiar respuesta al tratamiento, incluyendo el catéter de flotación pulmonar como gold standard*, así como técnicas más recientes incluyendo ecocardiografía y ultrasonido pulmonar, entre otros. Este artículo enfatiza los distintos mecanismos de choque observados en las unidades de cuidados cardiacos, con propuesta de abordaje y tratamiento.*

Palabras clave: *Choque circulatorio. Monitorización hemodinámica. Ecocardiografía. Ultrasonido pulmonar.*

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Introduction

Approximately one-third of the population in intensive care units is in a state of circulatory shock, whose rapid recognition is important to avoid tissue injury and death[1].

The shock state has usually been categorized according to its cause[2]. Septic shock is the most severe manifestation of sepsis with an approximate mortality rate of 30%; its incidence in patients admitted to intensive care units varies from 6 to 14%[3-5]. The cardiogenic shock commonly described in patients with acute myocardial infarction (AMI) has an incidence of 6-9% and its frequency has remained constant during the past decades with an approximate mortality rate of 50%[6].

There is little doubt about the physiopathological mechanisms of the different types of circulatory shock originally described by Weil and Shubin, however in the clinical practice at cardiac care units, it can be difficult to differentiate one mechanism from the other, which can hinder the treatment[7].

This article aims to better understand the hemodynamic mechanisms responsible for the shock according to the practical approach proposed by Gonzalez et al.[8]

Shock mechanism

Shock is a state that compromises life, defined by a circulatory failure in which there is loss of the physiological balance between the oxygen delivery (DO_2) and the oxygen uptake (VO_2) conditioning an anaerobic metabolism and cellular hypoxia[7]. The reduction of cardiac output and/or peripheral resistances is finally translated into an increase in oxygen extraction, with the consequent decrease in central venous oxygen saturation (SvO_2), which may even occur before the elevation of serum lactate. Elevation of lactate is directly proportional to the prognosis, initial values above 4.0 mmol/L and negative clearance are related to higher mortality[9-11].

Circulatory shock can be classified into four subtypes according to its mechanism: (1) loss of vascular tone that causes poor distribution of blood flow (distributive shock); (2) failure of the cardiac pump function (cardiogenic shock); (3) loss of circulating volume with decreased venous return (preload) either by internal or external losses (hypovolemic shock); and (4) obstruction caused by a pulmonary embolism, tension pneumothorax, or cardiac tamponade (obstructive shock). These shock states are not mutually exclusive and can be found simultaneously. Typically, the last three states are characterized by a low cardiac output with increased peripheral vascular resistance, while in the distributive shock cardiac output is normal or high with loss of the vascular tone[2,6,7].

Evaluation of circulatory shock

The diagnosis of circulatory shock is based on clinical components, hemodynamics, and biochemical data of tissue hypoxia. There are three types of "clinical windows" described by Vincent et al. through which we can see the effects of the altered tissue perfusion: the skin (coldness, cyanosis, and pallor), kidneys (oliguria with urinary output < 0.5 mL/kg/h), and the central nervous system (neurological alterations including drowsiness, disorientation, and confusional state). The presence of hypotension defined in the state of shock as a mean arterial pressure < 65 mmHg, systolic blood pressure < 90 mmHg or a decrease > 40 mmHg of baseline blood pressure is a component of shock[2,12].

The two main biochemical markers of tissue hypoperfusion are the serum lactate and the central venous oxygen saturation (SvO_2) obtained in a blood sample from the cavoatrial junction[9,11,12].

The evaluation of the circulatory shock, as mentioned above, can be done in a simple way by physical examination, evaluating the "windows" in search of hypoperfusion data; nevertheless, an integral approach is necessary for conjunction with the biochemical variables, and hemodynamic parameters Fig. 1[4,13].

Hemodynamic profiles

Once the circulatory shock has been identified, it is necessary to determine the main responsible mechanism. The clinical context and the physical examination are important, but in complex situations, as it happens in cardiac care units, reaching a correct diagnosis is usually a challenge. Each shock mechanism has different hemodynamic characteristics that allow us to identify them (Table 1).

Hypovolemic shock

It is characterized by a significant loss of intravascular volume resulting in an increase of sympathetic tone causing selective vasoconstriction of the skin, muscles, and splanchnic circulation to maintain venous return as well as cardiac output. If the intravascular volume loss continues, there is a decrease in the preload and subsequently in the cardiac output[12,13].

Table 1. Hemodynamic profile in different shock states

Shock subtype	Cardiac index	Systemic vascular resistances	Central venous pressure	Pulmonary capillary wedge pressure
Cardiogenic LV	Low	High (Can be low in 25% of cases)	High	High
Cardiogénic RV	Low	High	High	Low
Hypovolemic	Low	High	Low	Low
Obstructive Pulmonary embolism Tamponade Distributive	 Low Low Normal/High (Can be low in the late phase of sepsis)	 High High Low	 High High Low	 Low High Low

RV: right ventricular; LV: left ventricular.

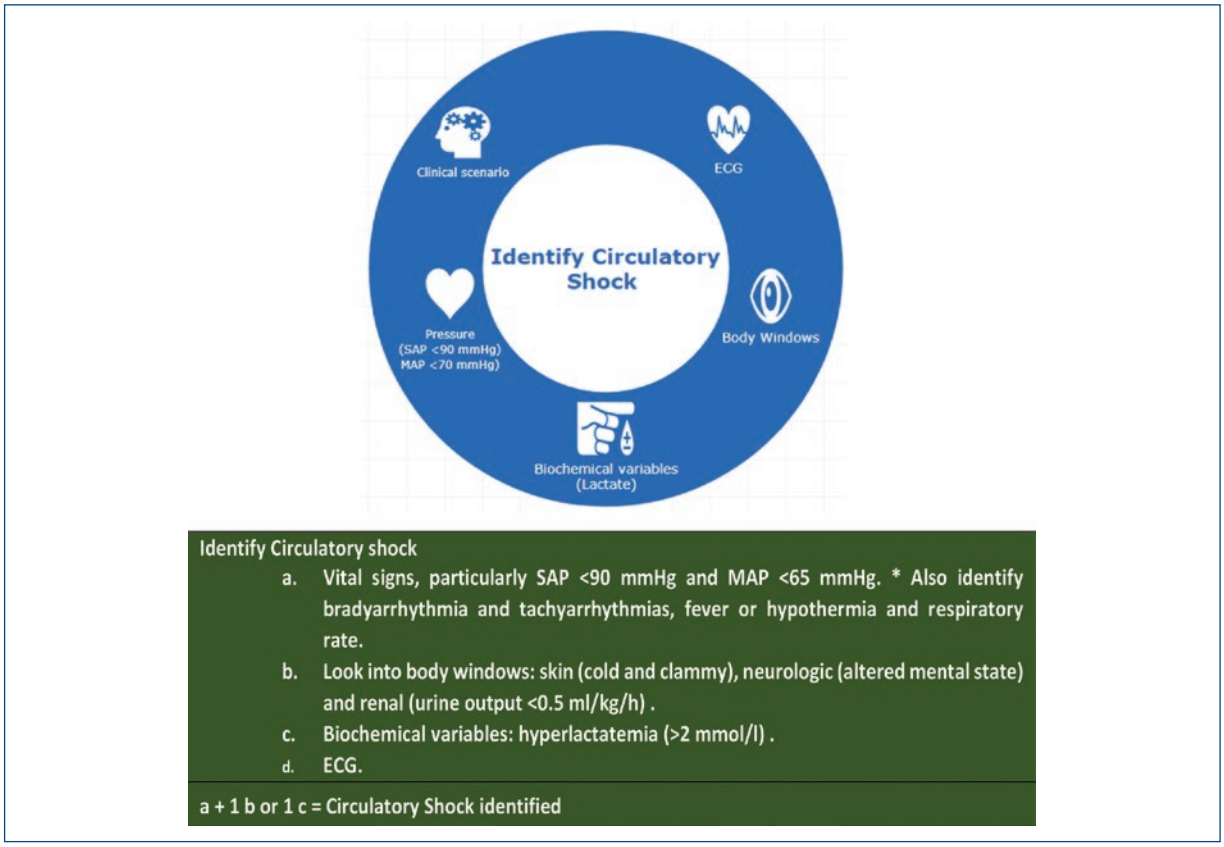


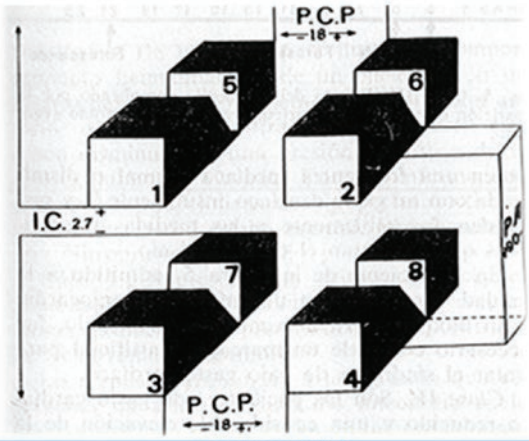
Figure 1. Identification of circulatory shock.

Cardiogenic shock

Any cause of left or right ventricular dysfunction or both can lead to cardiogenic shock, characterized by pump failure with increased ventricular filling pressures, and a low cardiac output with increased systemic vascular resistance[14].

Obstructive shock

It is caused by the inability to maintain adequate cardiac output despite normal intravascular volume and intrinsic myocardial function. An obstruction due to a pulmonary embolism, tension pneumothorax or cardiac tamponade causes a decreased cardiac output, an



Hemodynamic Profiles	
Group 1. Normal. Normal filling pressures, cardiac index and tissue perfusion.	Group 5. Normal cardiac index and filling pressures, tissue hypoperfusion at expense of low vascular resistances.
Group 2. Pump failure with high ventricular filling pressures, normal cardiac index and tissue perfusion.	Group 6. Patients with chronic high filling pressures maintaining cardiac index and unappropiate vasodilation due to a systemic process.
Group 3. Decreased intravascular blood volume and preload that conditions a low cardiac output, mantaining tissue perfusion at expense of systemic vascular resistances.	Group 7. Very decreased intravascular blood volume that condition a low filling pressures and low cardiac output, high systemic vascular resistances that are not enough to mantain tissue perfusion.
Group 4. Low cardiac index, and high filling pressures, maintaining tissue perfusion at expense of systemic vascular resistances.	Group 8. Cardiogenic shock and obstructive shock. Severe pump failure that conditions high filling pressures, low cardiac index and tissue hypoperfusion. Tipically high systemic vascular resistances.

Figure 2. Hemodynamic profile in cardial care units (*modified from* Los problemas hemodinámicos en el infarto del miocardio. *Arch Card Mex. 1980;50(3):319-26, with authorization from Dr. Jesus Antonio González Hermosillo*).

elevation in systemic vascular resistances and variable wedge pressure (pulmonary artery wedge pressure [PCWP]) depending on the etiology[15,16].

Distributive shock

It is caused by the loss of vascular tone with the resulting maldistribution of blood flow due to sepsis, anaphylaxis, or spinal cord injuries. Usually, the cardiac output is normal or high and a normal PCWP[13,15].

In 1980, Gonzalez et al. proposed a three-dimensional scheme to classify hemodynamic profiles according to three determinant variables: filling pressures, cardiac index and unlike the Forrester scale, adding the arterial pressure as a third variable with which they obtain eight possible hemodynamic states with different clinical expression and therapeutic approach, Groups 2-4 (systolic arterial pressure > 90 mmHg) correspond to patients with hemodynamic compromise but normal arterial pressure due to different compensatory mechanisms, these profiles were previously known as pre-shock, and if treated timely and properly can have a better prognosis; otherwise they will develop circulatory shock (Groups 5-8)[8].

Although this classification was initially aimed to assess the hemodynamic status during AMI, currently with the availability of new monitoring devices which allow a more accurate measurement of these and other hemodynamic parameters, we consider that its adjustment may be useful to classify the different hemodynamic states observed in the cardiac care units (Fig. 2).

An adequate initial assessment of the hemodynamic status can be achieved with the clinical examination and monitoring of certain basic hemodynamic parameters (heart rate, blood pressure, central venous pressure, respiratory variables, $SvcO_2$, electrocardiography, lactate, and urine output). However, when this fails, there are other monitoring modalities that guide the management of fluids and the inotropic/vasopressor support (PCWP, stroke volume variation, cardiac output, extravascular water, etc.) (Table 2).

Hemodynamic monitoring devices

Although still the gold standard, less used, the pulmonary artery catheter was introduced in 1970 by Swan, Ganz and Forrester as a method for the

Table 2. Hemodynamic parameters

Parameter	Equation	Normal Values
SaO_2 (Arterial oxygen saturation)		95-100%
$SvcO_2$ (Central venous oxygen saturation)		70%
Arterial blood pressure (TA)	Systolic diastolic	90-140 mmHg 60-90 mmHg
Pulmonary artery wedge pressure (PCWP)		5-12 mmHg
Cardiac output (CO)	HR × SV/1000	4.0-8.0 L/min
Cardiac index (CI)	CO/BS	2.2-4.0 L/min/m^2
Stroke volume	CO/HR × 1000	60-100 mL/beat
Systolic volume index (SVI)	CO/HR × 1000/BS	33-47 mL/m^2/beat
Systolic volume variation (SVV)	(maxSV – minSV)/Mean SV × 100	10-15%
Right atrium pressure (RAP)		0-5 mmHg
Systemic vascular resistances (RVS)	80 × (MAP – RAP)/CO	800-1200 dynas/s/cm

Table 3. Hemodynamic monitoring devices

Method	Examples	Calibration	Advantages	Disadvantages
Transpulmonary thermodilution (moderately invasive)	PiCCO® VolumeView® EV1000® LiDCO®	Calibrated	Intermittent and continuous CO and other variables	Need of central venous and arterial line
Pulse contour and pulse pressure variation (minimally invasive).	FloTrac/Vigileo® ProAQT® Pulsioflex® MostCare®/PRAM LiDCOrapid®	Non-calibrated	Continuos CO	Lack accuracy in unstable patients or during use vasoactive drugs

measurement of cardiac output, and it is with this that several studies have compared the majority of the new devices and techniques used[17].

Recently, multiple devices have been developed allowing cardiac output and other hemodynamic parameters to be obtained in real time. Among many others, these systems include PiCCO®, MostCare Vygon®, FloTrac Vigileo® Echocardiogram, and Lung Ultrasound, which provide information on preload, afterload and contractility variables, all aimed at improving both cardiac output and tissue perfusion[18,19].

Non-invasive monitoring devices can be moderately invasive or minimally invasive. The moderately invasive devices (require arterial catheter plus a central venous line) offer the advantage of a continuous analysis of cardiac output by means of the thermodilution principle and minimally invasive devices (only require an arterial catheter) allow an uncalibrated analysis (FloTrac®/Vigileo®, LiDCOrapid®, ProAQT®/Pulsiflex®).

With transpulmonary thermodilution, it is possible to determine the cardiac output, extrapulmonary extravascular water, pulmonary vascular permeability, and index of cardiac function and end-diastolic volume (Table 3)[20-21].

Pulmonary artery catheter

Catheter introduced by jugular, subclavian, or femoral access in the pulmonary artery. It allows the measurement of the PCWP, indicative of the filling pressures of the left atrium; it also allows the measurement of cardiac output by thermodilution, calculation of pulmonary and systemic vascular resistance as well as ventricular systolic volume. It is not considered a dynamic monitoring device and has wide inter-observer variability[17,21].

Table 4. Echo parameters for the assessment of circulatory shock

Cardiac output	LVOT Area × VTI (LVOT) × HR	LVOT Area = (aortic annulus in cm)^2 × 0.785 VTI LVOT = Sample volume of the pulsed Doppler 1 cm before the valve in apical approach three or five chambers, tracing with an electronic pencil the Doppler spectrum of the aortic flow
Fluid responsiveness	Spontaneous breathing Invasive mechanical ventilation	IVC collapsability index > 36% or IVC < 10 mm IVC distensibility index > 18% IVC variability 12% VTI and LVOT peak velocity variability > 12%
Filling pressures	Right atrium pressure Left Atrium pressure	IVC < 21 mm and > 50% collapse = 3 mmHg IVC > 21mm and < 50% collapse = 15 mmHg IVC < 21 mm and < 50% collapse or > 21 mm and > 50% collapse = 8 mmHg E/e' > 14 (High)
Diastolic function	Impaired relaxation Pseudonormal Restrictive	Filling pressures – Filling pressures +/– Filling pressures +
Left ventricle	EF (Simpson)	Men > 52% Women > 54%
Right ventricle	Longitudinal function Global systolic function	TAPSE > 17 S' > 9.5 FAC > 35%
Lung hemodynamics	PASP mPAP PVR	TR gradient + RAP 90 – (0.62 × RVOT acceleration time) (peak TR velocity/RVOT VTI) × 10 + 0.16

LVOT: left ventricular outflow tract; VTI: velocity-time integral; HR: heart rate; IVC: inferior vena cava; RVOT: right ventricular outflow tract; RAP: right atrial pressure; TR: tricuspid regurgitation; PVR: pulmonary vascular resistance; mPAP: mean pulmonary artery pressure; PASP: pulmonary artery systolic pressure.

PiCCO® system

It uses a central venous catheter and an arterial line that provides continuous measurement of cardiac output by thermodilution using a bolus of cold fluid injected through the central line. By means of an algorithm based on the analysis of the arterial pulse wave, continuous monitoring of cardiac output, and systolic volume is possible. The variation of the systolic volume and the variation of the pulse pressure are variables that can guide the response to fluid, although they are limited to completely sedated patients, under invasive mechanical ventilation and with the absence of arrhythmias. Unlike the pulmonary artery catheter, it is less invasive, allows to measure cardiac output continuously and assess the response to fluids[19,22].

FloTrac/Vigileo® system

Device uses the variation of pulse pressure and vascular tone to calculate the systolic volume and cardiac output[19,20,22].

Transthoracic echocardiogram

Useful to measure cardiac output by calculating the velocity-time integral of the left ventricular outflow tract by Pulsed Doppler, it is a dependent operator procedure. It is also useful to asses volume responsiveness. Table 4 summarizes the parameters that can be calculated using echocardiography[23].

Lung ultrasound

It is a tool that has been proposed for the assessment of circulatory shock using the Fluid Administration Limited by Lung Sonography-protocol first searching for pericardial fluid, right ventricle enlargement and tension pneumothorax (obstructive shock), if none of these is identified, the next step is to search for B-lines whose presence indicates pulmonary edema and cardiogenic shock as the likely cause. On the contrary, its absence, with a normal sonographic lung surface and fluid responsiveness indicate hypovolemic shock[24] Fig. 3.

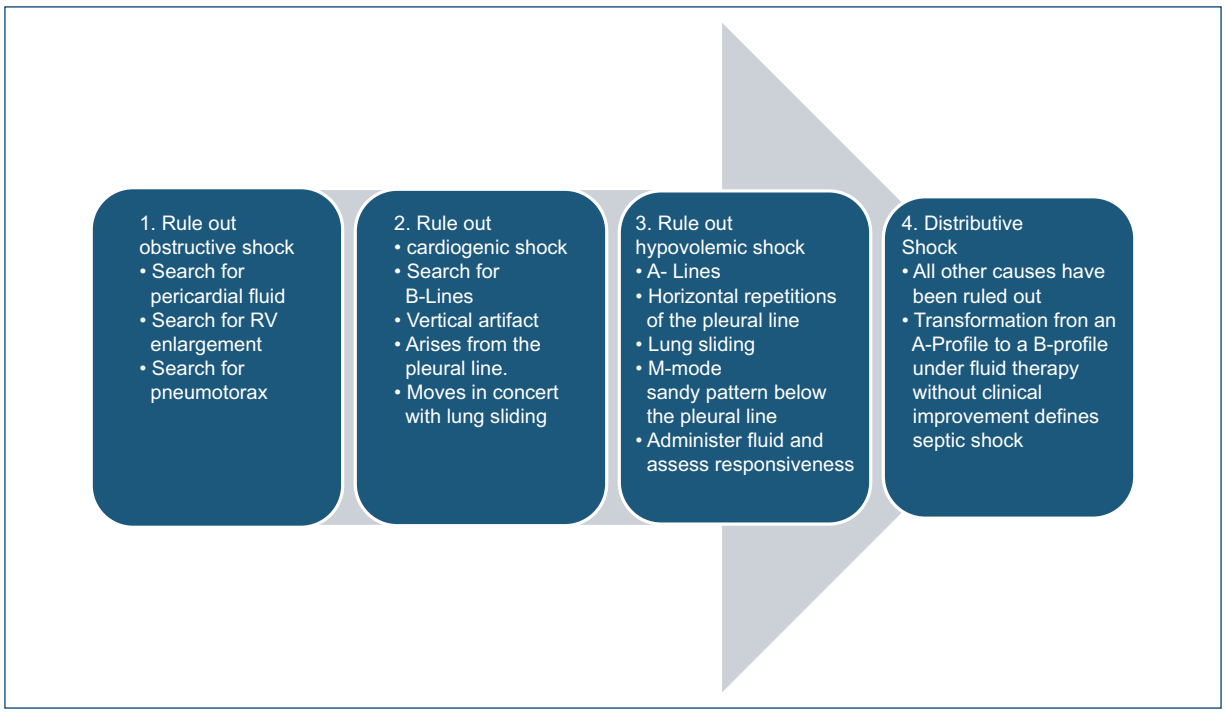


Figure 3. The Fluid Administration Limited by Lung Sonography-protocol.

Table 5. Pharmacologic and non-pharmacologic intervention

Class	Tissue perfusion	CI	Filling pressures	Example	Causes	Recommendation
1	→	→	→	Normal	NA	Requirements
2	→	→	↑	HFpEF	Multiple	Diuretic Vasodilator NIVM
3	→	↓	→	Hypovolemia	Losses (GI, diuretics, bleeding, etc.)	Crystalloids Blood
4	→	↓	↑	HFrEF	Multiple	Diuretic Vasodilator NIMV STVAD LTVAD
5	↓	→	→	Distributive shock	Sepsis Anaphylaxis Spinal cord injury	Vasopressor
6	↓	→	↑	Valvular heart disease/ HF + vasodilation	Mix	Vasopressor +/– Inotropic
7	↓	↓	→/↓	Hypovolemic shock	Losses (Surgery, diuretics, bleeding)	Vasopressor Crystalloid Blood
8	↓	↓	↑	Cardiogenic shock	MI Valvular Arrythmia	Inotropic PCI IABP Pacemaker VAD ST or LT

GI: gastrointestinal; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; STVAD: short-term ventricular assist devices; LTVAD: long-term ventricular assist device.

Goal directed therapy

The modification of all these variables (oxygen transport, preload, afterload, and vascular tone) is possible through pharmacological and non-pharmacological interventions[19,20]. The initial management of the shock should include ventilatory assistance, fluid resuscitation, and the use of vasoactive drugs according to the different hemodynamic profiles; occasionally, when these strategies fail and in the proper context it is necessary the use of circulatory assistance devices (Intra-aortic Balloon Pump, Extracorporeal Membrane Oxygenation, CentriMag, Impella, etc.) (Table 5).

Conclusion

The importance of the different tools is to be able to provide a better and easier assessment of the different hemodynamic profiles in circulatory shock. The cardiologist must have the ability to identify and assess different hemodynamic parameters in initial stages before circulatory shock; the failure to recognize and treat coexisting etiologies and contributors to the state of shock can lead to poor prognosis.

Conflicts of interest

None declared.

Ethical disclosures

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

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

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

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ARTÍCULO DE REVISIÓN

Left main coronary artery compression by the right pulmonary artery in a patient with congenital pulmonic stenosis

Compresión del tronco coronario izquierdo por la arteria pulmonar derecha en un paciente con estenosis pulmonar congénita

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Abstract

Congenital pulmonary stenosis (PS) can be associated with pulmonary artery (PA) dilatation. In some cases, this can cause compression of nearby structures including the left main coronary artery (LMCA). This compression causes angina and is considered an indication for surgical treatment. We present the case of a patient with PS and angina secondary to LMCA compression by the right PA and review the main indications and options for surgical treatment.

Key words: *Left main coronary artery. Pulmonary stenosis. Pulmonary artery. Angina. Mexico.*

Resumen

La estenosis pulmonar congénita se asocia a dilatación de la arteria pulmonar. En algunos casos esto puede causar compresión de las estructuras adyacentes incluyendo el tronco de la coronaria izquierda. Esta compresión causa angina y es considerada una indicación para tratamiento quirúrgico. Presentamos el caso de un paciente con estenosis pulmonar y angina secundaria a compresión del tronco de la coronaria izquierda por la arteria pulmonar derecha y revisamos las indicaciones y opciones de tratamiento quirúrgico.

Palabras clave: *Tronco coronaria izquierda. Estenosis pulmonar. Arteria pulmonar. Angina. México.*

Introducción

A 52-year-old man presented with a history of ventricular septal defect (VSD) and congenital pulmonary valve stenosis (pulmonary stenosis [PS]) who underwent pulmonary valve replacement with a biologic valve at 15 years old and VSD closure with pericardial patch at 17 years old in another institution. The indication and specifics of each procedure are unknown.

He had a 2-year history of stable angina (Class II of the Canadian Cardiovascular Society). An echocardiogram was performed which reported reopening of the VSD. He was referred to our institute for workup. During workup a transthoracic echocardiogram was performed,

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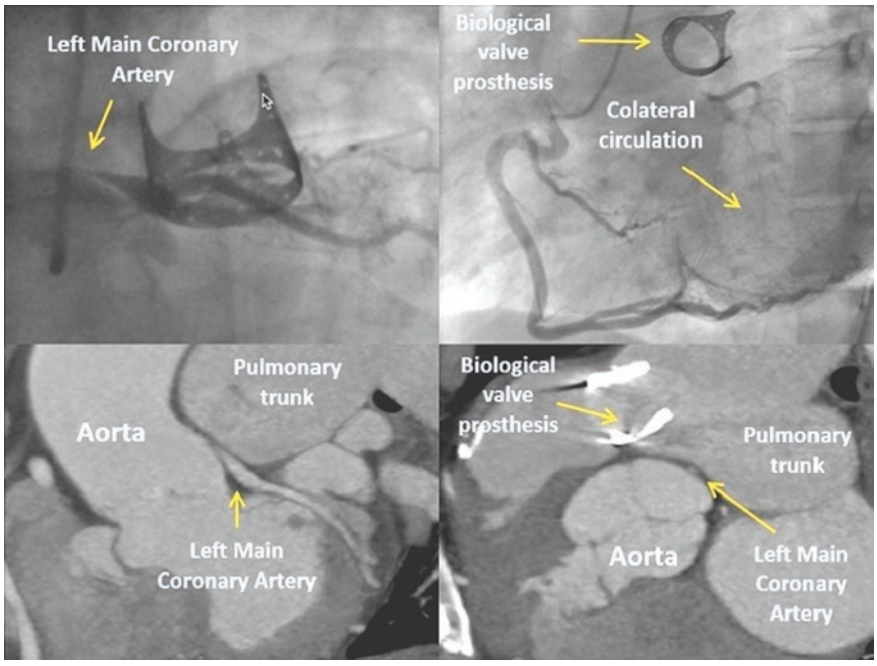

Figure 1. Extrinsic left main coronary artery (LMCA) compression of 90% and reduced blood flow to the left anterior descending with collateral circulation form de RCA in coronary angiography. LMCA compression by the pulmonary artery in computed tomography.

showing reduced right ventricular systolic function, left ventricle with anterior wall and septal hypokinesia and an ejection fraction of 45%, reopened VSD with left-right shunt and a dysfunctional prosthetic pulmonary valve (PPV) due to severe stenosis and severe regurgitation. A computed tomography showed obstruction of the left main coronary artery (LMCA) due to extrinsic compression by the right PA (RPA), left anterior descending (LAD), and left circumflex arteries where filled by collateral circulation, dilation of MPA, and its branches (MPA 52 mm, RPA 53 mm, and left PA 44 mm); VSD with a 17 × 14 mm diameter (Fig. 1). A right and left cardiac catheterization was performed which showed extrinsic LMCA compression with 90% stenosis and reduced blood flow to the LAD, PPV with a 60 mmHg gradient, and VSD with left-right shunt, mean pulmonary pressure of 20 mmHg and a Qp: Qs ratio of 1.2.

The patient was admitted for surgical treatment. He underwent pulmonary valve replacement with a prosthetic biological valve and RPA plasty. Coronary artery bypass of the LAD was attempted, but the artery could not be visualized during the procedure, so revascularization to the obtuse marginal artery with a radial artery graft was performed. The total surgical time was 11 h, with 361 min of extracorporeal circulation and aortic cross-clamping of 219 min. The patient was admitted to the post-operative intensive therapy with cardiogenic shock. He had a torpid evolution persisting in cardiogenic shock despite the use of vasopressin, norepinephrine, and dobutamine, eventually presenting multiple organ failure and 4 days after surgical procedure presented asystole and was declared dead after failure of advanced cardiopulmonary resuscitation.

Discussion

More than half the cases of PA dilatation are associated with congenital heart diseases mainly in cases with the left-right shunt, due to volume and pressure overload in the right cardiac system which causes hemodynamic stress on the vessel wall[1]. Congenital PS has also been associated with PA dilation. The mechanism of dilatation in PS is believed to be due to the jet of blood generated by the stenotic valve against the PA wall, without necessary relationship between the degree of stenosis and the degree of enlargement[2]. This condition can cause compression of nearby structures including the LMCA. We present the case of a patient with PS angina secondary to LMCA by the RPA. A relationship between PA diameter and

LMCA compression was determined in a study with 36 patients with pulmonary dilation and pulmonary hypertension (PH) of which 26 had angina. Compression was not seen in patients with pulmonary diameters < 40 mm and in patients with PA diameter ≥ 40 mm, 37% had compression of the LMCA[3].

The best treatment option for patients with PA dilatation is uncertain. There are no clear guideline indications for surgical intervention but some authors recommend surgical intervention when the PA diameter is ≥ 5.5 cm, if the diameter increases ≥ 0.5 cm in 6 months, compression of nearby structures occurs, thrombus formation in the aneurysm, presence of clinical symptoms, evidence of valvular pathologies or shunt, and if it presents signs of rupture or dissection[1]. In this case, the patient already had surgical indication for pulmonary valve replacement and due to the compression of the LMCA and presence of symptoms; he was also considered a candidate for RPA plasty, which was compressing the LMCA.

Surgical repair options for patients with PA dilatation include interposition of Dacron prosthesis or a homograft, reconstruction with pericardial patch or arterioplasty[4]. Our patient underwent pulmonary valve replacement, coronary bypass, PA and RPA plasty which was considered a high-risk surgery due to the procedure its self, the presence of biventricular dysfunction and the fact that it was his third cardiac surgery. All this combined eventually led to a bad outcome.

Conclusions

PA dilatation can cause compression of nearby structures, causing angina when it compresses the LMCA. There is an association between PS and PA dilatation being the jet of blood generated by the stenotic valve the pressumed cause. There is no clear consensus on the indications for surgical repair of PA dilatation although the presence of symptoms due to compression of other structures, like in the case presented, is generally considered an indication for intervention.

Conflicts of interest

None.

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Ethical disclosures

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

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

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

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ARTÍCULO DE REVISIÓN

Genes frecuentemente asociados con muerte súbita en miocardiopatía hipertrófica primaria

Genes frequently associated with sudden death in primary hypertrophic cardiomyopathy

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Resumen

La miocardiopatía hipertrófica (MCH) es el aumento de grosor de la pared ventricular izquierda no relacionada con otras alteraciones cardíacas. Es una enfermedad que puede presentar como primera manifestación clínica la muerte súbita y de ahí su relevancia clínica. Aunque se presenta sobre todo en la edad adulta, puede aparecer durante la infancia y adolescencia, en las que predominan los casos de origen hereditario. La MCH primaria, de causa genética, muestra en particular un patrón de herencia autosómico dominante en los 25 subtipos reconocidos en OMIM (Online Mendelian Inheritance in Man). Las proteínas codificadas por los genes mutantes forman parte del sarcómero en células musculares cardíacas, y las variantes patogénicas de filamentos gruesos son las de mayor frecuencia y peor pronóstico. En este artículo se describen la herencia mendeliana de la enfermedad y la relación con muerte súbita de los genes más frecuentemente encontrados en ella: MYBPC3 y MYH7.

Palabras clave: *Miocardiopatía hipertrófica. Genes. MYBPC3. MYH7. Variantes genéticas. Muerte súbita.*

Abstract

Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy without apparent cardiac justification. Sudden cardiac death may be the first manifestation of the disease. It occurs mainly in adulthood and can be seen in childhood and adolescence where genetic origin predominates. Primary HCM ("familial") is inherited in an autosomal dominant pattern in the 25 subtypes informed in Online Mendelian Inheritance in Man. The proteins encoded by the mutated genes are part of the sarcomere in the cardiac cells, being the thick filament the most frequently affected, with the worst prognosis. In the present article, we describe the Mendelian inheritance of the disease and the two most associated genes with sudden death: MYBPC3 and MYH7.

Key words: *Hypertrophic cardiomyopathy. Genes. Gene variants. MYBPC3. MYH7. Sudden cardiac death.*

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Introducción

La miocardiopatía hipertrófica (MCH) es una enfermedad cardíaca que se caracteriza por el aumento del grosor de la pared del ventrículo izquierdo sin que exista una sobrecarga de volumen sanguíneo o alguna otra enfermedad cardíaca que explique dicha hipertrofia.[1]

A lo largo de la historia se la ha conocido con diferentes nombres, entre ellos "hipertrofia ventricular hereditaria", "cardiomiopatía hipertrófica hereditaria", "cardiomiopatía hipertrófica familiar", "hipertrofia septal asimétrica" y "estenosis subaórtica idiopática". Para este trabajo se utiliza el término "miocardiopatía", y no "cardiomiopatía", por dos razones: a) "miocardiopatía" define la entidad, una enfermedad del miocardio, y b) el término "cardiomiopatía" es un anglicismo, un calco del inglés *cardiomyopathy*.

La *European Society of Cardiology* clasifica la MCH en dos grupos: a) MCH "primaria" o de origen genético causada por mutaciones en diversos genes[1] y b) MCH "secundaria" consecutiva a otra enfermedad, como hipertensión arterial sistémica, enfermedad valvular, o diversos síndromes metabólicos, como las enfermedades de Pompe, Fabry y Danon, que afectan la estructura del miocardiocito. Este trabajo se enfoca en la MCH primaria.

La MCH primaria se considera la enfermedad cardíaca de origen hereditario más frecuente, con una prevalencia de 1 en 500 individuos, de acuerdo con datos estadísticos obtenidos del estudio CARDIA (*Coronary Artery Risk Development in Young Adults*)[2], y es la sexta causa más frecuente de muerte súbita en niños y adultos jóvenes en países desarrollados, según un estudio realizado en Australia y Nueva Zelanda[3].

Los signos y síntomas se presentan en la tercera y cuarta décadas de la vida, con una amplia variación en el inicio y gravedad de las manifestaciones clínicas, desde individuos asintomáticos hasta la presencia de síncope, taquiarritmias o inicio con muerte súbita. Sin embargo, el diagnóstico de la enfermedad se establece por cambios morfológicos como el engrosamiento de la pared ventricular ≥ 13 mm (medido mediante ecocardiografía), con o sin obstrucción del tracto de salida del ventrículo izquierdo[4], y cambios electrocardiográficos en la repolarización, inversión de la onda T en las derivaciones cardíacas DI y aVL, además de prolongación de los intervalos QT[5], entre otros indicadores que reflejan la progresión del daño y el riesgo de muerte súbita cardíaca; este último es más alto en el grupo de edad de 14 a 35 años que tiene síntomas secundarios a la MCH[6].

Herencia mendeliana en MCH

Aunque se trata de una enfermedad con patrón de transmisión bien identificado, la MCH muestra una gran variabilidad clínica, con penetrancia dependiente de la edad, es decir, que el curso clínico tiene una gran heterogeneidad intrafamiliar e interfamiliar debido a factores modificadores que diversifican el fenotipo de cada paciente. Esta enfermedad es un buen ejemplo de "naturaleza versus crianza" ("*nature versus nurture*")[7].

Diversos estudios genéticos y genómicos han tratado de dilucidar las causas de esta anomalía hereditaria y han identificado modificaciones en el DNA conocidas como variantes genéticas, las cuales pueden ser benignas, probablemente benignas, de significado incierto, probablemente patogénicas o patogénicas y pueden ocasionar cambios estructurales en las proteínas sarcoméricas del músculo cardíaco, lo que favorece la hipertrofia de los ventrículos, de manera predominante del ventrículo izquierdo.

En general, la MCH primaria tiene un patrón de herencia mendeliano del tipo autosómico dominante, esto es, que los hijos de un afectado poseen 50% de riesgo de heredar el alelo mutado y por tanto padecerán la enfermedad. No obstante, se conocen casos *de novo* que no tienen antecedentes familiares y aun así el afectado muestra una variante patogénica identificada, la cual heredará con la misma probabilidad (50%) a su descendencia[8]; por otro lado, existen informes de casos que presentan mutaciones en los genes *MYL3, MYH7* y *MYBPC3* que sugieren un patrón de herencia autosómica recesiva, lo cual debe considerarse al momento de realizar la historia clínica. Es por ello que algunas investigaciones han tratado de dilucidar el efecto funcional de las variantes genéticas que dan origen a las alteraciones cardíacas, con el objetivo de facilitar el diagnóstico y ofrecer tratamiento temprano, incluso en pacientes asintomáticos. Por el momento, la identificación de las variantes causales, y su efecto funcional, ayuda a comprender el mecanismo que genera la hipertrofia y a predecir la gravedad del daño.

Gracias al uso de la secuenciación de nueva generación (SNG), el número de genes relacionados con la MCH se ha incrementado de forma notable en los últimos años[9–11], con más de 50 genes publicados y cerca de 8,000 variantes (Tabla 1) en la base de datos "PubMed" relacionados con esta enfermedad, de los cuales sólo 25 son consistentes con el compendio de genes *Online Mendelian Inheritance in Man* (OMIM; http: www.omim.org), en el que se describen las características

Tabla 1. Genes y tipo de variantes relacionadas con miocardiopatía primaria

Gen	Tipo MCH	Frecuencia	Sin inf	Tipo de variante descrita (OMIM)*		
				BEN	PAT	INC
ACTC1[12-17]	11[a]	Rara < 1%	29	8	29	30
TNNC1[18]	13[a]	Rara < 1%	17	4	7	8
TNNI3[13,14,19-24]	7[a]	Rara < 5%	47	7	73	39
TNNT2[13,14,19,21,22,25-27]	2[a]	Rara < 5%	65	11	81	53
TPM1[13,14,26,28,29]	3[a]	Rara < 5%	83	10	29	51
MYBPC3[13,14,17,21,22,26,30,31-55]	4[b]	15-25%	241	42	1014	302
MYH6[23,26,56]	14[b]	Rara < 1%	183	7	3	13
MYH7[13,14,17,21-23,30-32,49-52,55,57-69]	1[b]	15-25%	300	41	872	317
MYL2[13,17,29,70-72]	10[b]	Rara < 2%	37	18	25	24
MYL3[13,14,69,73-75]	8[b]	Rara < 1%	21	5	30	21
ACTN2[13-15,76,77]	23[c]	Rara < 1%	76	30	9	45
CSRP3[78,79]	12[c]	Rara < 1%	24	9	5	12
LDB3[80]	24[c]	Rara 1-5%	151	8	0	5
MYOZ2[67,81]	16[c]	Rara < 1%	36	1	8	2
MYPN[82]	22[c]	Rara < 5%	42	39	4	30
NEXN[83]	20[c]	Rara < 1%	35	10	4	45
TCAP[84]	25[c]	Rara < 1%	31	1	0	4
TTN[15,26,51,72,85]	9[c]	Rara < 5%	3949	2	12	20
VCL[86]	15[c]	Rara < 1%	54	24	3	30
CALR3[87]	19[d]	Rara < 5%	4	0	0	1
JPH2[88,89]	17[d]	Rara < 1%	6	13	6	15
PLN[90]	18[d]	Rara < 1%	7	0	5	5
CAV3[91]	1[e]	Rara < 5%	54	11	5	8
MYLK2[92]	1[e]	Rara < 5%	39	17	3	7
PRKAG2[93-98]	6[e]	Rara 1%	100	1	31	4

* Información obtenida de PubMed hasta abril del 2018.
OMIM: *Online Mendelian Inheritance in Man*; Sin inf: sin información en las publicaciones médicas; BEN: benigna; PAT: patogénica; INC: incierta; a: proteína de filamentos delgados; b: proteína de filamentos gruesos; c: proteína de discos Z; d: proteínas incluidas en el manejo de Ca+; e: otras proteínas relacionadas.

clínicas, los genes con las variantes patogénicas más comunes identificadas y las consecuencias fisiopatológicas de estos cambios moleculares.

Estructura de las células cardíacas y proteínas que subyacen a la MCH

El miocardiocito se encuentra constituido por cinco componentes: a) túbulos y sarcolema, b) retículo sarcoplásmico, c) elementos contráctiles, d) mitocondrias y e) núcleo. La unidad contráctil se conoce como sarcómero, el cual está formado por filamentos gruesos y delgados cuyas proteínas más importantes son miosina y actina (Fig. 1). Los filamentos gruesos están formados por cadenas pesadas de la proteína β-miosina. Ésta es una proteína hexamérica compuesta por dos cadenas ligeras esenciales, codificadas por el gen *MYL2*, dos cadenas ligeras regulatorias, codificadas

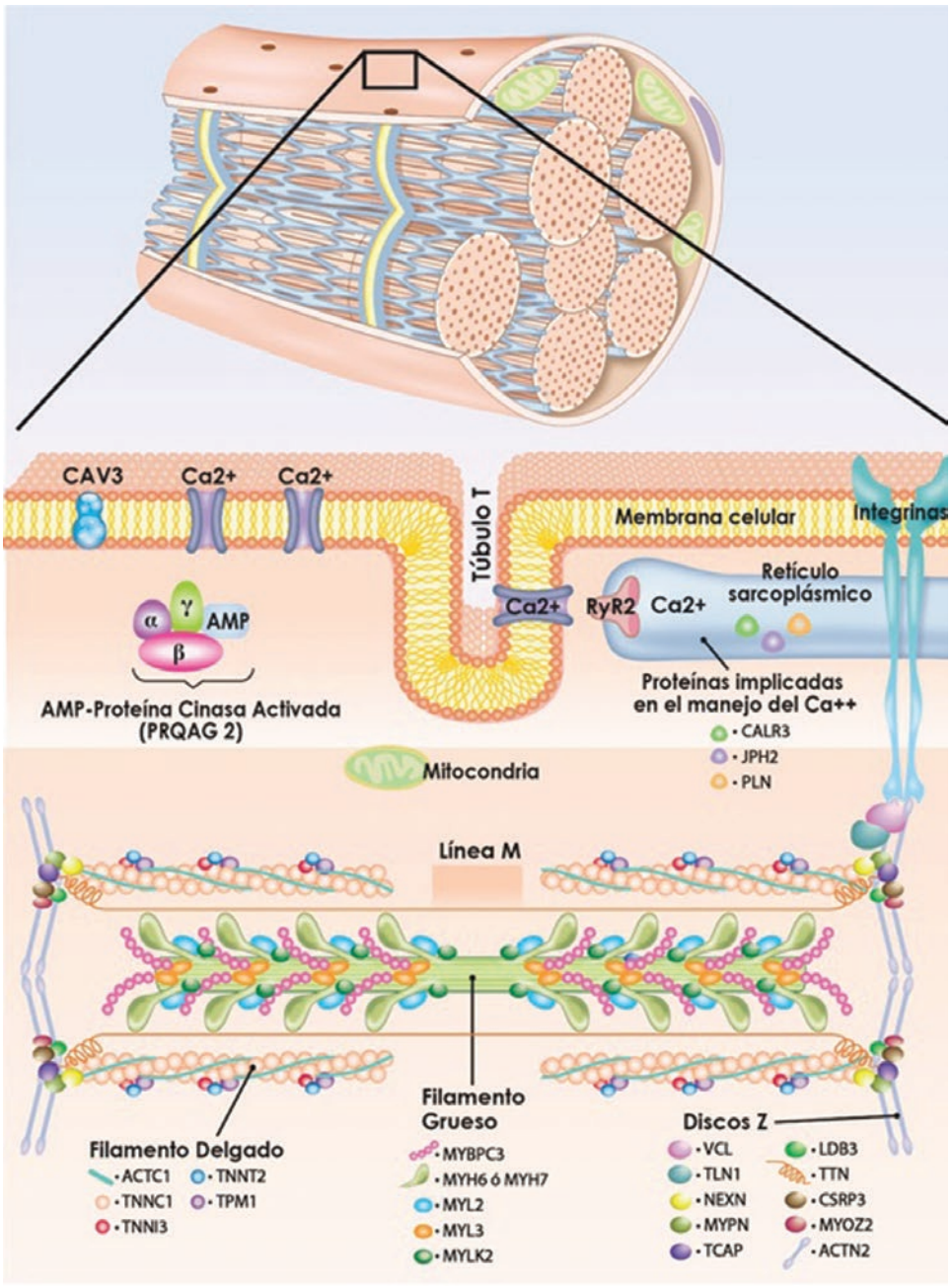

Figura 1. Sarcómero del músculo esquelético cardíaco. Se muestran las proteínas ubicadas en el sarcómero del músculo cardíaco y cuyas variantes patogénicas se relacionan con miocardiopatía hipertrófica primaria.

por el gen *MYL3*, y dos cadenas pesadas codificada por el gen *MYH7*, así como proteínas C de unión a miosina (gen *MYBPC3*). Los filamentos delgados están formados por actina (genes *ACTC1* y *ACTA1*), el complejo de troponina (genes *TNNC1, TNNI3, TNNT2*) y tropomiosina (codificada por el gen *TPM1*) (Fig. 1). La alteración de uno o varios componentes del miocardiocito tiene repercusiones directas o indirectas en el desarrollo de la MCH primaria[7,8].

Alteraciones en miofilamentos gruesos y delgados

Algunos estudios han demostrado que las variantes patogénicas en genes que codifican a proteínas de

Tabla 2. Los genes del sarcómero cuyas variantes patogénicas o probablemente patogénicas se relacionan con MCH y muerte súbita

Gen	Locus	Mim	Proteína	Herencia	HFMS
Genes que codifican a proteínas de filamentos delgados					
TNNC1	3p21.1	613243	Troponina C tipo 1	AD	Sí[18]
TNNI3	19q13.42	613690	Troponina I tipo 3	AD	Sí[19,20]
TNNT2	1q32.1	115195	Troponina T tipo 2	AD	Sí[25]
TPM1	15q22.2	115196	Tropomiosina 1	AD	Sí[28,99]
ACTC1	15q14	612098	Actina alfa del músculo cardíaco 1	AD	Sí[12]
Genes que codifican a proteínas de filamentos gruesos					
MYBPC3	11p11.2	115197	Proteína C cardíaca de unión a miosina	AD/AR	Sí[23,43,47,49,55,74,100-103]
MYH6	14q11.2	613251	Cadena pesada de miosina alfa	AD	Sí[56]
MYH7	14q11.2		Cadena pesada de miosina beta	AD/AR	Sí[46,49,55,57,58,67,100,104,105]
MYL2	12q24.11	608758	Cadena ligera de miosina regulatoria ventricular	AD	Sí[70,71]
MYL3	3p21.31	608751	Cadena ligera de miosina 3	AD/AR	Sí[36,73-75,106]

MIM: número correspondiente en la base de datos *Mendelian Inheritance in Man*; HFMS: historia familiar de muerte súbita; AD: autosómica dominante; AR: autosómico recesivo.

filamentos gruesos y delgados conducen a un incremento del gasto energético debido a la alteración en el uso y metabolismo del ATP[9,10]. Este "compromiso energético" podría resultar en una activación del sistema neuroendocrino con el fin de desarrollar una hipertrofia cardíaca compensatoria. Para estudiar los efectos funcionales de las variantes patogénicas, Coppini, et al.[11] realizaron un estudio prospectivo durante 4.5 años, en el cual dividieron a un grupo de individuos afectados según la estructura alterada, y se conformaron así dos grupos: uno en el que los pacientes (n = 80) portaban variantes patogénicas de filamentos delgados y otro (n = 150) con variantes patogénicas de los filamentos gruesos, y encontraron que los pacientes con alteraciones de filamentos delgados mostraban una mayor disfunción ventricular izquierda e insuficiencia cardíaca, en comparación con el grupo de alteraciones en los filamentos gruesos, que presentaron mayor fibrosis, menor hipertrofia con distribución atípica, disfunción diastólica grave, respuesta anormal de la presión arterial durante el ejercicio y antecedente familiar de muerte súbita cardíaca. Por otra parte, los individuos con variantes patogénicas que afectan a filamentos gruesos sufrieron mayor obstrucción del tracto de salida del ventrículo izquierdo debido a un crecimiento pronunciado de dicha pared ventricular[11]. En otro estudio, en el que se analizaron nueve genes en 197 casos índice de MCH (incluidos 172 casos familiares y 25 aparentemente esporádicos), Richard, et al.[107] encontraron variantes patogénicas en el 63% de los casos; de éstos, 42% se encontraba en la secuencia del gen *MYBPC3* y 40% en *MYH7*[7] Ambos genes codifican a proteínas de filamentos gruesos y cabe señalar que este tipo de hallazgos se repite a través de diversas investigaciones[108,109] en distintos grupos étnicos. Lo anterior convierte a los genes *MYBPC3* y *MYH7* como el principal objeto de estudio ante casos de MCH con antecedente de muerte súbita familiar o paro cardíaco no letal (Tabla 2).

El gen *MYBPC3* y su papel en la MCH

El gen *MYBPC3* se localiza en el brazo corto del cromosoma 11, el cual codifica a la isoforma cardíaca de la proteína C de unión a la miosina (MYBPC o MyBPC, *myosin-binding protein C*). Esta proteína se expresa sólo en el músculo cardíaco y se localiza de modo específico en las bandas A transversales del sarcómero, unida a las cadenas pesadas de miosina en los filamentos gruesos; por lo tanto, se la considera

miembro del complejo tripartito junto con la actina y la miosina, y regula así la contracción cardíaca a través de sucesos de fosforilación[101,110].

El mecanismo por el cual sus variantes patogénicas llevan al desarrollo de MCH aún es tema de debate, pero se han propuesto dos hipótesis. Una de ellas atribuye las manifestaciones clínicas a la haploinsuficiencia, con aumento de la sensibilidad al calcio[111], mientras que la segunda favorece la hipótesis de un efecto tóxico de la proteína alterada[112].

El estudio del gen *MYBPC3* cobró interés a raíz del uso cada vez más frecuente para el diagnóstico de las tecnologías de biología molecular, las cuales han encontrado una relación consistente entre variantes patogénicas de este gen y el desarrollo de MCH[113] y hasta el momento se han documentado más de 450 variantes patogénicas o probablemente patogénicas en la *The Human Gene Mutation Database* (HGMD; http://www.hgmd.cf.ac.uk).

El estudio molecular en casos de muerte súbita llevó a diversos investigadores a la vinculación con MCH debido a la presencia de variantes patogénicas en proteínas que intervienen en el funcionamiento del sarcómero. En este contexto, Cann, et al.[49] realizaron un estudio de necropsia molecular en 96 casos de muerte súbita cardíaca e identificaron 50 casos con miocardiopatía, de los cuales 15 tuvieron MCH y de éstos tres presentaron variantes patogénicas en el gen *MYBPC3* y tenían el antecedente de muerte súbita de origen cardíaco durante el ejercicio, inmediatamente después de realizar ejercicio o durante el sueño[49]. Las características clínicas de inicio tardío y alta frecuencia de antecedentes familiares de muerte súbita en los afectados se repiten a través de los múltiples estudios en distintas poblaciones alrededor del mundo[53,113].

El gen *MYH7* y su papel en la MCH

El gen *MYH7* se localiza en el brazo largo del cromosoma 14, codifica a la isoforma β de la cadena pesada de miosina (MYH o ß-MHC, *myosin heavy chain*), proteína que se expresa en el músculo estriado de los mamíferos (de forma predominante en los ventrículos) y que forma parte de los filamentos gruesos del sarcómero[114]. *MYH7* es el primer gen cuyas variantes patogénicas se relacionaron con MCH y cuyo efecto dominante negativo está bien descrito[115,116].

Hasta la fecha se han documentado más de 350 variantes patogénicas en el gen *MYH7* en HGMD, con fenotipos clínicos altamente variables, como es el estudio de cohorte de García-Castro, et al.[108] en 120 pacientes no emparentados con MCH. A los sujetos de este estudio se les realizó historia clínica y estudio molecular, y se identificaron 31 variantes patogénicas distintas en 32 pacientes, 8% de los cuales (10 pacientes) tenía alteración en el gen *MYH7*; la media de edad a la que se estableció el diagnóstico fue de 35 años y 3 de estos 10 pacientes (70%) tenían el antecedente familiar de MCH[108].

En cuanto al pronóstico de los portadores de variantes patogénicas del gen *MYH7*, Wang, et al.[117] informaron en 2008 que las variantes patogénicas de este gen producen fenotipos más agresivos en comparación con aquellas que afectan al gen *MYBPC3*, con manifestaciones de inicio temprano (16 años) y alto riesgo de muerte súbita[117].

Diversas investigaciones han tratado de establecer la correlación genotipo-fenotipo para facilitar el diagnóstico temprano en sujetos asintomáticos, pero esto ha sido difícil de establecer debido al gran número de variantes patogénicas identificadas en diversos genes (heterogeneidad de *locus*), a un posible efecto aditivo que modifique el fenotipo como en el caso de la edad de presentación y el pronóstico, a la gran variabilidad clínica de esta enfermedad y a la influencia del ambiente[48].

Variantes patogénicas o probablemente patogénicas localizadas en *MYBPC3* y *MYH7* en relación con muerte súbita

Hoy en día existe una decena de variantes patogénicas o probablemente patogénicas relacionadas con muerte súbita en diferentes poblaciones alrededor del mundo; la mayor parte de ellas produce un desplazamiento del marco de lectura y, como consecuencia, la proteína sintetizada es trunca debido a un codón de paro prematuro. A continuación se describen de forma sintética algunas de ellas en el contexto de la muerte súbita.

Variantes relacionadas con MCH y antecedente de muerte súbita para el gen *MYBPC3*

p.Glu542Gln: Este cambio se ha descrito en siete casos índices no relacionados. En el plano molecular se ve afectado el último nucleótido de un sitio consenso para corte y empalme (*splicing*) y como efecto se obtiene una proteína corta de 486 aminoácidos[118].

p.Cys719Arg: Este cambio se identificó en el año 2017 en un caso aparentemente esporádico de ascendencia

china cuya causa de muerte era desconocida y en el informe de defunción se concluyó muerte súbita[47].

p.Glu334Lys: Se identificó en un hombre de 48 años, de ascendencia coreana, diagnosticado por medios ecocardiográficos como una fenocopia del síndrome de Brugada al momento del diagnóstico de ingreso. Era un sobreviviente de un paro cardíaco no letal[100].

p.Pro108Alafs*9: Se trata de una inserción de los nucleótidos GCTGGCCCCTGCC en la posición 29 del exón 3. La variante se identificó de modo inicial en 13 familias del sur de España, por lo que se estudió a 107 familiares y de ellos 39 tenían MCH, con predominio del sexo masculino y con cinco casos de muerte súbita documentados y una mayor masa ventricular izquierda para los portadores de esta variante[43]. En la proteína, la longitud se reduce a 115 aminoácidos, ocho de los cuales son nuevos.

p.Gly1093Cys: Se analizaron 96 casos de necropsias de muerte súbita, en los cuales un probando falleció inmediatamente después de realizar ejercicio, motivo por el cual se solicitó prueba genética a 12 familiares, ocho de los cuales fueron positivos para este cambio y dos casos tenían síntomas cardíacos relacionados con MCH[49].

p.Arg668His: El caso índice falleció en apariencia durante el sueño, motivo por el que se estudió a 27 familiares de los cuales 10 resultaron positivos para la variante y cuatro experimentaron síntomas relacionados con MCH[49]. La variante se había notificado ya con anterioridad[119].

p.Arg502Trp: El caso índice falleció durante la realización de ejercicio, motivo por el cual se realizó estudio genético a cinco familiares, de los cuales tres fueron positivos, uno de ellos con síntomas relacionados con MCH[49].

IVS5+5G→C: Esta variante corresponde a una sustitución de guanina por citocina cinco pares de bases corriente abajo 5' del sitio donador de corte y empalme en el intrón 5 del gen *MYBPC3*. Esta modificación ocasiona un cambio en el marco de lectura y añade 15 aminoácidos después de la posición 165, lo que causa al final una proteína trunca. Lin, et al. informan el caso de una familia en la que existe el antecedente de muerte súbita en el hermano del probando, quien falleció a la edad de 20 años. Tanto el padre como el probando son portadores clínicos de MCH[120].

p.F305Pfs*27: Se trata de una deleción de dos timinas en el exón 11 que causa un codón de terminación y por lo tanto una proteína trunca. Calore, et al. estudiaron a una serie de 97 probandos de origen italiano con diagnóstico de MCH, de los cuales 19 fueron portadores de la variante, más 45 portadores detectados por tamizaje en cascada. La penetrancia en esta serie de pacientes fue del 75%; en ocho portadores hubo antecedente de muerte súbita, por lo cual el pronóstico es reservado para aquéllos con la variante después de la cuarta década de la vida[52].

Lys1209Serfs*28: En combinación con p.Gly100Ser localizada en *PRKAG2* (probable efecto aditivo), Zhao, et al. estudiaron a 18 pacientes con diagnóstico de MCH, entre los cuales un probando presentó dos variantes y el antecedente de muerte súbita en la madre y abuela materna; el fenotipo del probando es consistente con hipertrofia grave e inicio temprano de MCH[23].

Variantes relacionadas con MCH y antecedente de muerte súbita para el gen *MYH7*

p.Arg453Cys: En esta variante se observa un cambio de carga debido a un cambio de aminoácido, por lo que se ha informado un fenotipo más agresivo en comparación con Val606Met y Phe85Cys[121,122]. Ko, et al. estudiaron a un grupo de 20 individuos provenientes de una familia, todos ellos mayores de 16 años; en 11 casos se sospechó MCH clínica y en siete casos la enfermedad se confirmó por medio de ecocardiografía. Esta familia cuenta con el antecedente de tres casos de muerte súbita y dos con enfermedad cardíaca terminal[108].

p.Arg1045Leu: En esta familia cuyo probando falleció durante el sueño se estudió a cuatro individuos en quienes se identificó a un familiar con datos clínicos de MCH[49].

p.Arg719Trp: Anan, et al. realizaron un estudio genético en cuatro distintas familias con antecedente de MCH y por lo menos 22 casos de muerte súbita, lo que determinó un mayor riesgo de efectos adversos para los portadores de la variante[123].

p.Asn391Thr: Feng, et al. estudiaron a una familia extensa de la etnia han (China) con diagnóstico de MCH, la cual incluyó a tres generaciones y 22 individuos, de los cuales fallecieron tres con diagnóstico de MCH; la edad de inicio de los síntomas de la enfermedad en su mayoría fue < 20 años[58].

p.Gly716Arg: Hwang, et al. estudiaron a una familia coreana compuesta por 32 miembros en cuatro generaciones. En esta familia existía el antecedente de cuatro individuos con muerte súbita a edad temprana; las pruebas genéticas demostraron que 13 individuos eran portadores de la variante[124].

p.Arg403Gln: Marian, et al. estudiaron a una familia con siete casos positivos para esta variante. En esta

familia, el inicio de los síntomas ocurrió en promedio a los 22 años; sin embargo, un individuo masculino de 10 años estaba asintomático. El análisis de sobrevida de Kaplan-Meier mostró que los portadores de la variante p.Arg403Gln tienen 11% de probabilidad de seguir vivos a los 60 años[125]. Esta variante se había notificado antes con alta incidencia para muerte súbita en otras tres familias[126-128].

p.Arg453Cys: Esta variante se reconoció en el decenio de 1990 en una familia con 13 individuos afectados con MCH y el antecedente de seis casos de muerte súbita. De forma inicial, el tamizaje para detectar variantes se realizó con ayuda de estudios de protección de ribonucleasas y en el plano familiar se vinculó la enfermedad con la variante encontrada por medio de análisis de ligamiento; este cambio produce un cambio en la carga del aminoácido (-1) y se ha relacionado con una menor sobrevida[128].

p.Glu848Gly: Esta sustitución de ácido glutámico por glicina da lugar a un efecto dominante negativo mediante la alteración de uniones proteína-proteína (*MYH7-MYPC3*) que llevan a la disfunción sistólica y riesgo aumentado de muerte súbita[67].

p.Asn391Thr: Variante sin sentido hallada durante el estudio de una familia originaria de China con múltiples individuos afectados por MCH e historial de cuatro integrantes con muerte súbita[58].

Conclusión

La MCH es una enfermedad altamente heterogénea debido al gran número de genes afectados e identificados como causales; además, la presencia de una o más mutaciones en proteínas integrantes del aparato contráctil del músculo cardíaco y al final la influencia ambiental dan origen a un fenotipo particular con curso clínico variable, en el cual la muerte súbita puede ser la primera manifestación. Entre los genes que codifican a proteínas integrantes del aparato contráctil del músculo cardíaco, los genes de filamentos gruesos *MYBPC3* y *MYH7* son los identificados con más frecuencia como causales en las publicaciones médicas mundiales, tomadas en cuenta todas las poblaciones, con más de 350 variantes patogénicas o probablemente patogénicas notificadas en cada gen.

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Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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ARTÍCULO ESPECIAL

Joint Mexican position document on the treatment of atrial fibrillation

Posicionamiento conjunto acerca del tratamiento para fibrilación auricular

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Abstract

Atrial fibrillation (AF) is a frequent arrhythmia; its prevalence is near 2% in the general population; in Mexico, more than one-half million people are affected. AF needs to be considered as a public health problem. Because AF is an independent risk factor associated with mortality, due to embolic events, heart failure, or sudden death; early diagnosis is of utmost importance. In unstable patients with a recent onset of AF, electrical cardioversion should be practiced. In stable patients, once thrombo-embolic measures have been taken, it is necessary to assess whether it is reasonable to administer an antiarrhythmic drug to restore sinus rhythm or performed electrical cardioversion. For recidivating cases of paroxysmal and persistent presentation, the most effective strategy is performed pulmonary vein isolation with either radiofrequency or cryoballoon energy. Permanent AF is that in which recovery of sinus rhythm is not possible, the distinguishing feature of this phase is the uncontrollable variability of the ventricular frequency and could be treated pharmacologically with atrioventricular (AV) nodal blockers or with a VVIR pacemaker plus AV nodal ablation. The presence of AF has long been associated with the development of cerebral and systemic (pulmonary, limb, coronary, renal, and visceral) embolism. The prevention of embolisms in "valvular" AF should perform with Vitamin K antagonists (VKA). For patients with AF not associated with mitral stenosis or a mechanical valve prosthesis, a choice can be made between anticoagulant drugs, VKA, or direct oral anticoagulants. Antiplatelet agents have the weakest effect in preventing embolism.

Key words: *Atrial fibrillation. Drug treatment. Tromboprofilaxis. Cryoballoon ablation. Radiofrequency ablation.*

Resumen

La fibrilación auricular (FA) es una arritmia frecuente; su prevalencia es cercana al 2% en la población general, en México se ven afectados más de medio millón de personas por eso debe considerarse como un problema de salud pública. Debido a que la FA es un factor de riesgo independiente asociado a mortalidad, por eventos embólicos, insuficiencia cardíaca o

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muerte súbita, la identificación y diagnóstico temprano es de suma importancia. En el inicio reciente de FA en pacientes inestables, se debe practicar la cardioversión eléctrica. En pacientes estables, una vez que se han tomado medidas tromboembólicas, es necesario evaluar si es razonable administrar un medicamento antiarrítmico para restaurar el ritmo sinusal o realizar una cardioversión eléctrica. Para los casos que recidivan, ya sea paroxística o persistente, la estrategia más efectiva es realizar el aislamiento de la venas pulmonares con radiofrecuencia o crioablación con balón. La FA permanente es aquella en la que no es posible la recuperación del ritmo sinusal, la característica distintiva de esta fase de la FA es la variabilidad incontrolable de la frecuencia ventricular. Puede tratarse farmacológicamente con bloqueadores nodales AV o con un marcapasos VVIR mas ablación del nodo AV. La presencia de FA se ha asociado durante mucho tiempo con el desarrollo de embolia cerebral y sistémica (pulmonar, de extremidades, coronaria, renal y visceral). La prevención de embolias en la FA "valvular" debe realizarse con antagonistas de la vitamina K (AVK). Para los pacientes con FA no asociados con estenosis mitral o una prótesis valvular mecánica, se puede elegir entre medicamentos anticoagulantes, AVK o anticoagulantes orales directos (DOAC). Los agentes antiplaquetarios tienen el efecto más débil para prevenir la embolia.

Palabras clave: *Fibrilación atrial. Tratamiento farmacológico. Tromboprofiláxis. Crioablación. Ablación con radiofrecuencia.*

What is known about the epidemiology of atrial fibrillation (AF) in Mexico? Can it be considered a public health problem?

AF incidence and prevalence increase with age. Its prevalence is near to 2% in the general population, but it could be as high as 10% in those over 75 years[1,2]. Before the Mexican Registry of AF (ReMeFA) was published a study market was conducted in Mexico in 2007, finding that, for a population of 105'338,982 people the prevalence of cardiac arrhythmias was 2.4%, with tachyarrhythmias being the most common with 56% (1'402,453 people), of which, AF was the most frequent arrhythmia, occupying 60.7% of tachycardia (or a total of 851,489 cases)[3].

Today, we estimate that in Mexico, there are more than one and a half million people with AF, with a prevalence ranging from 0.43% in the 40 to 49 age group to 8.48% in those over 80 years old, for an average of 1.58% in a population over 40 years of age[3]. Permanent or chronic AF represents 51.5% (corresponding to 438,134, Mexicans). The ReMeFA[4] study was the first national multicenter registry, with clinical follow-up of 1 year, in 1201 subjects, on the comparison of AF treatment with a rhythm control strategy or with rate control. This study was carried out with the collaboration of 71 cardiologists and electrophysiologists. At 1 year follow-up, an incidence of 3% of ischemic cerebral vascular disease (CVD) was observed in the rate control strategy; significantly higher than 1% in the rhythm control strategy ($p = 0.04$)[2]. Worldwide, CVD is the second leading cause of death and the leading cause of disability[1]. CVD has become a health problem as a result of increased life expectancy and lifestyle changes, representing one of the leading causes of death in Mexico[2,3]. According to the Brain Attack Surveillance project in Durango, it is estimated that in Mexico the annual incidence of CVD is 232.3 cases per 100,000 inhabitants over 35 years of age, while its prevalence is eight cases of CVD per 1000 inhabitants, a figure that increases to 18 cases per 1000 in people over 65 years of age[5]. It is important to note that in recent years, CVD has occurred in younger people as a result of the continuing increase in risk factors, including unhealthy lifestyles and obesity. In a Pan American Health Organization report, indicators of premature vascular mortality (in people under 70) showed that in Mexico the rate in nondiabetics was 10.7/100,000, compared to 3.3 and 5/100,000 in Canada and the USA, respectively[6]. Based on these results, we consider AF to be the most frequent tachyarrhythmia in Mexico with a high percentage of CVD, so it should be considered a public health problem in Mexico[6].

Importance of early diagnosis

AF is an independent risk factor associated with mortality, increasing it twice in men and 1.5 times in women[1]; mortality due to embolic events can decrease with oral anticoagulation but other causes of cardiovascular death such as heart failure or sudden death continue to be frequent despite adequate treatment that is the reason why an early diagnosis is of outmost importance since AF can be asymptomatic (silent AF), and patients have it inadvertently, delaying proper treatment. The diagnosis of AF requires to be an event lasting at least 30 s and to be observed on an electrocardiogram (ECG), rhythm strip, or cardiac monitor, characteristically with the irregularity of RR intervals without clearly identifiable P waves or with visible "f" waves of fibrillation. An early electrocardiographic recording is cost effective for documenting chronic forms of AF, particularly in populations older than 65 years with a

prevalence of up to 2.3%, obtaining a "necessary to treat" number of 70 to find one with AF[1]. As for paroxysmal AF, the longer the record, the more likely it is to find silent events. Now the technology has evolved, so in Mexico, we already have 48-h recorders and implantable loop recorders whose duration is up to 3 years. The more we used these devices in high-risk patients, more likely the chance of found AF and being able to start appropriate treatment earlier[4].

Antiarrhythmics available in Mexico for rhythm control: how and when?

Recent onset AF: conversion to sinus rhythm in an unstable patient

If the AF paroxysm is associated with "angina pectoris," pulmonary edema, low blood pressure or shock, urgent electrical cardioversion should be practiced. It is recommended that the shock should be with the highest available energy 200 J biphasic or 360 J monophasic. It is not suggested to proceed in stages by increasing from lower energies. The reason for this is to reduce the number of shocks, use a lower cumulative dose of energy, and reduce the anesthetic time. For thromboembolic prophylaxis, unfractionated heparin (bolus according to body weight followed by infusion) should be administered, followed by oral anticoagulation[1]. Although embolism risk might be increased because of the emergency nature of the condition.

Stable patient

Assuming that the corresponding thromboembolic prevention measures have been taken and that the heart rate controlled with the isolated or combined use of beta-blockers, calcium antagonists, or digital, the clinician should assess whether it is reasonable to administer any antiarrhythmic drug to restore sinus rhythm. It is known that up to 50% of AF paroxysms may spontaneously remit within 24-48 h[7]. If AF persists after this period, pharmacological cardioversion with amiodarone (oral or preferably intravenous), propafenone or flecainide is indicated. Intravenous amiodarone is given at a loading dose of 5-7 mg/kg in 30-60 min, followed by a maintenance dose of 1.2-1.8 g/day until 10 g[1]. completed. The oral dose of propafenone is 600 mg in a single dose and that of flecainide is 300 mg in a single dose. Sinus rhythm conversion occurs in 80-90% of cases within the first few hours[8]. It should emphasize that sotalol, dronedarone, and digital are not indicated for conversion to sinus rhythm. If the episode becomes persistent despite the use of antiarrhythmics, electrical CV is indicated, preceded by a transesophageal echocardiogram to rule out intracavitary thrombus[1,9].

Maintaining sinus rhythm

Once the conversion to sinus rhythm has achieved, the clinician should assess whether it is appropriate to use an antiarrhythmic daily for the maintenance of sinus rhythm or whether it is preferable not to give preventive antiarrhythmic and choose a strategy of treating the episode with the "pill in your pocket" strategy[1,10]. For the maintenance of sinus rhythm, it is indicated to use one of the following antiarrhythmics: propafenone, flecainide, sotalol, dronedarone, or amiodarone. In the absence of structural heart disease, the use of propafenone or flecainide is recommended[10]. Sotalol may use in the presence of ischemic heart disease. Dronedarone is indicated only for cases of paroxysmal AF with preserved left ventricular ejection fraction, in the absence of heart disease and with preserved systolic ventricular function. Amiodarone is considered a second-line drug due to its side effects; however, it is the most effective alternative for maintaining sinus rhythm[1]. In the case of heart failure, the use of amiodarone is recommended. For the last three drugs (sotalol, dronedarone, and amiodarone), the duration of the QT interval should be monitored[11]. A single dose of 600 mg propafenone or 300 mg flecainide is recommended for the "pill in your pocket" strategy[1,8,10]. Caution should be exercised due to the possibility that these two drugs may unmask the electrocardiographic signs of Brugada syndrome or convert AF into an atrial flutter with a paradoxical increase in ventricular response (< 1% of cases)[12].

Recurrent AF (paroxysmal and persistent)

Unlike the first episode approach (or very sporadic recurrent cases), for recidivating cases of paroxysmal and persistent presentation, it is indicated to use antiarrhythmics for prevention. The therapeutic options are propafenone, flecainide, sotalol, dronedarone, and amiodarone. It should emphasize that dronedarone is only indicated to prevent recurrence of paroxysmal or persistent AF that have lasted < 6 months of evolution, in the absence of heart disease and with preserved left ventricular function. AF ablation (radiofrequency or cryoballoon energy) should be considered as a first-line alternative for drug-refractory or symptomatic cases (at least one antiarrhythmic Class Ic or III)[1,13].

Persistent AF lasting more than a year

This category was established to identify patients who may benefit from a rhythm control strategy because AF is permanent of those with a chance to convert to sinus rhythm. There are two therapeutic options: (1) facilitated electrical cardioversion with prior use of antiarrhythmics[14] and (2) AF ablation[1]. It is reasonable to proceed with facilitated electrical cardioversion with antiarrhythmic drugs as the first measure because if successful, although with early relapse, it demonstrates that the patient can maintain sinus rhythm and would be a suitable candidate for catheter ablation[1,13,14].

Immediate post-cardioversion recurrence

Electrical cardioversion is one of the cornerstones for rhythm control in AF. However, immediate recurrence or therapeutic failure, described in up to 26% of cases, limits its clinical application[15]. To increase the response rate, antiarrhythmics must give before the electric shock[13,14]. The use of verapamil, amiodarone, or sotalol has been reported to decrease the incidence of immediate recurrence[13-16]. Other drugs such as ibutilide (not widely available in Mexico), vernakalant (not available in Mexico), and ranolazine (available in our country) have also shown benefit in this area[1,17].

Postponed cardioversion (facilitated by antiarrhythmic)

It is indicated for persistent AF, mainly when the temporal progression is unknown or when a high probability of immediate recurrence is assumed. Amiodarone 600 mg/day administered for 1 month (total dose 16.8 g) is indicated for a better outcome. Pharmacological cardioversion has been observed to occur during loading in 16-18% of cases[1]. The success of electrical cardioversion is 88%. Besides, the ventricular response of the heart rate during AF is reduced from 100 ± 25 to 87 ± 27.5 beats/min ($p \leq 0.001$) by a negative dromotropic effect on the atrioventricular (AV) node[18].

How to manage rate control in permanent AF? What is the role of AV node ablation with pacemaker implant?

Much has been said about (AF) that can be summed up in three brief sentences: it is the most common arrhythmia, the easiest to diagnose, and the most difficult to treat[19-21]. Another no less ominous peculiarity is that AF is a progressive disease[22] and that itself is a condition that contributes to its perpetuation[23]. In other words, the sooner we try to revert and achieve sinus rhythm, the higher the chances of success (to keep the patient in sinus rhythm)[24].

Permanent (chronic) AF

Permanent AF is the one in which recovery of sinus rhythm is not possible[1,19]. The distinguishing feature of this phase of AF is the uncontrollable variability of the ventricular rate. It depends on the AV conduction and not on the sinus node function; it is the autonomic nervous system – sympathetic and vagal – that determines the AV conduction velocity and thus the ventricular frequency[25]. It is common to consider ventricular rate analysis only with a resting EKG record, however, this is not quite right because of the circadian heart rate variations. On the other hand, vagal tone during the early morning hours can delay AV conduction and cause considerable and sufficient ventricular pauses to cause low brain perfussion with its consequences. The therapeutic possibilities are: pharmacological and interventional[26,27].

Pharmacological treatment

The main limitation of drugs is because they slow nodal conduction it can produce very severe bradycardia, without avoiding abnormally fast frequencies[28]. Antiarrhythmic drugs such as amiodarone are ineffective, as, by definition, sinus rhythm is not intended to be restored[29]. Beta-adrenergic blockers may delay AV conduction, but decrease the force of ventricular contraction[1].

Interventional treatment

Once it has been demonstrated that the patient has a very high heart rate variability and maintains a rhythm above 140/min, heart failure is an imminent threat[1,30]. Ablation of the AV junction and placement of a variable frequency ventricular pacemaker (VVIR) are the indicated option. The use of anticoagulants is imperative even in patients who have regained sinus rhythm after isolating the pulmonary veins, so there is no argument against it[31,32]. Radiofrequency thermal injury of the AV junction causes an irreversible blockage. The injured tissue can be the AV node or the His bundle and can be achieved either from the tricuspid ring or from the left ventricle[1]. The success of this procedure is very close to 100%, and the possibility of recurrence is practically null. The

placement of a ventricular pacemaker is a routine procedure in any institution, with low risk and ventricular function improved by obtaining regularity of rate[1].

In a series of patients in the Unit of Arrhythmias of Experimental Medicine of the UNAM in the General Hospital of Mexico, 177 ablations of the AV junction and placement of ventricular pacemaker have been carried out. All patients showed a ventricular rate variability (ventricular function normal) > 140 bpm, when the normal is above 100 bpm. Many of them, during 6 min of walking, could not perform more than 250 m. In 159 of the patients, ablation of the AV Union achieved from the right atrium, and in 17 (10%), it had to be done from the left ventricle. In no case, there was a recovery of AV conduction. This study concludes that ablation of the AV node is affordable and feasible in cases of permanent AF. Isolation of pulmonary veins should not be performed as and attempt to recover sinus rhythm, even if other options have been exhausted. Anticoagulation is mandatory in almost all patients, with AF, regardless of its type.

What is the clinical benefit and what is the purpose of pulmonary veins isolation in AF

In general, there is no definitive cure for AF; the therapeutic goal is to control symptoms, delay disease progression, and prevent a cardiovascular event[33]. Electrical isolation of the pulmonary veins when there is recurrence with drug treatment may be the most effective strategy for maintaining sinus rhythm and keeping the individual asymptomatic[1,33]. Invasive electrophysiological treatment is relatively recent; it began when it was discovered that premature atrial contractions from the pulmonary veins were responsible for initiating AF; which led to the establishment of the selective elimination of these ectopic foci as a therapeutic objective[33]. At present, the strategy is broader, trying to make electrical isolation of all pulmonary veins from the antrum and not from the ostium to avoid side effects such as pulmonary stenosis. Other cases of more advanced disease require different ablation strategies such as supplemental lesion in the left or right atrium, or even both, as well as in the superior vena cava or cavotricuspid isthmus[1,33]. AF is a progressive disease, starting with tachycardia of the pulmonary veins (they usually arise from there, but they can be originated in other sites) that initiate AF; however, AF produces more AF with a remodeling, not only anatomical but also electrical process of the atria. If AF is prolonged enough, it becomes a biatrial disease with fibrosis, electrical remodeling, and dilation of both atria that causes rotor systems that support it, making it finally permanent[34-36]. Technology and knowledge have evolved with results of radiofrequency catheter ablation (RFCA) of 74% of patients in sinus rhythm at 1 year of follow-up[1,33]. AF ablation is recommended in paroxysmal, persistent, and persistent AF of long duration refractory or intolerant to antiarrhythmic drugs; it may also be considered as the first line in symptomatic paroxysmal AF[1]. The therapeutic objective is to create a series of lesions that prevent AF by eliminating the triggering extrasystoles or modifying the substrate that maintains it[1,33]. At present, ablation strategies depend on the type of AF; if it is paroxysmal AF, the success rate is higher, since the isolation of the pulmonary veins is sufficient to maintain sinus rhythm[1,33]. On the other hand, if it is persistent AF, the success rates are lower; in these cases, the therapeutic strategy is broader, requiring different ablation lines and searching for rotors not only in the left atrium but also in the right atrium, and even in other thoracic veins such as the coronary sinus, caval veins, or Marshall's vein[1,33,36]. This complexity leads to a significant reduction of the long-term success rate, requiring two or more procedures to make it more likely that the patient maintains sinus rhythm. Because of these results, patients with paroxysmal AF are now preferred for early intervention. Scientific evidence shows that the main factor for maintaining sinus rhythm is achieving complete electrical isolation of the pulmonary veins. In advancing stages the posterior wall, also plays an essential role in the maintenance in the maintenance of sinus rhythm.[1,33,34]. The techniques employed can be two, with RFCA using irrigation catheters or with cryoballoon ablation (CBA); the latter was limited only for paroxysmal AF but, nowadays it is safe to perform it in persistent AF with the advantage of being a less operator-dependent, with a faster learning curve and above all, fewer complications than RFCA[1], with comparable results in comparative studies[1,33,37]. In centers of high experience, it can give results of up to 85% of patients free of AF at a 12 month follow-up[38]. In Mexico, in the series published by the Instituto Nacional de Cardiología[39] (Clinicas Mexicanas de Cardiología) of RFCA, in a period of 8 years, in patients with paroxysmal AF, there is 78% success in a 12-month follow-up in a total of 121 patients. CBA is the first experience in Mexico from 2013 to 2014 in a multicenter study (unpublished data from Hospital Ángeles Interlomas, CMN Siglo XXI, CMN 20 de Noviembre and Servicios de Salud del Estado de Puebla) with 52 patients, exclusively with paroxysmal AF, was successful in 78% of cases with 18-month follow-up.

When and how should antithrombotic prophylaxis be given in the subject with AF? Antiplatelet drugs, Vitamin K antagonist (VKA), direct oral anticoagulants (DOAC) and left atrial appendage occluders (LAAO)

AF is a cause of stroke

The presence of AF has long been associated with the development of cerebral and systemic (pulmonary, limb, coronary, renal, and visceral) embolism[40]. Initially, only AF secondary to valvular disease, usually rheumatic heart disease, was considered thrombogenic[41], but since the Framingham study, AF of non-rheumatic origin is also recognized as a cause of embolism[42].

The prevention of embolisms in "valvular" AF should perform with VKA

For embolic risk purposes, "valvular" AF is considered to be the one associated with moderate or severe mitral stenosis or in the presence of a mechanical valve prosthesis[43]. Although acetylsalicylic acid was initially used in patients with rheumatic heart disease[44], subjects with valvular AF should now be anticoagulated with VKA, either acenocoumarin or warfarin[1,45]. The dose is that necessary to achieve an international normalized ratio (INR) between 2.0 and 3.0, except for patients with mechanical valve prostheses that require INR between 2.5 and 3.5. DOAC should not be used in valvular AF until the results of studies supporting this practice are available[46]. To improve the time in therapeutic intervals, it is recommended to: (1) establish anticoagulation clinics[47] and (2) self-monitoring of the INR with portable devices[48].

CHA_2DS_2-VASc scale and options for prevention of embolisms in "non-valvular" AF

For patients with AF not associated with mitral stenosis or a mechanical valve prosthesis, a choice can be made between anticoagulant drugs, VKA or DOAC. Antiplatelet agents have the weakest effect in preventing embolism[49]. In the joint analysis of randomized studies, the relative risk reduction of stroke by anabolic-androgenic steroids (AAS) compared to placebo was calculated at 19% while with VKA, it was 64%[50]. It is important to note that based on the results of the ACTIVE-W study, dual antiaggregation therapy (e.g. AAS and clopidogrel) is not recommended over oral anticoagulation[51].

The decision of which drug should be used in the prevention of cerebral infarction can be based on the use of the CHA_2DS_2-VASc1[52], scale (Table 1). For individuals with no points, (no risk factors, considered "low risk" by not observing any embolic event in a follow-up year) in general it is possible to choose not to give treatment; in those with a score of one ("intermediate risk" of 0.6% of an embolic event per year) if it is male or two if it is female, they benefit more with oral anticoagulation with VKA or DOAC[1]. The HAS-BLED or ATRIA scales can be used to assess the risk of bleeding (Table 1)[53].

For individuals scoring two or more on the CHA_2DS_2-VASc scale ("high risk," 3% embolic event per year), there is no doubt that formal anticoagulation with VKA or DOAC is required. There are currently three DOACs available in Mexico: dabigatran, rivaroxaban, and apixaban. Their mechanism of action is inhibition of thrombin (dabigatran) or inhibition of factor Xa (rivaroxaban and apixaban)[54].

Each has a different dosage, which varies with the individual's age (in the case of apixaban) and kidney function (all). None can be used in cases of renal failure with creatinine clearance < 30 mL/min. For a complete review of DOAC, including dosages, how to start them, switching from VKA to DOAC, drug interactions, and bleeding management, the clinical practice guidelines of the European Heart Rhythm Association are highly recommended[55].

LAAO

LAAO are an interventional option for the prevention of embolism that so far is only indicated for patients with high embolic risk and who have some contraindication to receive VKA or DOAC[56]. Outside of this select group of patients, implanting these devices as substitutes for anticoagulation do not yet have sufficient evidence. The most recent results on cost-benefit analysis using dedicated statistical models (e.g. Markov's stochastic decision model) have yielded contradictory results[57]. However, several studies are ongoing and are expected to produce positive results for occluders[58]. Like any invasive procedure, its efficacy in preventing stoke should weigh against possible complications of its implant.

Final remarks

AF, in its different forms, is considered to be the most frequent tachyarrhythmia in Mexico and should be considered as a public health problem. Its treatment

Table 1. Risk factors for cerebral infarction included in the "CHA_2DS_2-VASc" scale and hemorrhagic risk factors included in the "HAS-BLED" scale

CHA2-DS2-Vasc	Score	HAS-BLED	Score
C (Congestive heart failure) = Left-sided heart failure	1	H = Hypertension	1
H = Hypertension	1	A = Impaired liver or kidney function	1 each
A (Age) = ≥ 75 years	2	S (Stroke) = Cerebral vascular disease	1
A (Age) = Age 65-74 years	1	B (Bleeding) = Bleeding	1
D-Diabetes *mellitus*	1	L (Labil INR) = Highly variable INR (outside therapeutic intervals)	1
S (Stroke) = Previous stroke	2	E (Elderly)	1
S = Sex category	1	D (Drugs) = Drugs or alcohol	1 each
V = Peripheral vascular disease		1	
Risk of cerebral infarction: – Low = 0 – Intermediate = 1 – High = 2		Risk of bleeding in patients with AF with indication of oral anticoagulation: – Low = 0 – Intermediate = 1-2 – High = 3 or more	

INR: international normalized ratio; AF: atrial fibrillation.

includes "rhythm control" with a few antiarrhythmic drugs available in Mexico for this purpose. Ventricular rate control can be achieved with drugs or some interventional procedures, included AV junction ablation with a VVIR pacemaker implant. The role of pulmonary vein isolation is undoubted for clinical relief of symptoms with many ongoing studies on the possible effect on morbidity-morbidity. Thromboprophylaxis is a key and integral part of the management of any patient with AF. Recently, CENETEC (National Center for the Technical Excellence in Health, Health Ministry of Mexico) published guidelines on the antithrombotic treatment of AF[59].

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Conflicts of interest

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

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ARTÍCULO DE OPINIÓN

Ignacio Chávez Rivera. Un paradigma en la medicina

Ignacio Chávez Rivera. A paradigm in Medicine

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Resumen

Este documento sintetiza la vida de Ignacio Chávez Rivera, uno de los seis directores más valiosos que ha tenido el Instituto Nacional de Cardiología Ignacio Chávez Sánchez, su fundador y padre del ahora aludido. Su paso por la vida dejó un claro ejemplo a emular tanto en el ámbito científico, académico y docente como en los aspectos humano, familiar y social que lo convirtieron en el alumno más destacado del maestro Chávez. Su paso por la vida en la Academia Nacional de Medicina, la Universidad Nacional Autónoma de México, la Sociedad Interamericana de Cardiología, la Sociedad Mexicana de Cardiología y el propio Instituto ha dejado huella imperecedera en estas instituciones. El instituto Nacional de Cardiología se inclina reverente ante la figura de Ignacio Chávez Rivera.

Palabras clave: *Semblanza. Paradigma. Ignacio Chávez Rivera. México.*

Abstract

This article summarizes the life of Ignacio Chávez Rivera, one of the six most valuable directors that the National Institute of Cardiology has had "Ignacio Chávez Sánchez," founder of the same and father of the aforementioned. His time in life left a clear example to emulate both in the scientific, academic and teaching as well as in the human, family, social and friendly, which make him in the most outstanding student of Master Chávez. His time in life at the National Academy of Medicine, the National Autonomous University of Mexico, the Interamerican Society of Cardiology, the Mexican Society of Cardiology and the Institute itself, has left an indelible mark on these Institutions. The National Institute of Cardiology bows reverently to the figure of Ignacio Chávez Rivera.

Key words: *Semblance. Paradigm. Ignacio Chávez Rivera. Mexico.*

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Todos los que tuvimos el privilegio de conocer al mexicano ilustre (Fig. 1) que, entre otras tantas cosas, nos dejó como herencia el Instituto Nacional de Cardiología, que hoy orgullosamente lleva su nombre, consideramos un privilegio laborar en él y desde luego nos sentimos herederos de esta gloriosa tradición que lleva implícita la orden de continuarla, situación que ha ocurrido a través de los años desde la fundación del instituto en 1944 hasta la fecha. Sin embargo, el magno paradigma del cumplimiento de esta orden ocurrió de manera inusual en la persona de Ignacio Chávez Rivera, el propio hijo del maestro y uno de los seis directores que ha tenido el instituto.

En otras ocasiones, en las que por alguna razón he tenido que hacer uso de la palabra para describir la trayectoria y la personalidad de alguna celebridad, he señalado siempre que mi relación con ella se encontraba desprovista de cualquier afecto filial y que consecuentemente hablaba sólo del valor de la persona. Éste no es el caso cuando me refiero al Dr. Ignacio Chávez Rivera; a este hombre me une un sentimiento de afecto filial profundo e indestructible, basado en el reconocimiento de que le debo casi todo cuanto soy, que no es mucho, pero que para mí lo es todo y que deriva no del consejo, sino del ejemplo que me dio (sin que él se haya percatado y sin que jamás fuera su intento) con su trayectoria de vida, a través de una larga convivencia transcurrida a lo largo de 43 años, tiempo durante el cual he tratado de seguir su callada hidalguía.

Como dejé escrito en alguna ocasión[1], es sin duda alguna Ignacio Chávez Rivera el mejor de todos los discípulos que haya tenido Ignacio Chávez Sánchez, (que fueron muchos y muy valiosos).

Distinguidas personalidades, como las de los doctores Jesús Kumate, Guillermo Soberón, Bernardo Fishleder, Daniel Cosío Villegas, Pierre Duchosal, Antonio Bayes de Luna, José Narro, Juan Ramón de la Fuente, Adolfo Martínez Palomo, y muchos otros más, han hablado y escrito acerca de la grandeza de la obra de Chávez hijo y la modestia con la que fue manejada.

En su carrera médica, después del título de médico cirujano obtenido en la Universidad Nacional Autónoma de México en 1952, se desarrolló como internista en el Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán del cual fue residente y se preparó en cardiología como residente en el Instituto Nacional de Cardiología entre los años 1954 y 1956; con posterioridad fue Research Fellow en la Universidad de Harvard en el *Massachussets General Hospital* de Boston en 1957 y de nueva cuenta Research Fellow en el *Peter Bent Brigham Hospital* de 1958 a 1959.

Figura 1. Dr. Ignacio Chávez Rivera.

Desde temprana edad, la producción científica de Ignacio Chávez Rivera empezó a fructificar en numerosas publicaciones y en la creación de grandes obras cardiológicas que han quedado para la posteridad: *Coma, síncope y shock*, libro de 400 páginas editado en 1969 con reediciones en 1974 y 1976[2], *Cardioneumología fisiopatológica y clínica* de 1973[3] obra "titánica y enciclopédica" en dos volúmenes con 2,000 páginas y considerada en todo el mundo como obra de consulta obligatoria y fundamental de la cardiología, *Cardiopatía isquémica por ateroesclerosis coronaria*[4], libro de 518 páginas editado en 1979 y reeditado en 1982, *Hipertensión arterial esencial*[5] de 1984 y reimpreso en 1985, un libro de 300 páginas, *Cardiopatía coronaria e isquemia miocárdica*[6] de 1989 y *Cardiología*[7], dos volúmenes de 1,600 páginas editado en 1993.

En la obra de Ignacio Chávez Rivera destaca el academicismo de manera fundamental. En su ascendente carrera fue distinguido como Subjefe de médicos residentes en el Instituto Nacional de Cardiología en 1955 y Jefe de médicos residentes en el 1956. Desde Médico Adjunto, Jefe de Servicio Clínico, Jefe de la División de Enseñanza y hasta Director General del Instituto en

dos periodos renovados de 1989 a 1999.Tuvo más de 300 participaciones como conferencista invitado en la Ciudad de México, 100 más en toda la República Mexicana y en 10 países de América y Europa. Numerosas ponencias en Congresos y Jornadas Médicas, 30 artículos de investigación clínica, 66 de revisión de concepto o difusión y otros 200 diversos. Es coautor en seis libros. Fue Secretario Tesorero de la Sociedad Interamericana de Cardiología, Presidente de la Sociedad Mexicana de Cardiología, que más adelante lo designó como miembro honoris causa. Además, su destreza y afición por el dibujo lo llevó a colaborar en el excelente libro de ilustraciones médicas de Frank H. Netter[8].

Fue presidente de la segunda junta de gobierno del Consejo Mexicano de Cardiología; miembro asociado por invitación u honorario en 15 sociedades médicas en diferentes países; miembro de la Academia Nacional de Medicina desde 1970; secretario de ésta en 1971, y presidente en 1985.

En el seno de nuestra Universidad Nacional Autónoma de México, el Dr. Chávez tuvo una destacada labor, desde profesor de la asignatura en cardiología, profesor por oposición y titular de posgrado hasta miembro de la junta de gobierno de dicha casa de estudios de 1985 a 1997.

De vida modesta a pesar del entorno que lo rodeaba y habiendo nacido en el seno de una familia ilustre y muy conocida ya en el ámbito intelectual y social del México de la primera mitad del siglo pasado, y a diferencia de lo que ocurre con frecuencia, a Ignacio Chávez Rivera no le afectaba esto de modo desfavorable; por el contrario, le confirmaba más su idea de mantenerse callado, lejos de la presunción y el elogio y sobre todo del autoelogio que tanto se mira en la actualidad.

En Ignacio Chávez Rivera se viven, como en ningún otro de los discípulos del maestro Ignacio Chávez Sánchez, la honestidad, la modestia, la decencia y la lealtad, enlazando siempre (como señalaba el mismo maestro), la acción y el pensamiento.

En Ignacio Chávez Rivera se verifica también de manera cabal el dicho popular que reza: “Que el mejor predicador es Fray ejemplo”, prueba de lo cual son su actuar y su comportamiento. Siendo él director del Instituto, su modesto automóvil nunca estuvo estacionado en el lugar reservado para la dirección, sino en el estacionamiento general. O bien, habiendo comedor particular para los miembros de la dirección, siempre prefería comer en el comedor general acompañado de otros médicos, los adjuntos, los residentes, las enfermeras y aun del resto del personal administrativo o de la intendencia.

En algunas ocasiones su natural modestia fue confundida o mal entendida por algunos como falta de carácter o timidez, sobre todo por los que tuvieron menor talla intelectual que la de él.

No existe mayor carga que pueda llevar un hombre sobre sus espaldas toda una vida que la de ser hijo de uno de los hombres más ilustres que ha tenido nuestro país y, al mismo tiempo, ejercer la misma profesión del padre. El Dr. Chávez cumple callada, tranquila y serenamente su misión en la vida, soportando sobre sus hombros esta enorme cruz, con un gran orgullo interno sí, pero siempre sin abusar de privilegios, canonjías o prebendas que le habrían dispensado ser hijo de quien fue, sino con trabajo cotidiano, esmerado, dedicado y plagado del humanismo que le fue legado.

Que no se entienda mal ni por asomo algún descrédito que mis palabras pudieran sugerir para la eminencia del maestro Chávez Sánchez, quien además de todas sus virtudes y cualidades, como diría Bertrand Russell, el Maestro Chávez tenía una cualidad llamada brillo; sin embargo, es preciso señalar que los tiempos que les tocó vivir a Chávez padre y a Chávez hijo son totalmente diferentes, al igual que las oportunidades de transformación del medio. El México de los años de Chávez padre apenas florecía en la Posrevolución y con él una pléyade de intelectuales probos, bien intencionados, que formaron el grupo de sus primeros amigos en Morelia, haciendo honor al viejo dicho de que “Dios los creó y ellos se juntan” y otros posteriores como fueron los forjadores del Colegio Nacional.

En los logros del Instituto Nacional de Cardiología de la época de Chavez padre (lo señalaba él mismo) intervino cierta autonomía de gobierno que le fue permitida, pese a ser dependencia gubernamental de la Secretaría de Salud del gobierno federal de la República Mexicana, con la cual la Dirección de Chávez hijo ya no contó y, por el contrario, el mundo de Chávez hijo está plagado de sobrepoblación, pobreza, corrupción, menester social al por mayor y criminalidad desmedida, todo ello aunado a una excesiva burocratización de la instituciones gubernamentales. En el México actual, las personas no quieren *ser,* sólo quieren *tener* a costa de lo que sea.

Los valores de antaño han sido reemplazados. La mortalidad infantil ha disminuido de manera notable y, de la misma manera, la esperanza de vida para los viejos se ha prolongado de forma inusitada; cada vez nacen más y mueren menos, mientras que el tamaño del pan parece ser el mismo y muy pocos aportan para

que éste crezca. Es probable que la sociedad científica de un futuro no lejano y las instituciones religiosas recapaciten seriamente sobre esto y sobre el derecho a tener tantos hijos como la naturaleza y la inconciencia decidan.

Chávez Rivera dejó un caudal enorme de producción académica a las nuevas generaciones, que rebasó con mucho la obra académica escrita por su padre y que, para los que escribimos aun en muy pequeña escala, conocemos bien el esfuerzo, la dedicación y el trabajo que esto representa.

Entre sus múltiples cualidades figuran de manera notable la buena educación y la decencia y, en forma muy destacada, su habilidad para conocer el trasfondo de las diferentes personalidades, capacidad que le permitió en sus gestiones como director de nuestra casa y como presidente de la Academia de Medicina o en la Junta de Gobierno de nuestra universidad, delegar las diferentes responsabilidades en los hombres idóneos para cada mando, sin nepotismos, sin mimetismos, sin favoritismos, sin falsedades y, sobre todo, sin retórica.

Su concepto de la familia es también por demás envidiable, así como su fidelidad, lealtad y ejemplo transmitidos a sus hijos. Las decisiones que tomó Chávez Rivera nunca fueron atropelladas, nunca de manera arbitraria y jamás sin reflexión previa. En la vida de Ignacio Chávez Rivera destaca de manera promitente su gran compañera de toda la vida, Ofelia de la Lama de Chávez, mujer brillante, de intelecto agudo, cultura amplia y seleccionada, pero sobre todo de actitud positiva en la vida, especialmente en las adversidades. Ambas personalidades, la de Chávez y la de Ofelia, se complementaron y cristalizaron en una hermosa familia de universitarios, cultos y destacados.

El paso por la vida de Ignacio Chávez Rivera fue intachable y su valor moral imperecedero; los que tuvimos la fortuna de estar cerca de él enriquecimos sin duda alguna nuestro espíritu, nuestra moral y nuestra cultura.

Pero además, si hay algo digno de admiración y respeto en la vida de Chávez, es su absoluta congruencia, de acuerdo con los preceptos dictados por su padre de fusionar la acción y el pensamiento. El maestro Ignacio Chávez Rivera cumplió con creces la promesa hecha a su padre de labrarse él solo un nombre propio en la medicina y en la sociedad.

Maestro Ignacio Chávez Rivera, estimado e inmerecido amigo, le saludo.

Sergio Trevethan Cravioto

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Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

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ARTÍCULO DE OPINIÓN

Embarazo en pacientes adolescentes con cardiopatía

Pregnancy in teenagers with heart disease

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Resumen

La prevalencia de embarazo en mujeres adolescentes es muy alta en México, y representa un problema de salud pública. La adolescente embarazada con cardiopatía tiene altas posibilidades de complicaciones durante el embarazo y su resolución, lo que pone en riesgo la vida tanto de la madre como del producto. En muchos casos el embarazo debió ser evitado, planeado o interrumpido, sin embargo la mayoría a esta edad es vulnerable y si bien ciertos casos deben ser interrumpidos por su alto riesgo de muerte materno-fetal, es fundamental considerar la prevención y los aspectos legales. En algunos casos la mujer desea un embarazo aunque su condición de salud no se lo permite, pero existen opciones de adopción o recurrir a un vientre subrogado. Atendiendo este problema social cada vez más creciente, el Instituto Nacional de Cardiología Ignacio Chávez, en coordinación con la Comisión Coordinadora de la Secretaría de Salud y el Instituto Nacional de Perinatología, echaron a andar un módulo de prevención de embarazo dentro de una clínica de seguimiento de cardiopatía y embarazo. Esta revisión plantea el problema global en nuestro país, que ocupa el primer lugar en embarazos en adolescentes, con más de 400 mil embarazos al año y la forma de dar respuesta inmediata de manera multidisciplinaria.

Palabras clave: *Adolescente. Cardiopatía. Embarazo. Alto riesgo. Prevención. México.*

Abstract

The prevalence of pregnancy in adolescent women is high in Mexico and represents a public health problem. The pregnant teenager with heart disease has a high probability of complications during pregnancy and the delivery, which carries a risk of death of both the mother and the product. In many cases the pregnancy should have been avoided, planned or interrupted, however the majority at this age is vulnerable and although certain cases must be interrupted by their high risk of maternal-fetal death, prevention and legal aspects should be considered. In some cases the woman wants a pregnancy although her

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health condition does not allow it, but there are options of adoption or recourse to a surrogate belly. In response to this growing social problem, the National Cardiology Institute Ignacio Chávez and National Institute of Perinatology, with the coordination of Ministry of Health in Mexico, started a pregnancy prevention module within a clinic of follow-up of cardiopathy and pregnancy. This review raises the global problem in our country that occupies the first place in pregnancies in adolescents, with more than 400,000 pregnancies a year and the form of immediate response in a multidisciplinary way.

Key words: *Adolescent. Cardiopathy. Pregnant. High risk. Prevention. Mexico.*

Introducción

Recientemente la Organización para la Cooperación y el Desarrollo Económico reportó que de sus 35 miembros permanentes, México ocupa el primer lugar de embarazo en adolescentes, con cerca de medio millón de embarazos cada año[1]. De este grupo, el 60% es población de bajos recursos económicos, con incapacidad de acceder de forma óptima a los servicios de salud, a la educación, a una alimentación saludable y a mejores oportunidades de desarrollo tanto para la madre como para el niño. De acuerdo con la Encuesta Intercensal del Instituto Nacional de Estadística y Geografía (INEGI) en 2015, en México existen 48.7 millones de mujeres de 12 y más años, de las cuales el 67.3% han tenido al menos un hijo nacido vivo. Es importante señalar que el 7.8% de ellas con edades entre 12 y 19 años ya han procreado, ejerciendo su maternidad sin pareja en el 27.8% de los casos[2].

De este modo, las adolescentes se han convertido en uno de los grupos más vulnerables de nuestro país y esto representa un grave problema de salud pública, ya que las adolescentes embarazadas tienen dos veces más probabilidades de morir por complicaciones durante el embarazo o el parto en comparación con mujeres adultas[3], tanto así, que es la segunda causa de muerte entre los 15 y 19 años de edad. En la encuesta intercensal del INEGI en México, el análisis de la tasa global de fecundidad por nivel de escolaridad muestra que a mayor nivel de escolaridad es menor la fecundidad (Tabla 1) y en países en vías de desarrollo, las adolescentes suelen tener bajo nivel educativo y en muchos de los casos su embarazo puede estar relacionado con abuso o violencia sexual, que adiciona al problema obstétrico altas tasas de enfermedades de transmisión sexual, incluido el virus de la inmunodeficiencia humana, cuya carga es mayor en mujeres que en varones[4].

En la actualidad, los avances en los métodos de estudio diagnóstico, las técnicas quirúrgicas, la miniaturización de los circuitos de circulación extracorpórea y los cuidados postoperatorios han logrado mantener una supervivencia mayor al 85% en los pacientes con cardiopatías, especialmente las congénitas[3]. En el último caso la población infantil que sobrevive alcanzará la edad reproductiva, con lo que se crean nuevos riesgos de salud. En el Instituto Nacional de Cardiología Ignacio Chávez, entre 2003 y 2016 se operaron 4,000 pacientes pediátricos y para el 2016 ya se habían convertido en adultos 640 de ellos, de los cuales más del 50% fueron del sexo femenino, quienes representan un riesgo variable en caso de combinar el embarazo con una cardiopatía congénita[5]. Para el cardiólogo involucrado en el manejo de embarazadas con cardiopatía congénita o adquirida, el objetivo primordial debe ser la prevención de las complicaciones cardiovasculares. Sin embargo, las tasas de complicaciones son muy altas, sobre todo cuando existen cardiopatías que hacen muy alto el riesgo de morir durante la gestación, como son la hipertensión arterial pulmonar primaria y el síndrome de Eisenmenger, que tienen un riesgo de mortalidad de entre el 30 y el 50% durante el embarazo[6,7] (Tabla 2). Otro ejemplo de alto riego de morbimortalidad en este grupo es la necesidad de anticoagulación por arritmias y/o uso de prótesis mecánicas, lo que implica un mayor riesgo materno y fetal. Además del riesgo que la enfermedad cardiovascular genera para la madre, los fármacos cardiovasculares pueden significar un riesgo alto tanto para la madre como para el feto durante el embarazo[8,9].

En los casos de madres con cardiopatía congénita o adquirida, el riesgo fetal es del 18%, en comparación con el de la población general, que es del 7%, representado por retraso del crecimiento intrauterino, prematurez y hemorragia intracraneal entre otras[10]. Algunos defectos cardiacos tienen una herencia autosómica dominante, es decir que una madre con estos tipos de defectos puede tener un 50% de probabilidad de que el niño nazca con el mismo defecto genético.

Impacto emocional en la mujer con cardiopatía y embarazo

Desde los primeros años de este siglo, el tema «embarazo en adolescente» ha ocupado un espacio importante en la salud pública mundial porque afecta la salud física y emocional, y constituye un problema social y

Tabla 1. Tasa global de fecundidad (total de hijos que en promedio tendrá una mujer al final de su vida reproductiva) por nivel de escolaridad

Nivel de escolaridad	1997*	2009**	2014†
Sin instrucción	5.18	3.34	3.30
Primaria incompleta	4.06	3.26	3.21
Primaria completa	3.31	2.93	2.99
Secundaria	2.75	2.70	2.70
Media superior y superior	2.09	1.70	1.79

La tasa global de fecundidad se refiere al total de hijos que en promedio tendrá una mujer al final de su vida reproductiva.
*Corresponde al quinquenio 1992-1996.
**Corresponde al trienio 2006-2008.
†Corresponde al trienio 2011-2013.
Tomada de Instituto Nacional de Estadística y Geografía, 2016[2].

Tabla 2. Condiciones que ponen en alto riesgo a las embarazadas con cardiopatía congénita

Condiciones que ponen en alto riesgo a las embarazadas con cardiopatía congénita
– Síndrome de Eisenmenger
– Obstrucción grave del tracto de salida del ventrículo izquierdo
– Obstrucción grave del tracto de salida del ventrículo derecho
– Hipertensión arterial pulmonar grave
– Operadas de Fontan
– Atresia tricuspídea
– Transposición corregida
– Síndrome de Marfan

Tomada de Cossío-Aranda, 2002[8].

económico, especialmente en un grupo vulnerable de países con bajos ingresos económicos.

Existen investigaciones que demuestran que un alto porcentaje de adolescentes carece de educación e información sobre sexualidad y salud reproductiva. En México, las Secretarías de Salud y de Educación Pública han creado políticas con espacio físico y recursos humanos para facilitar la educación a adolescentes, y que ayudan a comprender su sexualidad y a protegerlos contra embarazos no deseados, infecciones de transmisión sexual y el riesgo subsiguiente de esterilidad. Sin embargo, estos programas merecen mayor difusión y acciones de la sociedad en general.

La adolescente gestante presenta alteraciones en el estado anímico, con sentimientos de frustración, enojo, irritabilidad, hostilidad, culpa y vergüenza. Conforme el embarazo avanza, desarrolla miedo, temor a morir, mayor estrés, síntomas de ansiedad y depresión, que impactan en la salud emocional de la madre y del producto. Por lo anterior, la atención psicológica orientada a la prevención de embarazos en adolescentes con cardiopatías es de gran importancia, haciendo efectiva la educación en sexualidad, centrada en los siguientes aspectos:

- Transmitir el concepto de «sexualidad integral» con responsabilidad.
- Desarrollar habilidades y actitudes que permitan formar personas autónomas, capaces de tomar decisiones para prevenir y/o enfrentar los riesgos que implican el ejercicio de la sexualidad.
- Generar autoconocimiento de la sexualidad.
- Desarrollar o fortalecer habilidades sociales y de comunicación asertiva.
- Desarrollar competencias, capacidades y actitudes, incidiendo en la autoestima.
- Motivar para culminar sus estudios.
- Informar a los padres las necesidades de las adolescentes en temas de sexualidad y cómo ayudarlas.

Salud reproductiva y prevención de embarazo en adolescentes

Ante el grave problema que implica la muerte materna, sobre todo en mujeres adolescentes con cardiopatía, la Comisión Coordinadora de los Institutos Nacionales de Salud y Hospitales de Alta Especialidad, dentro de un enfoque multidisciplinario con el Instituto Nacional de Perinatología y el Instituto Nacional de Cardiología Ignacio Chávez, ha desarrollado un programa de prevención de embarazos de alto riesgo.

Para el logro de este y con el apoyo de las autoridades médicas y de enfermería, se implementó en el Departamento de Consulta Externa del Instituto Nacional de Cardiología Ignacio Chávez un espacio de atención a pacientes en edad reproductiva y afección

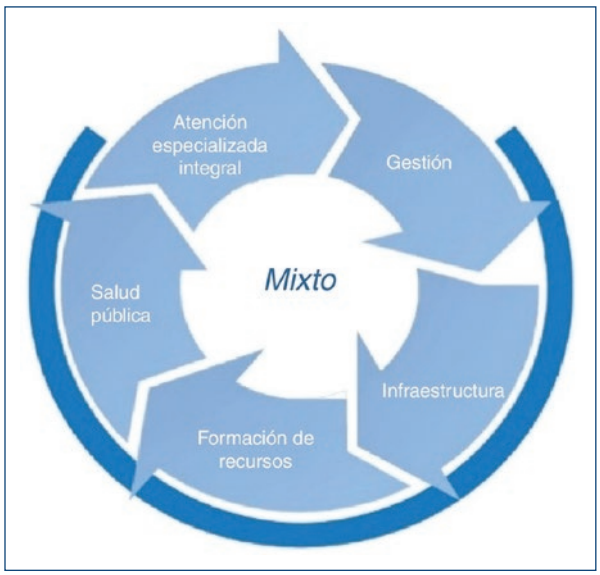

Figura 1. Vertientes de clasificación del proyecto de los módulos de alto riesgo reproductivo.

cardiovascular, denominado módulo de alto riesgo de reproductivo (MARR), que implica la prevención de embarazo en la cardiópata, especialmente la adolescente[11] (Fig. 1).

El personal médico y de enfermería en el MARR recibieron capacitación mediante cursos teórico-prácticos acerca de embarazo y métodos anticonceptivos en pacientes cardiópatas, así como del marco legal que debe regir en este contexto.

En este módulo se lleva un sistema de prevención mediante la información veraz y oportuna. Con la educación y difusión de mecanismos preventivos de embarazo, consejo genético y ayuda ginecológica para la prevención de embarazo. En un marco legal se informa a las pacientes adolescentes con cardiopatía sobre el riesgo de embarazo para la madre y el feto, y la forma de prevenirlo. Para promover el conocimiento acerca del riesgo reproductivo y métodos anticonceptivos se distribuye a las pacientes cardiópatas material informativo oficial de la Secretaría de Salud, y se realizan también actividades de consejo y apoyo psicológico para favorecer que las usuarias logren establecer un plan de vida reproductivo.

El uso de la agenda electrónica institucional permite mantener un registro de las pacientes atendidas y con esto se logra conformar una base de datos que facilita el informe que se debe generar a la Secretaría de Salud sobre los avances, logros y necesidades del módulo, y también permitirá medir el impacto del programa en este grupo de pacientes.

Marco legal, consecuencia y derechos del paciente y el médico

La Constitución Política de los Estados Unidos Mexicanos establece los derechos humanos que tiene toda persona, para estar informada de la prevención de embarazo en mujeres con cardiopatía congénita y el riesgo para su vida y/o al producto en gestación, para lo cual debemos tutelar estos derechos. El artículo 4.º de dicho ordenamiento establece que toda persona tiene derecho a decidir de manera libre, responsable e informada sobre el número y esparcimiento de sus hijos; asimismo contempla la protección del derecho a la salud, y en ese orden de ideas, la Declaración de Derechos Humanos, la Declaración de Derechos y Deberes del Hombre y el Pacto Internacional de Derechos Civiles y Políticos convergen en tener contemplado el derecho humano por excelencia que es «la vida», el cual deberá ser tutelado y/o protegido por encima de los demás derechos.

Las alternativas para la prevención del embarazo que tiene una mujer con cardiopatía congénita son la adopción y la maternidad subrogada. La adopción es el acto jurídico en virtud del cual una persona con capacidad de goce y ejercicio toma como propio a un hijo ajeno, con el fin de establecer con él una relación paternofilial, contrayendo así los mismos derechos y obligaciones que nacen de un vínculo consanguíneo. La ley prevé que para poder estar en posibilidades de adoptar, la persona que quiera hacerlo debe cumplir con una serie de requisitos, entre los cuales se cita una edad mínima de 25 años. La maternidad subrogada consiste en utilizar una práctica médica denominada técnica de reproducción asistida, cuyo objeto es realizar fecundación extracorpórea, es decir fuera del cuerpo de la madre. Para esto es necesaria la intervención de los tres agentes siguientes: la madre, la mujer gestante y el médico tratante, quien además de informar a los implicados sobre el procedimiento, realizará dicha técnica de reproducción asistida bajo su debida atención médica y supervisión a fin de llevar a buen término dicho embarazo. El artículo 3 de la iniciativa de Ley para Maternidad Subrogada define maternidad subrogada como «La práctica médica consistente en la implantación de mórulas humanas en una mujer, producto de la unión de un óvulo y un espermatozoide fecundados por una pareja unida mediante matrimonio o que vive en concubinato y que aportan su carga o material genético que concluye con el nacimiento». Así, la relación jurídica surge con el reconocimiento de la mujer a su hijo como suyo, es decir, en el momento posterior al parto, y en virtud de lo anterior una vez que el fin haya sido ejecutado, la mujer

gestora va a entregar al concebido a su madre biológica subrogándole todos los derechos y obligaciones adquiridos sobre el recién nacido; subrogar o sustituir se define jurídicamente como el acto de reemplazar en los derechos y obligaciones a una persona; ello va a dar lugar al vínculo jurídico denominado filiación. En suma, son dos los beneficios que se obtienen bajo esta opción: concebir al feto de forma viable en ejercicio de su derecho a la salud reproductiva al tiempo que se preserva el máximo bien jurídico tutelado por la ley: «la vida».

Considerando que la mujer decidiera no optar por la adopción o bien la maternidad subrogada y aun así su postura sea la de continuar con el periodo de gestación, la vía alterna para tutelar «la vida» es la interrupción legal del embarazo, procedimiento que la Ley de Salud del Distrito Federal y su Reglamento regula como gratuito y que puede ser realizado hasta antes de la decimosegunda semana de gestación.

La interrupción legal del embarazo puede practicarse después de la decimosegunda semana, sin caer en el tipo penal del aborto (interrupción del embarazo después de la decimosegunda semana de gestación) siempre y cuando se actualicen las hipótesis normativas del Código Penal del Distrito Federal, señaladas como excluyentes de responsabilidad penal en el delito, las cuales establecen que de no provocarse el aborto a juicio de un médico que le asista con apoyo del dictamen de otro médico determinen que corre peligro grave la vida de la mujer gestante, o bien cuando a juicio de dos médicos especialistas exista razón suficiente para diagnosticar que el producto presenta alteraciones genéticas o congénitas que puedan dar como resultado daños físicos o mentales al límite que puedan poner en riesgo su supervivencia.

Conclusiones

Ante un grave problema social y de salud en un grupo poblacional vulnerable como lo es la mujer adolescente, se debe ofrecer consejo de preconcepción a todas las mujeres con cardiopatía y mantener un cuidado multidisciplinario haciendo hincapié de forma constante en la prevención de embarazo en la adolescencia y en todos niveles.

Pese a la evidente diversidad existente entre las especialidades médicas, con la creación de un módulo de prevención de embarazo en mujeres adolescentes y adultos con alto riesgo de morbimortalidad por su cardiopatía, tenemos la esperanza de reunir, integrar y complementar lo necesario de la multidisciplinariedad, como lo exige la medicina de hoy, para conseguir el máximo *desideratum*: la prevención, esta vez en defensa de la edad fértil de la mujer.

Agradecimientos

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los utores declaran que en este artículo no aparecen datos de pacientes.

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IMÁGENES EN CARDIOLOGÍA

Shone's syndrome in an adult woman

Síndrome de Shone en una mujer adulta

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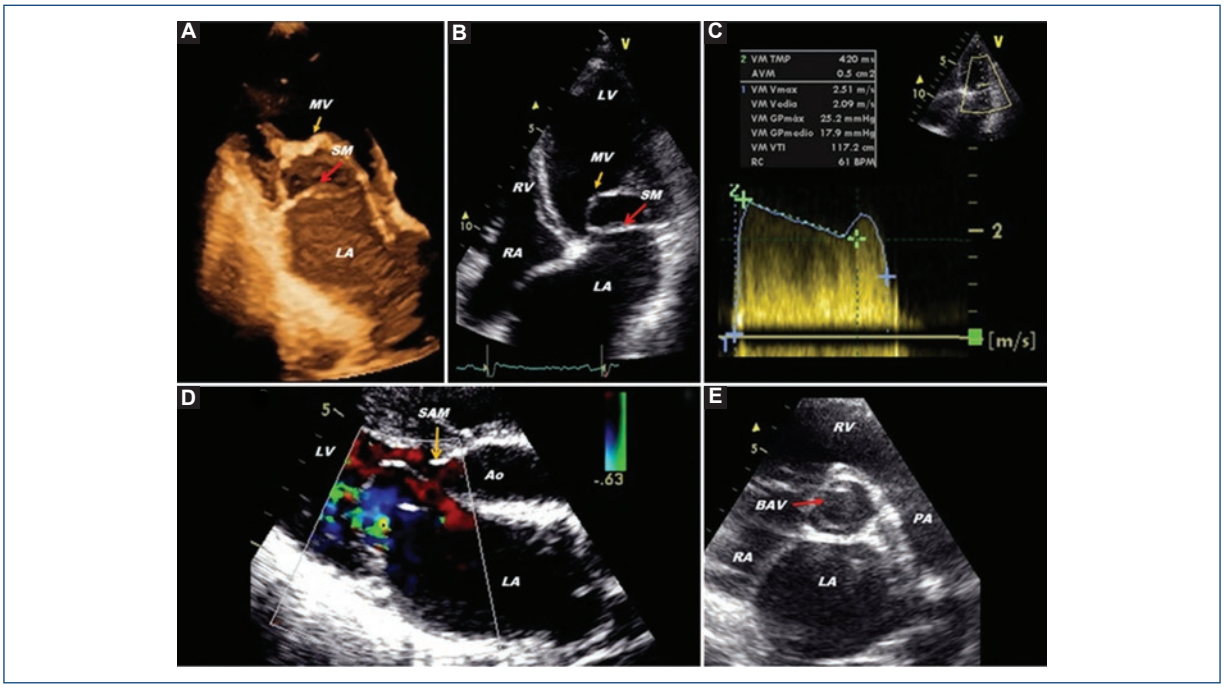

Figure 1. Transthoracic echocardiography. **A:** apical three-chamber view; **B:** apical four-chamber view; **C:** continuous Doppler, mitral valve gradient; **D:** parasternal long-axis color Doppler; **E:** parasternal short-axis view of aortic valve. BAV: bicuspid aortic valve; SM: supramitral membrane; MV: mitral valve; SAM: subaortic membrane; Ao: aorta; RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; PA: pulmonary artery.

A 22-year-old woman with history of heart murmur diagnosed in childhood was referred from a general hospital with dizziness, palpitation, and worsening of dyspnea (NYHA III).

Transthoracic echocardiography (TTE) revealed large atria with supramitral, non-restrictive membrane that extends from the mitral annulus to the lower portion of the left atrial appendage (Fig.1 A-B, red.arrow. Video S1). Mitral valve showed thickened leaflets, both leaflets inserted into anterolateral papillary muscle, and hypoplastic posteromedial papillary muscle was present, so a parachute mitral valve was described. The Doppler

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demonstrated significant mitral stenosis (mean gradient 17 mmHg, and valve area 0.5 cm^2) (Fig.1 C). Type I bicuspid aortic valve without raphe (Fig.1 E), non-restricted subaortic membrane (Fig.1 D, yellow. arrow. Video S2), aortic coarctation with gradient 28 mmHg and non-diastolic prolongation, preserved left ventricular systolic function, and tricuspid regurgitation gradient 52 mmHg were additional findings. Transesophageal echocardiography confirmed TTE diagnosis.

Cardiac catheterization showed pulmonary capillary wedge pressure 35 mmHg, transmitral gradient 10 mmHg, mean pulmonary pressure 47 mmHg, and non-significant aortic coarctation gradient (13 mmHg).

Surgery revealed supramitral membrane, anterior commissure fusion, and posterior mitral leaflet traction to anterolateral papillary muscle due to chordae tendineae. For those reasons, mitral commissurotomy was performed, supravalvular mitral membrane resection and mitral annuloplasty. Three months after the surgery, TTE showed a mean mitral gradient of 10 mmHg, and the treadmill exercise test demonstrated an improvement in the functional class (> 8 metabolic equivalents [METS]).

Shone's syndrome is a rare congenital anomaly of the mitral valve, and the survival is hardly ever until adulthood. There are different treatment techniques; one of them is the mitral plasty. Echocardiography is an excellent non-invasive method to establish the correct diagnosis.[1-4]

Conflicts of interest

We do not have conflicts of interest.

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Ethical disclosures

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

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

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

Supplementary data

Supplementary data are available at Revista Archivos de Cardiología de México online (http://www.archivoscardiologia.com/frame_esp.php?id=9). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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IMÁGENES EN CARDIOLOGÍA

Pseudoaneurisma gigante de la aorta ascendente fistulizado a la aurícula derecha

Giant ascending aortic pseudoaneurysm fistulized into right atrium

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Varón de 69 años, con historia de reemplazo valvular mecánico mitroaórtico y de la aorta ascendente por una prótesis tubular dos años atrás, que ingresó por insuficiencia cardiaca biventricular (predominantemente derecha). En el ecocardiograma destacó la existencia de un ventrículo derecho (VD) severamente dilatado y disfuncionante, prótesis con gradientes elevados e hipertensión pulmonar severa; el estudio transesofágico (ETE) descartó la trombosis protésica. Mediante tomografía computarizada se detectó la existencia de un pseudoaneurisma de la aorta ascendente (PAA) de 92x95 mm de diámetros que rodeaba el injerto aórtico

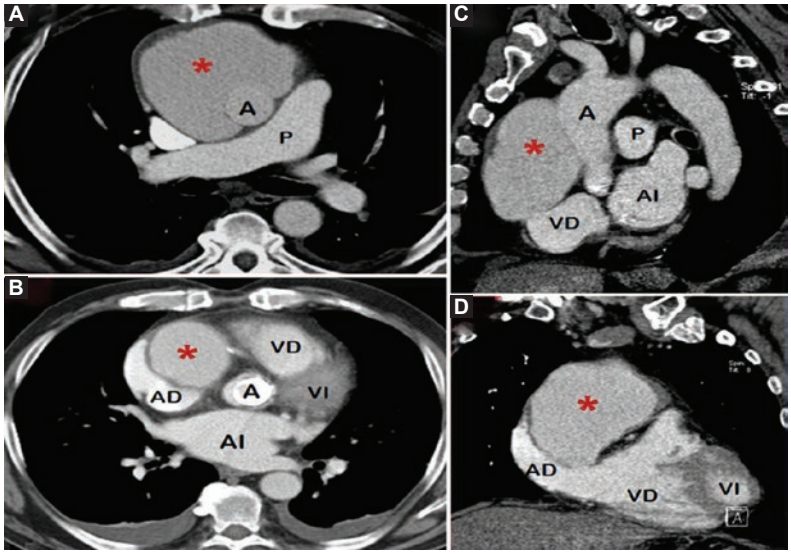

Figura 1. Imágenes de tomografía computarizada. **A y B:** cortes axiales donde se observa el gran pseudoaneurisma (*) formado entorno a la prótesis tubular aórtica y la compresión severa que ejerce sobre la AD. **C y D:** mismas alteraciones pero observadas en los cortes sagitales realizados a esos mismos niveles.
A: aorta; AD: aurícula derecha; AI: aurícula izquierda; VD: ventrículo derecho; VI: ventrículo izquierdo; P: arteria pulmonar.

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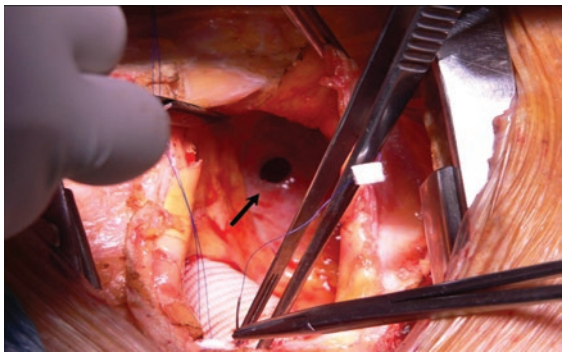

Figura 2. Imagen de la cirugía: apertura del pseudoaneurisma aórtico. Tras el drenaje del seudoaneurisma se observa la prótesis tubular aórtica, no epitelizada, y al fondo, en su pared, el orificio (flecha) de la fístula a la aurícula derecha.

y comprimía la aurícula derecha (AD) (Fig. 1 [*]); una segunda ETE demostró, además, la existencia de una fístula desde el PAA a la AD. El paciente fue intervenido: se cerró la fístula (Fig. 2 [flecha]), y la prótesis valvular aórtica junto con el injerto tubular aórtico (que no estaba epitelizado y presentaba roturas en sus anastomosis proximal y distal como orígenes del PAA), se sustituyeron por una prótesis aórtica tubular valvulada.

El PAA constituye una patología muy rara; su incidencia, tras una intervención aórtica, es < 1% y se ve favorecida por las infecciones perioperatorias[1]. Generalmente su origen está en los puntos de aortotomía, anastomosis o líneas de sutura (de prótesis o injertos de derivación aortocoronaria), o en puntos de punción, canulación o clampaje aórticos. La clínica varía según su localización, tamaño y compresión sobre estructuras adyacentes; sin embargo, resulta excepcional su presentación como disfunción cardiaca derecha (síndrome de vena cava superior, obstrucción de la entrada del VD, o fístula a arteria pulmonar, AD o VD)[2,3].

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Ninguno.

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Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

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Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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CARTA CIENTÍFICA

Reversible atrioventricular block after atrial septal defect closure with a Gore Cardioform Septal Occluder

Bloqueo auriculoventricular reversible post cierre de comunicación interauricular con dispositivo Gore Cardioform Septal Occluder

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Different degrees of atrioventricular (AV) block and other conduction disturbances have been previously reported after transcatheter closure of atrial septal defects (ASD).[1,2] Direct mechanical compression against AV node tissue followed by an inflammatory response due to device friction or to foreign body reaction has been mentioned as possible causes.[3-6] Although conduction disturbances may improve with time, progression has also been described.[2,4,5]

A 12-year-old boy with a normal basal electrocardiogram (ECG) was electively admitted for percutaneous ASD closure. Transesophageal echocardiography documented a 13 mm × 10 mm ostium secundum ASD, with a deficient aortic rim, 8 mm tricuspid rim, and 40 mm total septal length. All other rims were suitable for percutaneous closure. A 25 mm Gore Cardioform Septal Occluder device (GCSO™) (W.L: Gore and Associates, Flagstaff, Arizona) was initially chosen without balloon sizing (hospital policy with GCSO), but it moved easily during Minnesota maneuver. As a consequence, the device was removed, and a 30 mm GCSO was implanted uneventfully (Fig. 1). No arrhythmias or any degree of AV block were observed during or after the procedure. The following day, after a normal ECG (Fig. 2A) and a normal echocardiographic assessment, the patient was discharged.

Forty-eight hours later, the patient was re-admitted due to fever. Blood test was negative for acute phase markers (C reactive protein 2.4 mg/dL, and procalcitonin 0.06 ng/mL) and hence, a non-infectious origin of the fever was suspected. An echocardiogram showed a well-positioned device without complications. An ECG, however, revealed a first-degree AV block together with intermittent runs of second-degree AV block Mobitz I (Figs. 2B and 2C). Suspecting that the conduction disturbance was secondary to inflammation caused by the GCSO device, intravenous steroid therapy with methylprednisolone was initiated. In the following 48 h, the ECG showed a progressive normalization of PR interval (Fig. 2D), and a Holter recording performed the 4th day evidenced persistent sinus rhythm. The patient was discharged home with a descending schedule of oral steroid dosing. Nickel allergy was ruled out with a skin patch test 2 months after steroids discontinuation and during follow-up no AV block recurrence was documented in multiple Holter recordings. Two years later the patient remains asymptomatic.

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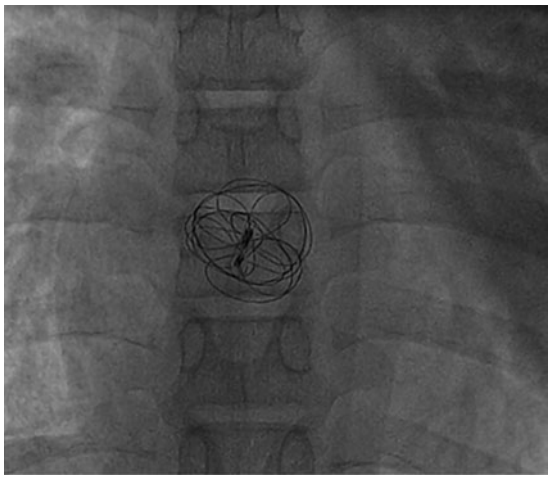

Figure 1. Fluoroscopy. Anteroposterior projection showing the GCSO device normopositioned.

Percutaneous closure of secundum ASD is considered safe and effective.[1,4,7-9] However, during or after closure, conduction disturbances may be occasionally observed.[2-4,6,7] The GCSO is a double-disc device with high compliance and flexibility, and it is made from nitinol covered by a polytetrafluoroethylene membrane.[1,10] Despite it is considered a "soft" device with low radial force and low compression stress on the tissue; a persistent GCSO-induced third-degree AV block has been reported.[3]

Although our patient was re-admitted due to fever, serial blood tests showed negative acute phase reactants and two blood cultures resulted negative. These lab data suggested more an inflammatory response than an infectious origin of the fever. Despite the fact that the exact mechanism of AV block after ASD closure remains unclear, a persistent mechanical compression, friction near AV node region, or a foreign body reaction, is all known to cause inflammation and edema that may damage AV node fibers and lead to different degrees of AV block.[3-6]

Use of large devices in young children, weight < 15 kg, small tricuspid or posterior-inferior rim has been discussed as risk factors for AV block. It may also occur, however, in patients with adequate margins.[2-4,6,9,11,12] In asymptomatic child's some authors recommend to post-pone the percutaneous ASD closure until preschool age (4 or 5 years of age) or weight >15 kg.[3,9]

The role of steroids for the treatment of AV conduction disturbances after percutaneous ASD closure remains debatable.[6-8,12] In fact, whether the conduction improvement is due to an steroid effect or it is spontaneous remains to be clarified. Suda et al. described one case of third AV block among ten patients with a new-onset AV block after ASD closure with amplatzer septal occluder (ASO). Corticosteroids were given and rapid improvement was observed with recovery of sinus rhythm within 2 weeks.[4] Similarly, Al Akhfash described a 7-year-old girl who 8 h after percutaneous closure of ASD with an ASO presented a second degree Mobitz I AV block and recovered sinus rhythm 4 days after being treated with prednisolone.[13] In our case, fever and inflammatory signs lead to trial with steroids with a good response. However, in other cases steroids may fail, or the initial improvement may be followed by conduction deterioration, requiring a surgical device extraction. Likewise, Al- Al-Anani et al. reported two cases and Amoozgar another one of AV block following percutaneous ASD closure where conservative treatment with steroids failed, and a surgical explantation was deemed necessary.[2,5]

Moreover, in the case herein described a negative skin patch test performed 2 months after steroid therapy excluded nickel allergy as a possible factor that could have damaged the AV node conduction through an allergic response to the nitinol device.

Of interest, in some patients there may be a spontaneous recovery that may be transient. This is the case described by Dittrich et al. of 36-month-old girl who presented a spontaneous improvement of a third-degree AV block after percutaneous ASD closure with a GCSO recovering sinus rhythm within 3 days. However, 11 months later deterioration of the AV conduction was observed when the patient suffered from undue fatigue associated with long-lasting episodes of complete heart block. A device explantation was then performed, but recovery was only partial since the patient was in sinus rhythm on day-time but she needed ventricular pacing while sleeping.[3]

Different degrees of AV block can be an early or a late complication after percutaneous ASD closure, even when using "soft" and flexible devices.[3,8] Recently, Sato et al. reported a 7-year-old male patient who developed a severe AV block 7 h after percutaneous ASD closure with the "soft and flexible" Occlutech Figulla® Flex II ASD occluder, requiring surgical removal.[8]

The distinct cases of AV block reported highlight the importance of extending monitoring of cardiac rhythm from already before the percutaneous procedure through the long-term follow-up.[6,7,13]

Although complete heart block needing device explantation has been described, this is, to the best

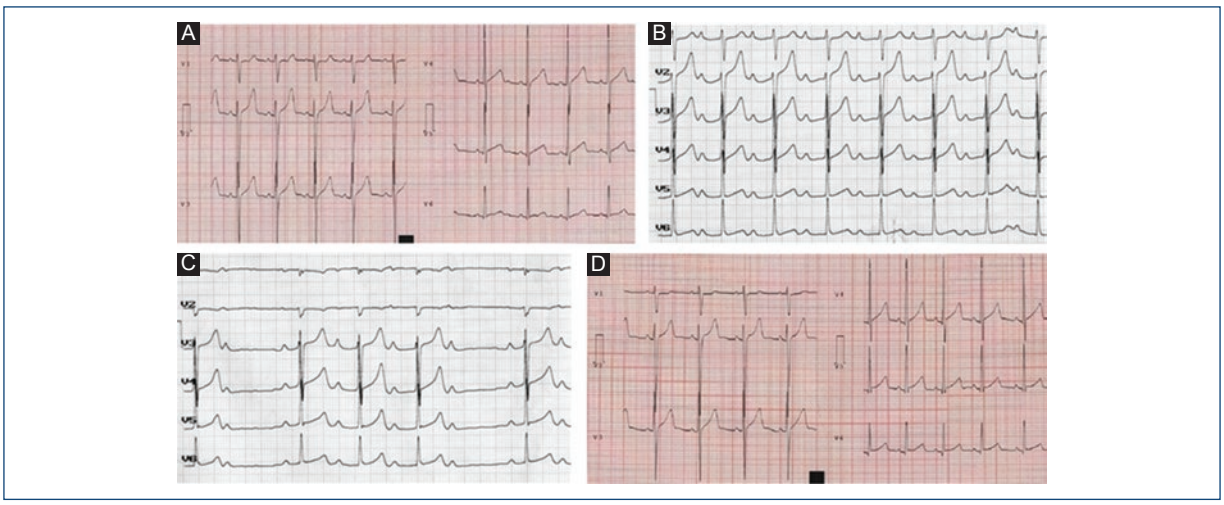

Figure 2. Electrocardiogram (ECG). **A:** Pre-procedure basal ECG showing sinus rhythm. **B:** Two days after Global Consortium for Sustainability Outcomes (GCSO) deployment showing first-degree AV block. **C:** Two days after GCSO deployment showing second-degree AV block, Mobitz I type. **D:** Four days after GCSO implantation showing sinus rhythm.

of our knowledge, the first reversible case of AV block after GCSO device implantation for ASD closure. In some occasions, early steroid therapy may prove effective by reducing AV node inflammation and restoring the sinus rhythm. In agreement with existing literature and to avoid pacemaker dependence, an early rather than a late removal of the device would seem reasonable whenever an inordinate and persistent pressure to the AV node region is suspected.

Conflicts of interest

None.

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None.

Ethical disclosures

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

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

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

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ARTÍCULO DE INVESTIGACIÓN

Underexpression of endothelial nitric oxide synthase leads to more severe pulmonary complex vascular lesions associated with HIV patients

La baja expresión de oxido nítrico sintetasa provoca mayor severidad en las lesiones vasculares complejas asociadas al VIH

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Abstract

Background: *Despite increase in survival of human immunodeficiency virus (HIV) patients due to highly active antiretroviral therapy, non-infectious complications are still prevalent such as presentation of lung vasculopathy, even in asymptomatic patients. Endothelial nitric oxide synthase (eNOS) is necessary to produce nitric oxide that causes pulmonary endothelial vasodilation. Participation of this protein in the pulmonary circulation in HIV patients has not been elucidated. This work studied the presence and expression of eNOS in pulmonary complex vascular lesions associated with HIV (PCVL/HIV).* **Methods:** *In lung tissues from patients who died from complications of HIV, we used immunohistochemistry and immune chemiluminescence (imageJ) to determine the different degrees of expression of eNOS in PCVL-HIV in comparison with non-PCVL/HIV. Reagents used were anti-eNOS and an automated system. All data are presented as mean and standard deviation. Differences were analyzed with Wilcoxon; $p < 0.05$ was accepted as statistically significant.* **Results:** *In 57 tissues, the histological evidence of pulmonary vasculopathy was showed as different types (proliferative, obliterative, and plexiform) and severe presentation of vasculopathy than non-PCVL/HIV. A statistically significant decrease of eNOS was observed in all PCVL/HIV tissue samples.* **Conclusion:** *eNOS has a relevant role in the pathogenesis of pulmonary vasculopathy in acquired immunodeficiency syndrome patients. It is necessary to determine in the future the participation of eNOS and other mechanisms involved in PCVL/HIV.*

Key words: *Nitric oxide synthase. Human immunodeficiency virus. Pulmonary circulation.*

Resumen

Antecedentes: *A pesar del incremento en la sobrevivencia del paciente con virus de inmunodeficiencia humana (VIH) debido al uso del tratamiento antiretroviral altamente efectivo, las complicaciones no infecciosas siguen ocasionando vasculopatía pulmonar, aun en pacientes asintomáticos. La óxido nítrico sintetasa (ONSe) es necesaria para la producción*

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de óxido nítrico la cual provoca vasodilatación pulmonar. La participación de esta proteína en la circulación pulmonar en los pacientes con VIH aún no se ha dilucidado. Este trabajo estudia la presencia y la expresión de ONSe en las lesiones vasculares pulmonares complejas asociadas al VIH (LVPC/VIH). Métodos: En tejidos pulmonares de pacientes que fallecieron por complicaciones del VIH, se utilizó inmunohistoquímica e inmunoquimioluminescencia (imageJ) para determinar los diferentes grados de expresión de la ONSe en LVPC/VIH. Los reactivos utilizados son anti-ONSe en sistema automatizado. Todos los datos son presentados en media y desviación estándar. Las diferencias son analizadas con la prueba de Wilcoxon; se aceptó como estadísticamente significativa una p < 0.05. Resultados: En 57 pacientes, la histología de la vasculopatía pulmonar mostró diferentes tipos (proliferativo, obliterativo y plexiforme) además de varias presentaciones de vasculopatía en tejidos no-LVPC/VIH. Se observó diferencia estadística en la disminución de ONSe en todos los tejidos LVPC/VIH. Conclusiones: La ONSe tiene un papel relevante en la patogénesis de la vasculopatía pulmonar en el VIH. Es necesario determinar en el futuro la participación de ONSe y otros mecanismos involucrados en LVPC/VIH.

Palabras clave: *Óxido nítrico sintetasa. Virus de inmunodeficiencia humana. Circulación pulmonar.*

Introduction

At present, the epidemic of human immunodeficiency virus (HIV) affects more than 36.7 million people globally, with a mortality rate of 1.1 million/year[1].

Many of these deaths were due to noninfectious complications like cardiovascular diseases. The first case reported of plexogenic pulmonary arteriopathy associated with HIV was carried out by autopsy[2].

HIV-1 infection is one of the major causes of pulmonary hypertension in the world[3].

This infection is a risk factor for the development of pulmonary arterial hypertension (PAH), increasing up to 2000-fold its odds[4].

The pathogenesis for the development of endothelial vascular lesion in lung circulation like PAH associated to HIV (PAH/HIV) is still unclear.

PAH/HIV is a devastating and life-threatening condition with recent cohort studies reporting prevalence ranging from 2.6 to 15.5%[5].

The survival rate of PAH/HIV patients is significantly reduced to one-half compared with HIV-infected individuals without PAH.

Nitric oxide (NO) is a potent pulmonary circulation vasodilator (Fig. 1) linked to homeostatic effects in different pathologies.

NO is synthesized from L-arginine and oxygen through a reaction catalyzed by endothelial NO synthase (eNOS)[6,7].

Myriad effects of NO on pulmonary vascular cell tone such as proliferation, apoptosis, and angiogenesis have been demonstrated. Once released, it rapidly diffuses across cell membranes to reach the cytoplasm of adjacent vascular smooth muscle cells, where it binds to soluble guanylate cyclase and increases intracellular cyclic guanosine monophosphate (cGMP) levels.

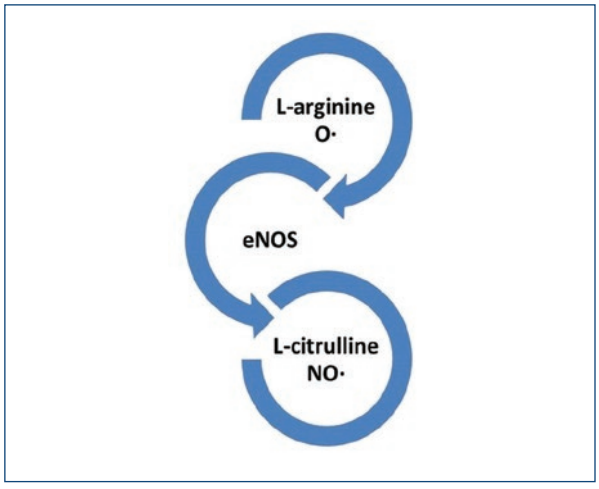

Figure 1. Synthesis of nitric oxide (NO) by endothelial nitric oxide synthetase, NO is produced when an electron from oxygen is transferred to an amino terminal nitrogen of L-arginine.

cGMP, in turn, phosphorylates cGMP-dependent protein kinase, which acts at several sites within the cell membrane and endoplasmic reticulum to lower intracellular calcium levels and reduce cross-linking of myosin light chain and decrease vascular tone[8].

Asymmetric dimethylarginine (ADMA) competitively inhibits eNOS and, thus, is a mediator of endothelial dysfunction. NO inhibits endothelial apoptosis and increases vascular endothelial growth factor expression to facilitate angiogenesis.

There is no definitive proof that HIV directly causes PAH or infects pulmonary endothelial cells. Nevertheless, HIV proteins (Nef, Tat, and Env) play key roles in PAH-associated pulmonary vascular remodeling because their interactions with molecular partners in the infected cells induce inflammation, oxidative stress, and

deregulate apoptosis and proliferation of vascular endothelial cells[9].

In this work, we looked at the presence and expression of eNOS in multiple grades of pulmonary complex vascular lesions in HIV patients (PCVL/HIV) and made a comparison to non-PCVL/HIV.

Methods

Tissue and histological examination

Pulmonary tissues of patients deceased from January 2006 to December 2016 for HIV-pulmonary complications were collected during autopsies; in addition, lung tissues of HIV patients who died from acquired immunodeficiency syndrome (AIDS) with no data of PCVL (non-PCVL/HIV) cases were included in the study.

Tissues collected were formalin fixed and paraffin embedded. Lung serial sections were stained with hematoxylin and eosin (H&E).

For this study, we used a simplified of the classical Heath and Edwards histopathology classification[10] (Table 1).

Immunohistochemistry and immunochemiluminescence

Reagent used for the immunohistochemistry was the endothelial anti-NO synthase (Abcam®, ab66127, Cambridge, MA)[11].

For the automated process of immunohistochemical staining, the Ventana® system (Tucson, Arizona) was used[12].

The eNOS quantification was measured by chemiluminescence on slides stained with H&E first and processed by the image processing software named *ImageJ*, download free provided by the National Institutes of Health of the United States[13].

The expression of the protein was measured in pixel units (arbitrary units).

Ethics

This work had the authorization of the Ethics and Research Committee of the National Institute of Respiratory Diseases (B-19-13).

Statistics

All the data are presented as mean and standard deviation (SD), the differences were analyzed with

Table 1. Heath and Edwards pulmonary circulation simplified pathology classification

Severity Grades
Grade I: Hypertrophy of the media of small arteries and arterioles and proliferation of the intima
Grade II: Thickening of the middle layer with hypertrophy and hyperplasia, showing plexiform lesions in the muscle
Grade III: Injury and cavernous angioma, with intimal hyalinization, fibrosis, and/or necrotizing artery

Table 2. Summary of demographic and disease characteristics HIV/AIDS study group

n	57
Mean age, years (range)	38.3 years ± 2.12 years (22-60)
Male (%)	88
HIV risk factor (%) Intravenous drug use Homosexual Heterosexual	 1 41 15
Pulmonary coinfections PCP Polymicrobial CMV Histoplasma sp. MTB	 21 16 10 6 4
Median CD4, SD cell count cells/µl (range)	36 ± 3 cells (1-115)
Viral load count, SD (range)	355,000 ± 165,000 (150,000-1 million)
Median follow-up, years (range)	3.0 ± 2.3 (0-9)
HAART 37 used before hospitalization 10 initiated at or after HIV diagnosis in hospital 10 never received	

PCP: *Pneumocystis jiroveci*; CMV: *Cytomegalovirus*; MTB: *Mycobacterium tuberculosis*; HAART: highly active antiretroviral therapy; AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; SD: standard deviation

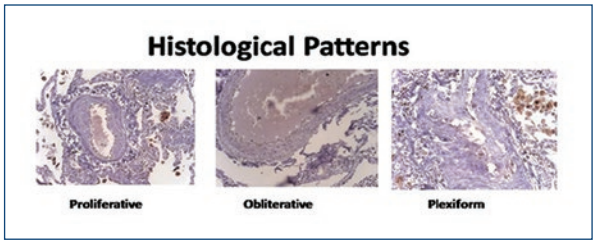

Figure 2. Examples of the most representative pulmonary circulation lesions in autopsy material of acquired immunodeficiency syndrome patients (hematoxylin and eosin staining).

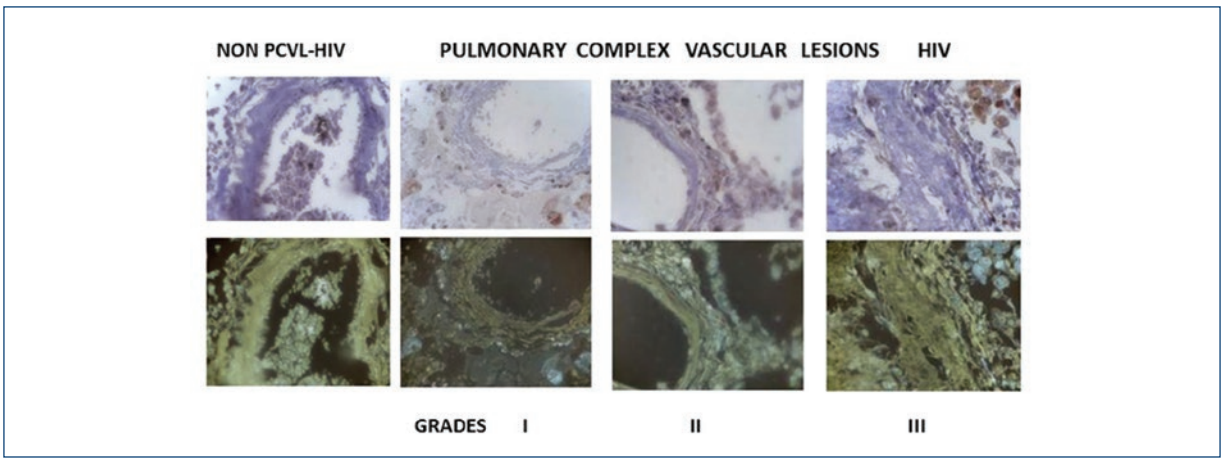

Figure 3. Seen at the top left by immunohistochemical nitric oxide synthetase staining (brown) in non-pulmonary complex vascular lesions (PCVL)-human immunodeficiency virus (HIV) lesions (all Grade III) and the different PCVL-HIV degrees (I-III).
At the bottom, the tissues are subjected to the image processor (*imageJ*) observed the expression of endothelial nitric oxide synthetase (gray).
*Non-PCVL-HIV: non-pulmonary complex vascular lesion in HIV patients.

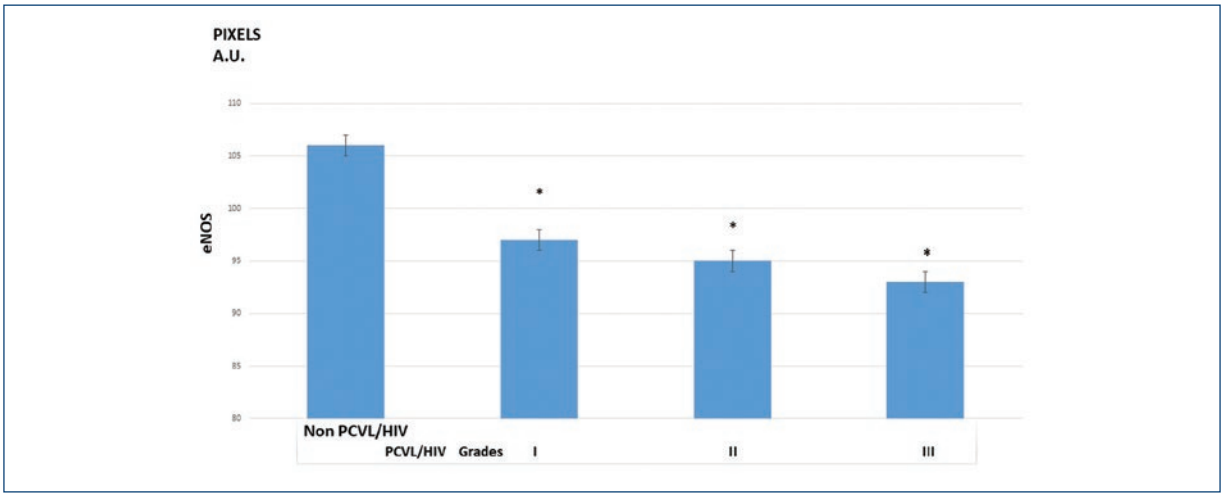

Figure 4. Difference in the expression of endothelial nitric oxide synthetase is observed in the intragroup different degrees of pulmonary complex vascular lesions/human immunodeficiency virus (PCVL/HIV) and with regard to the non-PCVL/HIV.
A.U.: arbitrary units.
*$p < 0.05$ Wilcoxon test.

non-parametric Wilcoxon rank-sum test, two samples; $p < 0.05$ was accepted as statistically significant, the Statistical Package for the Social Sciences (SPSS® version 20) was used.

Results

Lung tissues from a total a 57 subjects with HIV (52 men) with an average age of 38.3 years (SD 2.12). All patients were in AIDS (Stage C3) according to the classification of the Center for Disease Control and Prevention (CDC) in Atlanta, GA, USA.

The cause of death was mainly pulmonary complications (Table 2).

Lung tissues were paraffin embedded and H&E stained and processed for immunohistochemistry and were examined microscopically by an experienced pathologist in pulmonary circulation (M.R.R.R.) who

determined that 30/57 tissues (55%) showed PCVL with histological evidence of pulmonary vasculopathy or different types: proliferative (60%), plexiform (25%), and obliterative pattern (15%) (Fig. 2).

PCVL/HIV histological presentation: eight cases in Grade I, 7 in Grade II, and 15 in Grade III. eNOS *imagej* chemiluminescence showed a marked decrease expression associated with the severity of the lesion: non-PCVL/HIV group (17 lung tissues) had 106 pixels (SD 5.10) and PCVL/HIV group: 97 pixels (SD3.20) in Grade I, 95 pixels (SD 3.94) in Grade II, and 93 pixels (SD 3.70) in Grade III, statistical analysis of the Wilcoxon test showed significance ($p < 0.05$) among the four groups.

The statistical analysis of the Wilcoxon test showed significance ($p < 0.05$) after comparison of the intensity of Grade I compared with Grade II, and of this compared to Grade III, showing lower expression of eNOS to increased severity of PCVL (Fig. 3)

In all measurements of eNOS chemiluminescence in PCVL/HIV have significant diminution than in comparison with the caused by non-PCVL/HIV (Fig. 4).

Discussion

Infection with HIV infection induces a chronic inflammatory state and persistent immune activation and dysregulation that could indirectly induce the release of pro-inflammatory cytokines and growth factors that may be implicated in the pathogenesis of pulmonary vasculopathy.

These features include concentric laminar intimal fibrosis, medial hypertrophy, recanalized thrombi, and plexiform lesions. Additional hallmarks include increased expression of smooth muscle cell/fibroblast growth factors such as platelet-derived growth factor; inflammatory cells are present in the perivascular of HIV tissues, suggesting that HIV-induced chronic inflammation and immune hyperactivation may enrich the pro-inflammatory milieu implicated in vascular lesions.

Endothelial injury has been proposed to be a critical step in the initiation and progression of vascular remodeling associated with PAH[14].

Endothelial alterations precede the development of muscularization of pulmonary arteries in animal models[15].

It has been considered to the PCVL-HIV as a process of dysfunction of the vascular endothelium where you can engage different mechanisms such as the accessory proteins of HIV (Nef, Tat, and Env)[16] in the inactivation of NO conditioned by alterations in the role of eNOS. The exact role that NO plays in the pathophysiology of PAH is still unclear. Numerous studies have demonstrated that pulmonary hemodynamics and functional capacity can be improved in these patients by increasing NO delivery to the lung[17-19].

Our study is limited by the lack of hemodynamic data before death for a conclusive diagnosis of PAH, due to the lack of clinical suspicion by the treatment group (internal medicine, infectious diseases, and pulmonologist specialist) for the request of an echocardiogram in addition to the impossibility of performing right cardiac catheterization in a patient with severe sepsis.

Pharmacologic therapies that target the NO/cGMP pathway represent one of the major approaches to medical management or the patient with PAH[20,21].

Increase levels of ADMA are independently associated with HAP-HIV, the ADMA-NO axis is an important mechanism to be studied in the future[22].

In non-human primates as animal models like macaques the infection with Simian immunodeficiency virus/nef recombinant virus demonstrated pulmonary vascular remodeling without lesions were found in outside lung organs, suggesting a pulmonary-specific target[23].

Numerous pieces of the NO synthesis and signaling pathways are disrupted or altered in pulmonary vascular diseases. Although the data implicating NO deficiency in the pathogenesis of PAH are compelling, it is unclear which part of the biosynthesis pathway is impaired.

Evidence is accumulating that modification of deficiencies in NO synthesis and/or enhancement of its downstream signaling targets can attenuate pulmonary vascular remodeling.

Despite the increase in survival of HIV patients as a result of highly active antiretroviral therapy, pulmonary complications are still prevalent in the presentation of pulmonary vasculopathy even in asymptomatic patients. The accurate clinical diagnosis in the initial phase of the disease is necessary to improve the prognosis and survival.

These results show the preponderant reduce the presence of eNOS in pulmonary vasculopathy in AIDS patients. To the best of our knowledge, this is the first work that shows the significant diminution of eNOS in PCVL/HIV compared to non-PCVL/HIV.

It is important to continue the study in the future of NO and the inflammatory mechanism of the retroviruses on the pulmonary circulation, to promote a biological marker to detect PAH-HIV in asymptomatic patients and guide the therapy in the initial stages of this pathology[24,25].

Funding

Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”.

Conflicts of interest

The are no conflicts of interest.

Ethical responsibilities

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

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

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

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REPORTE DE CASO

On-pump beating heart treatment in pulmonary embolism and thrombus in transit

Tratamiento del tromboembolismo pulmonar y del trombo en tránsito con circulación extracorpórea sin clampeo

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Thrombi in transit (TT) in right cavities are an infrequent event and it is a medical emergency with very high mortality rate. Without treatment, mortality rate is about 90-100%. Right heart thrombi occur in about 4% of pulmonary embolism (PE)[1].

Three types of right heart thrombi can be distinguished by echocardiography: type A is the most common one; it is usually the result of deep venous thrombosis and it has the highest risk of embolization. Type B thrombus is thought to originate within the atrium or ventricle, and it is firmly attached to the chamber wall and it frequently has an ovoid shape. Finally, type C thrombus is rare and highly mobile. It often resembles cardiac myxomas[2].

Treatment modalities include anticoagulation therapy, systemic thrombolysis, percutaneous or surgical embolectomy[3]. In other words, optimal therapeutic approach is still a subject of discussion. We present a patient with a type A thrombus treated through a surgical approach.

Case report

A 47-year-old man was admitted for a syncopal episode and dyspnea. He was hemodynamically stable and eupneic with O_2 saturation 94%. As regards his cardiovascular history he referred: deep vein thrombosis and two episodes of pulmonary thromboembolism (PE) in the postoperative context of a hernia disc. Moreover, he completed 1 year of anticoagulation in 2003 which was subsequently suspended. We would like to highlight the mutation of Factor V Leiden as a relevant antecedent.

The transthoracic echocardiogram (ETT) reported a left ventricle (LV) of normal dimensions, with predominantly septal hypertrophy and preserved systolic function (ejection fraction of 64%). An Abnormal movement of interventricular septum secondary to right ventricle (RV) pressure overload was observed. Both the left cavities and the heart valves were normal. At the level of the right cavities we identified dilatation of RA (right atrium) and RV with mild deterioration of the systolic function of the RV: TAPSE 14 mm and DTI (Doppler tissue imaging) of the tricuspid annulus with S wave of 7 cm/s. He presented mild tricuspid insufficiency that allowed us to estimate a pulmonary hypertension of 90 mmHg. Finally, a homogeneous isoechoic mass with irregular borders, with great mobility was observed in the RA, which extended from the inferior vena cava with direction towards the tricuspid valve and protruded into diastole towards the RV. The image was interpreted as a thrombus in transit in right cavities (Fig. 1).

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His angiotomography of pulmonary arteries evidences multiple central filling defects which compromise the main lobar and segmental branches with predominance of the middle lobe and lobar superior right, compatible with acute thromboembolism (Fig. 2).

The patient was surgically treated with a full sternotomy. Aortic arterial and bicaval venous cannulation were performed. Assistance with extracorporeal circulation without clamping was initiated. Right atriotomy and resection of right atrial thrombus were performed. The patient also underwent right pulmonary arteriotomy and thrombectomy. The Pulmonary artery was closed with polypropylene 6-0 and bovine pericardium patch (Fig. 3).

The patient evolved without any complications and he was discharged on the sixth post-surgical day with enoxaparin.

During the initial stage we prefer low-molecular-weight heparins due to several advantages: adequate bioavailability, dose prediction, subcutaneous application. It allows us to use it without being monitored and with a low risk of thrombocytopenia.

One month after surgery we found normal pulmonary pressures (pulmonary artery systolic pressure: 23 mmHg) in the postoperative control. Currently, he is being periodically checked in hematology.

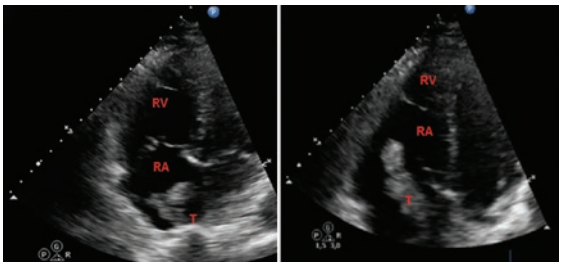

Figure 1. Transthoracic echocardiogram: RV: right ventricle; RA: right atrium; T: thrombus in transit.

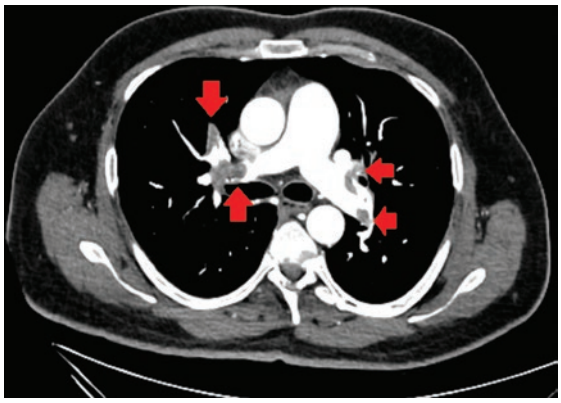

Figure 2. Angiotomography of pulmonary arteries evidences acute thromboembolism.

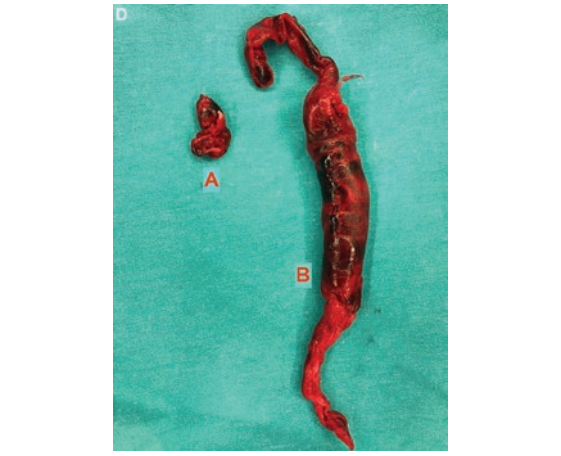

Figure 3. A. Thrombus of right pulmonary artery. **B.** Thrombus in transit.

Discussion

The treatment of TT is still controversial and difficult. Due to the complexity of the patients and the lack of randomized studies, we continue debating the best therapy for our patients. Different therapeutic approaches for acute PE with concomitant TT have been reported such as anticoagulation with unfractionated heparin (UFH), systemic thrombolysis with recombinant tissue plasminogen activator (rTPA), surgical embolectomy with exploration of the right chambers, pulmonary arteries under full cardiopulmonary bypass, and endovascular thrombectomy[1].

Pulmonary thromboembolism was present in 98% of the heart thromboembolism cases analyzed by Rose et al. The treatments administered were none in 9%, anticoagulation therapy in 35.0%, surgical procedure in 35.6%, or thrombolytic therapy in 19.8%. The overall mortality rate was 27.1%. The mortality rate associated with no therapy, anticoagulation therapy, surgical embolectomy, and thrombolysis was 100.0%, 28.6%, 23.8%, and 11.3%, respectively[4].

On the other hand, Athappan et al. studied 328 patients with right heart thrombi (RHT) and PE in a meta-analysis. The treatments administered were none in 11 patients (3.4%), anticoagulation (AC) with heparin in 70 patients (21.3%), thrombolytic in 122 patients

(37.2%), catheter-related treatments in five patients (1.5%) and surgical embolectomy in 120 patients (36.6%). The overall short-term mortality for the entire cohort was 23.2%. The mortality rate associated with no therapy was the highest at 90.9%. The mortality associated with AC alone was significantly higher than surgical embolectomy or thrombolysis (37.1% vs. 18.3% vs. 13.7%, respectively)[5].

To conclude, Galeano-Valle et al[1]. reported the surgical management of thrombus-in-transit and pulmonary embolism (PE) in four patients treated with early surgical embolectomy and anticoagulation. The initial treatment was unfractionated heparin (UFH) and urgent right atriotomy and manual removal of the thrombi. All patients survived after 30 days of follow-up.

In our clinical case, the surgical intervention decision was based on: the low pre-operative risk (EuroScore II calculated of 2.56% and EuroScore Logística of 9.91%) and the fact that our surgical team has experience in pulmonary thrombectomy. The patient is being monitored by clinical cardiology and hematology with a life-long anticoagulation based on his history of recurrent episodes of pulmonary thromboembolism and the mutation of factor V Leiden.

We emphasize the usefulness of the assistance with extracorporeal circulation without clamping, considering that it facilitates the procedure and minimizes risks.

Aortic clamping is not necessary and can be dangerous in elderly patients with calcified aortas (risk of stroke).

Although the evidence tilts the balance towards fibrinolysis and surgery as treatments with better results; we believe it is necessary to individualize the approach depending on the characteristics of the patients and the thrombi. To decide the appropriate treatment for each patient, it is essential to consider the following: the type of thrombus (Type A, B or C), pre-existing pulmonary diseases, deep vein thrombosis, hemodynamic state, experience of the treating team and availability of endovascular treatment[6].

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Conflicts of interest

Los autores no presentan conflictos de intereses.

Ethical responsibilities

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

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

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

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CARTA AL EDITOR

Nuevo enfoque en la prevención del ictus en pacientes con fibrilación auricular no valvular en hemodiálisis: cierre percutáneo de orejuela izquierda

New approach to the prevention of stroke in patients with non-valvular fibrillation in hemodialysis: percutaneous closure of left atrial appendage

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Señor editor:

La prevención de episodios cardioembólicos en pacientes con fibrilación auricular (FA) y alto riesgo hemorrágico supone un reto terapéutico, en la medida en la que debe valorarse la conveniencia o no de anticoagular frente al riesgo de sangrado.

Los pacientes con enfermedad renal crónica terminal (ERCT) tienen mayor prevalencia de FA que la población general (entre 12% y 27%), mayor tendencia a la hipercoagulabilidad y fenómenos trombóticos y mayor riesgo de hemorragia por alteraciones de la hemostasia primaria (disfunción plaquetaria)[1].

Los compuestos más usados como tratamiento anticoagulante en pacientes nefrópatas son los fármacos antivitamina K (warfarina y acenocumarol). En pacientes con ERCT su uso es controvertido, no sólo por el aumento del riesgo de sangrado, sino por las dificultades para mantener un INR en sus límites[2], la calcificación tisular, la calcifilaxia y el aumento de la arteriosclerosis, así como el mayor riesgo de hospitalizaciones de causa cardiovascular[3]. Además, el uso de los nuevos anticoagulantes de acción directa es limitado porque no hay evidencia científica que sustente su eficacia, ya que los pacientes con ERCT se excluyeron de los estudios clínicos que han demostrado beneficio de éstos respecto de la warfarina[4].

Por todo lo anterior, los pacientes con ERCT representan un escenario atractivo en el cual el cierre de la orejuela izquierda (COI) puede tener un beneficio clínico claro.

Seis pacientes con ERCT en programa de hemodiálisis, con diagnóstico de FA y problemas con la anticoagulación oral (ACO), se seleccionaron de forma conjunta entre los Servicios de Nefrología y Cardiología para COI, entre junio de 2017 y diciembre de 2018. Todos los pacientes otorgaron su consentimiento por escrito. Los criterios de exclusión fueron tener indicación de ACO por otra causa distinta de la FA, derrame pericárdico grave, cierre previo del tabique interauricular, trombo intracardíaco, hepatopatía crónica grave y el rechazo expreso del paciente. Las características clínicas de los individuos seleccionados se exponen en la tabla 1.

El dispositivo utilizado en todos los casos fue el Watchman® (Boston Scientific Corporation, Marlborough, Massachusetts, EE.UU.). El implante tuvo éxito en todos los casos y no se registraron complicaciones relacionadas ni con el dispositivo ni con el procedimiento.

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Tabla 1. Características clínicas de los pacientes incluidos y control a los tres a seis meses de la intervención

Paciente	1	2	3	4	5	6
Sexo	Hombre	Hombre	Mujer	Hombre	Mujer	Hombre
Edad	71	78	47	79	88	78
Causa: nefropatía	DM + NEA	DM + NEA	ERP	No filiada	NEA + ERP	Tumor renal
Tiempo de diálisis (m)	90.3	28.1	27.3	74.5	32.6	17.3
iCh	13	13	3	8	10	9
CHA_2DS_2VASc	6	5	3	4	4	3
HAS-BLED	6	5	4	6	6	5
AC por FA	Permanente	Paroxística	Paroxística	Paroxística	Paroxística	Paroxística
Tratamiento previo	HBPM + Clop	Clop	Acen	Acen + Clop	Warf	Acen
Indicación de COI	Hemorragia grave o recurrente	INR lábil	Hemorragia grave o recurrente	Hemorragia grave o recurrente	Hemorragia grave o recurrente	Hemorragia grave o recurrente
ETE Control 3-6 m	Sin fugas ni trombos en dispositivo	Sin fugas ni trombos en dispositivo	Sin fugas ni trombos en dispositivo	Sin fugas ni trombos en dispositivo	Fuga < 5 mm	Sin fugas ni trombos en dispositivo
Tratamiento	Ninguno	AAS	AAS	AAS	AAS	AAS
Episodios	Salida por sepsis	Sin episodios	Sin episodios	Sin episodios	Sin episodios	Muerte súbita a los 12 meses

DM: diabetes *mellitus*; NEA: nefroangioesclerosis; ERP: enfermedad renal poliquística; iCh: índice de Charlson; HBPM: heparinas de bajo peso molescular; Clop: clopidogrel; Acen: acenocumarol; Warf: warfarina; COI: cierre de la orejuela izquierda; ETE: eco transesofágico; AAS: ácido acetilsalicílico; AC: anticoagulación; FA: fibrilación auricular.

Tabla 2. Características técnicas del procedimiento

Morfología de la orejuela (%)	
"Ala de pollo" "Calcetín de viento" "Coliflor"	4 (66.6) 1 (16.7) 1 (16.7)
Diámetro máximo de *ostium* (mm)	22.2 ± 1.3
Diámetro mínimo de *ostium* (mm)	17.7 ± 1.5
Profundidad (mm)	23.5 ± 3.7
Tamaño del dispositivo (mm)	26.5 ± 1.2
Tiempo de endoscopia (min)	23.75 ± 3
Duración total implante (min)	75 ± 38
Cantidad de contraste (ml)	72.5 ± 15
Éxito en el implante (%)	6 (100)
Complicaciones durante el procedimiento (%)	0
Tratamiento tras el implante (%)	
Doble antiagregación	5 (93.3)

Todos los pacientes recibieron el alta en las 24 horas posteriores a la intervención. En la tabla 2 se resumen los principales detalles técnicos.

En la serie de los autores, la tasa de éxito es absoluta (100%) y la tasa de complicaciones durante el procedimiento inexistente (0%), sin perder de vista que el número de pacientes fue pequeño. Esto objeta la creencia de que los pacientes con ERCT sometidos a procedimientos cardiológicos intervencionistas tienen mayor riesgo de complicaciones, debido a que son sujetos más frágiles que la población general y con más cantidad de comorbilidades[5]. Chak, et al. comunicaron una serie de 196 pacientes sometidos a COI en la que se compararon dos grupos, con y sin ERC, encontrándose una mayor tasa de complicaciones periprocedimiento (9.9% vs. 2.4%, p = 0.04) en el grupo con deterioro de la función renal, a expensas del taponamiento cardiaco (8.5% vs. 0.8%, p = 0.01)[6]. Genovesi, et al., publicaron en fecha reciente datos de la mayor serie informada hasta el momento y demostraron en 50 pacientes que, a pesar de la edad avanzada y las múltiples comorbilidades que sufren los pacientes con ERCT, el implante del dispositivo es factible y seguro, con una tasa elevada de éxito (100%) y una tasa baja de complicaciones durante y después del procedimiento (sólo se describieron tres complicaciones menores[7]). Kefer, et al., por su

parte, publicaron una serie en la que se analiza el efecto que la ERC tiene en la prevención del ictus en pacientes sometidos a COI; en esta serie se consideró a pacientes con diversos grados de ERC, incluidos aquéllos con ERCT (estadio V). En ellos, la tasa de éxito en el procedimiento fue también alta (> 98%) y la de complicaciones baja (5.1%), sin observar diferencias entre los pacientes con deterioro de la función renal y sin ella, ni tampoco entre los que mostraban deterioro leve o ERCT[8]. El mayor conocimiento sobre la anatomía de la OI, el uso racional de las técnicas de imagen, la mayor experiencia acumulada en el implante de este tipo de dispositivos, así como los programas de proctorización que facilitan los fabricantes, hacen que este tipo de procedimientos sea algo seguro a pesar de que la unidad de hemodinámica se encuentre en la "curva de aprendizaje", como es este caso.

Durante una mediana de seguimiento de 272 días, y con controles con ecocardiografía transesofágica (ETE) a los tres, seis y 12 meses, no se han encontrado trombos relacionados con el dispositivo en ningún caso, y tan sólo una pequeña fuga en uno de ellos que no requirió intervención por ser menor de 5 mm. De la misma manera, hasta la fecha no se ha registrado ningún episodio de tipo cardioembólico ni sangrado significativo (BARC > 2).

A pesar de que la mortalidad relacionada con el procedimiento ha sido nula, dos pacientes han fallecido, uno por sepsis y otro por muerte súbita; si bien no se puede descartar que ésta fuera de causa embólica, lo más probable es que se debiera a la cardiopatía avanzada subyacente que presentaba el paciente.

La complejidad clínica de estos pacientes es muy alta y se ha tratado de medir con el índice de comorbilidad de Charlson (iCh), no tanto para evaluar a los pacientes sino para compararlos con los de otras series en el futuro. Se ha recurrido al iCh debido a que se ha empleado de forma amplia como variable de ajuste en distintos modelos pronósticos[9]. El iCh de la serie de pacientes de los autores es muy alto (media de 9.3): los dos sujetos fallecidos eran de los más altos (13 y 9). Es posible que en el futuro este índice pueda ayudar a seleccionar, dentro de esta población de pacientes, a aquellos que pueden beneficiarse más de esta medida preventiva a medio y largo plazos.

Aunque esta serie incluye a un número reducido de pacientes y no se pueden inferir conclusiones estadísticas, las perspectivas de la técnica son muy promisorias. Sin embargo, los estudios clínicos *Left atrial appendage occlusion vs. usual care in patients with atrial fibrillation and severe chronic kidney disease (WatchAFIB)* y el *The strategy to prevent hemorrhage associated with anticoagulation in renal disease management (STOP HARM) trial* se detuvieron a finales de 2018 por problemas en el reclutamiento de pacientes. En la actualidad está en marcha el Registro de cierre percutáneo de la orejuela izquierda con dispositivo Watchman® en pacientes con fibrilación auricular no valvular y enfermedad renal crónica en hemodiálisis (NCT NCT03446794), un registro multicéntrico español que cuenta con un objetivo combinado a los 24 meses de ictus o accidente isquémico transitorio, sangrado BARC-2 y embolia sistémica, así como objetivos secundarios de seguridad relacionados con el procedimiento y el seguimiento ecocardiográfico.

Es evidente que el nefrólogo es reticente en este momento a usar una técnica invasiva como medida preventiva, aunque ello suponga retirar la ACO a los pacientes y sus beneficios conocidos, y también el cardiólogo que es reacio *a priori* a tratar a pacientes con una comorbilidad considerable. Por lo tanto, los autores destacan la necesidad de establecer vías de comunicación entre ambas especialidades, que permitan una correcta selección de los pacientes y optimizar así el beneficio que esta técnica ofrece.

Conflicto de intereses

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Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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