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- Risk factors promoting atrial fibrillation
- Circadian variation of blood pressure obtained by ambulatory blood pressure monitoring
- Rare genetic cardiovascular diseases epidemiology
- Cruise ship Takotsubo syndrome
- Patient with lupus, syncope, AV block and His pacing
- Altered macrophage function and fatty liver disease

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Editorial

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Risk factors promoting atrial fibrillation

Factores de riesgo que inducen la fibrilación auricular

Elsa Verónica De la Chesnaye-Caraveo,* Gerardo Rodríguez-Diez‡

Atrial fibrillation (AF) is a chronic, progressive, degenerative, and multifactorial disease characterized by exacerbations and remissions of this arrhythmia.[1,2] It is the most common supra-ventricular tachycardia, affecting approximately 1.0% of the world's population;[2] in México, it is estimated that more than one and a half million people are affected.[3] Because this arrhythmia is associated with several components of the metabolic syndrome, nowadays considered a worldwide pandemic, such prevalence will increase within the following decades, resulting in a higher mortality rate.[1-4] At first, AF is mostly an isolated electrical disorder starting from rapid discharges mainly originating from the pulmonary veins; sustained rapid firing that provokes disorganization into fibrillatory waves that maintain AF, causing structural and functional atrial changes that promote fibrosis and atrial cardiomyopathy, which is the reason why the concept of AF generates more AF is more valid than ever.[1]

Non-modifiable and modifiable risk factors are responsible for producing and maintaining impaired circuitry within the cardiac atrium that contributes to the development of atrial fibrillation.[5] Gender and age are among the non-modifiable risk factors; unfortunately, elderly males will present a higher prevalence of atrial fibrillation than younger men or women, increasing by 8.48% in those over 80 years old.[3,5,6] Also, race and genetic mutations translated into ion channel impairment are associated with a higher prevalence of this arrhythmia. Caucasians have a higher risk for AF than the African ethnic group.[5] For example, a third of patients over 55 years of age with European ancestry will develop an AF episode.[4]

On the other hand, modifiable risk factors include ischemic disease, hypertension, heart failure, obstructive sleep apnea, dyslipidemia, type 2 diabetes mellitus, and obesity, all of which, through different pathophysiological mechanisms, lead to the generation of AF.[6] Inflammation, specifically, chronic inflammation is the common pathway within these risk factors that leads to atrial fibrillation due to the dysregulation of several pro-inflammatory proteins.[7] The high expression of these inflammatory markers, like cytokines or growth factors within cardiac tissue, leads to oxidative stress, myocardial apoptosis, fibrosis, and alteration of intracellular calcium concentration, resulting in the development of arrhythmogenic substrates in the atrium.[8]

Several studies have demonstrated that cardiomyocytes have an intrinsic inflammatory mechanism through proteins that are part of the NACHT-LRR- and pyrin domain-containing 3-inflammasome. Atrial cardiomyocytes synthesize many pro-inflammatory proteins and their respective receptors, stimulating different signaling mechanisms related to the surge of atrial fibrillation, such as the JAKs, STATs, MAPKs, and NF-kB pathways, which in turn upregulate the expression of genes encoding for inflammatory factors.[9] More importantly, it is well documented that modifiable risk factors trigger the pro-inflammatory signaling cascades mentioned above. For instance, within heart failure, connective tissue disruption, increment of left atrial size, ischemia, the reduction of electrical conduction, and the development of

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fibrosis due to the up-regulation of the renin-angiotensin system will promote the surge of atrial fibrillation.[10]

Interestingly, the correlation between dyslipidemia and AF is controversial because high levels of low-density lipoprotein and total cholesterol have not been singled out as a primary cause for AF development, but low concentrations of high-density lipoprotein, as well as high concentrations of triglycerides, are independently associated with the incidence of atrial fibrillation; the latter mainly because of the lack of high-density lipoprotein anti-inflammatory properties and the detrimental effects of hypertriglyceridemia within the cardiovascular system.[11-13] Also, advanced glycation end products present in diabetic subjects promote AF. According to Nayak et al.,[5] the circulating concentration of advanced glycation end products and their receptors link directly with the progression of paroxysmal to permanent atrial fibrillation through the pro-inflammatory pathway triggered by reactive oxygen species.

The relationship between AF and obesity is very complex because it modifies hemodynamic regulation, neurohumoral, metabolic inflammatory, and autonomic system functions and is considered a proinflammatory systemic state related to adipokine and cytokines dysregulation.[7,14] Pericardial fat and epicardial adipose tissue also induce an inflammatory immune response that leads to fat infiltration in the atrial myocardium, increasing fibrosis and favoring the onset and sustainment of AF.[14]

Nowadays, AF treatment aims to convert and maintain sinus rhythm (SR) at the earliest through the diagnosis. Because the control of all these risk factors leading to a chronic inflammatory process is not enough, an integral approach that includes the modification of such risk factors, the administration of anti-arrhythmic drugs, and a catheter ablation that will achieve the isolation of the pulmonary veins is necessary to prevent a high arrhythmia burn, in order to have an impact in the long-term follow-up, by retarding fibrosis and maintaining the patient in sinus rhythm as long as possible.[1,4]

In conclusion, atrial fibrillation is the most common arrhythmia affecting millions of people worldwide. Chronic inflammation is one of the main factors involved in its pathogenesis, producing dysregulation of different proteins. This alteration generates arrhythmogenic substrates within the myocardial atrium that promote atrial fibrillation.

To prevent the surge of this arrhythmia, in addition to the clinician's advice on modifying lifestyle and nutrition habits, many scientists have focused on identifying biomarkers that could accurately predict the appearance or recurrence of atrial fibrillation before and after catheter ablation of pulmonary veins.

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ORIGINAL RESEARCH

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Circadian variation of blood pressure obtained by ambulatory blood pressure monitoring in hypertensive individuals in Mexico City

Comportamiento circadiano de la presión arterial obtenida por monitoreo ambulatorio de presión arterial en individuos hipertensos en la Ciudad de México

René Rodríguez-Cruz,* Marco Antonio Sánchez-Hernández,‡ Liliana Isabel Ortega-Garibay,‡ Mónica Lizbeth Romero-Badillo,‡ María Guadalupe Velásquez-Cueto,§ Jessica Elizabeth García-Ramírez§

Keywords:
circadian rhythm, blood pressure, hypertension, Ambulatory Blood Pressure Monitoring.

Palabras clave:
ritmo circadiano, presión arterial, hipertensión, monitoreo ambulatorio de presión.

ABSTRACT

Introduction: the circadian rhythm of blood pressure has been associated with various vascular and metabolic effects contributing to increased mortality among individuals with hypertension. Thus, elucidating relevant variables could enhance understanding and potentially decrease mortality rates in this population. **Objective:** this retrospective study aimed to determine the circadian pattern of blood pressure in hypertensive individuals using Ambulatory Blood Pressure Monitoring (ABPM) in Mexico City. **Material and methods:** an observational, descriptive, cross-sectional study was conducted by reviewing PDF files of ABPM reports from a cardiology outpatient clinic. The study encompassed all individuals undergoing follow-up at a specialized clinic in Mexico City. **Results:** among the 648 patients included in the study, the physiological dipper pattern, considered normal, was present in 72.6% of hypertensive individuals. Additionally, 19% exhibited a non-dipper pattern, 22.5% displayed an inverse dipper pattern, and 12% showed an extreme dipper pattern. No significant differences were observed between genders. **Conclusions:** the circadian rhythm of blood pressure, characterized by the physiological dipper pattern, was observed in only 72.6% of hypertensive individuals, even among those with normal average blood pressure. The inverse dipper pattern represented the second most prevalent group at 22.5%. Minor differences were noted between men and women regarding the timing of peak hypertension.

RESUMEN

Introducción: *el comportamiento circadiano de la presión arterial se ha vinculado a múltiples efectos vasculares y/o metabólicos que incrementan la mortalidad en individuos hipertensos, por lo que el esclarecimiento de las variables relacionadas podría ayudar al mejor entendimiento, con el objetivo de fortalecer el descenso de la mortalidad de pacientes portadores de hipertensión arterial.* ***Objetivo:*** *establecer el comportamiento circadiano de la presión arterial en individuos hipertensos mediante la utilización del monitoreo ambulatorio de presión arterial (MAPA) en la Ciudad de México.* ***Material y métodos:*** *estudio observacional, retrospectivo, descriptivo y transversal, se realizó la revisión de los archivos en formato PDF de los reportes de MAPA realizados de la consulta externa de cardiología, se incluyeron todos aquellos individuos en seguimiento en una clínica de especialidades de primer contacto en la Ciudad de México.* ***Resultados:*** *de un total de 648 pacientes se encontró que el fenómeno dipper fisiológico considerado como normal ocurre en 72.6% de la población hipertensa, mientras que el no dipper ocurre en 19%, dipper inverso en 22.5% y finalmente el dipper extremo ocurre en 12% del total de la población. No existen diferencias significativas entre hombres y mujeres.* ***Conclusiones:*** *el comportamiento circadiano de la presión arterial considerado como fisiológico dipper sólo ocurre en 72.6% de las personas hipertensas aun en individuos con cifras de presión arterial promedio normal. El dipper inverso es el segundo grupo con mayor valor porcentual en la población estudiada con 22.5% de la población. Existen pequeñas diferencias entre hombres y mujeres con respecto al horario de mayor hipertensión.*

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Abbreviations:
ABPM = Ambulatory Blood Pressure Monitoring.
BMI = Body Mass Index.

INTRODUCTION

Blood pressure levels are intricately linked to various pathophysiological phenomena that underlie multiple diseases, predominantly of vascular origin. Investigating the circadian behavior of blood pressure holds promise in elucidating diagnostic and treatment challenges within the hypertensive population of Mexico City. Non-communicable diseases, particularly arterial hypertension, continue to dominate global mortality statistics, likely owing to their multifaceted modifiability. In Mexico, the prevalence of hypertension, as defined by the criteria established in the 2014 «Eighth Joint National Committee (JNC 8)»[1] American Hypertension Guidelines, was documented in the National Health Survey (ENSANUT) of 2022. The survey revealed a diagnosis of systemic arterial hypertension in 43.9% of adults, with a prevalence of 29.4% among individuals aged over 20, slightly higher in males at 31.3% and females at 27.7%.[2] However, some experts argue that these figures underestimate the true prevalence, prompting methodological refinements in various statistical trials better to capture the incidence and prevalence of arterial hypertension. This challenge was exemplified in 2005 by the «*Re-encuesta Nacional de Hipertensión Arterial (RENAHTA): Consolidación Mexicana de los Factores de Riesgo Cardiovascular. Cohorte Nacional de Seguimiento*» which, unfortunately, failed to demonstrate significant deviations from the earlier findings of ENSANUT.[3]

The complexities of hypertension extend beyond frequency and prevalence to encompass diagnostic criteria and optimal follow-up and treatment paradigms, as evidenced by a study published by García Zamora et al. In their analysis of the «PROSPERO» registry, encompassing four studies involving 29,820 patients with intensive arterial hypertension treatment, they found that despite intensive treatment, mortality rates remained unaltered. Specifically, the relative risk (RR) was found to be 0.89 with a 95% Confidence Interval (CI 95%): 0.68-1.07; p = 0.16, with no impact on total mortality (p = 0.45) for any of the evaluated causes.[4]

Currently, the established indications for Ambulatory Blood Pressure Monitoring (ABPM) remain relatively unchanged and fundamentally address three conditions.[5] Firstly, patients with elevated arterial hypertension readings in outpatient office settings termed the «white coat phenomenon». Secondly, individuals with blood pressure readings within the normal range during office visits but with a history of elevated pressure during daily activities are known as «masked hypertension».[6] Finally, continuous blood pressure monitoring is recommended to evaluate the nocturnal blood pressure behavior in cases of «isolated nocturnal hypertension».[7,8] However, the pathogenic aspects of the latter indication remain poorly understood,[9] as evidenced by various conditions associated with the nocturnal behavior of arterial hypertension, such as periodic limb movement. It seems that sympathetic discharges are the etiological cause with greater support. One study aimed at demonstrating the relationship between arterial hypertension and periodic limb movement took place in Cordova, a province of Spain. In this study, 11 individuals with a previous diagnosis of periodic limb movement were compared with seven control individuals using polysomnography. The patients with periodic limb movement had an average age of 57 ± 14 years, whereas the control group had an average age of 64 ± 6 years. However, the age difference between the two groups was not statistically significant (p = 0.284).

Contrary to the expected hypothesis, the results showed intriguing findings regarding blood pressure. The average blood pressure obtained over 24 hours by ambulatory blood pressure monitoring was lower in the periodic limb movement group compared to the control group. Specifically, the systolic pressure was 114.2 ± 11 mmHg in the periodic limb movement group versus 123 ± 11 mmHg in the control group, with a p-value of 0.095. Similarly, the diastolic pressure was 65.7 ± 5 mmHg in the periodic limb movement group and 74.4 ± 11 mmHg in the control group, with a p-value of 0.027.[10] These

unexpected findings raise questions about the underlying mechanisms and their implications for hypertension management. This prompts further investigation into whether circadian patterns of blood pressure behavior are linked to extravascular complications.[11] Multiple studies have sought to address this question. In 2018, a study in Cuba attempted to establish a link between the circadian behavior of blood pressure and specific conditions like left ventricular hypertrophy and insulin resistance among 46 hypertensive patients. Surprisingly, the initial hypothesis suggesting a direct relationship between insulin resistance and blood pressure behavior was not supported by the study's findings.

Nevertheless, the study shed light on the nocturnal behavior of blood pressure, uncovering significant anomalies. Among the participants, 58% exhibited abnormal nocturnal blood pressure patterns. This included 15% with the non-dipper phenomenon, 7% with Extreme dippers, and an additional 5% with Reverse dippers.[12] These findings underscore the existence of potential independent vascular risk factors within the hypertensive population, although their precise nature remains unclear.

MATERIAL AND METHODS

In an observational, retrospective, descriptive, and cross-sectional study, PDF files of Ambulatory Blood Pressure Monitoring (ABPM) reports obtained from the cardiology outpatient clinic were meticulously reviewed. This encompassed all individuals undergoing follow-up in a specialized first-contact clinic in Mexico City, dedicated to the control and monitoring of arterial hypertension, as well as the management of various cardiovascular pathologies, receiving referrals from health centers across the city. Evaluation of accepted indications for ABPM in the cardiology clinic was not conducted, adhering strictly to the prevailing normative criteria for specialty outpatient care in the institution.

Between June 1, 2018, and October 15, 2023, ambulatory blood pressure monitoring was conducted using a Schiller model BR 102 plus device. The device was programmed to record blood pressure at 30-minute intervals during daytime hours from 08:00 to 22:00 and during nighttime hours from 22:00 to 08:00 the following day. The decision to perform ABPM was solely based on clinical criteria and the follow-up protocol established by the responsible cardiologist.

A comprehensive database was constructed from the total ABPM records in PDF format, capturing essential variables such as age, sex, height, weight, body mass index (BMI), overall blood pressure averages, daytime, and nighttime blood pressure averages, as well as maximum blood pressure readings at various times and the corresponding hours of those peaks. An analysis of variance was conducted for multiple quantitative variables, and a Student's t-test was employed to determine differences between groups in independent variables, with a significance level set at $p < 0.05$.

RESULTS

A total of 768 ABPM reports obtained between June 1, 2018, and October 15, 2023, were scrutinized. However, 42 studies were excluded due to incomplete information for analysis. Among these, 26 lacked nighttime blood pressure recordings during ABPM, eight lacked weight and height measurements, and eight lacked age records in the ABPM report, rendering them unsuitable for analysis. Additionally, 78 ABPM studies performed to establish the diagnosis of arterial hypertension were set aside, constituting 10% of the total sample, as these patients were suspected to have the «white coat phenomenon and masked hypertension».

The groups of patients with previously diagnosed hypertension and established prior treatment totaled 648 individuals, who were further subdivided into two groups: those with information on office blood pressure measurements for comparison with ABPM averages.

Of the 648 studies conducted on hypertensive patients in follow-up, 425 corresponded to women (65.5% of the total records), while 223 corresponded to men (34.5%). Multivariate analysis revealed four

variables with statistically significant differences when comparing men and women *(Table 1)*.

1. The average body mass index for men was 28.77, and for women was 28.49, with a p-value of 0.03.
2. The time of maximum diastolic pressure for men was at 12:59 hours, and for women was at 12:23 hours, with a p-value of 0.0003.
3. The time of maximum nocturnal systolic pressure for men was at 21:56 hours, and for women was at 22:22 hours, with a p-value of 0.0001.
4. The time of maximum nocturnal diastolic pressure for men was at 22:39 hours, and for women was at 21:55 hours, with a p-value of 0.0004.

The remaining variables showed no statistical significance. Notably, no significant differences were found in the subgroup of patients with office blood pressure

Table 1: Comparative multivariate analysis of males and females.

	Males	Females	p
Age	65.03	64.13	0.3985
Weight	78.95	65.43	91.3993
Height	165.13	154.62	55.2257
BMI	28.77	28.49	0.0374
Global SP	122.53	121.66	0.3805
Global DP	73.61	68.67	12.1982
Global MAP	93.47	91.60	1.7500
Diurnal SP	124.36	123.32	0.5370
Diurnal DP	74.75	70.15	10.5721
Diurnal MAP	94.68	93.04	1.3551
Nocturnal SP	118.60	116.42	2.3760
Nocturnal DP	69.97	63.77	19.2136
Nocturnal MAP	89.62	87.22	2.8794
Reduction in SP	4.82	5.44	0.1975
Reduction in DP	6.09	8.88	3.8988
Maximum SP	154.08	154.99	0.4140
Time of maximum SP	12:33:48	12:50:48	6.9686
Maximum DP	100.75	98.95	1.6126
Time of maximum DP	12:59:12	12:23:18	0.0003
Maximum diurnal SP	152.90	156.34	5.9316
Time of maximum diurnal SP	12:58:07	13:02:11	3.9878
Maximum diurnal DP	99.68	97.76	1.8376
Time of maximum diurnal DP	13:33:33	13:37:20	3.4467
Maximum nocturnal SP	137.52	135.58	1.8890
Time of maximum nocturnal SP	21:56:55	22:22:56	0.0001
Maximum nocturnal DP	86.31	80.42	17.3725
Time of maximum nocturnal DP	22:39:56	21:55:46	0.0004
Mean HR	69.66	71.79	2.2714
Maximum HR	104.32	109.22	11.9851
Minimum HR	51.93	54.36	2.9567
In office SP	135.02	138.01	4.4588
In office DP	76.59	69.98	21.8460

BMI = Body Mass Index. DP = Diastolic Pressure. HR = Heart Rate. MAP = Mean Arterial Pressure. SP = Systolic Pressure.

Table 2: Nocturnal blood pressure variability: stratified by sex.

	Male N = 223 n (%)	Female N = 425 n (%)	Both N = 648 n (%)	p (T ≤ T) two-tailed
Inverse dipper –1 a –20%	53 (23.7)	93 (21.8)	146 (22.5)	0.3755
Non-dipper 0%	7 (3.1)	12 (2.8)	19 (2.9)	0.4842
Dipper 1 A 20%	159 (71.3)	312 (73.4)	471 (72.6)	0.0873
Extreme dipper 20%	4 (1.7)	8 (1.8)	12 (1.8)	0.4873

readings compared to the average values obtained in ABPM.

The circadian rhythm of systolic blood pressure allowed patients to be categorized into four distinct groups based on their nocturnal blood pressure behavior. These groups include:

1. **Inverse dipper:** patients exhibiting an increase in blood pressure during the night ranging from 0 to 20%.
2. **Non-dipper:** patients with no significant modifications in blood pressure values during nighttime.
3. **Dipper:** patients displaying a nocturnal reduction in systolic blood pressure of up to 20%.
4. **Extreme dipper:** patients with a substantial nocturnal reduction in systolic blood pressure exceeding 20%.[13]

Statistical analysis revealed small but significant differences in blood pressure behavior between men and women, with a calculated p-value of 0.059. Specifically, it was observed that 71.3% of women exhibited a dipper response, compared to 73.4% of men. The next most common group consisted of patients with inverse dipper patterns, accounting for 23.7% of women and 21.8% of men. Non-dipper behavior was less prevalent, accounting for 3.1% of men and 2.8% of women. Additionally, extreme dipper patterns were found in 1.7% of men and 1.8% of women. However, none of these individual percentages demonstrated statistically significant differences between genders *(Table 2)*.

In the gender-based analysis, notable disparities were observed in systolic and diastolic blood pressure values, primarily revolving around the timing of maximum peaks of hypertension. Additionally, a slight discrepancy in body mass index was identified between the inverse dipper and non-dipper groups, with values of 29.04 and 29.06, respectively, yielding a statistically significant p-value of 0.00018. Among men exhibiting dipper and extreme dipper responses, a marginal age difference was noted, with the first group averaging 64.05 years and the latter 64.5 years, resulting in a p-value of 0.09.

In cases where ABPM served as a diagnostic tool for arterial hypertension, no significant demographic distinctions were observed among the 79 individuals studied, comprising 58 women and 20 men. However, statistically significant differences were evident in the timing of maximum blood pressure values. For women, the hour with the highest systolic pressure was approximately 12:53 pm, while for men, it occurred around 2:09 pm, with a p-value of 0.001. Similarly, the hour of maximum nocturnal diastolic hypertension for women was recorded at 11:08 pm, whereas for men, it was at 10:10 pm, with a p-value of 0.0008. Notably, despite these temporal variations, average blood pressure values remained quite similar across genders.

The average blood pressure behavior among hypertensive patients in the study was slightly higher in men, with readings of 122/73 mmHg compared to 121/68 mmHg in women. During daytime hours, men exhibited an average blood pressure of 124/74 mmHg, whereas women recorded 123/70 mmHg. Nighttime blood pressure averaged 118/69 mmHg in men and 116/63 mmHg in women. Although men displayed a slightly greater reduction in systolic

blood pressure (4.8 mmHg) and diastolic pressure (6 mmHg) during nighttime, these differences did not reach statistical significance by gender. Moreover, no notable disparities were found between office blood pressure and average ABPM readings for hypertension diagnosis, as illustrated in *Table 3*.

DISCUSSION

The impact of abnormal circadian blood pressure patterns on vascular and metabolic diseases has been extensively documented in various studies, hinting at a common underlying etiology.[14] A recent systematic review delved into the cardiometabolic implications of circadian rhythm disruptions in the North American population, particularly associated with occupational factors. This review explored the interplay between meal timing, work schedules, and their correlation with body mass index, diabetes prevalence, hypertension, and cerebrovascular diseases. The findings revealed alarming statistics, including a 23% prevalence of obesity and overweight, a 14% increase in diabetes mellitus, and a metabolic syndrome prevalence ranging from 11% to 35% among individuals with disrupted circadian rhythms. Notably, hypertension exhibited a 10% prevalence but with a staggering 30% elevated risk of occurrence, underscoring the profound impact of circadian rhythm changes on health.[15]

The daily patient record was not consulted for the preparation of this study. However, the significance of this study potentially lies in its revelation that blood pressure behavior may deviate from expected norms even among individuals without significant changes in their daily activities. Surprisingly, only 71.5% of men and 73.4% of women exhibited a normal blood pressure pattern (dipper) despite their average blood pressure values falling within the normal range. Various efforts have been made to elucidate these phenomena, such as the research published by Murray E.C. et al., which investigated vascular response phenotypes in early hypertension. Their study, involving 73 newly diagnosed hypertensive individuals without standard treatment, compared with a control group of 79 hypertensive individuals matched for demographic characteristics, found that all newly diagnosed hypertensive individuals displayed vascular stiffness but not endothelial dysfunction.[16] This finding aligns with previous multicenter studies associating the duration of hypertension with vascular intima necrosis and greater endothelial dysfunction.

However, our study reveals gender-specific behavioral differences among individuals without a prior hypertension diagnosis. This aspect is particularly noteworthy as the timing of peak hypertension could unveil underlying factors yet to be fully understood between men and women. Despite similar systolic and diastolic pressure values, distinct differences in the times of peak hypertension were observed. These findings underscore the complexity of blood pressure regulation and the need

Table 3: Summary of blood pressure dynamics.

Study groups	Overall global blood pressure (mmHg)	Average diurnal blood pressure (mmHg)	Average nocturnal blood pressure (mmHg)	Systolic/diastolic reduction (%)
Overall blood pressure dynamics (M: 223/F: 435)	M: 122/73 F: 121/68	M: 124/74 F: 123/70	M: 118/69 F: 116/63	M: 4.8/6 F: 5.4/8.8
ABPM in hypertension diagnosis (M: 20/F: 58)	M: 121/72 F: 124/75	M: 123/74 F: 126/77	M: 112/64 F: 116/68	M: 7.3/11.1 F: 7.9/12.6
In office blood pressure records (M: 155/F: 314)	M: 123/74 F: 121/68	M: 125/75 F: 123/70	M: 118/69 F: 111/61	M: 4.5/5.9 F: 5.3/9.0

ABPM = Ambulatory Blood Pressure Monitoring. F = Female. M = Male.

Table 4: Individuals with indicated ambulatory blood pressure monitoring for hypertension diagnosis without prior diagnosis of arterial hypertension.

	Female	Male	Variance
N	58	20	722.00
Age	52.05	45.5	21.46
Weight	75.29	82.2	23.85
Height	155.20	166.4	62.64
BMI	30.30	29.65	0.20
Global SP	121.17	124.3	4.89
Global DP	72.70	75.35	3.49
Global MAP	93.79	95.2	0.98
Durnal SP	123.08	126.8	6.89
Diurnal DP	74.60	77.9	5.43
Diurnal MAP	95.74	97.5	1.54
Nocturnal SP	112.12	116.55	9.80
Nocturnal DP	64.98	68.45	6.01
Nocturnal MAP	85.53	87.75	2.45
SP reduction	7.37	7.9	0.13
DP reduction	11.18	12.6	0.99
Maximum SP	151.46	149.5	1.93
Time of maximum SP	13:12:40	14:33:18	0.00
Maximum DP	103.67	103.05	0.19
Time of maximum DP	13:39:00	13:27:00	0.00
Maximum diurnal SP	153.75	149.3	9.93
Time of maximum diurnal SP	12:53:43	14:09:18	0.00
Maximum diurnal DP	102.55	101.85	0.24
Time of maximum diurnal DP	14:16:22	12:57:00	0.00
Maximum nocturnal SP	129.05	134.15	12.99
Time of maximum nocturnal SP	13:03:37	12:55:30	0.00
Maximum nocturnal DP	81.10	84.7	6.46
Time of maximum nocturnal DP	11:08:48	10:10:30	0.00
Mean HR	73.13	71.95	0.70
Maximum HR	110.75	112.65	1.78
Minimum HR	54.75	52.6	2.32
In office SP	132.03	132.45	0.08
In office DP	71.96	79.45	28.04

BMI = Body Mass Index. DP = Diastolic Pressure. MAP = Mean Arterial Pressure. SP = Systolic Pressure.

for further investigation into gender-specific mechanisms influencing blood pressure patterns *(Table 4)*.

CONCLUSION

The circadian behavior of blood pressure, characterized by the physiological dipper pattern, was observed in only 72.6% of hypertensive individuals, even among those with normal average blood pressure values. The inverse dipper pattern emerged as the second most prevalent group in the studied population, comprising 22.5% of individuals. Minor disparities were noted between men and women regarding the timing of peak hypertension.

The group of researchers is developing work on the behavior of obstructive sleep apnea in cardiovascular disease, which could further enrich knowledge about this disease and its growing prevalence.

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Declaration of confidentiality and patients consent: the authors declare they have followed their workplace protocols for using patient data. Also, they certify that the patient has received sufficient information and has given written informed consent for his/her/their images and other clinical information to be reported in the journal, without names or initials, to protect the right to privacy.

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Rare genetic cardiovascular diseases: descriptive epidemiological data in a Mexican third-level cardiology hospital outpatient clinic

Enfermedades cardiovasculares genéticas raras: datos epidemiológicos descriptivos en la consulta externa de un hospital mexicano de tercer nivel de cardiología

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Keywords:
rare diseases, genetics, cardiovascular system, prevalence, epidemiology.

Palabras clave:
enfermedades raras, genética, sistema cardiovascular, prevalencia, epidemiología.

ABSTRACT

Introduction: rare cardiovascular diseases are conditions with low prevalence in the general population that affect the cardiovascular system. Most have a genetic etiology with a heritable potential denominated as Rare Genetic Cardiovascular Diseases (RGCVD). Currently, there are scarce epidemiological studies on RGCVD, and the overall prevalence is unknown. **Objective:** descriptive epidemiological analysis of RGCVD, emphasizing the overall prevalence estimation in a cardiovascular hospital. In addition, the cardiovascular phenotype distribution and other related demographic characteristics were analyzed. **Material and methods:** the study consists of a retrospective descriptive epidemiological analysis from January to December 2019 in the outpatient clinic of a cardiovascular third-level hospital in Mexico City. RGCVD patients were identified with an exhaustive review of all clinical records. The overall prevalence of RGCVD was estimated. In addition, the number of diseases, cardiovascular phenotype distribution, and other demographic data of these diseases were analyzed. **Results:** RGCVD comprised 794 of 31,487 patients in the outpatient clinic, corresponding to 104 diseases. The overall prevalence of RGCVD was 2.5% (95%CI, 2.3-2.7) patients. The prevalence of monogenic and chromosomal disorders was 2.1 and 0.4%, respectively. Congenital heart diseases were the most frequent cardiovascular phenotype (42.4%), and the less frequent were cardiac tumor disorders (0.9%). **Conclusions:** the study identified that almost one in 40 patients in the outpatient clinic of a cardiology hospital had an RGCVD. The study also provides useful epidemiological information for further research and planning cardiovascular health services.

RESUMEN

Introducción: *las enfermedades cardiovasculares raras son patologías de baja prevalencia en la población general que afectan al sistema cardiovascular. La mayoría tienen una etiología genética con potencial hereditario denominadas Enfermedades Cardiovasculares Genéticas Raras (ECVGR). En la actualidad, existen escasos estudios epidemiológicos sobre las ECVGR y se desconoce su prevalencia global.* ***Objetivo:*** *análisis epidemiológico descriptivo de las ECVGR, haciendo hincapié en la estimación de la prevalencia global en un hospital cardiovascular. Además, se analizaron la distribución del fenotipo cardiovascular y otras características demográficas relacionadas.* ***Material y métodos:*** *el estudio consiste en un análisis epidemiológico descriptivo retrospectivo de enero a diciembre de 2019 en la consulta externa de un hospital cardiovascular de tercer nivel de la Ciudad de México. Se identificaron pacientes con ECVGR con una revisión exhaustiva de todos los expedientes clínicos. Se estimó la prevalencia global de ECVGR. Además, se analizó el número de enfermedades, la distribución del fenotipo cardiovascular y otros datos demográficos de estas enfermedades.* ***Resultados:*** *las ECVGR comprendieron 794 de 31,487 pacientes de la consulta externa, correspondiendo a 104 enfermedades. La prevalencia global de ECVGR fue de 2.5% (IC95%, 2.3-2.7) de los pacientes. La prevalencia de los trastornos monogénicos y cromosómicos fue de 2.1 y 0.4%, respectivamente. Las cardiopatías congénitas fueron el fenotipo cardiovascular más frecuente (42.4%), y los menos frecuentes fueron los trastornos tumorales cardiacos (0.9%).* ***Conclusiones:*** *el estudio identificó que casi uno de cada 40 pacientes de la consulta externa de un hospital de cardiología tenía una ECVGR. El estudio también proporciona información epidemiológica útil para futuras investigaciones y para la planificación de los servicios de salud cardiovascular.*

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Abbreviations:
CI = Confidence Interval.
ICD = International Classification of Diseases.
OMIM = Online Mendelian Inheritance in Man.
RGCVD = Rare Genetic Cardiovascular Diseases.

INTRODUCTION

Rare diseases affect between 3.5 and 5.9% of the world's population, impacting around 350 million people at any time in life. Rare diseases are a heterogeneous group of disorders with a genetic etiology in almost 72%.[1-3] There is no global consensus about the definition of a rare disease, but in general terms, a rare disease is defined as a disease that affects < 50/100,000 people.[4]

Rare genetic cardiovascular diseases affect the cardiovascular system with or without extracardiac manifestations, with an individually low prevalence, mainly caused by rare and ultra-rare genetic variants with heritable potential.[2,5,6]

There are currently scarce epidemiological studies on rare genetic cardiovascular diseases that delineate their distribution and situation in different world regions, clinical settings, and healthcare systems.[7] Moreover, most studies are biased toward estimating the prevalence of some diseases, providing a fractioned and limited perspective of rare genetic cardiovascular diseases' global panorama.[3,8] These are routinely seen in cardiovascular clinical practice. However, the overall rare genetic and nongenetic cardiovascular prevalence in cardiology is hitherto unknown.

It is crucial to estimate the total number of people affected with rare genetic cardiovascular diseases to provide helpful information for improving medical care in the future. Furthermore, this information could establish some bases to encourage translational research that promotes the creation of health policies consistent with the needs of patients suffering from these diseases. Therefore, the objective herein was to conduct a descriptive epidemiological analysis of the rare genetic cardiovascular diseases in the outpatient clinic of a third-level cardiology hospital, emphasizing the estimation of their overall prevalence. Additionally, cardiovascular phenotype distribution, the outpatient prevalence per disease, type of genetic disease, type of rare disease, and other related demographic characteristics were analyzed to evaluate the situation of rare genetic cardiovascular diseases in a cardiovascular clinical setting.

MATERIAL AND METHODS

Study design and setting

The design was a retrospective, descriptive epidemiological study of the full range of patients with rare genetic cardiovascular diseases in a third-level cardiovascular hospital outpatient clinic in Mexico City (*Instituto Nacional de Cardiología Ignacio Chávez*) from January to December 2019. The hospital is a recognized national reference for the attention of pediatric and adult cardiovascular diseases.

Definitions, study population, and data collection

The operational definition of a rare genetic cardiovascular disease was a rare disease cataloged in the online rare diseases database Orphanet[2] with a genetic etiology (monogenic or chromosomal disorders) affecting the cardiovascular system with or without extra cardiovascular clinical features. The diagnoses of patients with rare genetic cardiovascular diseases were identified through an exhaustive review of all the diagnoses settled in the electronic clinical records of the 31,487 patients who visited the outpatient clinic. A medical geneticist conducted the review. The study included confirmed clinical diagnoses of patients with rare genetic cardiovascular diseases. The medical geneticist assessed each diagnosis to determine if it met the specific criteria of each rare genetic cardiovascular disease, regardless of whether a confirmatory genetic test was conducted. Diagnoses of common cardiovascular diseases or rare diseases without cardiovascular involvement were excluded from the study. In addition, the clinical data for each patient with a rare genetic cardiovascular disease, including the diagnosis (disease name), cardiovascular phenotype, age, and sex, were collected for further analysis. Each rare genetic cardiovascular disease name was matched with its related preferred disease term

and ORPHAcode, obtained from Orphanet.[2] In diseases without a specific ORPHAcode, the ORPHAcode of a group of disorders was assigned according to the phenotype.

Type of genetic disorder

Identified rare genetic cardiovascular diseases were classified according to the type of genetic disorder in two categories: chromosomal disorders and monogenic disorders. Chromosomal disorders include numerical and structural chromosomal abnormalities and genomic rearrangements. Monogenic include Mendelian inheritance patterns and non-Mendelian patterns. The information regarding the etiology was obtained from Orphanet[2] and OMIM (Online Mendelian Inheritance in Man).[9]

Type of rare disease

In order to analyze the situation of the rare genetic cardiovascular diseases identified in the outpatient clinic, each rare cardiovascular disease was categorized into three types of rare diseases according to the disease prevalence reported in Orphanet.[2] The prevalence reported for each disease could be related to the prevalence in the general population or birth prevalence. Therefore, the type of rare diseases was categorized as follows: rare (prevalence between < 1/2,000 - > 1/50,000),[4] ultrarare (prevalence between ≤ 1/50,000 - < 1/1'000,000),[10] and unknown prevalence.

Cardiovascular phenotype distribution

To analyze the distribution of the cardiovascular phenotype of the identified patients with rare genetic cardiovascular diseases, the cardiovascular phenotype of each patient was classified into one of the six groups (arrhythmic and conduction disorders, cardiac tumor disorders, cardiomyopathies, congenital heart diseases, vascular disorders, and other cardiovascular disorders) and its corresponding morphological subgroup.

Statistical analysis

The overall prevalence of rare genetic cardiovascular diseases, the prevalence per disease, and the prevalence of monogenic and chromosomal disorders were estimated using the total number of patients who attended the outpatient clinic in 2019 as a denominator. The 95% confidence interval (CI) was estimated for overall, monogenic, and chromosomal disorders prevalences. The prevalence per disease was calculated per 10,000 patients. Continuous variables were expressed as median (25^{th} - 75^{th} percentile). Categorical variables were expressed as absolute and relative frequencies, as appropriate. The differences in continuous variables among groups of cardiovascular phenotypes were calculated with the Kruskal-Wallis H test and, in categorical variables, with the χ^2 test. Data and statistical analyses were performed in Stata Statistical Software: Release 16 (StataCorp LLC. 2019).

RESULTS

Of the total population of patients who attended the outpatient clinic in 2019 (n = 31,487), 794 patients had a diagnosis of a rare genetic cardiovascular disease. The overall period prevalence of rare genetic cardiovascular diseases was 2.5% (95%CI, 2.3-2.7) of the patients in the outpatient clinic of the analyzed third-level cardiovascular hospital. The patients with rare genetic cardiovascular diseases corresponded to 104 disease names *(Table 1)*. The frequency of patients and the prevalence in the outpatient clinic per 10,000 patients for each rare genetic cardiovascular disease are shown in *Table 1*. Of the patients with rare genetic cardiovascular diseases, 51% were women, and the median age was 23 (13-38). Thirty-nine percent of patients correspond to pediatrics ages (0-18 years).

Eighty-seven out of 104 diseases observed corresponded to monogenic disorders, and 17 were chromosomal disorders *(Table 1)*. Therefore, the number of patients affected with monogenic disorders was 668/794 (84.1%), and patients with chromosomal disorders accounted for 126/794 (15.9%). The prevalence of monogenic and chromosomal disorders of the rare genetic cardiovascular diseases in the outpatient clinic was 2.1% (95%CI, 2.0-2.3) and 0.4% (95%CI, 0.3-0.5), respectively.

According to the reported prevalence for each disease in Orphanet,[2] 33 diseases

Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Marfan syndrome	558	178	56.5	Rare	Monogenic
Romano ward syndrome (long QT syndrome type 1, 2, and 3)	101,016	79	25.1	Rare	Monogenic
Noonan syndrome	648	72	22.9	Rare	Monogenic
22q11.2 deletion syndrome	567	43	13.7	Rare	Chromosomal
Williams syndrome	904	42	13.3	Rare	Chromosomal
Loeys-Dietz syndrome	60,030	38	12.1	Unknown	Monogenic
Left ventricular noncompaction	54,260	29	9.2	Unknown	Monogenic
Turner syndrome	881	24	7.6	Rare	Chromosomal
Brugada syndrome (types 1, 2, and 3)	130	21	6.7	Rare	Monogenic
Familial isolated dilated cardiomyopathy	217,656	20	6.4	Rare	Monogenic
Holt-Oram syndrome	392	18	5.7	Ultrarare	Monogenic
Familial isolated arrhythmogenic right ventricular dysplasia	154	16	5.1	Unknown	Monogenic
Supravalvular aortic stenosis	3,193	14	4.4	Rare	Monogenic
Classical Ehlers-Danlos syndrome	287	11	3.5	Rare	Monogenic
Familial thoracic aortic aneurysm and aortic dissection	91,387	11	3.5	Ultrarare	Monogenic
Heterotaxia (visceral heterotaxy)	450	9	2.9	Rare	Monogenic
Neurofibromatosis type 1	636	9	2.9	Rare	Monogenic
Andersen-Tawil syndrome	37,553	8	2.5	Unknown	Monogenic
Tuberous sclerosis complex	805	8	2.5	Rare	Monogenic
Congenital contractural arachnodactyly	115	6	1.9	Unknown	Monogenic
Jervell and Lange-Nielsen syndrome	768	6	1.9	Ultrarare	Monogenic
Vascular Ehlers-Danlos syndrome	286	6	1.9	Ultrarare	Monogenic
Hypermobile Ehlers-Danlos syndrome	285	5	1.6	Rare	Monogenic
Klippel-Feil syndrome	2,345	5	1.6	Ultrarare	Monogenic
CHARGE syndrome	138	4	1.3	Rare	Monogenic
Lown-Ganong-Levine syndrome	844	4	1.3	Ultrarare	Monogenic
Wolf-Hirschhorn syndrome	280	4	1.3	Rare	Chromosomal
Cardiofaciocutaneous syndrome	1,340	3	1	Unknown	Monogenic
Coffin-Lowry syndrome	192	3	1	Ultrarare	Monogenic
Cornelia de Lange syndrome	199	3	1	Ultrarare	Monogenic
Friedreich ataxia	95	3	1	Ultrarare	Monogenic
Hereditary hemorrhagic telangiectasia	774	3	1	Rare	Monogenic
Klippel-Trenaunay syndrome	90,308	3	1	Ultrarare	Monogenic
Sotos syndrome	821	3	1	Rare	Monogenic
Alagille syndrome	52	2	0.6	Ultrarare	Monogenic
Apert syndrome	87	2	0.6	Ultrarare	Monogenic
Crouzon syndrome	207	2	0.6	Ultrarare	Monogenic
Duchenne muscular dystrophy	98,896	2	0.6	Rare	Monogenic
Emery-Dreifuss dystrophy	261	2	0.6	Ultrarare	Monogenic
Frontonasal dysplasia	250	2	0.6	Unknown	Monogenic

Continue to Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Hereditary ATTR amyloidosis	271,861	2	0.6	Unknown	Monogenic
Johanson-Blizzard syndrome	2,315	2	0.6	Ultrarare	Monogenic
Kearns-Sayre syndrome	480	2	0.6	Ultrarare	Monogenic
MASS syndrome	156,532	2	0.6	Unknown	Monogenic
Noonan syndrome with multiple lentigines (LEOPARD)	500	2	0.6	Unknown	Monogenic
Smith-Magenis syndrome	819	2	0.6	Rare	Monogenic
Spondylocostal dysostosis	1,797	2	0.6	Unknown	Monogenic
47,XYY syndrome	8	1	0.3	Rare	Chromosomal
Aarskog-Scott syndrome	915	1	0.3	Rare	Monogenic
Achondroplasia	15	1	0.3	Rare	Monogenic
Acute intermittent porphyria	79,276	1	0.3	Ultrarare	Monogenic
Arterial tortuosity syndrome	3,342	1	0.3	Ultrarare	Monogenic
Autosomal dominant interatrial communication	1,478	1	0.3	Unknown	Monogenic
Autosomal recessive multiple pterygium syndrome	2,990	1	0.3	Ultrarare	Monogenic
Axenfeld-Rieger syndrome	782	1	0.3	Ultrarare	Monogenic
Becker muscular dystrophy	98,895	1	0.3	Ultrarare	Monogenic
Blackfan-Diamond anemia	124	1	0.3	Ultrarare	Monogenic
Carney complex	1,359	1	0.3	Unknown	Monogenic
Catecholaminergic polymorphic ventricular tachycardia	3,286	1	0.3	Rare	Monogenic
Complex chromosomal rearrangement; t(1;3)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(14;22)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(7;12)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(8;18)	263,708	1	0.3	Unknown	Chromosomal
Congenital heart block	60,041	1	0.3	Unknown	Monogenic
Costello syndrome	3,071	1	0.3	Ultrarare	Monogenic
Distal trisomy 18q	1,716	1	0.3	Unknown	Chromosomal
Distal trisomy 6p	1,745	1	0.3	Ultrarare	Chromosomal
Ellis Van Creveld syndrome	289	1	0.3	Unknown	Monogenic
Fabry disease	324	1	0.3	Rare	Monogenic
Familial atrial fibrillation	334	1	0.3	Unknown	Monogenic
Familial dilated cardiomyopathy with conduction defect due to LMNA mutation	300,751	1	0.3	Unknown	Monogenic
Fragile X syndrome	908	1	0.3	Rare	Monogenic
Incontinentia pigmenti	464	1	0.3	Ultrarare	Monogenic
Kabuki syndrome	2,322	1	0.3	Rare	Monogenic
Kallmann syndrome-heart disease syndrome	2,326	1	0.3	Ultrarare	Monogenic
Kyphoscoliotic Ehlers-Danlos syndrome	536,545	1	0.3	Unknown	Monogenic
Larsen syndrome	503	1	0.3	Ultrarare	Monogenic
McCune Albright syndrome	562	1	0.3	Ultrarare	Monogenic
Meckel syndrome	564	1	0.3	Rare	Monogenic
Mosaic trisomy 8	96,061	1	0.3	Unknown	Chromosomal

Continue to Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Mucopolysaccharidosis type 2 (Hunter)	580	1	0.3	Ultrarare	Monogenic
Mucopolysaccharidosis type 6 (Maroteaux-Lamy)	583	1	0.3	Ultrarare	Monogenic
Muenke syndrome	53,271	1	0.3	Rare	Monogenic
Multiminicore myopathy	598	1	0.3	Unknown	Monogenic
Oculopharyngeal muscular dystrophy	270	1	0.3	Ultrarare	Monogenic
Opitz GBBB syndrome	2,745	1	0.3	Ultrarare	Monogenic
Partial duplication of the long arm of chromosome 13; t(13;14)	262,932	1	0.3	Unknown	Chromosomal
Partial duplication of the long arm of chromosome 13; t(13;15)	262,932	1	0.3	Unknown	Chromosomal
Partial duplication of the short arm of chromosome 11	262,785	1	0.3	Unknown	Chromosomal
Pfeiffer syndrome	710	1	0.3	Unknown	Monogenic
Pseudopseudohypoparathyroidism	79,445	1	0.3	Unknown	Monogenic
Robinow syndrome	97,360	1	0.3	Unknown	Monogenic
Rubinstein-Taybi syndrome	783	1	0.3	Ultrarare	Monogenic
Seckel syndrome	808	1	0.3	Ultrarare	Monogenic
Short QT syndrome	51,083	1	0.3	Unknown	Monogenic
Shprintzen-Goldberg syndrome	2,462	1	0.3	Ultrarare	Monogenic
Steinert myotonic dystrophy	273	1	0.3	Rare	Monogenic
Stickler syndrome	828	1	0.3	Rare	Monogenic
TARP syndrome	2,886	1	0.3	Ultrarare	Monogenic
Tel Hashomer camptodactyly syndrome	3,292	1	0.3	Ultrarare	Monogenic
Tetrasomy 12p (Pallister-Killian syndrome)	884	1	0.3	Rare	Chromosomal
Trisomy X	3,375	1	0.3	Rare	Chromosomal
TTR-related cardiac amyloidosis	85,451	1	0.3	Unknown	Monogenic
Van den Ende-Gupta syndrome	2,460	1	0.3	Ultrarare	Monogenic

CHARGE = coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital abnormalities, and ear abnormalities. ATTR = transthyretin-related amyloidosis. MASS = mitral valve, aorta, skeletal, and skin. LMNA = lamin. GBBB = first letter from the last names of the families that was first diagnosed. TARP = talipes equinovarus, atrial septal defect, robin sequence, and persistence of left superior vena cava. TTR = transthyretin.

* According to the diseases prevalences in Orphanet;2 rare (< 1/2,000 - > 1/50,000), ultrarare (≤ 1/50,000 - < 1/1'000,000), and unknown prevalence.

correspond to the definition of rare diseases with a prevalence between < 1/2,000 and > 1/50,000, 38 correspond to ultrarare diseases (≤ 1/50,000 - < 1/1,000,000), and 33 had an unknown prevalence in the general population or at birth *(Table 1)*. Ultrarare diseases and rare genetic cardiovascular diseases with an unknown prevalence comprise a diverse spectrum, including skeletal dysplasias, cardiac neoplasm syndromes, unbalanced reciprocal translocation syndromes, muscular dystrophies, inborn errors of metabolism, and other syndromes, as shown in *Table 1*.

The cardiovascular phenotype presented in each rare genetic cardiovascular disease patient was classified to determine its distribution. The frequency per cardiovascular phenotype groups and subgroups is shown in *Table 2*. The most frequent cardiovascular phenotype was congenital heart diseases (42.4%;

Table 2: Cardiovascular phenotype distribution of the 794 patients with rare genetic cardiovascular in the outpatient clinic.

Cardiovascular phenotype	n (%)
Arrhythmic and conduction disorders	
Primary electrical diseases	117 (90.0)
Preexcitation syndrome	5 (3.9)
Atrioventricular block	3 (2.3)
Other cardiac arrhythmias*	3 (2.3)
Atrial fibrillation and flutter	2 (1.5)
Cardiac tumor disorders	
Cardiac rhabdomyoma	6 (85.7)
Cardiac myxoma	1 (14.3)
Cardiomyopathies	
Left ventricular noncompaction	29 (32.6)
Dilated cardiomyopathy	27 (30.3)
Arrhythmogenic right ventricular cardiomyopathy	16 (18.0)
Hypertrophic cardiomyopathy	15 (16.9)
Restrictive cardiomyopathy	2 (2.2)
Congenital heart diseases	
R-sided and L-sided obstructive lesions‡	161 (47.8)
Septal defects§	67 (19.9)
Conotruncal heart defects¶	45 (13.3)
Valvular heart diseases‖	38 (11.3)
Other congenital heart diseases**	16 (4.7)
Heterotaxy	10 (3.0)
Vascular disorders	
Thoracic aortic aneurysm and dissection	211 (97.7)
Arteriovenous malformation	3 (1.4)
Varicose veins	2 (0.9)
Other cardiovascular disorders	
Primary pulmonary hypertension	6 (40.0)
Cardiac dysautonomia	5 (33.3)
Ischemic heart disease	2 (13.3)
Pericardial effusion	1 (6.7)
Ventricular dysfunction	1 (6.7)

* Sinus node disease, supraventricular tachycardia, and ventricular premature depolarization.
‡ Right-sided obstructive lesions (pulmonary stenosis, stenosis of the pulmonary arteries, and pulmonary atresia with intact ventricular septum) and left-sided obstructive lesions (aortic stenosis, bicuspid aortic valve, coarctation of the aorta, supravalvular aortic stenosis, hypoplastic left heart syndrome, mitral stenosis, and mitral double outlet).
§ Atrial septal defects, ventricular septal defects and atrio ventricular septal defects (with or without minor abnormalities).
¶ Tetralogy of Fallot, pulmonary atresia with ventricular septal defects, double outlet of the left ventricle, pentalogy of Fallot, pulmonary valve agenesis, truncus arteriosus, transposition of great arteries, and interrupted aortic arch.
‖ Mitral prolapse valve, pulmonary, and tricuspid, aortic and mitral insufficiency.
** Total and partial anomalous pulmonary venous return, Epstein's anomaly, vascular ring, patent arterial duct, persistent left superior vena cava, and anomalous pulmonary venous drainage.

n = 337/794), followed by vascular disorders (27.2%; n = 216/794), arrhythmic and conduction disorders (16.4%; n = 130/794), cardiomyopathies (11.2%; n = 89/794), and the less frequent phenotypes were other cardiovascular disorders (1.9%; n = 15/794) and cardiac tumor disorders (0.9%; n = 7/794). There was a statistically significant difference among the cardiovascular phenotype groups in age (χ^5 = 106; p= 0.0001) *(Figure 1)* and sex (χ^5 = 17.9; p = 0.003) *(Figure 2)*. The youngest and oldest cardiovascular phenotype groups were cardiac tumor disorders (4 [1-13] years) and cardiomyopathies (37 [24-50] years), respectively *(Figure 1)*. In addition, cardiac tumor disorders had a higher proportion of females (85.7%) *(Figure 2)*. Sixty-two percent of all patients (n = 489/794) with rare genetic cardiovascular diseases corresponded to three cardiovascular phenotype subgroups. The cardiovascular phenotype subgroup related to thoracic aortic aneurysm and dissection had the largest number of patients, corresponding to 26.6% of all patients (n = 211/794), followed by obstructive congenital heart disease lesions (20.3%; n = 161/794) and primary electrical diseases (14.7%; n = 117/794) *(Table 2)*. These three subgroups of cardiovascular phenotypes correspond principally to Marfan syndrome, Loeys-Dietz syndrome, Noonan syndrome, Williams syndrome, Romano-Ward syndrome, Brugada syndrome, and others.

DISCUSSION

Scarce studies have addressed the number and prevalence of rare cardiovascular diseases because of their low prevalence and difficulty in recognition.[1,7,8] However, knowing the prevalence of rare genetic cardiovascular diseases is of utmost importance since there is an increase in prevention and follow-up algorithms,[11,12] new treatments, and gene therapies that may benefit patients.[13] Rare genetic cardiovascular diseases are frequently encountered in clinical practice, but the overall prevalence of rare genetic cardiovascular conditions in a clinical setting was previously unknown in Mexico and worldwide. In the present research, the overall period prevalence of rare genetic cardiovascular diseases was

2.5%; in other words, almost 1 in 40 patients has a rare genetic cardiovascular disease in a cardiovascular outpatient clinic. Although the prevalence may appear low relative to other cardiovascular diseases, it is not insignificant, especially considering that a significant proportion of rare genetic cardiovascular diseases harm the quality of life, reduce life expectancy, and have economic implications that could cause higher medical care costs.[14-16]

In the present study, the prevalence of monogenic rare genetic cardiovascular diseases was 2.1%. In this regard, a recent study estimated the prevalence of monogenic cardiovascular diseases in patients referred to cardiac catheterization with an unbiased whole-exome sequencing approach. The prevalence of patients with pathogenic and likely-pathogenic variants with a clinical phenotype was 1.7%.[17] Nevertheless, the estimated prevalence includes both common genetic diseases and rare genetic cardiovascular diseases without reporting the overall estimated prevalence for those rare diseases. The higher prevalence of monogenic disorders observed in the present study could be related to a broader spectrum of conditions in the cardiovascular outpatient clinic and the inclusion of pediatric ages.

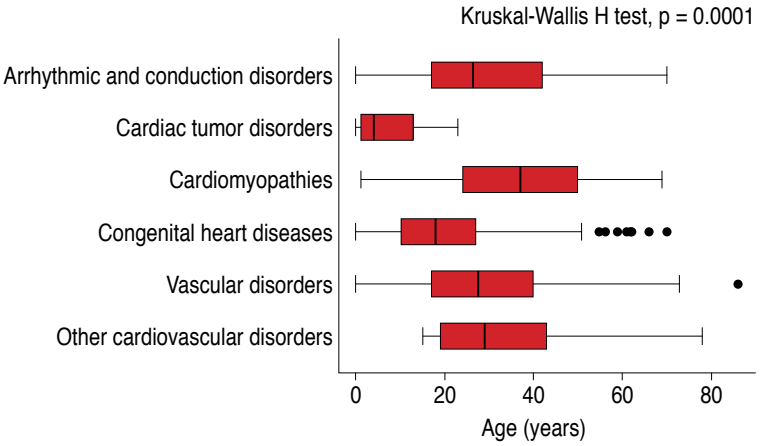

Figure 1: Distribution of age of patients with rare genetic cardiovascular diseases among cardiovascular phenotype groups.

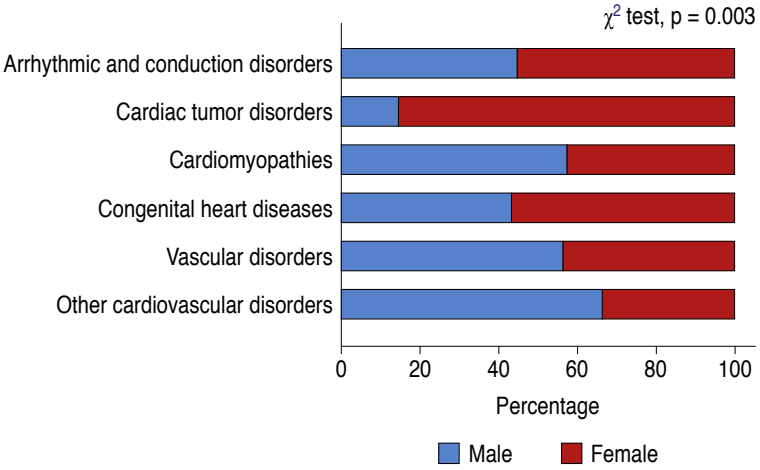

Figure 2: Distribution of sex of patients with rare genetic cardiovascular diseases among cardiovascular phenotype groups.

A curated database initiative (PhenoDis)[5] has annotated the existence of 327 rare cardiac diseases so far,[5] without counting those that affect the vascular system or other rare cardiovascular diseases. The present study detected the broad spectrum of rare genetic cardiovascular diseases that can occur in cardiovascular clinical practice. The spectrum includes rare genetic cardiovascular diseases affecting the heart structure and functioning, blood vessels, cardiac conduction, autonomic systems, and others. A total of 104 different rare genetic cardiovascular disease diagnoses were identified, not limited to a few widely known syndromes. We should be aware that a great proportion of the rare genetic cardiovascular diseases found in the present study have an unknown prevalence or are considered ultrarare diseases with an extremely low prevalence (≤ 1/50,000 - < 1/1'000,000) in the general population.[10] Ultrarare diseases are routinely excluded from public health policies and comprise highly heterogeneous phenotypes with complex molecular mechanisms. Therefore, it is essential to highlight the importance of its recognition to promote comprehensive diagnostic approaches, the formation of doctors specialized in them, drug development, novel therapies, and the creation of health policies consistent with the needs of the patients suffering from these diseases.[18]

The cardiovascular phenotype distribution observed among rare genetic cardiovascular diseases showed some expected results, such as a higher frequency of congenital

heart diseases[19] and a lower frequency related to rare genetic disorders with cardiac tumors.[20] Unexpectedly, cardiomyopathy disorders had a lower frequency compared to other cardiovascular phenotypes. In this regard, it is widely known that hypertrophic cardiomyopathy as a composite is one of the most common genetic diseases, with a prevalence between 1/200 and 1/500 in the general population.[21] Although not all the subtypes of hypertrophic cardiomyopathies are rare,[12] a higher proportion of cases was expected than observed. Several factors related to characteristics inherent to these types of rare genetic cardiovascular diseases, such as variable expressivity, attenuated phenotypes, incomplete or reduced penetrance, atypical phenotypes, absence of genetic family history, or lack of genomic diagnosis that could make its recognition, referral, and diagnosis difficult may be contributing to this.[21-23] A finding to consider was the proportion of cases corresponding to thoracic aortic aneurysms and dissection disorders (Marfan syndrome, Loeys-Dietz syndrome, and others) that represented almost a third of all cases with rare genetic cardiovascular diseases in the outpatient clinic. The early recognition and diagnosis of these diseases are crucial to conducting proper follow-up, genetic counseling, treatment, and surgical procedures to prevent fatal outcomes.

The retrospective design has well-known limitations, and probably some rare genetic cardiovascular diseases could have been masked among highly prevalent diseases or were not suspected yet.[22,23] Nevertheless, the retrospective design offers a good alternative for detecting low-prevalence disorders in the absence of registries, insufficient epidemiological data, and missing specific International Classification of Diseases (ICD) codes for rare diseases.[3] Moreover, no studies have been conducted regarding the prevalence of rare genetic cardiovascular disease in a cardiovascular clinical setting or other hospitals. Although the cardiology hospital studied is a cardiovascular reference in Mexico, the prevalence per disease in the outpatient clinic reported in the present study remained as newly descriptive data to inform about the situation of these diseases and could not be compared with the general population or regional disease prevalences. However, the number and prevalence observed in the present study could increase in the future with the improvement and implementation of more diagnostic technologies and the incorporation of cardiogenetics clinics. Despite the limitations, the present study sets a step forward to close knowledge gaps concerning rare cardiovascular disease prevalence and, hopefully, encourage further research.

CONCLUSIONS

Rare diseases face considerable challenges because of their low prevalence in the general population. Scarce studies have focused on knowing the number and distribution to delineate the magnitude in different clinical contexts. The current study has provided the first estimate of the overall prevalence of rare genetic cardiovascular diseases in a cardiovascular hospital. In this hospital, almost one in forty patients was affected. Moreover, the present study identified the vast spectrum of rare genetic cardiovascular diseases and their most common cardiovascular phenotype in a cardiovascular clinical setting.

Further research in other cardiovascular hospitals and the general population is needed to achieve a global panorama concerning these diseases. Recognition and visibility of rare diseases are the first steps toward better clinical care. Also, it is imperative to create comprehensive clinical registries for rare genetic and nongenetic cardiovascular diseases. This study reminds us that rare genetic cardiovascular diseases are rare, complex, and not easy to recognize but not invisible.

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Clinical trial registration and approval number: the study was not a clinical trial and did not involve interventions of any kind in patients. The Institutional Research Committee evaluated and communicated an exemption, and no sanction by committees was required (INCAR-DG-DI-CI-096-2022).

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Takotsubo syndrome in a cruise ship port, a single center experience

Síndrome de Takotsubo en un puerto de buques crucero, experiencia de un solo centro

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Keywords:
Takotsubo syndrome, cruise ships, heart failure, cardiogenic shock, vacations.

Palabras clave:
síndrome de Takotsubo, cruceros, insuficiencia cardiaca, choque cardiogénico, vacaciones.

ABSTRACT

Introduction: Takotsubo syndrome is an infrequent problem characterized by transitory apical dilatation and ballooning of the left ventricle, frequently resulting from mental or physical stress; it mimics other acute cardiac problems. There are few publications about these conditions in vacation centers, especially on cruise ships. **Results:** the paper describes 15 patients from a vacation center with high cruise ship volume, from 2014 through 2023, nine of them on Killip-Kimbal class 3-4; the average ejection fraction of all patients was 36%. All the patients had negative coronary angiography or non-significant stenosis, and all of them had complete recovery before leaving the hospital, on Killip-Kimball class 1 and 58% average left ventricle ejection fraction. **Discussion and conclusion:** the present TS single-center experience at a top vacation cruise line center offers significant insight into travelers' triggers, demographic characteristics, and illness management. Post-menopause, women are especially vulnerable to the syndrome. TS usually shows ST-segment but is distinguished from acute coronary syndromes by the early return of ventricular function, conditions observed in our patients. Echocardiography, coronary angiography, and electrocardiography are vital for distinguishing myocardial infarction from TS. Supportive therapy and identifying and correcting triggering variables are part of the management; this care may include intravenous and device-based ventricular support.

RESUMEN

Introducción: *el síndrome de Takotsubo es un problema poco frecuente que se caracteriza por la dilatación apical transitoria y el abombamiento del ventrículo izquierdo, que suele ser consecuencia del estrés físico o mental; imita otros problemas cardiacos agudos. Existen pocas publicaciones sobre estas afecciones en centros vacacionales, especialmente en cruceros.* ***Resultados:*** *el artículo describe 15 pacientes de un centro vacacional con un gran volumen de cruceros, desde 2014 hasta 2023, nueve de ellos con una clase Killip-Kimbal 3-4; la fracción de eyección promedio de todos los pacientes fue del 36%. Todos los pacientes tenían una angiografía coronaria negativa o estenosis no significativa y todos se recuperaron por completo antes de salir del hospital, con una clase Killip-Kimball 1 y una fracción de eyección promedio del ventrículo izquierdo del 58%.* ***Discusión y conclusión:*** *la experiencia actual de un solo centro de TS en un centro de una importante línea de cruceros vacacionales ofrece una perspectiva significativa sobre los desencadenantes de los viajeros, las características demográficas y el manejo de la enfermedad. Después de la menopausia, las mujeres son especialmente vulnerables al síndrome. El síndrome de Takotsubo suele mostrar segmento ST, pero se distingue de los síndromes coronarios agudos por el retorno temprano de la función ventricular, condiciones observadas en nuestros pacientes. La ecocardiografía, la angiografía coronaria y la electrocardiografía son vitales para distinguir el infarto de miocardio del síndrome de Takotsubo. La terapia de apoyo y la identificación y corrección de las variables desencadenantes son parte del tratamiento; esta atención puede incluir asistencia ventricular intravenosa y basada en dispositivos.*

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INTRODUCTION

Takotsubo syndrome (TS) consists of sudden functional deterioration and deformity of the left ventricle, typically with apical segment dyskinesis and ballooning, with the preservation of the basal segment's mobility. It frequently results after a mental or physical stressing condition, especially in women, under complex pathophysiological aspects such as paradoxical adrenergic-load triggered myocardial microvascular dysfunction, stress-triggered altered neuronal activity, metabolic derangements, and epigenetics.[1,2]

This kind of cardiomyopathy mimics other acute cardiac problems, especially myocardial infarction, and myocarditis, with all the possible heart failure spectrum up to cardiogenic shock, cardiac arrest, and death, being sometimes unrecognized and making particular diagnostic challenges, with its final clinical diagnostic feature, the complete or almost complete quick left ventricle function and shape recovery.

The mental stress triggering TS might result from a sad personal catastrophe, extreme joy, physical trauma, or general disease; nonetheless, sometimes, there is a lack of stress. The present paper discloses our experience of TS in patients who attended a hospital located in a port that receives cruise-ship travelers. Up to these cases, there is only one published case of a woman suffering from TS on a cruise ship.[3]

TS, which primarily affects postmenopausal women, represents 1-2% of all suspected cases of acute coronary syndrome. While most patients with TS recover fully, complications can occasionally result in significant morbidity and mortality.[4]

MATERIAL AND METHODS

Our private hospital attends to the local population, destination tourists, and cruise ship travelers. The current paper is a case report resulting from the retrospective review of our patients considered with a diagnosis of TS, based on the occurrence of sudden myocardial infarction symptoms and heart failure, with echocardiography-tailored transitory segmental akinesia with angiography-confirmed lack of significant coronary stenosis and documented clinical and echocardiography recovery before discharge. Our experience includes a small case number from a low-volume heart service, with results expressed as case presentations with an average of the numerical variables.

RESULTS

We gathered data from 12 women and two men –one of them is a ship crew member– with TS between 2014 and 2023. Their average age was 61.8 years, with an average hospital stay of 4.9 days and an average body mass index of 29.5. Ten patients were from cruise ships, three were tourists, and one was a local patient. Nine patients were on Killip-Kimbal class 3-4 and five class 1-2, with an average class of 2.7.

The average ejection fraction at admission was 36%; seven patients started with chest pain, 12 had dyspnea, three had delirium, three patients needed mechanical invasive ventilation, while four on cardiogenic shock received intravenous amines, none of them had mechanical cardiac support. Only three patients had initial ST elevation, two had left bundle branch block, 12 had troponin I, and 12 had proBNP elevation. We found three patients with mental stress before the event, and eight had physical trauma: three during snorkeling, one on scuba diving, one during beach gaming, one after intense diarrhea, one after severe bladder retention, and one during abdominal sepsis. Four patients had a history of depression, one of them after melanoma.

All the patients had coronary angiography, eleven catheter-based and three by computed tomography; 12 had coronaries without significant and two with borderline stenosis; nine catheterized patients had TIMI-3 and two TIMI-2 flow. All the patients left the hospital (four by air-ambulance transfer, ten to home) on Killip-Kimbal class 1; the discharge ejection-fraction average was 58.4%.

Table 1 shows the patients' origin and demographics. *Table 2* shows the basal patient's characteristics, *and Table 3* displays the diagnostic angiography and outcomes; *Figure 1* displays the Killip-Kimbal class progress *and Figure 2* the ejection fraction; *Figure 3* shows an example of the echocardiographic in one of our patients, showing the characteristic apical

Table 1: Patient demographics and medical history.

Patient	Sex	Age (years)	Origin	Weight (kg)	Height (cm)	BMI	DM	HTN	Depression	Smoking	Previous heart disease
1	F	59	Cruise	80	172	27	No	Yes	Yes	Yes	No
2	F	83	Local	69	148	31	Yes	Yes	No	No	Yes
3	F	73	Cruise	91	152	39	No	Yes	No	No	No
4	M	34	Cruise	87	168	31	No	No	No	No	No
5	F	68	Cruise	113	170	39	No	Yes	Yes	No	Yes
6	M	79	Cruise	81	171	28	No	No	No	No	Yes
7	M	58	Germany	68	168	24	Yes	Yes	No	No	No
8	F	51	Canada	92	175	30	No	No	No	No	No
9	F	68	Cruise	85	170	29	Yes	No	Yes	No	Yes
10	M	24	Cruise	83	178	26	No	No	No	No	No
11	F	60	Cruise	NA	NA	NA	No	No	No	No	No
12	F	75	Argentina	70	155	29	No	Yes	No	No	No
13	M	59	Cruise	93	175	30	No	Yes	No	No	Yes
14	F	75	Cruise	50	152	21	No	No	Yes	No	No

BMI = body mass index. DM = diabetes mellitus. F = female. HTN = hypertension. M = male.

Table 2: Clinical presentation and laboratory.

	Angina	Dyspnea	Ventilation	Emotional trauma	Trauma etiology	Troponin elevated	proBNP elevated	ST elevation	Initial KK	Final KK	Admission ejection fraction	Discharge ejection fraction
1	Yes	Yes	Yes	Yes	Excursion	Yes	Yes	No	4	1	25	72
2	No	Yes	Yes	No	No	No	Yes	No	3	1	30	50
3	No	Yes	No	No	Snorkel	Yes	Yes	No	1	1	73	73
4	Yes	Yes	Yes	No	No	Yes	Yes	No	4	1	15	52
5	Yes	Yes	No	Yes	No	Yes	Yes	No	3	1	50	50
6	No	No	No	No	No	Yes	No	No	1	1	64	67
7	Yes	Yes	Yes	No	Snorkel	Yes	No	No	1	1	38	70
8	Yes	Yes	No	No	Scuba diving	Yes	Yes	Yes	3	1	28	50
9	Yes	Yes	No	No	No	Yes	Yes	No*	3	1	25	44
10	Yes	Yes	No	No	Sepsis	Yes	Yes	Yes	2	1	20	40
11	No	Yes	No	No	Beach playing	Yes	Yes	Yes	3	1	25	60
12	No	Yes	No	No	No	Yes	Yes	Yes	4	1	25	55
13	No	No	No	No	Urination pain	Yes	Yes	No*	2	1	55	66
14	No	Yes	Yes	Yes	Snorkel	No	Yes	No	4	1	32	68

* Left bundle branch block. KK = Killip-Kimbal class.

ballooning on dotted lines and the typical basal contractility shown by the arrows.

DISCUSSION

The present TS single-center experience at a top vacation cruise line center offers significant insight into travelers' triggers, demographic characteristics, and illness management. Any major changes in circumstances that are stressful for the person might also serve as triggers for the beginning of TS; significant atmosphere changes caused by lengthy overseas travels, together with physical and psychological history, may significantly contribute to TS.[5]

Post-menopause, women are especially vulnerable to the syndrome due to hormonal fluctuations that intensify stress responses and endothelial impairment, possibly after the expected estrogen levels decline with consequent morbid changes in autonomic regulation and endothelial function, impairing the cardiovascular stress response.[6]

Myocardial stunning, microvascular dysfunction, and catecholamine surges are all implicated in the pathophysiology of TS,

Table 3: Procedures and outcome.

Patient	Coronary angiogram	Coronary stenosis	TIMI flow	Days of stay	Discharge
1	Invasive	Non-significant	2	2	Air ambulance
2	Invasive	Non-significant	3	13	Home
3	Computed tomography	Non-significant		4	Home
4	Invasive	Non-significant	3	13	Home
5	Invasive	Non-significant	3	1	Air ambulance
6	Invasive	Borderline	3	4	Home
7	Computed tomography	Non-significant		3	Home
8	Computed tomography	Non-significant		4	Home
9	Invasive	Non-significant	3	0	Home
10	Invasive	Non-significant	3	3	Home
11	Invasive	Non-significant	2	4	Air ambulance
12	Invasive	Non-significant	3	9	Home
13	Invasive	Borderline	3	3	Home
14	Invasive	Non-significant	3	6	Home

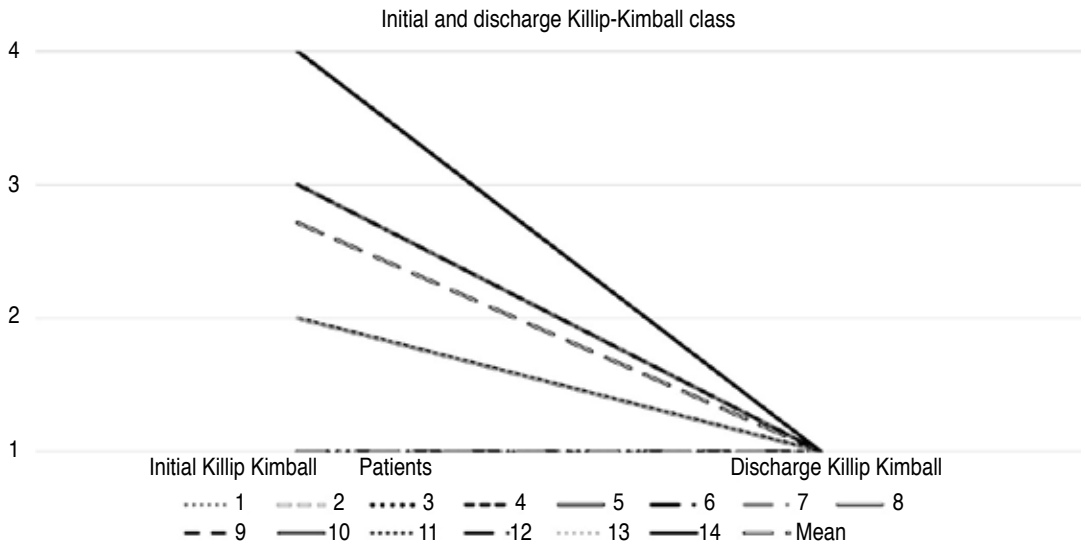

Figure 1:

The graphic displays every patient's Killip-Kimball class on admission and discharge.

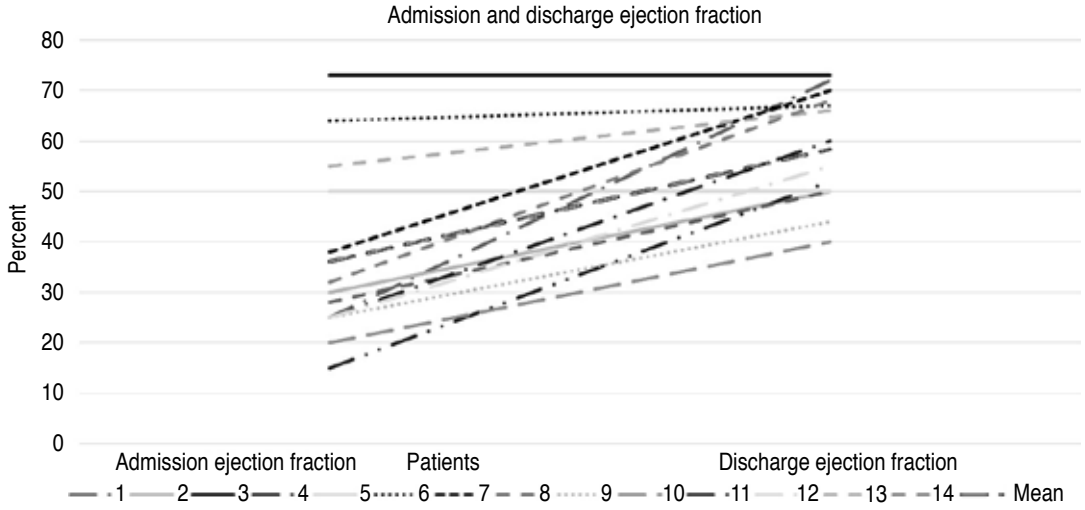

Figure 2: The graphic displays every patient's ejection fraction on admission and discharge.

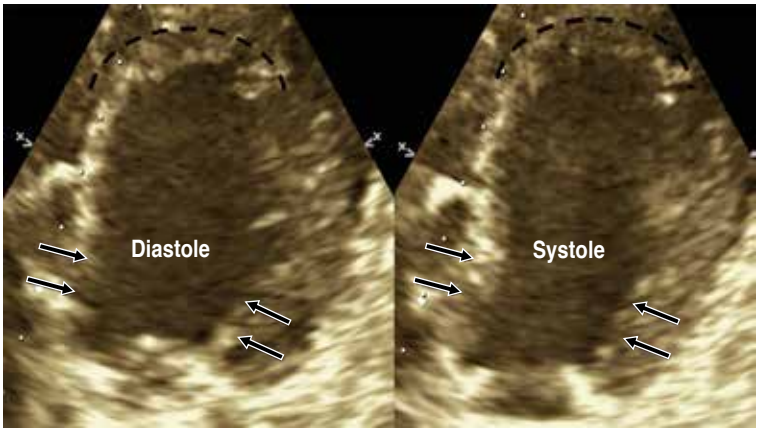

Figure 3: Typical left ventricle ballooning on systole and diastole, the arrows show the basal segments contractility, and the dotted lines show the apical ballooning.

possibly for dysregulation of the hypothalamic-pituitary-adrenal axis, which leads to increased sympathetic response and, in turn, left ventricular dysfunction.[7]

TS usually shows ST-segment elevation, dyspnea, and chest discomfort that resembles myocardial infarction, as well as presenting with any degree of heart failure, including cardiogenic shock, but distinguished from acute coronary syndromes by the early return of ventricular function, conditions observed in our patients.

Echocardiography, coronary angiography, and electrocardiography are vital for distinguishing myocardial infarction from TS. Supportive therapy and identifying and correcting triggering variables are part of the management; this care may include intravenous and device-based ventricular support.

Even though the majority of patients restore their ventricular function on their own in a matter of days to weeks, persistent psychological stress could increase the chance of recurrence worth preventive strategies for TS recurrence, including neurohormonal therapies that target the sympathetic nervous system. In our patient list, we do not describe another three patients who came for cardiological assessment due to TS preexistence.

CONCLUSIONS

In conclusion, this single-center experience underscores the need for heightened vigilance in diagnosing and managing TS, particularly in high-stress settings like sea travel, warranting further research to explore the long-term outcomes of TS and the efficacy of stress management interventions in preventing recurrence.

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Systemic lupus erythematosus, syncope, high degree atrio-ventricular block and Hisian pacemaker

Lupus eritematoso sistémico, síncope, bloqueo auriculoventricular de alto grado y marcapasos de estimulación hisiana

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Keywords: systemic lupus erythematosus, atrio-ventricular block, Hisian stimulation, right bundle branch block, syncope.

Palabras clave: *lupus eritematoso sistémico, bloqueo auriculoventricular, estimulación hisiana, bloqueo de rama derecha, síncope.*

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) is frequently associated with ischemic heart disease, whereas other connective tissue diseases induce electrical conduction disturbances. **Presentation of case:** a 54-year-old female had SLE diagnosed in 2008 and systemic arterial hypertension. The patient presented with syncope and dizziness. The electrocardiogram (ECG) showed bradycardia, Right Bundle Branch Block (RBBB), and 2º Mobitz II Atrio-Ventricular Block (AVB) while having hypokalemia. The electrolyte unbalance was corrected. A Holter and new ECG showed RBBB, anterior fascicle block, and 2º Mobitz II AVB again. A stress echocardiogram was negative for ischemia and showed an antegrade Wenckebach phenomenon at 110 beats per minute (545 ms). That sort of AVB suggested high requirements of ventricular stimulation. Thus, a double chamber pacemaker (DDD) with Hisian stimulation was implanted without acute complications. The patient has been followed up for four years and showed important shifts in stimulation thresholds, impedance, and in the selective (or not) His capture, sometimes determined by atrio-ventricular delay. This prompted recurrent programming changes. **Conclusion:** His's stimulation in this subject has prevented new syncope episodes, but the behavior of stimulation thresholds and impedance in the presence of SLE seems unstable and requires frequent surveillance. Ventricular stimulation through the left bundle branch would now be preferred, but due to the scarcity of conduction disorders in SLE patients, more information is required.

RESUMEN

Introducción: *el lupus eritematoso sistémico (LES) suele asociarse con enfermedad isquémica cardiaca, a diferencia de otras colagenopatías que provocan trastornos de la conducción eléctrica.* ***Presentación del caso:*** *una mujer de 54 años con LES diagnosticado en 2008 e hipertensión arterial sistémica presenta síncope y mareos. El electrocardiograma (ECG) muestra bradicardia, bloqueo de la rama derecha (BRD) y bloqueo auriculoventricular (BAV) de 2o Mobitz II con hipocalemia. Se corrigió el trastorno electrolítico y se hizo Holter que muestra BAV 2o MII. Bloqueo de rama derecha del haz de His (BRD) y bloqueo de fascículo anterior del haz de His (BFAS). El ecocardiograma de estrés es negativo para isquemia, pero muestra un punto de Wenckebach anterógrado a 110 latidos por minuto (545 ms). El tipo de bloqueo presupone requerimientos de estimulación ventricular elevados y se implanta marcapasos de doble cámara (DDD) con estimulación hisiana sin complicaciones. Durante cuatro años de seguimiento ha habido variaciones importantes en los umbrales de estimulación e impedancia, así como en la captura selectiva o no selectiva del His, a veces asociada con el retraso auriculoventricular, por lo que es necesario hacer ajustes recurrentes en la programación.* ***Conclusión:*** *la estimulación hisiana ha prevenido nuevos síncopes en este caso, pero el comportamiento de los umbrales de estimulación e impedancia en presencia de LES es inestable y requiere de vigilancia frecuente. Se comenta la posibilidad de preferir estimulación de rama izquierda, pero dada la rareza de los trastornos de conducción en LES, se requiere de más información.*

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Abbreviations:
AVB = Atrio-Ventricular Block.
bpm = beats per minute.
BUN = Blood Ureic Nitrogen.
DDD = double chamber pacemaker.
ECG = Electrocardiogram.
LVEF = Left Ventricular Ejection Fraction.
PM = Pacemaker.
RBBB = Right Bundle Branch Block.
RNP = Ribonucleoprotein.
RNP = Systemic Lupus Erythematosus.
SLE = Systemic Lupus Eritematosous.

INTRODUCTION

Rheumatologic diseases are associated with cardiovascular disorders that may range from serositis to vasculitis-induced coronary artery disease and ischemia, valvular heart disease (Libman Sacks' endocarditis, for example) and even rhythm disturbances such as sinus node disease or Atrio-Ventricular Block (AVB) due to chronic inflammation and fibrosis. Systemic Lupus Erythematosus (SLE) is often associated with vasculitis and, thus, atherosclerotic ischemic heart disease.[1,2] Approximately 50% of SLE patients will show some cardiovascular disease.[3] The most common seems to be serositis (pericarditis is present in 25% of patients). Autopsy reports have shown myocarditis in up to 40% of SLE patients, but it is clinically evident in only 10% of them. This condition tends to disappear spontaneously, but it can progress to dilated cardiomyopathy, a substrate for tachycardia or bradyarrhythmia. It is noteworthy that 40% of SLE patients might have subclinical ischemic heart disease, but it will be manifested only in 12%. Unless there are advanced stages of myocardial disease derived from ischemia or myocarditis, the chances that SLE induces conduction disturbances are scarce, especially when there is no apparent inflammatory activity. This case shows a symptomatic advanced AV block in an SLE patient, without further evidence of cardiac or pericardiac involvement, that needed pacing with high requirements of ventricular stimulation.

CASE PRESENTATION

With previous consent from the patient, we present the case of a 54-year-old female who was evaluated by rheumatology in 2008 and diagnosed with SLE based on clinical criteria and antinuclear antibodies. The patient received prednisone and leflunomide as immunomodulators. She complained of frequent fatigue and occasional back and joint pain. Arterial hypertension was diagnosed in 2010 and received treatment with amlodipine and chlortalidone by internal medicine.

The patient was referred to a cardiology consultation in December 2019 because of syncope while washing her car and frequent dizzy spells. In that first evaluation, her electrocardiogram (ECG) showed a Right Bundle Branch Block (RBBB) with superior axis deviation, suggesting a concomitant anterior fascicle block, 2º Mobitz II AVB, and bradycardia. At that moment, she had a serum potassium level of 2.7 mEq/L with indicators of renal impairment (creatinine 1.3 mg/dL, urea 80 mg/dL, and Blood Ureic Nitrogen [BUN] 37.4 mg/dL) but normal general urine test.

The patient was started on volume and potassium repositioning. An echocardiogram showed a structurally normal heart with 57% Left Ventricular Ejection Fraction (LVEF) without segmental mobility abnormalities. When she reached a serum potassium level of 3.8 mEq/L, the ECG still showed the bifascicular block (RBBB and fascicle block), but the AVB was apparently corrected.

After discharge, a 24-hour Holter monitoring showed again 2º Mobitz II AVB during sleep periods, without significant pauses. Then, a negative-for-ischemia dobutamine-stress echocardiogram induced antegrade Wenckebach phenomenon at 110 beats per minute (bpm) (545 ms cycle length).

With this information and the evidence that the AV-block was symptomatic, a double chamber (DDD) pacemaker (PM) was proposed. Since the possibilities of high ventricular stimulation requirements were elevated, a bifascicular block was present, and the patient was 54 years old, a physiological stimulation approach was preferred, and thus, a His bundle stimulation device was implanted (Medtronic Ensura ENS01DR, Medtronic inc. Minneapolis, USA).

The procedure was performed without complications. The His-bundle stimulation

threshold was 1 V with a pulse width of 0.6 in unipolar stimulation. The impedance was 232 Ohms, and the R wave amplitude was 3.3 mV. The baseline QRS measured 160 ms, and after His stimulation, it shortened to 100 ms. *Figure 1* shows the baseline ECG as well as the ECG and chest X-ray control prior to discharge the day after PM implantation. The stimulated AV delay was set to 180 ms and the sensed one to 160 ms. Since then, the patient has not presented any new syncope events.

Four months after the implant, she reported dyspnea while housekeeping but not on exertion (brisk walking her dog). At that moment, the His stimulation threshold was 1.25 V and 0.4 ms with monopolar stimulation. The impedance had increased to 475 Ohms with no evidence of rupture or displacement of the electrode. With lower output voltage, there was non-His selective capture up to 0.5 V.

At the ninth follow-up month, she complained of a «twitching sensation» near the generator in the pectoral muscle. The ECG showed a loss of selective capture and right bundle branch block, apparently related to the monopolar stimulation. The PM was set to bipolar stimulation, and the sensation disappeared. The new selective capture threshold was 1.5 V with 0.5 ms pulse width.

During 2021, the patient did not receive presential follow-up visits because of the COVID pandemic, although she reported herself sometimes fatigued, with tolerable short bouts of joint pain and asymptomatic periods by e-mail communications.

In December 2021, during an office visit, the His stimulation threshold was again elevated (3.75 mV), monopolar stimulation was painful, and induced pectoral muscle contractions. His' output was again set to bipolar. At that point, the patient still showed RBBB morphology in stimulated beats. *Figure 2* shows the threshold, impedance, and sensitivity values during follow up.

In July 2022, she underwent a surgical left shoulder ligament repair, and in September, she had a *Clostridium difficile* gastric infection without any evidence of endocarditis.

Finally, in November 2023, the patient reported herself to be asymptomatic, active,

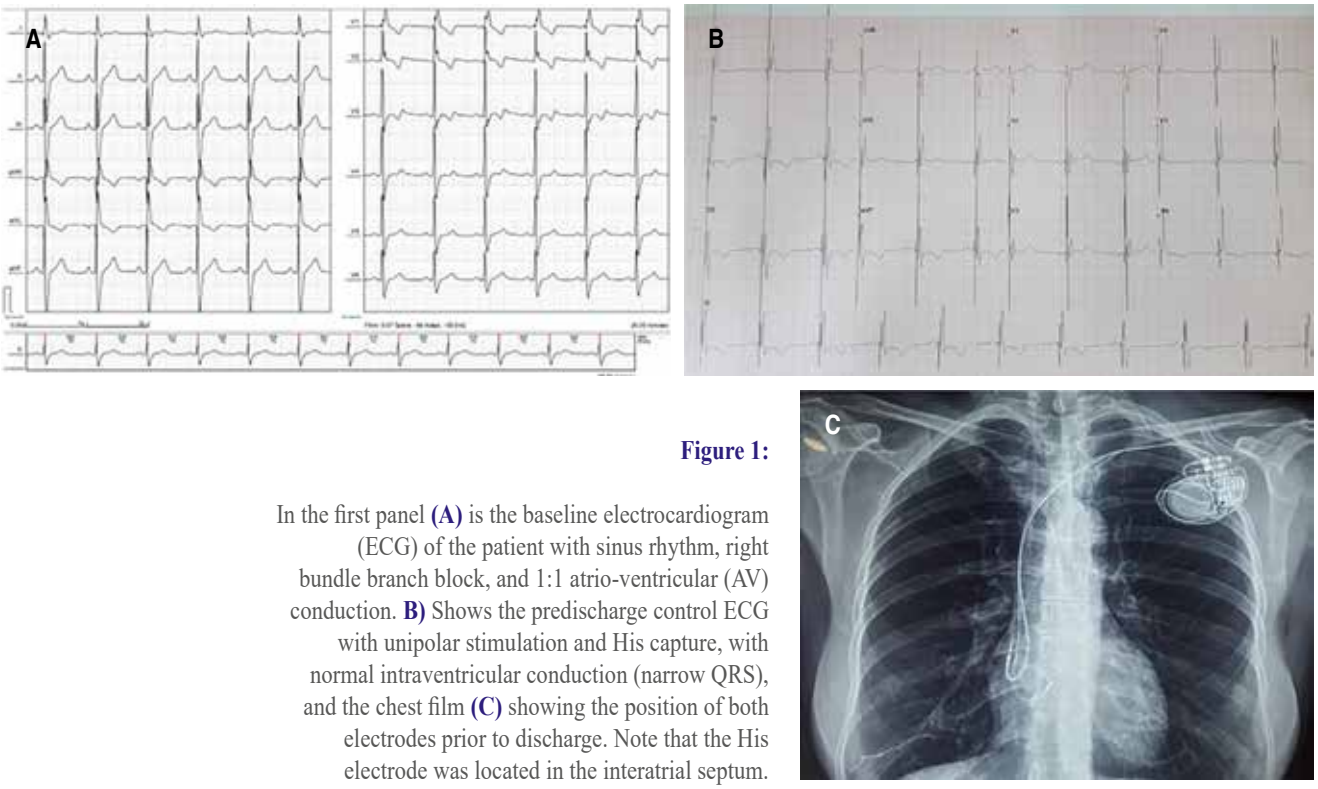

Figure 1:

In the first panel **(A)** is the baseline electrocardiogram (ECG) of the patient with sinus rhythm, right bundle branch block, and 1:1 atrio-ventricular (AV) conduction. **B)** Shows the predischarge control ECG with unipolar stimulation and His capture, with normal intraventricular conduction (narrow QRS), and the chest film **(C)** showing the position of both electrodes prior to discharge. Note that the His electrode was located in the interatrial septum.

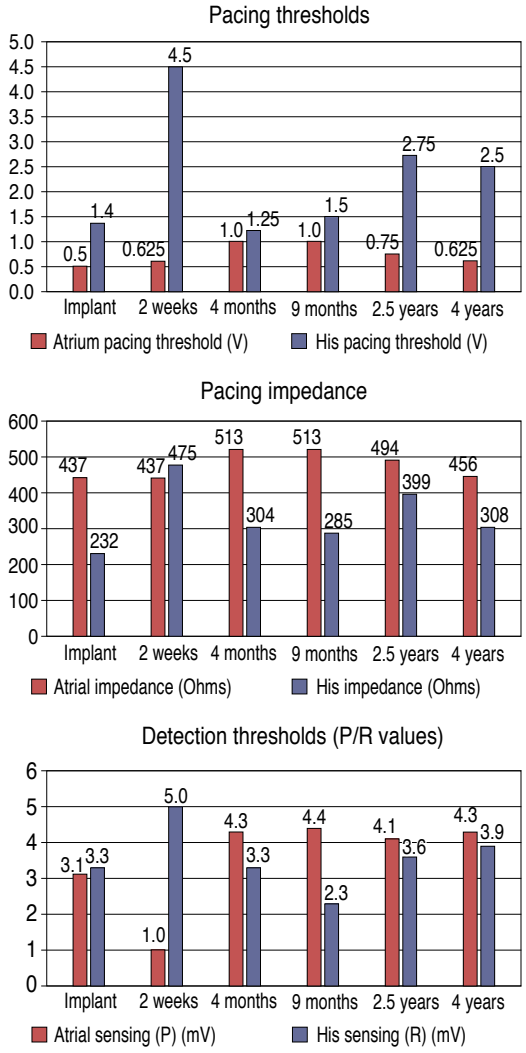

Figure 2: The different graphs show the chronic behavior of several electric parameters of the pacemaker: pacing threshold (volts), pacing impedance (Ohms), and detection thresholds (millivolts) during a four-year follow up.

NYHA functional class I, without any further syncope episodes since the pacemaker's implant. The ECG showed ventricular stimulation with left bundle branch morphology and a 2.25 V RV threshold with 0.5 ms pulse width. During the tests, it was noticed that when the AV-delay is shortened by 20 ms, there is selective capture by His bundle or, at least, a shortening of the QRS duration, so the PM was programmed according to these new findings *(Figure 3)*. During follow-up, no new electrolyte disturbances were identified. Serum creatinine levels returned to normal values after the first interventions and have remained so far within normal limits. She had a complement (C3 and C4) determination in 2020 that was within normal ranges. The only parameter that has consistently remained within 13 and 12.5 mg/dL is the hemoglobin determination.

DISCUSSION

To our knowledge, this is the first reported case of SLE with a high degree of AVB and His stimulation. At the present moment, the patient would be a more suitable candidate for selective left bundle branch stimulation, but at the time of implant, it was not available. We ought to offer her a physiological stimulation mode that would not compromise ventricular function since high stimulation requirements were anticipated.

Rheumatologic disease poses a complex context: inflammation might affect many organs and structures with variable intensity and at different moments. Many times, inflammation may go unnoticed for long periods. The immunologic modulation treatments may also exert some effects on the clinical presentation or lack of presentation of symptoms.

Several mechanisms for cardiovascular involvement have been proposed, including type 1 interferon pathway (IFN-1, IFNα, and IFNβ), autoantibodies, CD16 monocytes, Th17 cells, and low-density granulocyte-mediated damage.[4] Usual cardiovascular risk factors (diabetes, hypertension, dyslipidemia, obesity) also promote atherosclerotic plaque formation and endothelial dysfunction, which are responsible for the main cardiovascular manifestations of SLE.[1] Several risk scores have been developed (Urowitz, Petri, QRISK3), but they focus on ischemic heart disease detection since SLE itself and its treatment promote atherosclerosis and pro-coagulant states instead of rhythm disturbances. It is also known that SLE increases cardiovascular risk by two to 10-fold compared to the general population.[1,3,5]

The incidence of atrio-ventricular conduction disturbances is low in SLE patients.

A report by Natsheh et al. from 2019 mentioned their case and 31 more.[6] The mechanisms are not well understood but seem to be associated with a positive ribonucleoprotein (RNP) antibody.[7] Other actors might be the anti-SSA and anti-SSB antibodies, which might also explain congenital AV-block.[8-10] It is clear that complex immune interactions must play a role, and etiologies other than atherosclerosis or myocarditis must be explored, including the immune-mediated effects on autonomic regulation.

In the present case, since the PM implant, the patient has shown a satisfactory functional class and has had no syncope recurrence. Nonetheless, the stimulation thresholds have changed, and the RBBB has become apparent again unless a fine-tuning of the stimulation parameters (AV-delay, stimulation polarity, His output) achieves a selective capture pattern.

Similar behavior was documented in a case presented by Kishihara J et al.[10] in an SLE patient with conventional ventricular stimulation. They suggest an anatomic-functional interaction: a shorter right ventricular filling interval might lead to different RV dimensions. This will induce discrete modifications in the contact between the lead and the myocardium and a probable accumulation of fluid around the electrode tip that can modify the impedance. The present case showed significant differences in impedance in the first year of stimulation simultaneously with automatic pacing output adjustments. In another case report, a patient without autoimmune disease, a 2:1 AV-block, and His stimulation had a transient increase in the pacing threshold.[11] During follow-up, he presented atrial fibrillation and was started on amiodarone, which was deemed responsible for the increased pacing threshold. The patient, in this case, did not receive any threshold-modifying drugs (mainly antiarrhythmic),[12] so the changes observed are possibly attributable to SLE itself, either from an inflammatory nature or secondary to the fluid accumulation around the tip of the electrode as described by Kishihara. There is scarce information about a direct pro-arrhythmic mechanism linked to SLE, but work by Pisoni C. et al.[13] suggests that positive anti-Ro/SSA antibodies and high IL-1β can modulate cardiac ion channel function and induce prolonged corrected (QTc) interval.

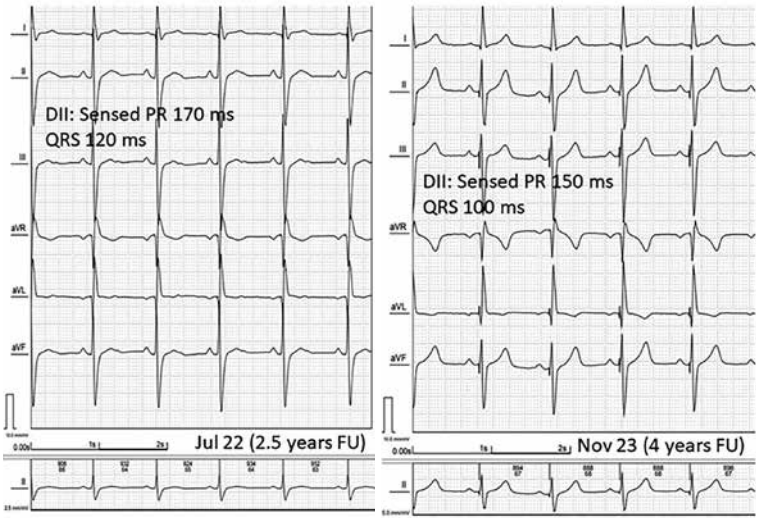

Figure 3: Electrocardiogram (ECG) from one of the latest follow-up visits where the adjustments in the atrio-ventricular (AV) delay show changes in QRS duration when near-selective pacing capture is reached.

CONCLUSIONS

We present here a patient with SLE and His bundle pacing with important variations in stimulation thresholds that forced frequent output, AV-delay duration, and polarity programming changes during a four-year follow-up. Because of the little experience with the matter, many conjectures arise, but it seems apparent that the impedance and threshold behavior when pacing His bundle are not different from pacing other right ventricular areas in SLE. Close monitoring of these rare patients is warranted to evaluate the pacemaker's performance and safety as well as the expected device's longevity. Special attention must be given to the optimal AV delay programming for selective His stimulation. This case could add to the current tendency to prefer left bundle branch pacing over His' stimulation in patients with similar conditions or other rheumatologic diseases.

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Fe de erratas

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Altered macrophage function and its impact on fatty liver disease

Disfunción de macrófagos y su impacto en la enfermedad del hígado graso

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ABSTRACT

Nonalcoholic Fatty Liver Disease (NAFLD) is a prevalent global disease, affecting at least a third of the world population and having an estimated prevalence that could be greater than 50% in Mexico. NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, generally associated with metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Kupffer cells are specialized hepatic macrophages essential for liver health and immune regulation but become pathogenic in NAFLD and contribute to liver inflammation and fibrosis through cytokine secretion and signaling pathways such as the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and the Peroxisomes Proliferators Activated Receptors Gamma (PPAR-γ). Chronic macrophage activation in NAFLD is influenced by factors such as saturated fatty acids, leading to polarization of the M1 phenotype and promoting inflammation. Currently, there are no FDA-approved drugs specifically targeting macrophage dysfunction. However, several therapeutic approaches are under investigation that may indirectly influence macrophage activation and further polarization to suppress inflammation and prevent disease progression. Promising strategies include modifying this macrophage polarization and targeting specific signaling pathways. Targeting chemokines such as the chemokine ligand 16 (CXCL16) also can potentially reduce liver inflammation and steatohepatitis. Targeting hepatic macrophage activation offers a promising approach for mitigating NAFLD progression.

RESUMEN

La enfermedad del hígado graso no alcohólico (NAFLD, por sus siglas en inglés) es una enfermedad global prevalente, que afecta al menos a un tercio de la población mundial y tiene una prevalencia estimada que podría ser mayor al 50% en México. La NAFLD varía desde la esteatosis simple hasta la esteatohepatitis no alcohólica (NASH, por sus siglas en inglés), fibrosis y cirrosis, generalmente asociadas con trastornos metabólicos como obesidad, diabetes tipo 2 y enfermedad cardiovascular. Los macrófagos juegan un papel crítico en la NAFLD, contribuyendo a la inflamación, fibrosis y progresión de la enfermedad. Las células de Kupffer, macrófagos hepáticos especializados, son esenciales para la salud del hígado y la regulación inmunológica, pero se vuelven disfuncionales en la NAFLD. Exhiben un comportamiento dinámico, responden a diversos estímulos y contribuyen a la inflamación y fibrosis del hígado a través de la secreción de citocinas y vías de señalización como el factor nuclear potenciador de la cadena ligera kappa de las células B activadas (NF-κB) y el receptor gamma activado por el proliferador de peroxisomas (PPAR-γ). La activación crónica de los macrófagos en la NAFLD está influenciada por factores como los ácidos grasos saturados, lo que lleva a la polarización del fenotipo M1 y promueve la inflamación. Actualmente, no existen medicamentos aprobados por la FDA que se dirijan específicamente a la disfunción de los macrófagos. Sin embargo, se están investigando varios enfoques terapéuticos que pueden influir indirectamente en la activación de los macrófagos y una mayor polarización para suprimir la inflamación y prevenir la progresión de la enfermedad. Las estrategias prometedoras incluyen la modificación de esta polarización de los macrófagos y la focalización en vías de señalización específicas. La focalización de quimiocinas como la quimiocina ligando 16 (CXCL16) también puede reducir potencialmente la inflamación hepática y la esteatohepatitis. La focalización de la activación de los macrófagos hepáticos ofrece un enfoque prometedor para mitigar la progresión de la NAFLD.

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Abbreviations:

Ω-3 PUFA = Ω-3 Polyunsaturated Fatty Acids.
CVC = Cenicriviroc.
CXCL16 = Chemokines such as the Chemokine Ligand 16.
DAMPs = Danger-Associated Molecular Patterns.
FFAs = Free Fatty Acids.
GLP-1 RAs = Glucagon-Like Peptide-1 Receptor Agonists.
HSCs = Hematopoietic Stem Cells.
IFN-γ = Interferon-γ.
IL = Interleukin.
iNOS = Inducible Nitric Oxide Synthase.
LCM = Liver Capsular Macrophages.
LPS = Lipopolysaccharides.
M1 = Classically Activated Macrophages.
M2 = Alternatively Activated Macrophages.
MCP-1 = Monocyte Chemoattractant Protein-1.
M-CSF = Macrophage Colony-Stimulating Factor.
MoMFs = Monocyte-Derived Macrophages.
NAFLD = Nonalcoholic Fatty Liver Disease.
NASH = Nonalcoholic Steatohepatitis.
NF-Kb = Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells.
OCA = Obeticholic Acid.
oxLDL = Oxidized Low-Density Lipoproteins.
PAMPs = Pathogen-Associated Molecular Patterns.
PPAR-δ = Peroxisome Proliferator-Activated Receptor Delta.
PPAR-γ = Peroxisomes Proliferators Activated Receptors Gamma.
PRRs = Pattern Recognition Receptors.
ROS = Reactive Oxygen Species.
TGF-β = Transforming Growth Factor-beta.
TLRs = Toll-Like Receptors.
TNF-α = Tumor Necrosis Factor-α.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a prevalent condition globally, affecting almost a third of the population worldwide. It is recognized as the most common liver disease in Western countries. Mexico is a country prone to this condition due to its population having several risk factors; the estimated prevalence of the disease could surpass 50%.[1] NAFLD encompasses a spectrum of liver conditions, from simple steatosis to Non-Alcoholic Steatohepatitis (NASH), fibrosis, and cirrhosis.[2] The disease is associated with metabolic dysregulation and can progress to severe complications such as hepatic cirrhosis and hepatocellular carcinoma.[3]

The prevalence of NAFLD is rising globally, with estimates suggesting that around 25 to 30% of the world population is affected by the disease.[4] Lifestyle factors such as physical inactivity and poor dietary habits contribute to the increasing prevalence of NAFLD.[5] Furthermore, the disease is closely associated with other metabolic disorders like obesity, type 2 diabetes, and cardiovascular diseases,[6] which are, in turn, risk factors for NAFLD, including obesity, insulin resistance, dyslipidemia, and hypertension.[7]

In NAFLD, macrophages are involved in inflammation, fibrosis, and disease progression to more severe stages.[8] The disease is characterized by hepatic steatosis, where macrophages contribute to the inflammatory response within the liver, leading to the development of NASH and fibrosis.[2] Additionally, macrophages regulate metabolic homeostasis in NAFLD, highlighting their importance in the pathogenesis of the disease.[8]

PHYSIOLOGY AND NORMAL FUNCTION OF MACROPHAGES IN THE LIVER

The liver contains three main populations of macrophages: Kupffer cells, which make up 80-90% of the body's total macrophage population, and Liver Capsular Macrophages (LCM), recently identified on the outer surface of the liver.[7] Kupffer cells are the only resident population of macrophages in the liver and play a crucial role in defending against pathogens and resolving inflammation; they are long-lived, self-renewing, and do not typically require recruitment from the bloodstream. Kupffer cells are strategically located in the liver sinusoids, allowing them to monitor blood flow from the gastrointestinal tract. This unique positioning enables them to efficiently phagocytose (engulf) pathogens, dead cells, and debris that enter the liver. Besides their role in pathogen clearance, Kupffer cells are critical for maintaining tolerance to harmless substances absorbed from the gut and modulating immune responses. They help suppress excessive inflammation under normal conditions but can also become polarized to release pro-inflammatory cytokines when pathogens or liver damage are detected. Their ability to regulate inflammation is central

to preventing chronic liver injury. Meanwhile, LCM unlike Kupffer cells, which handle internal immune surveillance, LCMs are believed to serve as a first line of defense against infections that breach the liver capsule from the peritoneal cavity. The third non-resident population is called monocyte-derived macrophages (MoMFs), which migrate into the liver during injury, infection, or inflammation in response to signals like cytokines and chemokines released. Unlike long-lived and self-renewing Kupffer cells, monocyte-derived macrophages are recruited for temporary responses to acute conditions.[7]

Development and differentiation of macrophages in the liver

The origin of Kupffer cells has been a subject of scientific inquiry. Research indicates that Kupffer cells have a unique developmental pathway, distinct from Hematopoietic Stem Cells (HSCs). Studies suggest that Kupffer cells can be derived from yolk sac-specific progenitor cells,[9] which settle in the hepatic sinusoids and can persist in adult mice independently of HSCs.[10] However, the debate over the origin and cell kinetics of Kupffer cells continues, with some researchers arguing for a monocytic origin while others support the idea of self-replication.[11]

Kupffer cells exhibit a heterogeneous nature, with different subsets demonstrating distinct functional properties. Both Kupffer cells and macrophages of monocytic origin can express a wide range of cytokines. While monocytic macrophages are typically more associated with the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-18, Kupffer cells can also produce these cytokines under specific conditions. Conversely, both cell types have the potential to express anti-inflammatory cytokines, including IL-10, TGF-β, IL-4, and IL-13, depending on their activation state. The hepatic microenvironment plays a crucial role in shaping the development and function of these cells, particularly through the influence of the Macrophage Colony-Stimulating Factor (M-CSF), which supports their survival and proliferation.[12]

While Kupffer cells originate from the fetal yolk sac and are embryonically derived and self-renewing, liver LCM are derived from infiltrated bone marrow-derived monocytes/macrophages and are replenished from blood monocytes in the steady state.[13,14] These macrophages are identified as F4/80+ cells beneath the liver surface, distinct from F4/80+ monocytes, indicating a different cell type.[15]

MoMFs in the liver originate from bone marrow-derived Ly-6C high monocytes that are recruited into the liver in response to acute and chronic injuries. These monocytes are primarily attracted via the CCL2-CCR2 axis, where they differentiate into hepatic Ly-6C+[16] with either pro-inflammatory or anti-inflammatory functions based on the local environment.[17]

Kupffer cells have unique morphological features. They include vacuoles containing membrane-bound granules, increased lysosomes in the cytoplasm, crystal clefts and lipid droplets, and multiple cytoplasmic extensions. These features enable the cells to patrol the sinusoidal lumen effectively.[18,19] Additionally, they express a variety of surface receptors, including pattern recognition receptors such as Toll-Like Receptors (TLRs), scavenger receptors, and complement receptors. When activated, these cells exhibit specific histopathological changes such as karyomegaly and increased phagocytic activity.[20]

Role in liver homeostasis, metabolism, and interaction with other hepatic cells

Kupffer cells, as the only liver-resident macrophages, play a crucial role in maintaining liver homeostasis through their interactions with other hepatic cells, particularly hepatocytes. These interactions are essential for responding to various stimuli, such as sensing necrotic cells and inducing the production of chemokines like CXCL1 in hepatocytes. Additionally, Kupffer cells contribute to liver injury in conditions like endotoxemia, where their communication with hepatocytes is a key factor.[21,22]

Moreover, Kupffer cells are responsible for most of the phagocytic activity in the liver, as evidenced by the predominantly localization of nanoparticles in them.[23] They are also involved in lipid metabolism and have been implicated in modulating hepatocyte lipid metabolism, contributing to hepatic steatosis in response to high-fat diets. Kupffer cells can internalize

and degrade oxidized low-density lipoproteins (oxLDL), playing a role in both lipid homeostasis and the prevention of atherosclerosis.[24] Kupffer cells can also activate stellate cells through the secretion of Transforming Growth Factor-beta (TGF-β), leading to extracellular matrix deposition and fibrogenesis.[25]

Kupffer cells can be identified by the expression of CD68, prominently found on their surface and within their cytoplasm, as well as by the upregulation of CD14, particularly in response to lipopolysaccharide (LPS) exposure. Additionally, these cells exhibit heterogeneous surface expression of M1 and M2 markers, including iNOS and CD206, reflecting their functional diversity.[26-30]

ALTERATION OF MACROPHAGE FUNCTION IN FATTY LIVER DISEASE

NAFLD is a multifaceted disorder marked by the pathological accumulation of lipids within hepatocytes. This condition encompasses a spectrum that ranges from benign hepatic steatosis to more severe NASH, which poses significant risks for the development of liver fibrosis, cirrhosis, and HCC. The pathogenesis and progression of NAFLD are driven by a complex interplay of genetic predispositions, environmental influences, and metabolic dysregulation, reflecting the intricate nature of this disease.[31]

Insulin resistance and dysregulated lipid metabolism are closely linked and play central roles in the development of the disease. Insulin resistance causes an increase in the release of free fatty acids from adipose tissue into the bloodstream. The liver then takes up these FFAs, storing them as triglycerides or undergoing de novo lipogenesis, a process that is also promoted by insulin resistance. In a state of insulin resistance, the liver's ability to control lipid metabolism becomes impaired. Normally, insulin inhibits hepatic glucose production and encourages lipid oxidation, but in insulin-resistant conditions, this regulation is disrupted. This leads to an increase in lipogenic pathways, resulting in excessive triglyceride synthesis, while fatty acid oxidation is reduced due to concurrent mitochondrial dysfunction. This imbalance between lipid synthesis and disposal leads to hepatic steatosis, the main characteristic of NAFLD. Mitochondrial dysfunction also contributes to the generation of reactive Oxygen Species (ROS). In response to oxidative stress, Kupffer cells and recruited immune cells release pro-inflammatory cytokines, which perpetuate hepatic inflammation. This inflammatory environment leads to the activation of HSC, which is responsible for the deposition of extracellular matrix proteins and contributing to the development of fibrosis. The oxidative stress damages cellular components, including lipids, proteins, and DNA, which triggers hepatocellular injury and inflammation.[31-34]

It is observed that imbalanced gut bacteria also play a role in NAFLD by affecting the integrity of the intestinal barrier. Research has indicated that high-fat diets can reduce the expression of tight junction proteins like occludin, which are crucial for maintaining the integrity of the gut barrier. This disruption allows harmful substances such as lipopolysaccharides (LPS) to enter the bloodstream, leading to inflammation in the liver. The gut-liver axis is responsible for the transfer of microbial by-products, such as short-chain fatty acids, which can benefit liver metabolism. However, an imbalance in gut bacteria can impact the production of these beneficial by-products.[35-38]

The pathological changes result in macrophages remaining chronically activated, a state known as polarization, where they adopt specific functional states or phenotypes. Macrophages can polarize into two primary phenotypes: classically activated macrophages (M1), which are pro-inflammatory, and alternatively activated macrophages (M2), which are anti-inflammatory and promote tissue repair. M1 macrophages, induced by LPS and interferon-γ (IFN-γ), are renowned for their pro-inflammatory roles. They release significant amounts of pro-inflammatory cytokines, such as IL-1β, inducible nitric oxide synthase (iNOS), and Tumor Necrosis Factor-α (TNF-α). On the other hand, M2 macrophages, activated by interleukin (IL)-4 and IL-13, are recognized for their anti-inflammatory functions. These macrophages secrete anti-inflammatory factors, including IL-10, transforming growth factor-β (TGF-β), and arginase 1. Research has demonstrated

that saturated fatty acids polarize Kupffer cells/macrophages towards an M1-predominant phenotype, while Ω-3 polyunsaturated fatty acids (Ω-3 PUFA) polarize them towards an M2 phenotype. The polarization process consists of the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) signaling pathways; these pathways are favored by excessive consumption of high-energy diets, which contributes to fat accumulation in adipose tissue, which releases Free Fatty Acids (FFAs) and adipokines into the bloodstream. This results in elevated levels of circulating triglycerides and free fatty acids. High-energy diets can also cause gut leakage, leading to the translocation of bacterial products such as lipopolysaccharides (LPS) into the bloodstream. LPS are detected by pattern recognition receptors (PRRs) such as TLR4/NF-κB. This Activating of TLR4/NF-κB or specifically their adapter protein Myeloid Differentiation Primary Response Protein 88 (MyD88) signaling pathway by M1-polarized macrophages significantly diminishes expression of arginase 1, induces the production of pro-inflammatory cytokines and promotes lipid synthesis, and accumulation in hepatocytes, favoring hepatic steatosis. Furthermore, the pro-inflammatory signals (e.g., TNF-α, IL-1β, IL-6, TGF-β) from Kupffer cells activate hepatic stellate cells, which differentiate into myofibroblasts. Myofibroblasts are responsible for producing extracellular matrix components, leading to fibrosis in the liver. Persistent activation of these cells contributes to the progression of liver disease, ultimately leading to cirrhosis *(Figure 1)*. Additionally, the inhibition of

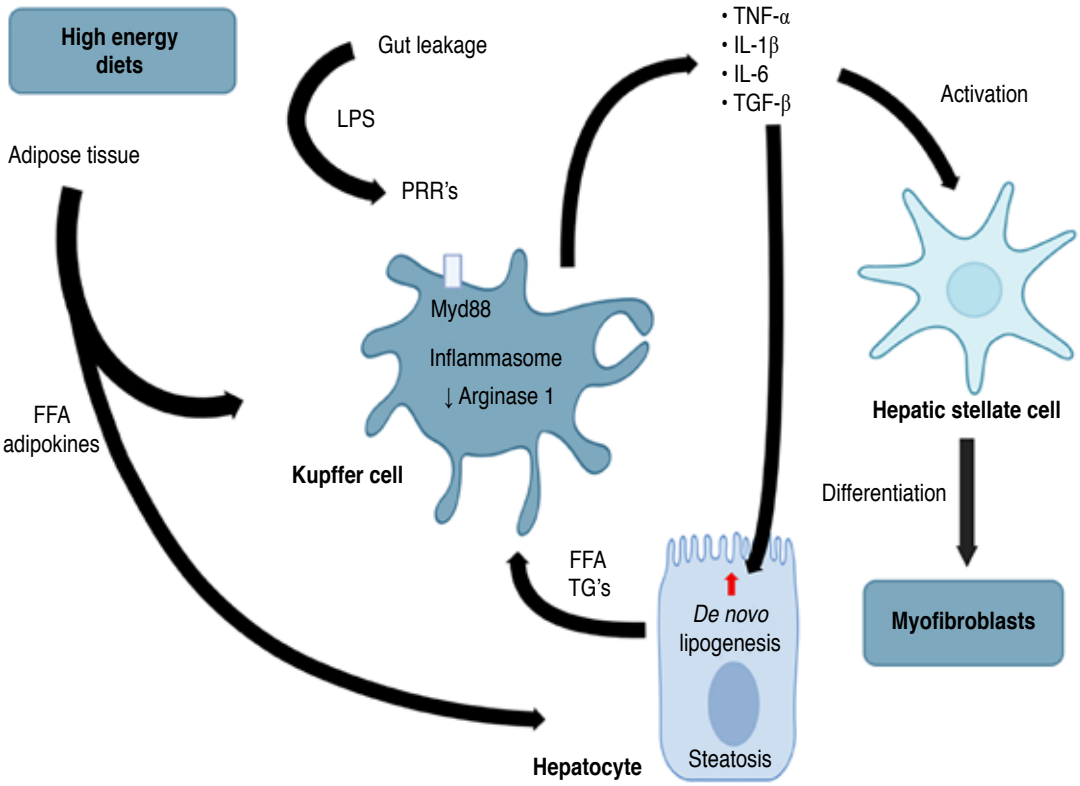

Figure 1: Altered macrophage dysfunction. Different stimuli, including Lipopolysaccharides and *de novo* lipogenesis, can classically activate macrophages (M1). Myd88 receptors, an adapter protein for the TLR/NF-κB-mediated inflammation in macrophages, finally generate pro-inflammatory cytokines, eventually favoring the activation of hepatic stellate cells and fibrosis, contributing to the progression of Nonalcoholic Fatty Liver Disease (NAFLD).
FFA = Free Fatty Acids. LPS = Lipopolysaccharides. PRR = Pattern Recognition Receptors. TG = Triglyceride.

hepatic macrophage apoptosis by Chitinase 3-like 1 can lead to macrophage accumulation and activation, exacerbating liver fibrosis. Interestingly, PPAR-γ upregulation can reverse M1 macrophage polarization and reduce the activity of TLR4/NF-κB, having anti-inflammatory and anti-fibrotic effects in NAFLD.[39-41]

The NLRP3 inflammasome is one of the most extensively studied inflammasomes, which are multiprotein complexes found within cells of the immune system. Under normal circumstances, inflammasomes detect harmful stimuli, such as Pathogen-Associated Molecular Patterns (PAMPs) from infections or Danger-Associated Molecular Patterns (DAMPs) from cell damage. Their activation facilitates the activation of the enzyme caspase-1 processes and activates pro-inflammatory cytokines like IL-1β and IL-18, which are then released to induce inflammation and help fight the infection or repair damaged tissue. However, chronic activation of NLRP3 in hepatic macrophages can lead to innate inflammatory responses and pyroptosis-regulated signaling pathways, which is required for the development of fibrosis in NAFLD.[42] Pharmacological inhibition of the NLRP3 inflammasome has emerged as a promising therapeutic strategy for various inflammatory diseases. Compounds such as MCC950 and CP-456,773 have demonstrated efficacy in suppressing NLRP3 activation, thereby reducing the production of pro-inflammatory cytokines like IL-1β and alleviating associated pathologies in animal models.[43] In another example, sulforaphane, a known NLRP3 inhibitor, has demonstrated protective effects against NAFLD in high-fat diet-induced mouse models by reducing hepatic inflammation and lipid accumulation.[44]

Additionally, the dysregulation of macrophage-hepatic stellate cell interactions targeting macrophage PPAR-γ can exacerbate NAFLD progression.[45,46]

CURRENT THERAPIES

Non-pharmacological therapies

Research has shown that exercise can significantly change the behavior of liver macrophages. It promotes a shift from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages in the liver. This shift enhances the M2 macrophage phenotype and inhibits M1 macrophages, thereby reducing chronic inflammation.[47] This is corroborated by findings from O-Gorman et al., who reported that aerobic exercise led to significant reductions in hepatic TNF-α levels and resident macrophage infiltration in a controlled trial.[48] Similarly, it was demonstrated that voluntary distance running in mice resulted in decreased levels of pro-inflammatory cytokines and changes in the intrahepatic immune environment, which are critical for mitigating liver injury.[49]

Resistance exercise has been demonstrated to reduce liver fat and its mediators independently of weight loss, indicating that the benefits of exercise go beyond mere caloric expenditure.[50] The underlying mechanisms through which exercise exerts its beneficial effects on liver macrophages include the enhancement of autophagy and the reduction of oxidative stress, thereby preventing the overactivation of the innate immune response in NAFLD.[51]

Extensive research has been conducted on the effects of caloric restriction on liver macrophages and their functions. One-way caloric restriction influences liver macrophages is by activating SIRT1, which is a protein deacetylase that regulates metabolic pathways. The activation of SIRT1 has been associated with inhibiting inflammatory pathways in macrophages, improving insulin sensitivity, and reducing the production of pro-inflammatory cytokines. Caloric restriction also triggers autophagy through SIRT1 and AMPK mediation, which are vital for maintaining macrophage function and longevity. For aged macrophages, the decline in autophagic activity is linked to dysfunctional lysosomes and increased inflammatory responses.[52-55]

Novel pharmacological therapies

As of the most recent updates, there are no FDA-approved drugs specifically targeting macrophage dysfunction. However, several therapeutic approaches are under investigation

that may indirectly influence macrophage function as part of broader strategies to treat NAFLD and NASH. One approach involves modifying macrophage polarization by restraining M1 activation or promoting M2 activation. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) engage the GLP-1 receptor, leading to a reduction in the population of pro-inflammatory monocytes in the liver. This modulation of macrophage polarization can help suppress inflammation and prevent the advancement of NAFLD.[56]

Peroxisome proliferator-activated receptor delta (PPAR-δ) can also be helpful in regulating the polarization of Kupffer cells towards the anti-inflammatory M2 phenotype by inhibiting the pro-inflammatory transcription factor NF-κB, which is crucial for M1 macrophage activation and promotes a shift towards M2-like phenotype. These agents also enhance liver histology in NASH.[57-59]

Cenicriviroc (CVC) or TAK-652 is a medication that works by targeting the C-C chemokine receptors CCR2 and CCR5. Its primary mechanism of action involves reducing inflammation and fibrosis in the liver by inhibiting the infiltration of monocytes and macrophages. CVC effectively blocks the migration of CCR2+ monocytes to the liver by disrupting the CCL2-CCR2 pathway.[16,60]

In addition, CVC has been shown to encourage a transition in macrophage polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype. This modulation not only helps decrease inflammation but also assists in improving liver fibrosis, as indicated by enhancements in fibrosis scores in clinical trials.[61,62]

Obeticholic acid (OCA) is also a potential drug option. It is a semi-synthetic bile acid that acts as a potent agonist of the farnesoid X receptor, which is mainly found in the liver, intestine, and kidney. This receptor regulates bile acid homeostasis, lipid metabolism, and immune responses within the liver.[63-65] OCA treatment has been linked to a decrease in inflammatory cell infiltration in the liver, as evidenced by reduced levels of monocyte chemoattractant protein-1 (MCP-1) mRNA, which is essential for macrophage recruitment.[63,66] Furthermore, OCA has been reported to enhance gut barrier function and reduce bacterial translocation improving gut integrity and decreasing systemic exposure to bacterial products that can activate liver macrophages and exacerbate inflammation.[67]

Targeting specific signaling pathways has shown promise in regulating macrophage activation in NAFLD. For instance, the Rictor/Akt/FoxO1 signaling pathway has been identified as a critical player in activating proinflammatory macrophages and disease progression in NAFLD.[56] The heme oxygenase system has been suggested as a potential therapeutic target to modulate macrophage polarization towards the anti-inflammatory M2 phenotype.[68]

Recently, the chemokine CXCL16 has emerged as a significant player in the pathogenesis of NAFLD, particularly in its progression to NASH and liver fibrosis. CXCL16 is primarily known for its role in recruiting immune cells, particularly natural killer T cells, to the liver, where it contributes to inflammatory processes and liver injury.[69,70] Elevated CXCL16 levels in NAFLD patients suggest its role in disease progression and potential as a biomarker for liver inflammation. The upregulation of the CXCL16/CXCR6 axis in response to liver injury has been linked to increased macrophage infiltration and activation of hepatic stellate cells.[71-74]

The mechanism by which CXCL16 influences NAFLD involves its interaction with the CXCR6 receptor, which is expressed on various immune cells, including NKT cells. This interaction promotes the accumulation of these cells in the liver. Pharmacological inhibition of CXCL16 has been shown to reduce liver macrophage infiltration and ameliorate steatohepatitis in experimental models.[69,70]

In conclusion, modulating hepatic macrophage activation in NAFLD is a promising area of research. Various therapeutic avenues are being explored to target macrophage polarization, signaling pathways, and specific molecules to mitigate inflammation and disease progression in NAFLD.

Authors' point of view

We emphasize the critical role that macrophages, especially Kupffer cells, play in the development

and progression of NAFLD. We believe it is essential to understand how macrophages contribute to hepatic inflammation, fibrosis, and metabolic dysregulation. The connection between steatosis, insulin resistance, and the polarization of macrophages towards pro-inflammatory phenotypes (M1) is a key factor in the worsening of this disease. We also explore the potential of targeting macrophage polarization and signaling pathways as therapeutic strategies for NAFLD. Our analysis highlights how interventions like exercise, caloric restriction, and new pharmacological agents hold promise in modulating macrophage activity and improving liver histology. Through this discussion, we advocate for continued research into the modulation of hepatic macrophages to alleviate the impact of NAFLD, particularly in populations with high prevalence rates and significant risk factors.

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