CARDIOVASCULAR AND METABOLIC SCIENCE

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ASOCIACION NACIONAL DE CARDIOLOGOS DE MEXICO

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Cardiac risk of transgender, let us take it seriously

Riesgo cardiaco de los transexuales, tomémoslo en serio

Rafael Moguel-Ancheita,* Beatriz Moguel-Ancheyta[‡]

The cardiovascular community must face human rights regarding gender identity that demands specific knowledge and skills for cardiac disease prevention, diagnosis, and multidisciplinary interaction.

We are not discussing genetic and phenotypic sexual determination at birth, but the personal perception of a non-originally assigned gender, called transgender, in which someone seeks for medical interventions to alter the body to change from the born gender through the self-perceived one, on two conditions:

Transgender men, transmen, female-to-men, or FTM. The born women switch or want to change to men.

Transgender women, transwomen, male-to-female, or MTF. The born men switch or want to change to women.[1]

To anticipate how often a person will need professional attention, let us look at the Mexican national statistics, considering that these concepts are relatively new and may exclude older people who feel uncomfortable declaring their gender identity. The National Institute of Statistics and Geography (INEGI from *Instituto Nacional de Estadística y Geografía*) estimates 0.9% transgender from the Mexican population that may seek medical services in all public institutes and private practice.[2] This information brought a recently published Mexican cardiology opinion.[3]

The current evidence points towards a myocardial infarction risk increase of over two-fold in FTM compared to cisgender men and four-fold compared to cisgender women. Contrarily, MTF has over two-fold risk against cisgender women, suggesting FTM receives a significant risk impact.[4] This problem was mentioned in the Mexican Consensus on Chronic Ischemic Heart Disease. Non-invasive diagnosis, classification, and stratification. Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE).[5]

Hormonal basics in cisgenders indicate a progressive increase in cardiovascular risk in men. In contrast, there is a rapid rise in women after menopause, especially in early menopause, either natural or surgical.[6] The gender-affirming hormone therapy may be responsible for the risk mentioned above but also associates to double the risk for ischemic stroke on MTF against cisgender men, especially in prolonged hormonal therapy for more than six years. On prolonged oral hormone therapy, the same group has 20 to 40 times the risk for thromboembolic complications.[7,8]

Different publications render conflicting results regarding cardiovascular risk factors. Nonetheless, transgender people may have more incidence of smoking, increased body weight, alcohol and other substance abuse, sedentarism, inadequate nutrition (more fast-food preference), dyslipidemia, and especially HIV infection. The relationship between these risk factors and cardiac events is unclear, except for HIV infection, which unequivocally gives evident high risk.[9]

Minority stress deserves particular attention, yet being transgender is not easy but quite difficult and stressful due to the self-perception of rejection caused by transphobia, which leads to physical and psychological violence and isolation from society. The latter may be the

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more significant problem that this population face, provoking a higher tendency towards discrimination, depression, addictions, suicidal ideas and acts, poverty, margination from professional, family, and recreative activities, underemployment, self-medication and possible involvement in illegal activities.[10-12]

Finally, the more interesting issue concerns transgender people's medical service, which is unequal, delayed, less efficient, and not inclusive due to fear of mistreatment from the subjects and rejection from clinical staff, including physicians and other patients. This phenomenon creates a vicious circle that perpetuates and aggravates mental and physical morbidities.[13]

Concerning the so-called conscientious objection of medical and health personnel, recognized and protected by the Political Constitution of the United Mexican States, The Supreme Court warned (unconstitutionality action 54/2018) of the superlative risk that the absolute and unlimited exercise of this right could entail, especially against the sexual and reproductive rights of women and people of sexual and gender diversity, from the problematic situation in which they find themselves and their historical discrimination. It states that the objection must be compatible and not sacrifice the rights of the beneficiaries of health services. Consequently, the Supreme Court invalidated the article of the General Health Law that authorized the conscientious objection of medical and nursing personnel. That means that, as of today, Mexican law does not protect conscientious objection and that denying health service for reasons of conscience could lead to administrative, civil, or even criminal liability. Besides, refusing health services to sexually/gender diverse people puts their lives at risk by not addressing their high health risks.[14]

Based on these concepts, our professional community should have a substantial change in transgender care, as follows:

Transgender is real, not fiction.
Transgender people need and seek medical attention for mental and physical morbidities.
They do not need our opinion regarding sexual genetic considerations.

Medical care must be inclusive and egalitarian.
Cardiologists should interact in the prevention of cardiovascular deterioration.
Mexican law does not currently protect conscientious objection.
This historical moment is a time for adaptation and interdisciplinary construction to improve transgender people's smooth and easy life.

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A reflection on the results of the ENSANUT 2022 on high blood pressure in Mexican adults

Una reflexión sobre los resultados de la ENSANUT 2022 sobre hipertensión arterial en adultos mexicanos

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INTRODUCTION

National health surveys are essential in elaborating a punctual diagnosis of the public health of a particular nation over a selected period, identifying the most conspicuous health problems, permitting found scientifically applicable political policies, as well as diagnostic and treatment guidelines, and finally, monitoring the behavior of various risk factors, diseases, conditions, and various complications over time.[1,2]

Renowned epidemiologists and public health experts from the National Institute of Public Health have conducted these national health assessments for lustrums in our country. They have the financial resources, the backup of the Mexican State, and the technical and statistical know-how to bring about these complex and costly surveys. Certainly, no one else has such capacity in this country. The entire society, not only the health State agencies and institutions, should benefit from the knowledge derived from these epidemiological enquires. A clear understanding of the current epidemiological profile of our population can and should influence medical practice and the teaching of medicine at all levels. In this context, the results of the national surveys must be analyzed and judged by everyone involved in health affairs because all of us are directly interested in their problems and solutions. In the past, many of us have been critical of

the results and interpretation of some data of the more recent national inquiries on health and nutrition without falling into the rude insinuation that the results of these searches were illusive or elusive, complying more with a political compromise than with the scientific truth. This text reveals its authors' opinion, critical but respectful, about the scientific value of National Surveys on health.

The recent publication of the 2022 version of the National Health and Nutrition Survey[3] results regarding high blood pressure (HBP) should have numerous consequences in developing sound public policies required to face the challenge of the hypertensive epidemic. These policies have yet to be generated or have only been applied insufficiently or partially.

Epidemiologic scientific knowledge is focused on the population behavior of the factors determining the origin, magnitude, characteristics, and velocity of propagation of a disease, syndrome, or other clinical condition. The certainty of an epidemiological inquiry is based on the quality of unbiased data from a probabilistic sample: their collection, the statistical analysis, and the derived biological or medical interpretation. The process must inform about the frequency and the pattern of the factors and determinants of the assessed disease, syndrome, or condition. Consecutive surveys report the tendency over time of the disease, syndrome, or conditions and their risk factors and determinants. The results of

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national serial surveys done under a similar methodology must be precise and consistent so that the medical and scientific community can accept them as genuine. But if the results of serial surveys are grossly inconsistent, or some of them are unreasonably unexpected or contrary to medical knowledge or simple logic, the rejection of the survey generates confusion or perplexity. It opens the door to all kinds of interpretations, some of them irrational and insulting, especially in a community like ours with an innate distrust of all government actions and tasks. If such is the case, the entire exercise of the epidemiological study depreciates and becomes unprofitable, despite its high cost and the effort of the researchers.

The more recent national health surveys consider numerous variables such as sociodemographic data, housing conditions, the state of health of children, adolescents, and adults, nutritional status, overweight and obesity, tobacco and alcohol consumption, violence, vaccinations, reproductive health, diabetes, dyslipidemias, and HBP, among many others. In this review, we only examine the topic of blood pressure (BP).

In 1985 the first national health survey was carried out,[2] which is now untraceable. In 1993 the ENEC[4] (National Survey on Chronic Diseases) was brought about, followed by the National Health Survey[5] in 2000. Since 2006, the so-called National Health and Nutrition Surveys (ENSANUTs) began to be carried out every six years, corresponding to each presidential period (ENSANUTs 2006,[6] and 2012[7]). Then, in the middle of the presidential six-year period next past, for some reason, the so-called Halfway National Survey on Health and Nutrition was conducted (ENSANUT MC 2016[8]). In 2018 was done the corresponding survey (ENSANUT 2018[9]) in which BP was not measured, and only the proportion of people who knew they had HBP was reported. In the same year, another survey was done on vulnerable populations residing in towns with less than 100,000 inhabitants (ENSANUT 100K 2018[10]). Since that year, the surveys have been carried out continuously every year (ENSANUT 2020,[11] ENSANUT 2021 on COVID-19,[12] ENSANUT 2022[3]).

The National Health and Nutrition Survey[3] (ENSANUT 2022). This survey comprehended 8,647 adult persons comprising a probabilistic sample representing 83,697,700 adults ≥ 20 years old. BP was measured with an electronic device. HBP was defined using the cutoff values recently proposed by the binomial American College of Cardiology (ACC) and the American Heart Association (AHA)[13] (130/80 mmHg) or the older (140/90) than the authors attribute to the «Eighth» Joint National Committee JNC 8.[14] We quoted «Eight» because this last version of the Joint National Committee report was not, as the previous documents were, endorsed by the National Heart, Lung, and Blood Institute (NHLBI) of the United States (US). Instead, it was the product of a group initially appointed by the NHLBI to elaborate on the JNC 8 report. But later, that institute withdrew its endorsement, leaving the participants of the group alone with no representation other than their own.[15] But even more, the recommendations of the appointed panelist to the JNC 8 did not address any definitions of hypertension and prehypertension, as indeed did the JNC 7 (140/90 mmHg).[16]

How has HBP evolved in Mexico, according to the ENSANUTs. Our country experienced an accelerated and geographically heterogeneous epidemiological transition in the last decades that put heart diseases, diabetic mellitus, and malignancies in the first place as causes of general mortality. Hand in hand with a pandemic of overweight and obesity, conditions that affect more than 70% of the population, the prevalence of type 2 diabetes mellitus, atherogenic dyslipidemia, HBP, and ischemic heart disease rose significantly.

The prevalence of the common atherosclerotic risk factors does not change abruptly in a few years unless a natural or socioeconomic cataclysm occurs, like a catastrophic war, a prolonged famine, a devastating economic crisis, and the like. Inversely, after successfully applying solid public policies and population programs to obtain a massive detection of HBP and better therapeutic management, many years are needed to observe substantial changes.

Table 1 shows some inconsistencies in the results of the national surveys on HBP over almost three decades. We found three probable

Table 1: Prevalence of HBP according to diverse national surveys.								
	ENEC 1993	ENSA 2000	ENSANUT 2006	ENSANUT 2012	ENSANUT MC 2016	ENSANUT-100 K 2018	ENSANUT 2020	ENSANUT 2022
Women	140/90 28.1%	140/90 26.3%	140/90 31.1%/47.3%*	140/90 30.8%	140/90 26.1%	140/90 33.8% 130/80 46.8%	140/90 28.6% 130/80 44%	140/90 27.7% 130/80 42.4%
Men	140/90 37.5%	140/90 34.2%	140/90 32.4%/40.3%*	140/90 33.3%	140/90 24.9%	140/90 31.4% 130/80 52.2%	140/90 31.9% 130/80 53%	140/90 31.3% 130/80 53.8%
Total	140/90 32.8%	140/90 30.5%	140/90 30.8%/43.2%*	140/90 32%	140/90 25.5%	140/90 32.7% 130/80 49.2%	140/90 30.2% 130/80 49.4%	140/90 29.4% 130/80 47.8%

ENEC = National Survey on Chronic Diseases. ENSA = National Health Survey. ENSANUT = National Health, and Nutrition Surveys. MC = halfway. 100 K = towns of less than 100,000 inhabitants.

Cutoffs for diagnosing HBP: 140/90 (JNC 7) or 130/80 (ACC/AHA).

* Data from ENSANUT 2006: the first number corresponds to the official report, and the numbers with a single asterisk indicate those published in an article written by the same investigators.[6,17]

causes of these disparities: first, sloppy handling of calculations. With the data from ENSANUT 2006[6] and the cutoff values of 140/90 mmHg, the official report of that inquiry informed an HBP prevalence in both genders of about 30%. Later, in an article[17] on the HBP topic, the same investigators estimated an amazing prevalence greater than 40% using identical data. Which was the correct one? Everything suggests that the lower number is true because it coincides with the prevalence found in the previous surveys and the one that followed in 2012.[7] Secondly, in ENSANUT 2016 Halfway,[8] the methodology for blood pressure measurement changed, and a digital manometer was used. That modification was correct because the mercurial sphygmomanometers are perilous to the environment. The prevalence of HBP was less than in previous inquiries, about 25%. The authors[8] attribute this disparity to the different techniques employed. However, with the same methodology, the HBP prevalence found in ENSANUT 2020 was 30.2%, using the same cutoff value of 140/90 mmHg.[11] Furthermore, a recent meta-analysis on the usefulness of digital devices found a sensitivity of 79% and a specificity of 91%, signaling that both methods have similar accuracy.[18] Therefore, another explanation for this disparity would have to be sought. Finally, the most important reason for the survey's inconsistent results is the inclusion of the ACC/AHA's newest cutoff values for HBP (130/80 mmHg). To begin with, the 140/90 mmHg ciphers were the cutoffs accepted by Mexican health authorities, as stated in both the Mexican Official Norm and the project for a new one.[19,20] Although our government's intention to suppress many Official Mexican Norms (NOM) is in process, among them that of arterial hypertension, they are still in force to date and are obligatory throughout the country. Since ENSANUT 100 K to the last survey, the authors included the newest and the older cutoffs. According to the latter, the prevalence of HBP is slightly higher than 30%, coincident with the historical values and with the findings of some non-governmental academic-based epidemiological studies.[21] If we discard the results obtained with the ACC/AHA recent cutoff, the prevalence of HBP in adults in our country has remained stable since 1993 to date, around 30%.

The change of the HBP diagnostic paradigm. Has it been accepted? The diagnostic cutoffs of blood pressure are still up for debate. For many years ago, the limits between normotension and hypertension were figures ≥ 140/90 mmHg. In 2017, numerous US medical societies headed by the two greater cardiovascular societies, the ACC and the AHA, decided to lower the normotension threshold to less than 130/80 mmHg *(Table 2)*.[13] The European Societies of Cardiology and Hypertension (ESC/ESH) did not support this position, but without modifying the diagnostic values of ≥ 140/90 mmHg, lowered the blood pressure targets to < 130/80 mmHg.[22,23] Similarly, the International Society of Hypertension,[24] the Canadian 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children,[25] the Japanese Society of Hypertension,[26] the Korean Society of Hypertension,[27] the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension,[28] the Australian National Heart Foundation,[29] the British National Institute for Health and Care Excellence (NICE),[30] the 7th Brazilian Guideline of Arterial Hypertension,[31] the Latin American Society of Hypertension Guidelines on the management of arterial hypertension and related comorbidities in Latin America,[32] and the Argentine Consensus on Arterial Hypertension (*Consenso Argentino Hipertensión Arterial*)[33] among many others around the world, have not modified the old diagnostic criteria. Even in the US, not all major medical associations agree with changing cutoff values: the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) have rejected the paradigm modification.[34,35] So, it is evident that the ACC/AHA definition of hypertension, based on the cutoff point of 130/80 mmHg, it is rejected worldwide by most of the cardiological and hypertension societies, and national and international guidelines. In addition to the uncertainty about the usefulness of lowering SBP to less than 130 mmHg, some members of the AAFP have raised some ethical considerations. The Chair of the Steering Committee of the SPRINT study (whose results were taken as the main evidence for the modification of the cutoff point) was also Chair of the ACC/AHA guideline organism in charge of recommending the paradigm modification. That in Spanish is called being a «judge and part» of a process and is a clear example of intellectual conflict.

What is the rationale for modifying the traditional cutoff points from which HBP is diagnosed? To state it at once, all BP cut points are pragmatic, set by expert opinion and epidemiological evidence. In other words, no physiologic threshold has been established to separate hypertension from normotension. As the relationship between BP values and cardiovascular risk is exponential, the selected cutoff threshold signals a point from which a small increment of BP is associated with a significant increase in risk. Consequently, the need to treat medically is based on these values. The higher the BP, the more frequent and serious the vascular complications of all kinds. But what is the physiologic level of BP in which it fulfills its function of properly perfusing the tissues without damaging the structure and function of blood vessels? HBP is perceived as a «civilization disease», rare in communities that live, still in our time, under the norms of the stone age. Among these tribal persons, the prevalence of HBP is very low, and the average population pressure is less than 120/80 mmHg in both genders and all age groups.[36] So, that must be the physiologically adequate level of BP. But it is impossible to compare these very primitive societies with modern, complex, and sophisticated contemporary human communities. Modern society is plagued by excessive consumption of salt and alcohol, poor ingestion of fresh fruit, vegetables, and dietary fiber, lack of physical exercise, and

Table 2: New blood pressure categories proposed by the ACC/AHA and associated societies.[13]	
Category	Blood pressure values, mmHg
Normal	SBP < 120 and DBP < 80
Elevated	SBP 120-129 and DBP < 80
Hypertension, stage 1	SBP 130-139 or DBP 80-89
Hypertension, stage 2	SBP > 140 or DBP > 90
SBP = systolic blood pressure. DBP = diastolic blood pressure.	

considerable sociopsychological stress, among other numerous vascular damage factors.[36] Conversely, the genetic homology between modern chimpanzees and humans is about 96%.[37] They are the closest living beings, genetically speaking, to us. It is impossible to measure the BP in wild apes and very difficult indeed in captive ones, as it is necessary to sedate them, altering in the process the physiologic levels of the BP.[38] Despite all difficulties and shortcomings, BP has been measured in captive adult chimpanzees. The median normotension found is 126/63 mmHg, like the adequate human BP.[39] These anthropometric and comparative zoology data show doubtlessly that the optimal blood pressure level should be at least 120/80 mmHg or less. In fact, the general opinion is that these figures, and even lower, are healthier and desirable. On the other hand, although observational studies have shown that each increment of 20 mmHg of systolic blood pressure (SBP) and 10 mmHg of diastolic blood pressure (DBP) double the risk of cardiovascular (CV) death,[40] the contrary, diminishing 20 mmHg and 10 mmHg in SBP and DBP reduces in different proportions the absolute CV risk.

Behind the modification of the diagnostic cutoffs of BP is the concept that the lower, the better. But, as in any therapeutic or preventive intervention, lowering BP must consider a balance between the risks and benefits. A therapeutic-driven excessive reduction of some biological parameters could yield undesirable effects, sometimes catastrophic, except in the case of LDL-cholesterol. As an example, in a patient with diabetes, lessening the blood sugar to 80 mg/dL theoretically must have advantages to a discrete reduction to 120 mg/dL. Whatever the benefits of such a reduction, the risk of hypoglycemia, even fatal, makes strict glycemic control ill-advised. Regarding BP, a so-called J-curve signals the occurrence of outcomes, mainly coronary, when BP descends too much. Although more robust evidence is lacking in this respect, observational data indicate that an excessive reduction of DBP, principally in the frail elderly or in patients with or without diabetes but with coronary atherosclerotic plaques, can cause a dangerous diminution of coronary flow and adverse outcomes.[41]

A single study, the SPRINT,[42] aimed to establish a better target for SBP to diminish CV risk, it is the foundation on which all the arguments regarding the lowering of the cut-off point and the reclassification of HBP are built.

The SPRINT[42] study: its results have provoked a very broad discussion, especially based on the differences in the methodology used to measure blood pressure. This controlled, randomized, open-label study was sponsored (but not endorsed) by the National Heart, Lung, and Blood Institute from the US and carried out in several clinical centers in this country and Puerto Rico. The study group comprised 9,361 hypertensive patients with SBP 130-180 mmHg and increased CV risk (Framingham 10-yr cardiovascular disease risk score) but without diabetes or previous stroke or younger than 50 years old, 91% of which received some antihypertensive medication. Women and persons aged ≥ 75 years were represented (35.6% and 28.2%, respectively). The participants were randomly assigned to two groups, one in which SBP was lowered with intensive treatment to less than 120 mmHg and another in which the SBP was reduced to less than 140 mmHg with standard therapy. In an open-label fashion, patients were treated with any antihypertensive drugs. The defined primary composite outcome was myocardial infarction, another acute coronary syndrome not resulting in myocardial infarction, stroke, acute heart failure, or death from cardiovascular causes. Additionally, renal outcomes in patients with chronic kidney disease (CKD) were a composed final renal outcome of a decrease of 50% of the glomerular filtration rate (eGRF), worsening of the CKD, or the need for dialysis or transplant. In those without CKD, the final renal outcome was a decrement of 30% in basal eGFR and a doubling of the AUC (urinary albumin/creatinine) ratio. The study compared the time of the first primary outcome in both groups, the one with an intensive and the other with standard treatment. *Table 3* shows some results obtained from the data displayed in the published article.

Intensive treatment reduced the relative risks of the primary outcome, total and cardiovascular mortality, heart failure, and a combination of death or incidence of the primary outcome to a great extent, 22 to 57%. Relative risk is

Table 3: Main results from the SPRINT study.						
Variable	Intensive treatment, %	Standard treatment, %	Hazard ratio	RRR, %	p	RAR, %	NNT
Primary outcome	5.2	6.8	0.75	25	< 0.001	1.6	62
Death from any cause	3.3	4.5	0.73	27	0.003	1.2	83
Death from CV cause	0.8	1.4	0.43	57	0.005	0.6	166
Heart failure	1.3	2.1	0.62	38	0.002	0.8	125
Primary outcome or death	7.1	9	0.78	22	< 0.001	1.9	52
Complications	Intensive treatment, %	Standard treatment, %	Hazard ratio	IRR, %	p	IAR, %	NNH
Hypotension	2.4	1.4	1.70	70	0.001	1	100
Acute kidney injury	4.4	2.6	1.69	69	0.001	1.8	55
Syncope	3.5	2.4	1.45	45	0.003	1.1	90
30% ↓ eGFR in patients without CKD	3.8	1.1	3.45	345	0.001	2.7	37

RRR = reduction of relative risk. RAR = reduction of absolute risk. IRR = increment of relative risk. IAR = increment of absolute risk. NNT = number needed to treat. NNH = number needed to harm.

Although consistent, there are small variations between these estimates and those provided by the authors in the original article.

the probability that an event will happen in one group exposed to a factor or treatment compared to a nonexposed group. Meanwhile, absolute risk is the probability of an event in a group. In this case, the reduction of relative risk (RRR) measures the comparative size of the therapeutic intervention. At the same time, the reduction of absolute risk (RRA) estimates the crude proportion of curtailing an event because of the intervention. The RRR overestimates the real effectiveness of an intervention, so RAA is the most reliable statistical tool to estimate its true significance.[43] The inverse of RRA yields the number of patients needed to be treated (NNT) to obtain a reduction of an event. Of course, the larger the RRA, the fewer patients needed to treat. An NNT of less than 50 in prevention means an acceptable pharmacoeconomic effect. Compared with the larger RRR in the study, the RRA numbers were rather small, yielding a very large NNT. For example, treating HBP intensively in 160 patients is necessary to prevent a single death. And what was the prize to obtain that meager

success? Many complications, none labeled by the authors as severe, but anyway limiting, and probably perilous in the long-range, as the decrease of eGFR. Truly, the estimations of NNH, the number of patients needed to put in evidence an undesirable outcome, are also very large. For example, it is necessary to treat 90 patients intensively to cause a single case of syncope. So, the study results are not as spectacular as they seem (looking at the reduction of absolute instead of relative risks), and their limited benefits are balanced by complications such as hypotension, syncope, acute kidney injury, and decreased glomerular filtration rate in patients without previous kidney disease. In addition, as the study does not include diabetic or stroke patients, its results are insufficient to justify drastically lowering the BP thresholds. Furthermore, in the study, BP was measured by an automatic device, without any human intervention, following the strict recommendations of the AHA,[44] which generally are not observed in daily medical practice. This disparity in how BP is measured

makes it difficult to transfer the study's findings to the real clinic. For all the above mentioned facts, ENSANUT researchers should give less importance to this controversial study.

CONCLUSION

Being HBP the most important and prevalent cardiovascular risk factor, its control is crucial for public health. Sequential national surveys must operate as an unchallenged indicator of the epidemiological course of the disease and of the correctness or not of the public policies and the clinical and therapeutic measures addressed for its control. It would be highly desirable for our esteemed epidemiologists and public health experts in charge of the now continuous ENSANUTs to articulate efforts with the cardiovascular community to carry out future evaluations jointly. As individuals and representatives of diverse cardiovascular societies or associations, we can offer, in good faith, our wide and deep knowledge of HBP, a rather intricate syndrome, one of the major enemies of the health of our fellow Mexicans.

A point of caution must be placed on the fact that establishing precise cutoff points in a continuous and fluctuating variable, such as BP, can impact decision-making in public health. Furthermore, applying this concept in the daily clinic, in which the measurement of BP is very inaccurate, requires an educated judgment of the treating physician and the participation of an informed patient in making decisions about the presence or not of HBP and its adequate management. All this requires the development of a lifetime program, which generally requires significant behavioral modifications and the permanent taking of medications for the rest of the patient's life.

In conclusion, our opinion as clinical cardiologists, nephrolgists, and internists, who have dedicated long years to the study of HBP and the care of victims of this disease is that the lowering of the established cutoffs of 140/90 mmHg just brings a modest benefit which is canceled by the complications derived from a significant decrease in BP. We courteously suggest to the researchers in charge of the National Health Surveys to discard the cutoff point proposed only by the ACC/AHA, rejected by most of the world's hypertension and cardiovascular associations, in the following surveys.

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ORIGINAL RESEARCH

Cardiac arrhythmia among hospitalized COVID-19 patients at Gunung Jati General Hospital, Indonesia

Arritmia cardiaca entre pacientes hospitalizados con COVID-19 en el Hospital General Gunung Jati, Indonesia

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ABSTRACT

Introduction: arrhythmia is one of the most common extrapulmonary complications of coronavirus 2019 (COVID-19). **Objectives:** this study aimed to assess the outcomes of hospitalized COVID-19 patients with and without arrhythmia from asymptomatic to life-threatening disease severity and the predictors of the in-hospital outcomes. **Material and methods:** a total of 257 patients with confirmed COVID-19 who had at least one electrocardiogram recording from April 01 to December 31, 2021, were enrolled in this cross-sectional study. **Results:** arrhythmia occurred in 36.6% of patients. The mean age of patients with arrhythmia was 52.48 ± 13.936 years, with a male preponderance (57.4%). The most common arrhythmia was sinus tachycardia (69.1%). Pre-existing atrial fibrillation (AF) and new-onset AF occurred in 10.6% and 2.1% of patients, respectively. Total atrioventricular block occurred in 2.1% of patients. Heart failure (20.2%), previous arrhythmia (10.6%), hypertension (46.8%), diabetes mellitus (DM) (42.6%), and chronic kidney disease (55.3%) were more prevalent in patients with arrhythmia. Patients with arrhythmia had a significantly higher need for Intensive Care Unit (ICU) (50%), need for intubation and mechanical ventilation (MV) (7.4%), hypotension requiring vasopressor (16%), and in-hospital mortality (44.7%) compared to patients without arrhythmia. After multivariate analysis, DM was associated with a higher need for ICU, hypotension requiring vasopressor, and in-hospital mortality. History of stroke/ transient ischemic attack (TIA) and thrombocytopenia during admission was associated with a higher need for intubation and MV. **Conclusions:** the in-hospital outcomes in patients with COVID-19 and arrhythmia are the worst. In patients with arrhythmia, DM is associated with higher need for ICU, hypotension requiring vasopressor, and in-hospital mortality. A history of stroke/TIA and thrombocytopenia during admission are associated with higher need for intubation and MV.

RESUMEN

Introducción: las arritmias son una de las complicaciones extrapulmonares más comunes del coronavirus 2019 (COVID-19). Objetivos: este estudio se realizó para evaluar la evolución de los pacientes hospitalizados por COVID-19, desde asintomático hasta grave, que presentaban con y sin arritmias, e investigar los predictores de desenlaces hospitalarios. Material y métodos: se hizo un estudio transversal que incluyó un total de 257 pacientes con COVID-19 confirmado y que contaban con al menos un registro de electrocardiograma entre el 1 de abril y el 31 de diciembre del 2021. Resultados: se observaron arritmias en 36.6% de los pacientes. Su edad promedio fue de 52.48 ± 13.93 y predominaron los de género masculino (57.4%). La arritmia más común fue la taquicardia sinusal (69.1%), seguida por fibrilación auricular (FA) preexistente y la FA de reciente aparición, que ocurrieron, respectivamente, en 10.6% y 2.1% de los pacientes. Hubo bloqueo auriculoventricular completo en 2.1%. Las comorbilidades más frecuentes en el grupo de arritmias fueron: la insuficiencia cardiaca (20.2%), arritmia previa (10.6%), hipertensión arterial (46.8%), diabetes mellitus (DM) 42.6% y enfermedad renal crónica (55.3%). Los pacientes con arritmia tuvieron una mayor necesidad de cuidados intensivos (CI) (50%), intubación y ventilación mecánica (VM) (7.4%), vasopresores (16%) y mayor mortalidad hospitalaria (44.7%). El análisis multivariante asoció la DM con mayor necesidad de CI y necesidad de vasopresores y mortalidad hospitalaria. La historia de accidente cerebrovascular o ataque isquémico transitorio (AIT) y trombocitopenia al momento de la admisión se asoció con mayor necesidad de intubación y VM. Conclusión: los resultados intrahospitalarios en pacientes con COVID-19 y arritmia son los peores. Los pacientes con arritmias y DM requirieron con mayor frecuencia de CI, vasopresores y tuvieron mayor mortalidad hospitalaria, aquellos con historia de accidente cerebrovascular y AIT eran más susceptibles de ser intubados y recibir VM.

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INTRODUCTION

The coronavirus 2019 (COVID-19), first identified in Wuhan in December 2019, primarily affects the respiratory system.[1,2] However, COVID-19 is also known to affect the other system in the body and can lead to extrapulmonary involvements, including cardiac arrhythmia.[3,4] An early study from Wuhan reported an incidence of arrhythmia in 16.7% of hospitalized COVID-19 patients.[5] In addition, the incidence was higher in patients admitted to the Intensive Care Unit (ICU) and reached 44%.[5] However, the study did not describe the specific type of arrhythmia.[5] The severity of the disease was also found to correlate with the incidence of arrhythmia, with a higher incidence in patients with severe disease compared to mild disease.[6]

In some COVID-19 patients, arrhythmia may be the first infection symptom, preceding the respiratory symptoms.[6] COVID-19-related arrhythmia can manifest as tachyarrhythmia or bradyarrhythmia.[7-11] Atrial fibrillation (AF) was the most commonly reported supraventricular tachyarrhythmia.[12,13] In addition, ventricular tachyarrhythmia such as ventricular tachycardia (VT) was reported in hospitalized COVID-19 patients.[8,14,15] Several studies also reported bradyarrhythmia in the form of sinus bradycardia, total atrioventricular (AV) block, and sinus pause.[8,10,11,14,15]

Despite accumulating evidence, there is still variation in the type and outcomes of arrhythmia associated with COVID-19 in hospitalized patients. Some retrospective studies did not include COVID-19 patients with asymptomatic and mild disease severity. Therefore, this study aims to investigate and to compare the outcomes of hospitalized COVID-19 patients with and without arrhythmia from asymptomatic to life-threatening disease severity and to investigate the predictors that may influence the in-hospital mortality, the need for intensive care (IC), the need for intubation and mechanical ventilation (MV), hypotension requiring vasopressor, thromboembolic event (deep vein thrombosis and pulmonary embolism), major bleeding, and stroke or transient ischemic attack (TIA).

MATERIAL AND METHODS

Inclusion and exclusion criteria. This study included moderate, severe, and critically ill COVID-19 patients ≥ 18 years who were hospitalized with the primary indications of COVID-19 and tested positive with real time-polymerase chain reaction (RT-PCR) between April 1, 2021, and December 31, 2021, at Gunung Jati General Hospital, Cirebon. We also included patients admitted to our hospital due to other medical indications with positive RT-PCR tests. The COVID-19 severity of patients admitted due to other medical indications will be assessed and categorized as asymptomatic, mild, moderate, severe, or critically ill. Patients who were pregnant, discharged, or transferred by their intention before fulfilling treatment were excluded.

Data collection. Data on patients' demographic, clinical characteristics, comorbidities, history of cardiovascular procedures, electrocardiography, management during hospitalization, outcomes were directly collected from hospital medical records. Two cardiologists interpreted the electrocardiography. Any disagreement in the electrocardiography interpretation was resolved through discussion. Continuous telemetry monitoring was performed on all patients admitted to the ICU. We included major arrhythmias (supraventricular tachycardia, new-onset atrial fibrillation, new-onset atrial flutter, pre-existing atrial fibrillation, pre-existing atrial flutter, atrioventricular block, sinus pause, sinus arrest, ventricular tachycardia, ventricular fibrillation) and non-major arrhythmias (sinus tachycardia, sinus bradycardia, premature atrial complex, premature ventricular complex).[7,8] New-onset atrial fibrillation (NOAF) or atrial flutter is defined as electrocardiographic evidence of atrial fibrillation or atrial flutter during admission or hospitalization in patients without a medical history of atrial fibrillation or atrial flutter. Pre-existing atrial fibrillation (PEAF) or atrial flutter is defined as patients with a medical history of atrial fibrillation or atrial flutter. The outcomes were in-hospital mortality, the need for IC, the need for intubation and mechanical ventilation, hypotension requiring vasopressor, thromboembolic event (deep

vein thrombosis and pulmonary embolism), major bleeding, and stroke/TIA. Our hospital's ethics committee approved this study with the number No. 087/LAIKETIK/KEPKRSGJ/VI/2021.

Statistical analysis. Descriptive statistics were used to summarize the data. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk or Kolmogorov-Smirnov normality test was performed as appropriate. Normally distributed data for continuous variables were summarized as mean and standard deviation. Otherwise, the data were presented as the median and interquartile range (25th percentile = P25, 75th percentile = P75). The independent T-test or Mann-Whitney U-test was performed to compare continuous variables between patients with and without arrhythmia. Chi-square (χ^2) and Fisher's exact were used to compare dichotomous variables between patients with and without arrhythmia. Results were considered significant at p-value < 0.05.

Furthermore, the χ^2 test or Fischer's exact test was performed to compare and determine the independent variables according to the outcomes of patients with arrhythmia that will be included in the multivariate logistic regression analysis. Variables with χ^2 or Fisher's exact p-value logistic regression and backward method were applied. The statistical analysis was conducted using SPSS version 22.0.

RESULTS

This cross-sectional studies included 257 patients admitted due to confirmed COVID-19, from April 1 to December 31, 2021, for study analysis. A total of 94 patients (36.6%) had arrhythmia during hospitalization. The patients' demographic data are shown in *Table 1*. Most patients were male (n = 137, 53.3%), and the mean age was 53.49 ± 13.34 years old. The proportion of IHD in patients with arrhythmia was almost twice that of patients without arrhythmia, although the difference did not reach statistical significance.

As seen in *Table 2*, patients with arrhythmia had more severe disease (48.9% vs. 22.7%; p < 0.001) than those without arrhythmia, as reflected in clinical presentation and laboratory results. Compared to patients

without arrhythmia, patients with arrhythmia had lower oxygen saturation during initial admission (90.5 vs. 96; p < 0.001). Patients with arrhythmia had a higher level of leukocytes (9,465 vs. 8,070/µL; p = 0.019), neutrophil-to-lymphocyte ratio (NLR) (6.53 vs. 4.62; p < 0.001), creatinine (1.34 vs. 1.14 mg/dL; p = 0.022), and d-dimer level (2,061 vs. 1,167 ng/mL; p < 0.001) compared to patients without arrhythmia, as presented in *Table 3*. The high-flow nasal cannula [23 (24.5%) vs. 15 (9.2%); p = 0.001], anticoagulant [80 (85.1%) vs. 117 (71.8%); p = 0.015], and plasma convalescent [28 (29.8%) vs. 27 (16.6%); p = 0.013] were more commonly prescribed in patients with arrhythmia compared to those without arrhythmia, as seen in *Table 4*.

In this study, 94 patients (36.6%) displayed arrhythmia during hospitalization. The electrocardiographic parameter between patients with and without arrhythmia can be seen in *Table 5*; the arrhythmias are listed in *Table 6*. The patients can present with single or multiple arrhythmias during hospital admission. From patients with single arrhythmia, the most common arrhythmia was sinus tachycardia (69.1%) and followed by pre-existing AF (10.6%). New-onset AF occurred in 2.1% of patients during the hospitalization period. Total AV block also occurred in 2.1% of patients. For patients with multiple arrhythmias, the most common arrhythmia was sinus tachycardia with premature atrial complex (3.2%), followed by sinus tachycardia with premature ventricular complex (1.1%) and sinus bradycardia with first degree AV block and premature ventricular complex (1.1%).

Overall, patients with arrhythmia had significantly worse outcomes than those without during hospitalization, as shown in *Table 7*. The need for intubation and mechanical ventilation [7 (7.4%) vs. 2 (1.2%); p = 0.009] and hypotension requiring vasopressor [15 (16%) vs. 5 (3.1%); p < 0.001] were more commonly observed in patients with arrhythmia compared to patients without arrhythmia. Due to higher disease severity and complications, the need for IC was significantly higher in patients with arrhythmia compared to those without arrhythmia [47 (50%) vs. 38 (23.3%); p < 0.001].

Age ≥ 65 years old (OR 3.203; 95% CI 1.117-9.186; p = 0.026), DM (OR 2.918; 95% CI 1.248-6.824; p = 0.012), leukocytosis during admission (OR 2.616; 95% CI 1.134-6.033; p = 0.023), and NLR > 6.82 during admission (OR 2.641; 95% CI 1.139-6.123; p = 0.017) were associated with the need for IC in univariate analysis. After multivariate analysis, only DM (adjusted OR 2.656; 95% CI 1.114-6.333; p = 0.028) remained associated with the need for IC and can be seen in *Table 8*.

In univariate analysis, history of stroke/TIA (OR 17; 95% CI 1.965-147.046; p = 0.027) and NLR > 6.82 (OR 8.914; 95% CI 1.028-77.292; p = 0.041) were associated with the need for intubation and mechanical ventilation as seen in *Table 8*. After multivariate analysis, history of stroke/TIA (adjusted OR 46.426; 95% CI 1.64-1314.392; p = 0.024), thrombocytopenia during admission (adjusted OR 17.131; 95% CI 1.623-180.777; p = 0.018), and NLR > 6.82 (adjusted OR 0.67; 95% CI 0.005-0.882; p = 0.04) associated with the need for intubation and mechanical ventilation. In univariate analysis, new-onset AF and premature atrial complex (PAC) numerically increased the need for intubation and mechanical ventilation.

In univariate analysis, age ≥ 65 years old (OR 5.802; 95% CI 1.79-18.805; p = 0.004),

Table 1: Basic demographic.			
	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Male sex	137 (53.3)	54 (57.4)	83 (50.9)	0.312
Age (years), mean ± SD	53.49 ± 13.344	52.48 ± 13.936	54.08 ± 12.998	0.355
Duration of hospitalization (days), median [IQR]	12 [9-16]	13 [7-16.5]	11 [9-16]	0.87
BMI (kg/m^2), median [IQR]	23.88 [22.03-26.62]	24.425 [22.108-26.68]	23.74 [21.87-26.57]	0.48
Active smoker	11 (4.3)	5 (5.3)	6 (3.7)	0.537
Ischemic heart disease	22 (8.6)	12 (12.8)	10 (6.1)	0.067
Heart failure	27 (10.5)	19 (20.2)	8 (4.9)	< 0.001
Previous arrhythmia	11 (4.3)	10 (10.6)	1 (0.6)	< 0.001
Hypertension	89 (34.6)	44 (46.8)	45 (27.6)	0.002
Diabetes	85 (33.1)	40 (42.6)	45 (27.6)	0.014
Chronic kidney disease	121 (47.1)	52 (55.3)	69 (42.3)	0.045
Obesity	105 (40.9)	42 (38.4)	63 (66.6)	0.344
COPD	0	0	0	–
Bronchial asthma	3 (1.2)	0	3 (1.8)	0.301
Active cancer	11 (4.3)	1 (1.1)	10 (6.1)	0.06
Stroke or TIA	9 (3.5)	4 (4.3)	5 (3.1)	0.728
Tuberculosis on treatment	7 (2.7)	6 (6.4)	1 (0.6)	0.011
HIV	4 (1.6)	2 (2.1)	2 (1.2)	0.626
Autoimmune disease	2 (0.8)	1 (1.1)	1 (0.6)	1
Valvular heart disease	2 (0.8)	1 (1.1)	1 (0.6)	1
History of PCI	2 (0.8)	0	2 (1.2)	0.534
History of CABG	1 (0.4)	0	1 (0.6)	1

BMI = body mass index. CABG = coronary artery bypass grafting. COPD = chronic obstructive pulmonary disease. IQR = interquartile range. PCI = percutaneous coronary intervention. SD = standard deviation. TIA = transient ischemic attack.

Variable	All patients (N = 257)	Arrhythmia (N = 94)	Non-arrhythmia (N = 163)	p
Table 2: Vital signs during admission and COVID-19 symptom severity.				
Vital signs during admission, median [IQR]				
Systolic blood pressure (mmHg)	130 [110-140]	130 [118.75-150]	130 [110-140]	0.075
Diastolic blood pressure (mmHg)	80 [70-90]	80 [70-90]	80 [70-82]	0.106
Heart rate (bpm)	95 [84-104]	103.5 [90.5-117]	89 [83-99]	< 0.001
Respiratory rate	24 [22-28]	27.5 [24-30]	24 [21-26]	< 0.001
Oxygen saturation (%)	95 [88-97.5]	90.5 [82-96]	96 [89-98]	< 0.001
Temperature (ºC)	36.6 [36.35-36.8]	36.7 [36.5-37]	36.6 [36.3-36.8]	0.034
COVID-19 symptom severity, n (%)				
Non severe and critical	174 (67.7)	48 (51.1)	126 (77.3)	< 0.001
Severe and critical	83 (32.3)	46 (48.9)	37 (22.7)	< 0.001

IQR = interquartile range.

Table 3: Laboratory results during admission.			
	All patients (N = 257) Median [IQR]	Arrhythmia (N = 94) Median [IQR]	Non-arrhythmia (N = 163) Median [IQR]	p
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Hemoglobin (g/dL)	12.8 [11.2-14]	12.9 [11.2-14.125]	12.7 [11.2-13.9]	0.439
White blood cells (µL)	8,590 [6,335-11,970]	9,465 [6,610-13,182.5]	8,070 [6,040-10,750]	0.019
Platelets count (10^3/µL)	240 [176.5-322.5]	228 [169.5-305.5]	251 [179-329]	0.156
Red blood cells (million/µL)	4.5 [3.925-4.945]	4.61 [4.048-5.115]	4.4 [3.8-4.88]	0.033
Neutrophils (%)	77.8 [68.95-86.25]	80.7 [74.075-87.025]	74.6 [65.4-84.5]	0.001
Lymphocytes (%)	15 [8.35-21.5]	12.65 [7.65-17.75]	17.2 [9.9-24.5]	< 0.001
NLR	5.06 [3.17-10.525]	6.53 [4.2-11.25]	4.62 [2.56-8.42]	< 0.001
Ureum (mg/dL)	39 [25.95-68.1]	50.75 [29.15-81.275]	34 [24.5-56.7]	0.003
Creatinine (mg/dL)	1.23 [0.96-1.775]	1.34 [1.04-2.025]	1.14 [0.88-1.56]	0.022
eGFR, mean ± SD	59.297 ± 32.604	57.137 ± 30.415	60.542 ± 33.831	0.421
Sodium (mmol/L)	139.2 [134.375-142.4] N = 233	138.9 [134.2-142.45] N = 89	139.4 [134.325-142.375] N = 144	0.949
Potassium (mmol/L)	4.22 [3.718-4.765] N = 233	4.29 [3.815-4.975] N = 89	4.145 [3.56-4.725] N = 144	0.227
Random blood glucose (mg/dL)	126 [104-191]	135 [109.25-208]	119 [100-178]	0.036
CRP (mg/L)	49.84 [19.12-92.408] N = 178	59.705 [24.42-119.29] N = 66	46.655 [16.8-79.49] N = 112	0.058
D-dimer (ng/mL)	1,384 [675.75-3,568.25] N = 234	2,061 [1,203.25-5,087.75] N = 84	1,167 [592-2,657.25] N = 150	< 0.001

CRP = C-reactive protein. eGFR = estimated glomerular filtration rate. IQR = interquartile range. NLR = neutrophil-to-lymphocyte ratio.

Table 4: Treatments during hospitalization.			
	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Azithromycin	162 (63)	58 (61.7)	104 (63.8)	0.737
High flow nasal cannula	38 (14.8)	23 (24.5)	15 (9.2)	0.001
Vitamin C	233 (90.7)	86 (91.5)	147 (90.2)	0.729
Vitamin D	200 (77.8)	78 (83)	122 (74.8)	0.131
Zinc	80 (31.1)	31 (33)	49 (30.1)	0.627
N-acetylcysteine	150 (58.4)	61 (64.9)	89 (54.6)	0.107
Oseltamivir	40 (15.6)	9 (9.6)	31 (19)	0.044
Remdesivir	154 (59.9)	60 (63.8)	94 (57.7)	0.332
Favipiravir	58 (22.6)	24 (25.5)	34 (20.9)	0.388
Antibiotic	124 (48.2)	51 (54.3)	73 (44.8)	0.143
Anticoagulant	197 (76.7)	80 (85.1)	117 (71.8)	0.015
Unfractionated heparin	137 (53.3)	55 (58.5)	82 (50.3)	0.204
Low molecular weight heparin	53 (20.6)	13 (24.5)	30 (18.4)	0.247
Fondaparinux	7 (2.7)	2 (2.1)	5 (3.1)	1
Corticosteroid	90 (35)	34 (36.2)	56 (34.4)	0.769
Insulin	39 (15.2)	19 (20.2)	20 (12.3)	0.087
Anti IL-6	0	0	0	0
Plasma convalescent	55 (21.4)	28 (29.8)	27 (16.6)	0.013
IVIG	2 (0.8)	2 (2.1)	0	0.062

IL = interleukin. IVIG = intravenous immunoglobulin.

Table 5: Electrocardiography results.			
	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Duration of QRS complex (ms), median [IQR]	80 [80-100]	80 [80-100]	80 [80-100]	0.471
Duration of QT corrected (ms), median [IQR]	401 [373-426]	389.5 [362.5-429.75]	401 [376-423]	0.239
ST-T changes	13 (13.6)	17 (18.1)	18 (11)	0.113
Right bundle branch block	15 (5.8)	4 (4.3)	11 (6.7)	0.412
Left bundle branch block	3 (1.2)	3 (3.2)	0	0.048
Non-specific intraventricular conduction delay	4 (1.6)	0	4 (2.5)	0.3

IQR = interquartile range.

DM (OR 7.286; 95% CI 1.895-28.007; p = 0.001), CKD (OR 3.9; 95% CI 1.021-14.892; p = 0.036), leukocytosis during admission (OR 4.039; 95% CI 1.181-13.810; p = 0.019), and NLR > 6.82 during admission (OR 4.492; 95% CI 1.311-15.387; p = 0.011) were associated with hypotension requiring vasopressor. After multivariate analysis, only DM (adjusted OR 4.850; 95% CI 1.172-20.078; p = 0.029) remained associated

with hypotension requiring vasopressor, as shown in *Table 8*.

Regarding in-hospital mortality, age ≥ 65 years old (OR 5.785; 95% CI 1.901-17.598; p = 0.001), DM (OR 8.315; 95% CI 3.270-21.141; p < 0.001), CKD (OR 2.813; 95% CI 1.199-6.6; p = 0.016), leukocytosis during admission (OR 2.778; 95% CI 1.199-6.346; p = 0.016), and NLR > 6.82 during admission (OR 2.745; 95% CI 1.183-6.371; p = 0.017) were associated with in-hospital mortality in univariate analysis. Atrial arrhythmias were also found to increase the risk of in-hospital mortality. After multivariate analysis, only DM (adjusted OR 6.52; 95% CI 2.445-17.387; p < 0.001) remained associated with in-hospital mortality, as shown in *Table 8*.

DISCUSSION

This study involved 257 patients with confirmed COVID-19. The prevalence of arrhythmia in our study was 36.6%, which was higher than the previously reported prevalence.[5,6,16,17] We found that the most common arrhythmia was sinus tachycardia. This type of arrhythmia was in line with the previous study.[7] No VT or ventricular fibrillation was detected in our study. The need for IC, intubation and MV, hypotension requiring vasopressor, and in-hospital mortality were significantly higher in patients with arrhythmia than those without arrhythmia.

Table 6: Frequencies and type of arrhythmia in COVID-19 patients.

Arrhythmias	n (%)
Single arrhythmia	
Sinus tachycardia	65 (69.1)
Pre-existing atrial fibrillation	10 (10.6)
PVC	6 (6.4)
Sinus bradycardia	3 (3.2)
New-onset atrial fibrillation	2 (2.1)
Total atrioventricular block	2 (2.1)
First degree atrioventricular block	1 (1.1)
Multiple arrhythmias	
Sinus tachycardia and PAC	3 (3.2)
Sinus bradycardia, PVC, and first degree atrioventricular block	1 (1.1)
Sinus tachycardia and PVC	1 (1.1)

PVC = premature ventricular complex. PAC = premature atrial complex.

Table 7: Outcomes during hospitalization period.

	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
The need for ICU	85 (33.1)	47 (50)	38 (23.3)	< 0.001
Intubation and mechanical ventilation	9 (3.5)	7 (7.4)	2 (1.2)	0.009
Hypotension requiring vasopressor	20 (7.8)	15 (16)	5 (3.1)	< 0.001
Thromboembolic event	0	0	0	0
Major Bleeding	5 (1.9)	3 (3.2)	2 (1.2)	0.359
Stroke or TIA	2 (0.8)	1 (1.1)	1 (0.6)	1
Death	70 (27.2)	42 (44.7)	28 (17.2)	< 0.001

ICU = Intensive Care Unit. TIA = transient ischemic attack.

Table 8: Multivariate logistic regression analysis of the need of ICU in patients with arrhythmia.					
Univariate			Multivariate		
Variables	Unadjusted odds ratio (95% CI)	p	Variables	Adjusted odds ratio (95% CI)	p
The need for ICU					
Male sex	1.691 (0.741-3.860)	0.211	Diabetes mellitus	2.656 (1.114-6.333)	0.028
Age ≥ 65 years old	3.203 (1.117-9.186)	0.026	Leukocytosis during admission	2.354 (0.996-5.565)	0.051
Any cardiovascular comorbidity	2.074 (0.888-4.843)	0.09			
Diabetes mellitus	2.918 (1.248-6.824)	0.012			
Chronic kidney disease	1.681 (0.740-3.818)	0.213			
Leukocytosis during admission	2.616 (1.134-6.033)	0.023			
Thrombocytopenia during admission	0.393 (0.112-1.379)	0.135			
NLR > 6.82 during admission	2.641 (1.139-6.123)	0.017			
The need for intubation and mechanical ventilation					
History of stroke or TIA	17 (1.965-147.046)	0.027	History of stroke or TIA	46.426 (1.64-1314.392)	0.024
Leukocytosis during admission	3.224 (0.593-17.535)	0.24	Thrombocytopenia during admission	17.131 (1.623-180.777)	0.018
Thrombocytopenia during admission	5.775 (1.125-29.638)	0.053	NLR > 6.82 during admission	0.67 (0.005-0.882)	0.04
NLR > 6.82 during admission	8.914 (1.028-77.292)	0.041	New-onset atrial fibrillation	17.673 (0.777-402.004)	0.072
New-onset atrial fibrillation	14.333 (0.794-258.607)	0.144			
Premature atrial complex	7.083 (0.559-89.744)	0.209			
Hypotension requiring vasopressor					
Age ≥ 65 years old	5.802 (1.79-18.805)	0.004	Age ≥ 65 years old	3.288 (0.911-11.861)	0.069
Obesity	2.091 (0.687-6.444)	0.193	Diabetes mellitus	4.850 (1.172-20.078)	0.029
Tachycardia during admission	2.549 (0.748-8.69)	0.126	Leukocytosis during admission	3.039 (0.814-11.343)	0.098
Any cardiovascular comorbidity	2.87 (0.75-10.979)	0.112			
Diabetes mellitus	7.286 (1.895-28.007)	0.001			
Chronic kidney disease	3.9 (1.021-14.892)	0.036			
Leukocytosis during admission	4.039 (1.181-13.810)	0.019			
NLR > 6.82 during admission	4.492 (1.311-15.387)	0.011			

Continuos Table 8: Multivariate logistic regression analysis of the need of ICU in patients with arrhythmia.					
Univariate				Multivariate	
Variables	Unadjusted odds ratio (95% CI)	p	Variables	Adjusted odds ratio (95% CI)	p
In-hospital mortality					
Age ≥ 65 years old	5.785 (1.901-17.598)	0.001	Age ≥ 65 years old	3.404 (0.981-11.818)	0.054
Obesity	1.76 (0.722-4.012)	0.177	Diabetes mellitus	6.52 (2.445-17.387)	< 0.001
Hypoxia during admission	1.937 (0.848-4.422)	0.115	Leukocytosis during admission	2.289 (0.866-6.054)	0.095
Any cardiovascular comorbidity	2.143 (0.904-5.081)	0.081			
Diabetes mellitus	8.315 (3.270-21.141)	< 0.001			
Chronic kidney disease	2.813 (1.199-6.6)	0.016			
Leukocytosis during admission	2.778 (1.199-6.436)	0.016			
NLR > 6.82 during admission	2.745 (1.183-6.371)	0.017			
Atrial arrhythmias (AF & PAC)	2.091 (0.678-6.444)	0.193			

CI = confidence interval. AF = atrial fibrillation. ICU = Intensive Care Unit. NLR = neutrophil-to-lymphocyte ratio. PAC = premature atrial complex. TIA = transient ischemic attack.

The mean age of arrhythmia patients was 52.48 ± 13.94 years old. The mean age from our study was younger compared with earlier studies.[5-7,14] The younger study population may be explained by the admission criteria in our hospital. Our hospital is one of the referral COVID-19 hospitals in West Java. Therefore, we included patients transferred from other hospitals and primary healthcare facilities and traced from communities.

Based on previous studies, arrhythmia was associated with a critical illness.[6,16] From our findings, severe and critical disease severity was more commonly observed in patients with arrhythmia compared to patients without arrhythmia. Higher proportions of severe and critical COVID-19 cases may contribute to elevated in-hospital mortality among hospitalized patients with arrhythmia. Disease severity was reflected in vital signs, comorbidities, and laboratory results in patients with arrhythmia. The oxygen saturation was significantly lower in patients with arrhythmia during initial admission. Low presenting oxygen saturation was associated with severe disease.[18] Previous studies reported that several comorbidities, such as hypertension, DM, HF, and previous arrhythmia, were more prevalent in patients with arrhythmia.[6,16] Indeed, patients with arrhythmia in our study had significantly higher comorbidities (e.g. hypertension, HF, DM, CKD) than those without arrhythmia. The presence of comorbidities, including PEAF, increased the susceptibility to develop a severe COVID-19 disease.[19] Moreover, the neutrophil count, NLR, and D-dimer were significantly elevated compared to patients without arrhythmia. These inflammatory markers were significantly elevated in severe or critical COVID-19 cases.[20] Furthermore, the level of C-reactive protein (CRP), one of the inflammatory markers, was higher in patients with arrhythmia than in patients without, although the difference was not statistically significant.

Based on our cohorts, severe COVID-19 disease was more prevalent in patients with arrhythmia than those without, potentially increasing the risk of poor hospital outcomes for patients with arrhythmia. Theoretically, the combination of low oxygen saturation, high levels of inflammatory markers, and high level of proinflammatory cytokine during severe COVID-19 disease may lead to clinical deterioration during hospitalization.[21-23] In addition, arrhythmia-related changes in heart rate, whether too fast or too slow, may cause clinical instability.[11,24,25] However, our univariate and multivariate analysis did not find arrhythmia to be a predictor of in-hospital outcomes, as shown in *Tables 8 to 12*. Moreover, the most common arrhythmia in this study was sinus tachycardia, a minor arrhythmia with multifactorial aetiologies. Sinus tachycardia may reflect the more severe clinical features of COVID-19 disease but is less likely to cause clinical deterioration. On the other hand, NOAF and AV block may be more significant predictors of in-hospital outcomes than sinus tachycardia. However, neither NOAF nor AV block achieved a p-value < 0.25 and were not included as variables in our multivariate analysis. Thus, it appears that arrhythmia in hospitalized COVID-19 patients may be a marker of the disease's severity rather than a variable that worsens the COVID-19 disease. In addition,

univariate analysis was performed to identify the association between atrial fibrillation type and in-hospital outcomes, as presented in *Tables 9 to 12*. Neither NOAF nor PEAF were associated with in-hospital outcomes. However, NOAF is more easily attributable to the COVID-19 infection itself compared to PEAF. Suggesting the NOAF may act as a risk marker of COVID-19 infection, while PEAF may act as a risk factor to worse COVID-19 infection during hospitalization period.

From our study, the need for IC, hypotension requiring vasopressor, and in-hospital mortality were higher in patients with arrhythmia. Our study found an in-hospital mortality rate as high as 44.7%, and this in-hospital mortality rate of patients with arrhythmia was higher than in the previous studies.[6-8,16] Multivariate analysis showed that DM in patients with arrhythmia was associated with the need for ICU, hypotension requiring vasopressor, and in-hospital mortality. Diabetes mellitus can increase disease severity and progression to cardiorespiratory failure by increasing inflammatory cytokines, natural killer cells, reactive oxygen species, interleukin-6, D-dimer, and fibrinogen levels.[26] Diabetes mellitus in COVID-19 was also associated with a two-fold increase in mortality compared to those without DM.[27] Moreover, the presence of DM in our patients with arrhythmia was higher than

Table 9: Type of arrhythmia and the need for Intensive Care Unit.		
Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	0.897 (0.359-2.240)	1.000
Pre-existing atrial fibrillation	1.573 (0.414-5.981)	0.740
PVC	1.573 (0.414-2.134)	0.740
Sinus bradycardia	0.319 (0.32-3.182)	0.617
New-onset atrial fibrillation	–	0.495
Total atrioventricular block	–	0.495
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	–	0.056

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

Table 10: Type of arrhythmia and the need for intubation and mechanical ventilation.		
Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	2.286 (0.261-19.991)	0.671
Pre-existing atrial fibrillation	–	1.000
PVC	–	1.000
Sinus bradycardia	–	1.000
New-onset atrial fibrillation	14.333 (0.794-258.607)	0.144
Total atrioventricular block	–	1.000
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	3.458 (0.332-36.000)	0.327

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

Table 11: Type of arrhythmia and hypotension requiring vasopressor.		
Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	1.544 (0.397-6.000)	0.752
Pre-existing atrial fibrillation	0.556 (0.65-4.742)	1.000
PVC	1.365 (0.260-7.170)	0.659
Sinus bradycardia	–	1.000
New-onset atrial fibrillation	5.571 (0.329-94.371)	0.295
Total atrioventricular block	–	1.000
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	2.897 (0.593-25.629)	0.179

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

in previous studies.[6-8,16] During the period of data collection, the shortage of doctors, nurses, personal protective equipment, ventilators, and COVID-19 drugs occurred in our hospital. Furthermore, Indonesia ranked first with the most COVID-19 cases in Southeast Asia, according to the Center for Strategic and International Studies (CSIS).[28] Combined, this may contribute to higher in-hospital mortality rates compared to previous studies from developed countries and may also explain the higher need for IC and hypotension requiring vasopressor in patients with arrhythmia.

History of stroke, thrombocytopenia during admission, and NLR > 6.82 during admission were associated with the need for intubation and mechanical ventilation. However, the confidence interval was too wide to draw firm conclusions, and NLR > 6.82 during admission reduced the risk for intubation and mechanical ventilation after multivariate analysis. This finding was contrary to the previously reported

study.[29] A relatively small number of patients with arrhythmia who required intubation and mechanical ventilation may explain this difference.

From our study, we reported zero incidences of thromboembolic events. At the time of writing this article, our hospital could not perform urgent Doppler ultrasonography for confirming deep vein thrombosis and urgent computed tomography pulmonary angiography or invasive pulmonary angiography for confirming pulmonary embolism. Therefore, the true incidence of either deep vein thrombosis or pulmonary embolism may be missed.

The main limitation of our study was the inability to perform continuous electrocardiographic monitoring on patients outside the ICU ward. Hence, the arrhythmia prevalence in patients with asymptomatic and mild disease may be missed. Second, the study design was cross-sectional, and data were retrospectively collected based on medical records. Changing the study design to a prospective one and contemplating the inclusion of patients with known pre-existing arrhythmia only when they have been diagnosed with COVID-19 could be a valuable consideration. Third, we failed to establish a causal link or a comparative effect between primary arrhythmia and in-hospital outcomes. Fourth, we included patients admitted due to other medical indications that tested positive for COVID-19. Fifth, the relatively small sample size of patients with arrhythmia was included in the multivariate logistic regression analysis resulting in a wide confidence interval. Sixth, some laboratory data, such as electrolyte, CRP, and D-dimer, were not complete and were not included as variables in the multivariate logistic regression analysis. Finally, markers of myocardial injury and pro-inflammatory cytokines were not measured, preventing us from assessing their association with arrhythmia in hospitalized COVID-19 patients.

CONCLUSIONS

According to our data, the in-hospital outcomes in patients with COVID-19 and arrhythmia are the worst. Severe and critical COVID-19 disease was more commonly observed in patients with arrhythmia than in patients without arrhythmia. The arrhythmia may be a marker of severe COVID-19 disease rather than a variable that worsens COVID-19 disease. Diabetes mellitus is associated with a higher need for IC, hypotension requiring vasopressor, and in-hospital mortality in patients with arrhythmia. A history of stroke/TIA and thrombocytopenia during admission are associated with a higher need for intubation and mechanical ventilation. Further prospective trials with a larger sample size are needed to confirm this finding.

Table 12: Type of arrhythmia and in-hospital mortality.		
Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	1.038 (0.413-2.608)	1.000
Pre-existing atrial fibrillation	2.000 (0.525-7.615)	0.334
PVC	0.807 (0.212-3.070)	1.000
Sinus bradycardia	–	0.125
New-onset atrial fibrillation	–	0.500
Total atrioventricular block	–	0.197
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	1.923 (0.306-12.079)	0.653

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

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Initial experience with zero or near zero-fluoroscopy to perform catheter ablation of supraventricular tachycardias in a private practice setting

Experiencia inicial para la realización de ablaciones con catéter de taquicardias supraventriculares sin fluoroscopia, o casi 0-fluoroscopia en una práctica privada

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ABSTRACT

Introduction: fluoroscopy has been the main navigation tool in electrophysiology for decades, but it has inherent risks to both patients and the medical team. Zero-fluoroscopy systems have been used for several years now and they show a safer profile, although their costs are of concern. **Material and methods:** in 2022, we collected information about patients selected for electrophysiological study and supraventricular arrhythmia ablation in our group in central Mexico City and presented them as a series of cases. **Results:** ten patients were treated without fluoroscopy or with minimal radiation exposure during the year. They were mostly young (43.6 ± 20.8 years old) female subjects (80%). The mean procedure duration time was 118 ± 17.1 minutes. There were no immediate complications, and all the procedures were successful regarding the elimination of the arrhythmia substrate. **Conclusions:** this is a small series of patients representing an initial approach in our community to introduce 0-F procedures with good results and within safe limits for patients and the medical team.

RESUMEN

Introducción: la fluoroscopia ha sido la herramienta de navegación empleada en electrofisiología por décadas, sin embargo, tiene riesgos inherentes para el paciente y el equipo médico. Los sistemas de cero-fluoroscopia se han usado desde hace varios años y han mostrado ser seguros, aunque los costos deben considerarse. Material y métodos: durante 2022 se recopilaron los datos de pacientes consecutivos sometidos a estudio electrofisiológico y ablación por arritmias supraventriculares en una ciudad del centro de la República Mexicana. Se presentan los datos como una serie de casos. Resultados: durante el año se trataron 10 pacientes sin fluoroscopia o con una exposición mínima a radiación. Fueron predominantemente mujeres (80%) jóvenes (43.6 ± 20.8 años). El tiempo promedio de duración del procedimiento fue de 118 ± 17.1 minutos. No hubo complicaciones inmediatas y se logró la eliminación del sustrato arrítmico en todos los casos. Conclusiones: esta es una pequeña serie de pacientes que representa la experiencia inicial en nuestra comunidad para introducir procedimientos de 0-fluoroscopia con buenos resultados y seguridad tanto para el paciente como para el equipo sanitario.

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INTRODUCTION

Interventional electrophysiologic procedures have increased both in frequency and complexity. Fluoroscopy has been the main imaging technique to perform intracardiac catheter navigation for a long time. Nonetheless, it has deterministic risks (dose-related) as skin lesions and stochastic risks (dose-independent) as increased neoplasia risk and genetic damage.[1,2]

Those deleterious effects from radiation are worrisome in obese subjects, young persons or patients that will receive long, complex or

repeated procedures. On the other hand, the medical team (operators, nurses, technicians) is exposed on a daily or nearly daily basis to significant ionizing radiation doses that increase the risk of cancer, cataract and congenital defects, especially in high volume centers and even with the use of protective personal equipment, that in some instances (such as in low volume centers) is not always available or is suboptimal.[2-4] In Mexico, many facilities outside large medical centers do not have enough personal protection equipment or do not totally comply with the «Reglamento general de seguridad radiológica»;[5] although this is a non-published observation.

New navigation technologies without fluoroscopy, which also allow obtaining electro-anatomic intracardiac maps, significantly reduce radiation exposure during diagnostic and therapeutic-ablation procedures, even in complex cases.[4,6-11] The ALARA principle «As low as reasonably achievable» to reduce as much as possible ionizing radiation exposure is an old recommendation of the American College of Cardiology[12] that remains paramount for safety.

Several studies have shown that procedures without fluoroscopy are safe and effective, with a relatively fast learning curve and they show a significant reduction in radiation exposure for the patient and the medical team.[13,14] This was the reason to start a zero-fluoroscopy (0-F) or «near-zero fluoroscopy» program in our group. We ought to evaluate its viability in a private practice setting of a middle size city (1,049,777 inhabitants according to the 2020 national census) and present here an initial series of cases of patients submitted for electrophysiologic study and ablation for different arrhythmias.

MATERIAL AND METHODS

A descriptive study was performed. Data were prospectively collected from consecutive cases referred for supraventricular tachy-arrhythmia ablation from January 2022 to December 2022. A meeting before the intervention was devoted to explain the technique to the patients and their nests of kin, the expected benefits and the risk of complications of the procedure. After their doubts were answered, all patients signed an informed consent according to the hospital's policies. The patient's confidentiality was respected and no individual data was revealed to or used by other parties. All patients had medical insurance so that expensive electroanatomic mapping systems could be used. Complex cases (Atrial fibrillation, ventricular premature beats, atrial tachycardias) were performed with electro-anatomical mapping systems (Biosense Webster CARTO© or Abbott EnSite©), but we did not discard a priori fluoroscopy use. The analysis is mainly based on subjects with atrio-ventricular reentry through accessory pathways and atrio-ventricular node reentry tachycardia since these are less complex arrhythmias to treat and more suitable to gain experience.

We included demographic, initial and final electrophysiologic data, use or not of fluoroscopy, procedure time-length and location of the successful ablation site. Recurrences during the follow-up period in 2022 were also recorded.

In every patient an individualized clinical review was performed, as well as an electrocardiogram (ECG) analysis in sinus rhythm and, when available, with the symptomatic tachycardia (either 12-lead ECG or Holter monitoring tracing). According to this evaluation, we planned the vascular access, usually beginning with right femoral vein punctures (two or three) guided by ultrasound under local anesthesia. If needed, we inserted a femoral artery catheter (usually the ablation catheter) to reach left side accessory pathways, also with ultrasound guidance.

We routinely placed a decapolar catheter in the coronary sinus and a tetrapolar catheter in the atrio-ventricular node area to identify a His bundle potential. The EnSite mapping system depicts the vascular trajectory from the iliac vein to the superior vena cava and cardiac chambers. We performed an initial diagnostic electrophysiologic (EP) study during which we measured conduction intervals, atrial and ventricular refractory periods and antegrade and retrograde Wenckebach points. A decapolar coronary sinus catheter and a tetrapolar right atrial catheter were inserted for that purpose. Both were the initial mapping tools to reconstruct the intracardiac

anatomy. If the arrhythmia was induced with these maneuvers, we interrupted it by stimulation (entrainment, extrastimuli, or override pacing). Once the baseline study was finished and the diagnosis was established, the radiofrequency (RF) ablation catheter was introduced (either by venous or arterial approach), and we searched for the best ablation site with the electroanatomical mapping functions, as well as the conventional signal recording of the catheter to the polygraph. We used irrigated catheters to apply RF, and once the responsible structure was eliminated, we did a new tachycardia induction protocol. In all cases, we used radiofrequency as the energy source, and the RF generator was adjusted according to the area to be ablated by temperature, impedance and power. If the ablation was successful, we waited for 20 to 30 minutes to repeat the induction protocol, and if the absence of arrhythmia was corroborated, we concluded the procedure and catheters and introducers were withdrawn. In every case, there were adaptations to the technique based on anatomical and functional characteristics that would be too long to depict here, and it is not the objective of this presentation.

Statistical analysis

Categorical variables are expressed in total and percent values. Continuous variables are shown in averages ± standard deviation. We did a comparison between the initial and final electrophysiological variables of the study using a paired T-test for the continuous variables.

RESULTS

During 2022 we performed 28 electrophysiologic studies and ablations. We present ten consecutive cases of supraventricular tachycardia treated without fluoroscopy or with near-0 fluoroscopy. There were seven female patients (80%), and the group's average age was 43.6 ± 20.8 years. The mean procedure time in the group was 118 ± 17.1 minutes, including the described waiting period after ablation to ensure a lack of immediate recurrence. The mean fluoroscopy time was 1.2 ± 2.1 seconds for the whole group, but as seen in *Table 1*, fluoroscopy was only used in three patients to ensure the femoral introducers' guidewire position or, in one case, evaluate the fluoroscopic aspect of a coronary sinus catheter. The shortest X-ray exposure was two

Table 1: General description of the cases. N = 10.										
Case number	Age (years)	Gender	Arrhythmia	Procedure duration (min)	Fluoros duration (seg)	Mapping system	Venous accesses	Arterial accesses	Radio frequency duration (min)	Successful ablation
1	53	Female	AVNRT	150	0	Ensite	2	0	2.54	Yes
2	48	Female	AVNRT	140	0	Ensite	2	0	2	Yes
3	34	Female	AVNRT	120	0	Ensite	3	0	2.5	Yes
4	81	Female	AVNRT	120	0	Ensite	3	0	2.5	Yes
5	68	Female	AVNRT	130	0	Ensite	3	0	3	Yes
6	15	Male	AVRT right PS	90	5	Ensite	3	0	2	Yes
7	14	Male	AVRT left post	140	0	Ensite	3	1	2	Yes
8	40	Female	AVRT left lateral	120	5	Ensite	3	1	2.5	Yes
9	45	Female	AVNRT	110	2	Ensite	3	0	2	Yes
10	38	Male	AVRT left antero-lateral	60	0	Ensite	2	1	3	Yes

AVNRT = atrio-ventricular node re-entry tachycardia. AVRT = atrio-ventricular re-entry tachycardia. PS = postero-septal. Post = posterior. Lat = lateral.

Table 2: Electrophysiologic parameters.			
Electrophysiologic parameter	Pre-ablation	Post-ablation	p
Atrium-his interval (AH)	68.13 ± 16.49	65.43 ± 17.8	0.33
His-ventricle interval (HV)	46.1 ± 14.7	51.6 ± 6.52	0.39
Anterograde Wenckebach point (PWA)	341.25 ± 82.3	330 ± 42.4	0.25
Retrograde Wenckebach point (PWR)	313.3 ± 73.03	432 ± 113.9	0.301

Figure 1:

Cartographic location of the slow pathway in an atrioventricular node reentrant tachycardia.

The projection is a right anterior oblique, almost in a lateral position, as can be seen in the tracking image in the superior right corner of the image.

seconds, and the longest was five seconds. All the vascular accesses were performed under vascular ultrasound guidance.

In one patient, we had to do an electro-anatomic «remap» because the electrogram signals obtained by the intracardiac catheter were not accurately concordant with the position of the catheter in the represented electroanatomic map.

If a fast nodal rhythm appeared during RF administration, for example, in the case of a slow nodal pathway ablation, RF was immediately stopped and the ablation catheter was repositioned to a safer zone, more distal to the His bundle area-electrogram. The same happened with a postero-septal accessory pathway. This is why the main number of RF pulses was not included; instead, we recorded the total RF time.

Table 1 shows the main characteristics of the patients. Six had atrio-ventricular node reentry tachycardia, and 4 had atrio-ventricular reentry through an accessory pathway. Table 2 shows the electrophysiologic parameters before and after ablation. The main cycle length of the AVNRT was 287.5 ± 41.1 ms, and for the accessory pathways (AVRT), it was 309.6 ± 60.25 ms. Figure 1 shows a common cartographic map of Koch's triangle, the area suitable for the ablation of a slow conduction pathway in the case of a patient with AVNRT.

In all the patients submitted to ablation with the present protocol, there was a successful

elimination of the arrhythmia in the acute setting, and during follow-up (that went from 11 months to one month) there were no recurrences in the treated patients, nor chronic complications. We had no acute complications during the procedures, and since the vascular approach was performed under ultrasound guidance, there was only one patient with a minimum hematoma in the puncture site that did not require further treatment prior to his discharge the following day after the cardiac ablation procedure.

DISCUSSION

Electrophysiology procedures without fluoroscopy have become a safe and doable option in many places in the world. To the health team in charge of doing them, reducing ionizing radiation exposure has significant advantages. A study by Marazziti et al.[15] in 2015 found that interventional cardiologists have a high risk of presenting problems ranging from neuropsychological deterioration of cognitive functions related to the left hemisphere to brain neoplasia and orthopedic lesions. So, a reduction of exposure may limit those problems. Patients also show benefits from reduced radiation exposure, as mentioned in the introduction.[1,2] When initiating zero or near-zero fluoroscopy interventions, starting with «simple» substrates located in the right cavities is recommended: reentrant tachycardia in the atrioventricular node or common atrial flutter for example. We did not include flutter, instead, we ablated accessory pathways. In order to gain confidence, large centers suggest that radiological protection can be worn, and the position of the catheters obtained from the navigator and electroanatomical mapping can be confirmed with conventional fluoroscopy. In our cases, the few seconds of fluoroscopy were mostly used to confirm a guidewire position in the venous or arterial position next to the puncture site.

Once enough confidence has been obtained, the use of radiation protection garments could be discontinued to achieve another advantage of the Zero-Fluoroscopy procedure: avoid spinal injuries. The next step is to gradually increase the number and complexity of the arrhythmic substrates to be treated.

In this series of cases, there were more female subjects. Chen et al.[16] observed a higher prevalence of women in the 0-F group, as in another study with fewer patients,[17] but as the number of subjects included is higher, that appreciation loses its significance. We are aware that there is a selection bias in our series due to the higher proportion of young women of fertile age that were included. This difference might be reduced as more patients are included in the future.

Several studies have demonstrated that there are no significant differences in the success rate of different tachycardias ablation with any of both approaches.[2,13,17-20] None of the patients in this series had structural heart damage, a fact that helps in the overall positive success rate, as showed in the study by Kawakami et al.[21] They made extensive use of intracardiac echocardiography (ICE) and ultrasound-guided venous and atrial septal puncture (transesophageal echo), thereby obtaining a reduction in intervention-related complications. In the present cases, no further ultrasound support was required.

There were no significant differences in the EP parameters before and after the procedure. This finding suggests that the technique is as safe as the conventional approach and somehow reinforces the concept that it is not associated with higher complication rates, as has been found in similar work with 14 patients by Robledo et al.[22] The precise location of anatomical structures such as the atrio-ventricular node in an electroanatomic map might reduce the risk of damage with RF.

Prolic et al.[18] showed a longer duration of the ablation procedures when performed without fluoroscopy, but Chen et al.,[16] found that the difference between fluoroscopy-guided and 0-F procedures disappeared as the team acquired more experience with the navigation systems. This fact is usually attributed to the learning curve of the operators.[13,19,23]

Limitations

This article is a descriptive case series study. Even if the data collection was prospective

and in consecutive patients, the navigation method choice was biased by the kind of patient, gender, age and the arrhythmia diagnosed by a 12-lead ECG. As we gather more experience, the probability to produce comparative results between a 0-F group and a conventional one, with different types of arrhythmias will be higher. Nonetheless, even while complying with the ALARA principle, complex arrhythmias might require a combined approach (fluoroscopy-electroanatomic mapping) to achieve successful results.

The number of patients is another limitation, partly explained by the intervention costs, the selection mode and the frequency at which EP procedures can be performed out of a specialized center.

CONCLUSIONS

The present study shows that a 0-F program is feasible in a private practice setting in a medium size city, although the time to reach a considerable volume of patients might be longer than desired. Our results are comparable to the findings of others and suggest that these 0-F or near 0-F ablations are achievable within safe limits for the patients and the medical team.

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Palpitations as manifestation of lipomatous hyperplasia interatrial septum: case report and review of the literature

Palpitaciones como manifestación de hiperplasia lipomatosa del tabique interauricular: reporte de caso y revisión de literatura

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ABSTRACT

Lipomatous hypertrophy of the interatrial septum is increasingly recognized and should be considered as part of the differential diagnosis of any cardiac tumor. We present the case of a 70-year-old patient who presented to the outpatient service for palpitations. Transthoracic echocardiogram (TTE) detected thickening of the interatrial septum with proximal predominance with respect to the fossa ovalis. The diagnosis was confirmed by cardiac magnetic resonance imaging. In such cases, the opinion of a cardiologist with expertise in cardiac imaging would help to avoid misdiagnosis and unnecessary intervention. This condition is more common than initially thought and remains under-recognized by most physicians.

RESUMEN

La hipertrofia lipomatosa del tabique interauricular se reconoce cada vez más y debe considerarse como parte del diagnóstico diferencial de cualquier tumor cardiaco. Presentamos el caso de un paciente de 70 años que acudió al servicio ambulatorio por palpitaciones. El ecocardiograma transtorácico (ETT) detectó engrosamiento del septo interauricular de predominio proximal con respecto de la fosa ovalis. El diagnóstico fue confirmado por resonancia magnética cardiaca. En tales casos, la opinión de un cardiólogo experto en imagen cardiaca ayudaría a evitar un diagnóstico erróneo y una intervención innecesaria. Esta condición es más común de lo que se pensó inicialmente y sigue siendo poco reconocida por la mayoría de los médicos.

INTRODUCTION

Lipomatous hypertrophy of the interatrial septum (LASH) is a benign lesion characterized by an excessive accumulation of adipose tissue in the interatrial septum exceeding 2 cm in thickness and forms part of the differential diagnosis between malignant and benign tumors of the atrium.[1] As most patients with this condition remain asymptomatic, cases are usually detected as an incidental finding at the time of cardiac imaging, surgery or necropsy.[2] Consequently, this condition remains under-recognized by most physicians and therefore can easily be mistaken for a malignant lesion, subsequently leading to unwarranted surgical removal.

We present a case of a patient with persistent palpitations as a manifestation of an LASH, discuss the main features of this lesion and the importance of the diagnostic role of noninvasive imaging modalities, and briefly review the current literature.

DESCRIPTION OF THE CASE

A 70-year-old woman with a history of hypertension and dyslipidemia. The patient consulted for a long-standing clinical picture of occasional irregular palpitations, without

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syncope, attended cardiology consultation where Holter was taken with evidence of frequent supraventricular ectopias with arrhythmic load of 1%, echocardiogram with image suggestive of lipomatous hyperplasia *(Figure 1)* cardiac MRI was performed with evidence of left ventricle with normal function and size confirming the diagnosis without evidence of late enhancement *(Figures 2 and 3)*, beta-blockers were added and the patient is currently under follow-up with improvement of the initial symptoms.

DISCUSSION AND LITERATURE REVIEW

Lipomatous hypertrophy of the cardiac interatrial septum is a rare but increasingly recognized benign anomaly of the heart.[3] It was first described in 1964 following postmortem examination.[4] Since then, this condition has been extensively documented in various case reports and original articles. The lipomatous lesion derives mainly from the superior and/or inferior part of the interatrial septum, typically respecting the fossa ovalis, giving a characteristic, considered by some to be pathognomonic, hourglass-shaped image, with a tendency to stand out in the right atrium, which may be related to a thickening of the terminal ridge *(Figures 1 and 2)*.

Lipomatous hypertrophy of the interatrial septum is a frequent finding on echocardiography
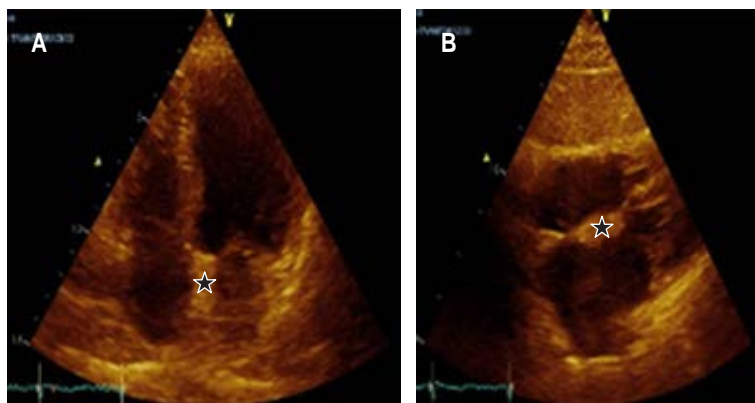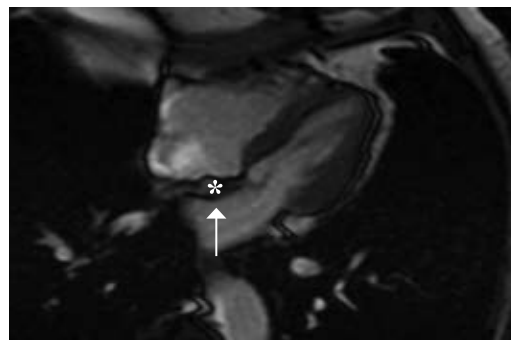
Figure 2: 4-chamber cine. Lesion in the interatrial septum with high signal intensity in relation to the myocardium (asterisk). The lesion presents artifact in India ink (low intensity line surrounding the lesion), indicating the presence of fat (arrow).

with a reported incidence of 1 to 8% of the general population.[5] Cases previously described in the literature were based on incidental autopsy, surgical, and clinical imaging findings or were associated with the symptomatic course of the disease.[6] Risk factors for LASH include emphysematous pattern with use of steroid therapy in higher frequency for elderly women, in which predisposition to mediastinal and intracardiac deposition of fatty tissue, cerebrotendinous xanthomatosis, mediastinal-abdominal lipomatosis and long-term parenteral nutrition are observed.[7] Lipomas account for about 10% of cardiac neoplasms and are discrete accumulations of tissue grade that are usually extramyocardial and present as a defined rounded mass.[8] While similar in tissue characterization to lipomas, LASH on TTE respects the boundaries of the atrial septum and usually respects the fossa ovalis.[9] On transesophageal echocardiogram, LASH appears as an echodense globular thickening of the interatrial septum that is best seen in the bicave projection.[10]

Although it is a benign tumor that remains asymptomatic in most people, it may be associated with atrial arrhythmias that often require antiarrhythmic drugs. The arrhythmia, rarely associated with LASH, was first observed in 1969 by Kluge.[11] The mechanism of its occurrence has not been well explained, however, it appears to be related to infiltration of fatty tissue that interferes with the structure of atrial myocytes, thus disrupting normal

Figure 1: A) Four-chamber view shows increased thickness of the interatrial septum. **B)** Subcostal view, thickening of the interatrial septum with proximal predominance with respect to the fossa ovalis («hourglass sign»).

★ = interatrial septum.

conduction pathways.[3] The arrhythmia manifests mainly in atrial fibrillation, atrial extrasystoles, supraventricular arrhythmias, ectopic and junctional rhythms. The incidence of atrial arrhythmia is also presumed to be related to septal thickness.[12]

This case highlights that while most LASH has the standard «dumbbell» appearance on TTE, there are cases where it may appear more like an adherent mass causing a wider differential. Noncontrast cardiac computed tomography (CT) can be used to confirm LASH by presenting low attenuation values for tissue (-80 to -120 HU) in the area of the atrial septum.[7] Alternatively, CMR (cardiac magnetic resonance imaging) can be used for tissue characterization and confirmation of LASH. Steady-state pre-contrast free precession T2/T1-weighted cine CMR images show high signal

Figure 3: Axial T1 FSE **(A)** and 4-chamber STIR **(B)**. Lesion in the interatrial septum (asterisk), of «dumbbell» or «hourglass» morphology, with high signal intensity in T1 **(A)**, with signal drop in fat saturation sequence **(B)**, suggesting the presence of fat. The morphology of the lesion and the presence of fat suggest the diagnosis of lipomatous hypertrophy of the interatrial septum.
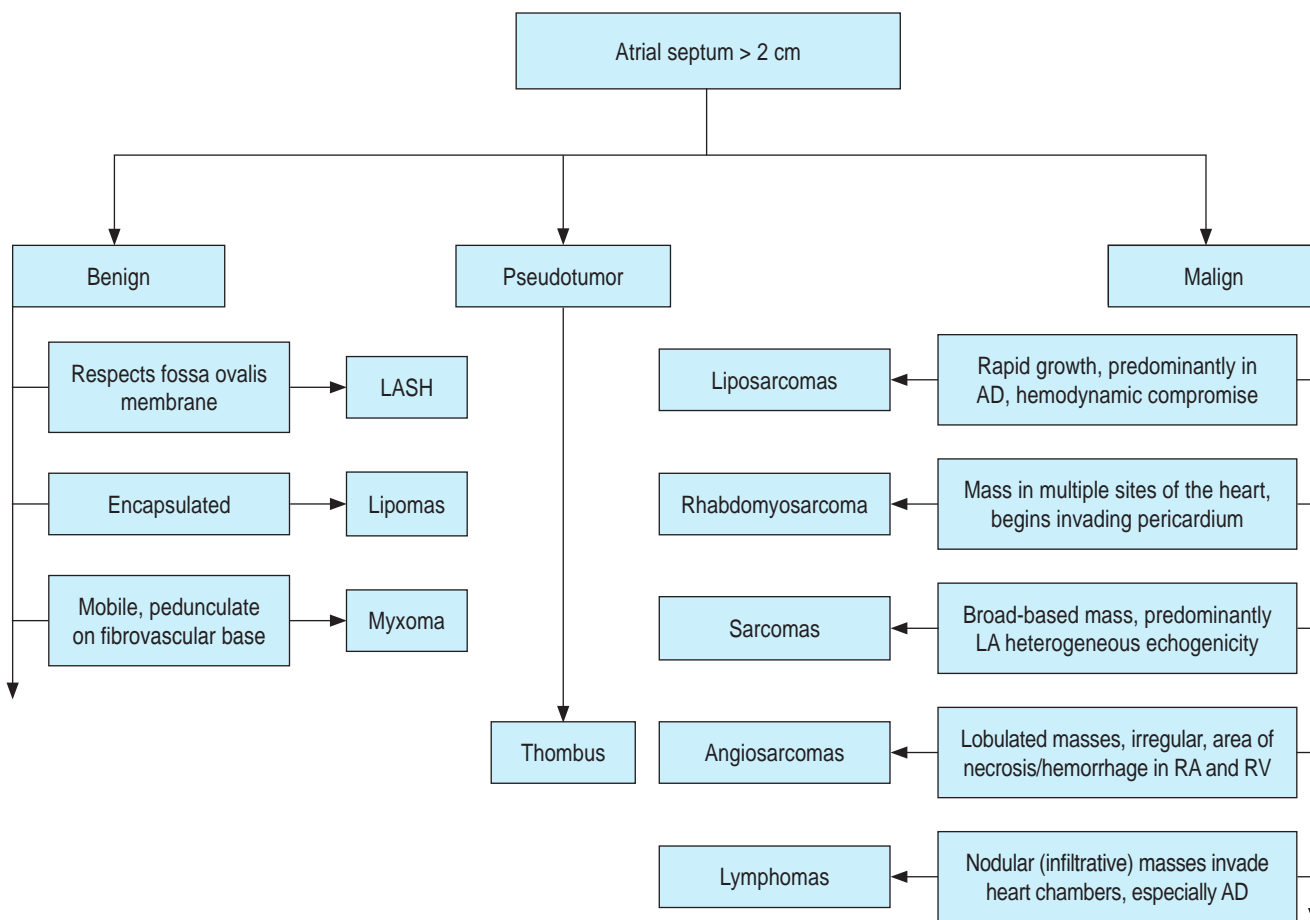
Figure 4: Atrial septal thickening approach.

intensity in the area of LASH and elicit a black limiting/hypointense effect between fat and myocardium *(Figures 2 and 3)*.[13] Because the structural features of this lesion are so distinct from any other intracardiac mass, definitive diagnosis without the need for tissue biopsy is now widely accepted.

Making the differential diagnosis of LASH from other cardiac neoplasms based on conventional imaging findings can be difficult. Myxomas are the most common primary cardiac tumors and account for 30% to 50% of all cases.[14] Most myxomas are solitary and are located in the atria. They arise from the interatrial septum in the vicinity of the foramen ovale, whereas the foramen ovale is always spared in LASH. In addition, most myxomas are pedunculated on a fibrovascular stalk, which differentiates them. Cardiac lipoma is a true neoplasm occurring in younger patients. Lipomas are encapsulated, which is never seen in LASH.[14] Rhabdomyomas and fibromas are common cardiac tumors in infants and children, and usually occur in the ventricles. Cardiac liposarcoma, a rare entity occurring predominantly in the right atrium, is a rapidly growing tumor with early signs of local invasion and hemodynamic compromise.[15] Intraseptal cardiac liposarcomas have never been described. Its incidence is high in malignant melanoma, lymphoma and leukemia, where it occurs in the context of extensive disease.[16]

In our case presented with the «typical» hourglass appearance seen on TTE, a multimodality approach was used to narrow the differential diagnosis and arrive at a definitive diagnosis of LASH without requiring tissue biopsy. Lipomatous hypertrophy of the interatrial septum is a benign condition in most cases. Rarely, if severe interatrial hypertrophy is present, patients may develop right atrial filling obstruction (marginal obstruction of the superior vena cava or right atrium), shortness of breath and/or symptoms of heart failure. LASH can coexist with other intracardiac malignancies, which would warrant resection of the lesion with simultaneous interatrial septal plasty.[17] Our case does not present these conditions and therefore was not a candidate for surgical management.

Considering the increase in life expectancy of the general population, the evolution of non-invasive imaging techniques and the increase in the prevalence of obesity, the probability of identifying this lesion will increase. We suggest a diagnostic algorithm for atrial septal hypertrophies in order to have a timely diagnosis and an adequate approach *(Figure 4)*.

CONCLUSIONS

LASH is a benign lesion of the atrial septum, often asymptomatic. The role of multimodality imaging techniques in the diagnosis of LASH is essential. Making a correct and timely diagnosis prevents the patient from undergoing futile examinations with probable economic, social and psychological consequences, since in most cases of LASH, management consists of rapid diagnosis, reassurance and periodic follow-up.

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Glycated hemoglobin fundamentals. Value and advantages in practical clinical

Fundamentos de la hemoglobina glicada. Valor y ventajas en la práctica clínica

Mariana Sue Camarena-Hidalgo,* Eduardo Meaney,‡ Pilar Ortiz-Vilchis‡

ABSTRACT

The glycated hemoglobin (HbA1c) test is a useful, economic, and practical clinical tool for long-term glycemic control in patients with diabetes mellitus (DM). Historically, since 1955, the HbA1c was described for the first time by Kunkel and Wallenius as a minor fraction of human hemoglobin. However, until the 70s, the molecule was recognized as a glycemic control marker. The HbA1c is a conjugated protein (heteroprotein, hemoglobin-glucose) formed through the non-enzymatic and post-translational process called glycation (Maillard reaction) as a stable Amadori product. If the reaction continues, the final results are irreversible products called advanced glycation end products (AGEs). AGEs are responsible for modifying proteins of the whole tissues and contribute to inflammatory reactions mediated by the AGE receptor and complications of DM. Additionally, HbA1c levels of less than 7% have been associated with reducing microvascular and macrovascular lesions. An adequate evaluation and monitoring routinely of HbA1c levels would allow adequate glycemic control and help to reduce the risk of future complications.

RESUMEN

La prueba de hemoglobina glucosilada (HbA1c) es una herramienta clínica útil, económica y práctica para el control glucémico a largo plazo en pacientes con diabetes mellitus (DM). Históricamente, desde 1955, la HbA1c fue descrita por primera vez por Kunkel y Wallenius como una fracción menor de la hemoglobina humana. Sin embargo, hasta la década de los 70, la molécula fue reconocida como un marcador de control glucémico. La HbA1c es una proteína conjugada (heteroproteína, hemoglobina-glucosa) formada a través de un proceso no enzimático y postraduccional llamado glicación (reacción de Maillard) como un producto estable de Amadori. Si la reacción continúa, los resultados finales son productos irreversibles llamados productos finales de glicación (AGE, por sus siglas en inglés). Los AGE son responsables de modificar las proteínas de todos los tejidos y contribuyen a las reacciones inflamatorias mediadas por el receptor AGE y las complicaciones de la DM. También, los niveles de HbA1c inferiores a 7% se han asociado con la reducción de lesiones microvasculares y macrovasculares. Una adecuada evaluación y monitorización rutinaria de los niveles de HbA1c permitiría un adecuado control glucémico y ayudaría a reducir el riesgo de futuras complicaciones.

INTRODUCTION

Glycated hemoglobin (HbA1c), still in recent times, is the most useful, economical, and practical clinical tool for long-term glycemic control in patients with diabetes mellitus (DM).[1,2] Unfortunately, many aspects regarding its basic biology, assay and standardization techniques, sensitivity, pitfalls, and shortcomings, and its correlation with micro and macrovascular lesions in DM, remain not fully understood by many practitioners. This review aims to make this important clinical instrument's basic and clinical foundations available to caregivers, especially in medical care's first and second levels. After this brief introduction, the paper is organized as follows. The HbA1c history is presented.

The Hb variants section presents the principal features of hemoglobin, different types of Hb, and Hb variants caused by genetic alterations. The glycation and glycosylation

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reactions are detailed in the following sections (glycation, glycated hemoglobin, glycation vs glycosylation). Some important points about glycemic control are presented in the measurement of HbA1c, HbA1c in the initial diagnosis of diabetes mellitus, and shortcomings of HbA1c sections. Next, HbA1c and the microvascular and microvascular diabetic complications are supported. Finally, this paper is concluded.

HBA1C HISTORY

The history of HbA1c started in 1955 when Kunkel and Wallenius reported the separation of minor fractions of human hemoglobin (Hb) by electrophoresis.[3] Subsequent studies using chromatographic techniques confirmed the presence of adult and fetal types of Hb,[4] and five minor subtypes of adult Hb (HbA1c) were named a, b, c, d, and e.[4,5] In 1962, Huisman,[6] through cellulose acetate electrophoresis, found an HbA minor variant in diabetic patients, while Rahbar, in 1969, observed that one of these Hb bands generated a rapid positional movement, later described as a «fast-moving abnormal hemoglobin band», and recognized it as the subfraction HbA1c.[7,8] Since the 70s, the molecule has been recognized as an excellent marker of glycemic control and micro and macrovascular diabetic complications.[9]

HB VARIANTS

Hb is a protein found in red blood cells, composed of two globin dimers associated with a heme group whose primary role is oxygen transport.[10] The two αβ dimers (named α1β1 and α2β2) are arranged around a 2-fold axis of symmetry resulting in a large central water cavity (deoxygenated structure) and a thinner cavity oxygenated structure.[11] Through electrophoresis, different types of Hb were identified, as already stated, allowing a classification according to subunits conformation (a, b, or g dimers)[12] in three main groups: hemoglobin A1 (HbA), which is the most abundant type in adults (~96%), hemoglobin A2 (HbA2, frequency about 2.3-2.8%), generally found in small amounts in adults and hemoglobin F (HbF < 2%), mainly

found in fetuses and newborns.[5] In addition, there are abnormal genetic hemoglobinopathies such as α- and β-thalassemia syndromes and structural Hb variants (HbS found in sickle cell anaemia, and the variants of HbE and HbC diseases, among others).[13-15]

Furthermore, many Hb variants are secondary to gene deletions, insertions, polymorphisms, or mutations, which are the basis of different types of hemoglobinopathies.[16,17]

More recently, the interactions among genes, certain pathologic conditions, and environments have been described that potentially can influence the glycemic control of patients with type 2 DM (DM2). In other cases, these can affect the production and structure of Hb, the lifespan of red blood cells, iron metabolism, resistance to malaria, and many other functions and traits.[16,17] Additionally, several subfractions are recognized, according to their migrating velocity: slower or faster, depending on the sugar bound: HbA1a1 (glycation with fructose 1-bisphosphate); HbA1a2 (glycation with glucose 6-phosphate); HbA1b (glycation with pyruvic acid), and HbA1c (glycation with glucose).[18]

GLYCATION

Glycation is a non-enzymatic chemical reaction in which some sugar is directly added to proteins, lipids, or nucleic acids biomolecules *(Figure 1)*. It is involved in the so-called Maillard reaction or non-enzymatic browning process, resulting from adding amino groups and reducing sugars, which produces a discoloration of food exposed to thermal effect.[19] The Maillard reaction occurs not only in food or beverage processing but also in other industrial conditions and even in the metabolism of mammals.[20] *In vivo*, the early step of the Maillard reaction is an autoxidative reaction involving the addition of oxidized glucose with other biomolecules, mainly amino groups, such as lysine or arginine residues. The second phase occurs when the glucose-amino adducts form the so-called Schiff bases (the condensation of primary amines and carbonyl functional groups), such as glycosylamine, that are naturally unstable.[21] Then, the base suffers a molecular rearrangement. This phenomenon first generates a large series of
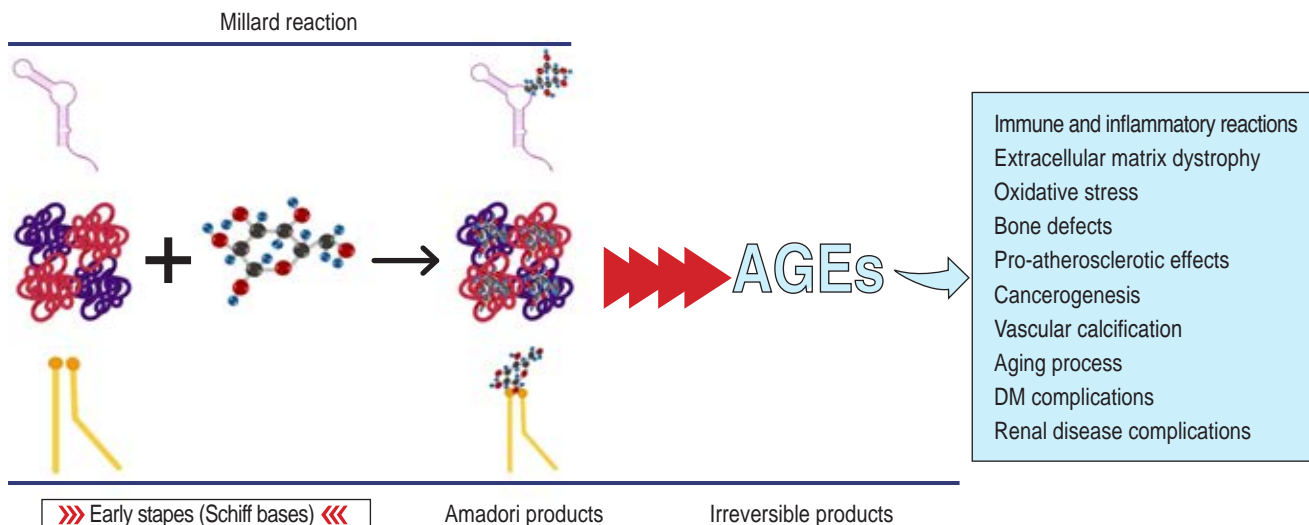
Figure 1: Glycation reaction, products and their effects.
AGEs = advanced glycated end products.

intermediate molecules and, finally, the more stable Amadori products (such as HbA1c and fructosamine, among others). In the last phase of the Maillard reaction, these early adducts are further transformed into more glycated compounds.[22,23] These final irreversible products are called advanced glycated end products (AGEs) and have crucial importance in the genesis of tissue damage in disorders like DM *(Figure 1)*.[24] AGEs are not solely generated endogenously but are components of processed food and beverages and are also generated by aging, ultraviolet radiation, tobacco smoking, diverse chemical agents and air pollution, among other conditions.[19] In the advanced glycation process, some proteins are modified by oxoaldehydes, mainly glyoxal, methylglyoxal, and 3-deoxyglucosone.[25,26] These proteins modified by AGEs can harm every body cell and tissue, eliciting an inflammatory reaction mediated by the so-called AGE receptor,[27,28] which recognizes as ligands not only AGEs products but also a vast set of molecules as S100/calgranulins, high mobility group box one (HMGB1), a chromatin-associated protein family, and specific amyloid molecules, among many others. All these substances can detonate complex functional and structural phenomena of immune and inflammatory reactions, extracellular matrix dystrophy, oxidative stress, bone defects, pro-atherosclerotic effects, cancerogenesis, and vascular calcification, among other catastrophic consequences.[28-30] Precisely, the increment of AGEs precursors, the carbonyl highly reactive compounds, named carbonyl stress,[31] contributes to the aging process, too many complications of DM and renal disease, and some of the derangements of dysmetabolic obesity, among many other severe pathological events *(Figure 1)*.[31] The concept of carbonyl stress signals that the excess oxidation of sugars and lipids, associated with a poor removal (as it happens in renal failure) of carbonyls, by itself or generating AGEs, exerts a powerful deleterious effect in several tissues.[31,32] One of the therapeutic benefits of metformin is the drastic decrease of serum glycating agents dicarbonyls in patients with dysmetabolic obesity, treated with an even small dose of the drug.[33]

GLYCATED HEMOGLOBIN

The HbA1c is a conjugated protein (hemoglobin-glucose), a heteroprotein. It is formed through the non-enzymatic and post-translational processes described above. The union of glucose to the β-N-terminal valine residues of globin forms the Amadori product named HbA1c. Hence, as the

amount of plasma glucose increases, it also raises HbA1c.[34] As this process is irreversible throughout the 120-day lifespan of non-transfused erythrocytes,[35,36] there is a direct relationship between the mean concentration of glucose and the amount of HbA1c. This fact makes Hba1c an excellent long-range marker of glycemic control.[36]

GLYCATION VS GLYCOSYLATION

Even though there are striking differences between glycosylation and glycation, both chemical processes are misunderstood and frequently misused.[18,37] As stated above, protein glycation is an irreversible, non-enzymatic reaction where the amino groups of proteins are conjugated with reduced sugars, forming brown polymers (browning o Maillard reaction).[23] Such a reaction depends on the substrate concentration (free glucose) and is characterized by forming a ketoamine at the N end of the beta chain of Hb. Similarly, nucleic acids, lipids, and intracellular and extracellular proteins can be modified by glycation.

On the other hand, glycosylation refers to a post-translational modification in which carbohydrates combine with other biomolecules (proteins, lipids, or nucleic acids) under the effect of multiple enzymes, with strict control in binding sugars to residues such as serine, asparagine, and hydroxylysine in enzymatic glycosylation. This phenomenon is necessary for certain normal functions, such as protein folding and stabilization. Abnormalities of glycosylation can result in inflammation processes, altered immunity, extracellular matrix dysfunction, stimulation of malignant metastasis, and other severe health problems. This process will allow them to fulfill a wide variety of functions, such as a longer protein survival, facilitation of protein secretion from its cell of origin, molecular traffic, cell signalization, the formation of specific receptors for hormones and other humoral substances, and the provision of a barrier or protective layer, and others.[35,37] Although use makes customs and customs make laws, from the scientific point of view, the terms glycation and glycosylation cannot be used as synonyms since they indicate totally different biological and biochemical processes.[37]

THE MEASUREMENT OF HBA1C

When the assay of HbA1c is certified by the National Glycohemoglobin Standardization Program (NGSP),[38,39] which describes the measurement techniques (using a high-performance liquid chromatography [HPLC] system and a BioRex 70 CE resin column) and standardization follows the specifications derived from the diabetes control and complications trial (DCCT);[40] the main use is to assess the glycemic control in the last three months.[38] In general, it is accepted that among diabetic patients, a value of HbA1c less than 7% signals a good control of the disease. The ADA counsels the measurements of HBA1c twice or thrice a year in stable patients but more frequently in patients with labile or uncontrolled glycemia.[38] The ADA recommends achieving a value of Hba1c < 7% in diabetic, non-pregnant patients as a good marker of good glycemic control, with a low risk of hypoglycemia.[38] Later, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) introduced a new method for measuring the concentration of a single molecular species of glycated A1c.[36,41] The reason was the lack of uniformity of HbA1c results of many laboratories, using different assay methods and kits from different manufacturers. So, the task group of the IFCC established international reference methods and obtained pure samples of HbA1c for calibration purposes.[42,43] Anyhow, the percentage values of HbA1c continue to be the most widely used method. Both methods, however, correlate well with the estimated average glucose *(Table 1)*.

Until recently, glycemic control in patients with DM was based on frequent self-monitoring of blood glucose (SMBG) and the periodical estimation of HbA1c, so far, the gold standard for long-term glycemic monitoring. The so-called «Point-Of-Care» tests (POCT, also called extra-laboratory or close-patient glucose measurements) have clear advantages over the more time-consuming central analytical laboratory glucose measurements regarding feasibility, promptness of results, and probably costs in both the intrahospital and home milieus. Modern POCT devices are light, economical, and accurate, allowing better

Table 1: Relations among DCCT and IFCC values of HbA1c and estimated average glycemia.		
HbA1c (NGSP/DCCT) %	HbA1c (IFCC) mmol/mol	Estimated average glucose (eAG) mg/dL
5	31	97
6	42	126
7	53	154
8	64	183
9	75	212
10	83	240
11	96	269
12	107	298
13	118	355

Adapted from: American Diabetes Association Professional Practice Committee[38] and Agrawal SN.[59]

control of hyperglycemia.[44] In this context, the measurement in capillary blood of HbA1c with high-sensitivity POCT devices also allows better long-term glycemic control.[45] Continuous glucose monitoring (CGM) is another tool that allows better long-term glycemic control in insulin-treated patients or those with great variability of glycemic values, making glycemic control more difficult. HbA1c can be derived from the average glycemia, although its value occasionally differs from the compound's lab assay. CGM apparatus detects interstitial and no intravascular glucose concentrations, so the provided glucose values could also differ from the capillary glycemia measured with oxidase reagents, generating hydrogen peroxide, by the POCT devices.[46,47] CGM has some advantages over HbA1c. The latter cannot detect the abrupt glycemia oscillations observed in patients with type 1 DM (DM1) or those under intensive antidiabetic treatment, mainly with complex associations of different insulins. Some of these important fluctuations can provoke threatening hypoglycemic episodes. It is evident that HbA1c measurement cannot detect this kind of event.[46] Nevertheless, it also seems that in most patients with stable DM2, non-insulin users, and with low risk of hypoglycemia, it is mainly treated with modern incretins, glucagon-like peptide analogues, or sodium-glucose cotransporter (SGLT2) inhibitors, the higher cost of CGM is not rewarded with better clinical outcomes.[48]

HBA1C IN THE INITIAL DIAGNOSIS OF DM

Most clinicians, together with fasting plasma glucose (FPG), use the HbA1c value for the initial diagnosis of DM, given that it is easier and faster than determining blood glucose 2 hours after an oral intake of a 75 g load (2-h PG). However, the latter is a more accurate and earlier marker of DM. Both glucose measurements show marked variability depending on diet, exercise, medications, and mental and social stress, among other factors.[49,50] The technique of obtaining and transporting the sample and the delay in performing the analysis can also influence the result.[50]

In contrast, HbA1c is more stable, providing, by inference, the estimated average glycemia in a long lapse. Nevertheless, HbA1c does not represent the direct measure of serum glucose, only the glycation phenomenon. The results deserve less credibility if the assay is not performed according to international standardization norms (as in many Mexican laboratories of private and institutional hospitals and clinics). The abundant sources of errors and shortcomings (see below) in the assessment of HbA1c require that the result be taken with caution and accompanied by careful clinical criteria and other laboratory techniques (FPG and 2-h PG). The result of the HbA1c assay is usually expressed as the glycated percentage of the total Hb content. It has been established that people without prolonged hyperglycemia have HbA1c values of less than 5.6%, while persons with uncontrolled DM exhibit values ≥ of 6.5%.[38] Between these two limits are those with a high probability of developing DM («pre-diabetes»).[38,51]

SHORTCOMINGS OF HBA1C

Along with advantages and virtues, HbA1c has a lot of pitfalls and shortcomings, both as a diagnostic marker for diabetes and as an indicator of glycemic control.[38,50,51] A set of conditions can influence the results of the HbA1c assay. Among those falsely increasing HBa1c

value are deficient anemias (iron, vitamin B12), alcohol abuse, some hemoglobinopathies, advanced renal failure, and splenectomy. In the opposite situation, normal pregnancy, erythropoietic-stimulating drugs, vitamins E and C, certain hemoglobinopathies, hypersplenism, and use of drugs like aspirin (in great doses), opiates, and antiretrovirals, among others, can decrease HbA1c values.

HBA1C AS A MARKER OF MICROVASCULAR DIABETIC COMPLICATIONS

A long time ago, it was confirmed that in patients with DM1, HbA1c is an excellent risk marker that predicts the development and aggravation not only of microvascular diabetic lesions but also of macrovascular ones, well.[52,53] According to the DCCT,[40] lowering HBa1c in young patients with DM1 less than 7% was associated with a 50-76% reduction of microvascular diabetic lesions,[54] while the UKPDS trial showed that a value of HbA1c of 7% diminished the risk of all diabetes-related endpoints by 12-32%.[55] Diabetic microangiopathy includes the classical retinal, renal, and peripheral nerve lesions and those affecting the brain, the skin, and myocardial microcirculation. The so-called «therapeutic legacy» describes the fact that patients with better HbA1c at the beginning, many years later, continue to obtain benefits and reduced outcomes due to micro and macroangiopathy.[56] However, since diabetic vascular lesions are not entirely due to persistent hyperglycemia, regardless of the value of HbA1c, not all diabetic patients exhibit the same incidence and extent of vascular damage. Genetic, metabolic, and nutritional factors can exert a protective role. Moreover, some trials testing the effect of intensive treatment to get tight glycemic control failed to show a substantial reduction in cardiovascular outcomes.[57]

HBA1C AND MACROVASCULAR DIABETIC COMPLICATIONS

A graded relationship between HbA1c and the occurrence of coronary syndromes and mortality has been established since normal values of the variable.[58] There is also a relation with ischemic stroke but not with hemorrhagic cerebral events.[58,59] An important message is that hyperglycemia also has a pathogenic role in macrovascular diabetic lesions, dyslipidemia, and HBP, underlying the holistic approach in the diabetic patient, with the obligatory reduction of all risk factors.

CONCLUSIONS

Hba1c is a conjugated protein formed through the glycation process termed and recognized as a glycemic control marker in diabetic patients since the last century. The glycation should not be confused or used as a synonym for glycosylation. Hba1c is a remarkable clinical tool useful in the management of diabetes mellitus and the prediction of microvascular and macrovascular lesions. The clinician must know its value, limitations, and advantages to use it wisely in the initial diagnosis of DM and the follow-up of the disease as an excellent marker of long-term control and the prevention of vascular complications.

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Myocardial infarction with non-obstructive coronary arteries and, ischemia non-obstructive coronary arteries, COMECITE recommendations

Infarto de miocardio con arterias coronarias no obstructivas e isquemia de arterias coronarias no obstructivas, recomendaciones de COMECITE

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ABSTRACT

Myocardial infarction with non-obstructive coronary arteries (MINOCA), and ischemia with non-obstructive coronary arteries (INOCA) are controversial concepts. A non-obstructive lesion with ≤ 50% stenosis in acute coronary syndromes may have an atherosclerosis process with plaque erosion or fracture and thrombus formation, which are time-dependent and not easily shown by intravascular imaging methods. The largest MINOCA Registry is the Swedish, which included 9,092 patients with MINOCA, supported only by coronary angiography without intravascular imaging, led to unknown dissection, erosion, or fracture, and did not discriminate Takotsubo, myocarditis, or cardiomyopathies. MINOCA must have positive cardiac markers or enzymes, electrocardiographic (ECG) changes, regional wall motion abnormalities (WMA), coronary angiography, and intravascular image to confirm the diagnosis. In INOCA a positive ischemic stress test, coronary angiography, and coronary hyperemic physiologic studies as fractional flow reserve (FFR), and coronary flow reserve (CFR) should be present to confirm the diagnosis.

RESUMEN

El infarto y la isquemia del miocardio sin lesiones coronarias obstructivas (MINOCA, INOCA, por sus siglas en inglés) son conceptos controvertidos. Una lesión no obstructiva ≤ 50% implica la presencia de aterosclerosis que puede complicarse con ruptura o erosión de placa y trombosis presentes en los síndromes coronarios agudos, los cuales son tiempo dependientes y no fácilmente detectables por imagen intravascular. El mayor registro de MINOCA es el sueco, que reportó 9,092 pacientes utilizando angiografía coronaria únicamente, sin imagen intravascular, lo que deja poco claro si hubo disección, erosión o ruptura de placa; así como tampoco especifica la presencia de enfermedad de Takotsubo, miocarditis o cardiomiopatía. El diagnóstico de MINOCA debe tener elevación de marcadores o enzimas cardiacas, con o sin cambios electrocardiográficos y anomalías en la movilidad segmentaria, angiografía coronaria e imagen intravascular. INOCA debe tener un estudio inductor de isquemia positivo, angiografía coronaria, estudio fisiológico coronario hiperémico con la determinación del flujo de reserva fraccional (FFR, por sus siglas en inglés) y el flujo de reserva coronaria (CFR, por sus siglas en inglés) para el diagnóstico de certeza.

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INTRODUCTION

The Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE for the name in Spanish: Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular) formed the consensus group with a designated chairman and co-chairman; that later distributed functions to the rest of the members. Every member searched and analyzed relevant publications about MINOCA and INOCA disease. The authors used the Cochrane Handbook[1] for systematic reviews of interventions and A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2): a critical appraisal tool for systematic reviews that included randomized or non-randomized study trials of healthcare interventions.[2] The members also reviewed single papers on special anatomical conditions. The consensus group discussed each paper in an expert panel format, nominal group, and anonymous Dolphy survey.[3] The consensus timing process took from October 13, 2022, to February 28, 2023. The authorship for publication follows the International Committee of Medical Journal Editors (ICMJE).[4]

MINOCA

Cardiac event characterized by clinical symptoms of an ischemic episode with chest pain or equivalent, lasting more than 10 minutes, elevated cardiac enzymes or markers, with or without electrocardiographic ST depression or elevation (type 2 myocardial infarction); non-obstructive disease (luminal stenosis < 50%) or dissection on coronary angiography and without evidence of plaque rupture or erosion with intravascular ultrasound (IVUS) or optical coherence tomography (OCT).[5]

INOCA

Myocardial ischemia acute or chronic with or without symptoms, with positive ischemic exercise or pharmacological stress test, non-obstructive coronary artery disease in coronary angiography (< 50% stenosis), and coronary hyperemic physiologic study with normal FFR, and abnormal CFR and index of microvascular resistance (IMR).[6]

CLINICAL FEATURES

Chest pain is cardinal, but other symptoms may be present in MINOCA and INOCA. The incidence of MINOCA with Non-ST segment elevation myocardial infarction (NSTEMI) is about 8-10%, while ST-Segment Elevation Myocardial Infarction (STEMI) is 2.8-4.4%. Patients with MINOCA tend to be younger, and less likely to have risk factors such as hyperlipidemia, hypertension, diabetes, and smoking. The male-female ratio for MINOCA is 2.5:1 compared with 4:1 for atherosclerotic disease.[7] Symptoms and signs of INOCA are often misdiagnosed in young and middle-aged women and men because they do not present typical anginal symptoms; the prevalence is 13-39%, patients are younger, female, and had fewer atherosclerosis risk factors,[8] which is also associated with impaired quality of life, higher disability, morbidity, mortality, and higher number of hospital readmission and repeat coronary angiographies.[6,9]

NON-INVASIVE DIAGNOSTIC APPROACH FOR MINOCA AND INOCA

Electrocardiogram (ECG)

STEMI criteria

1. S-T segment elevation straight or convex upward, blends with T to form a dome in two contiguous leads with 1.0 mV = 10 mm standardization.
2. Wide upright T or inverted T.
3. ST-segment elevation or T wave may approximate or exceed QRS height.
4. 1 mm in all standard leads other than V2 and V3.
5. 2.5 mm in leads V2 and V3 in men younger than age 40, 2 mm in leads V2 and V3 in men aged 40 and older, and 1.5 mm in these leads in women.
6. Concomitant T-wave abnormalities (wide, ample, or inverted T-waves).
7. Q waves.

8. ST depression in the reciprocal leads.
9. New left bundle branch block (LBBB).[10]

Non-STEMI criteria

1. Absence of persistent ST-segment elevation
2. ST-depression
3. Transient ST-segment elevation
4. T-wave changes[11]
5. Normal ECG

CARDIAC MARKERS AND ENZYMES

Two types of cardiac troponin (cTn) I and T are proven as biomarkers for myocardial damage. The Baseline concentration depends on the diagnostic system and varies in men, women, and age. In myocardial infarction (MI), cTn concentration peaks at 10-20 hours after occluded coronary arteries reperfusion and 24-50 hours in vessels without reperfusion. cTnI is released in a single peak, while cTnT exhibits biphasic kinetics; the first peak concurs with cTnI, and the second peak occurs after 80 hours of the first ischemic episode without reperfusion. Troponin remained increased up to 10-14 days after MI.

Other pathologies that increase cTn include heart failure, atrial fibrillation, pulmonary embolism, endocarditis, myocarditis, cardiac trauma, stable coronary artery disease, cardiotoxic agents, drugs of abuse, carbon dioxide, and venoms of spiders, scorpions, snakes, or jellyfish, stroke or brain trauma, physical exercise, skeletal muscle disorders, sepsis, SARS-CoV-2 infection or renal failure.[12]

Creatine kinase (CK) and CK subfraction MB should be performed in myocardial infarction. Their peak levels were lowest in patients with MINOCA as compared to acute coronary syndromes (ACS) with a single vessel or multivessel disease.[13]

D-dimer in ACS has prognostic value, and levels were an independent predictor of unfavorable outcomes.[14] N-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP) is also an independent biomarker and is a powerful determinant of short-term cardiac risk in ACS,[15] both markers would be especially useful in the acute myocardial setting.

ECHOCARDIOGRAPHY

The technique is essential for patient assessment with myocardial infarction, chronic or acute cardiac ischemic, myocarditis, cardiomyopathy, and Takotsubo setting. CFR with adenosine or dipyridamole could be evaluated.[16,17]

Findings

1. Wall motion abnormalities with absence or reduction of systolic thickening.
2. Decreased motion score:
   a. Hypokinetic
   b. Akinetic
   c. Dyskinetic (systolic bulging)
   d. Aneurysmal
3. Compensatory hyperkinesis of non-ischemic wall.
4. Global longitudinal strain (GLS) segment abnormalities.
5. GLS Post-systolic shortening.
6. Tissue synchrony imaging abnormalities.
7. Diastolic dysfunction.
8. Mechanical complications (thrombus, right ventricular infarction, acute mitral insufficiency, septal defects, free wall rupture or pericardial effusion, and tamponade).[18-20]

Brachial flow-mediated dilation (FMD) is a useful non-pharmacological tool for endothelial function evaluation. It is positively associated with future cardiovascular events[21] and could be a surrogate marker of microvascular dysfunction.

CARDIAC COMPUTED TOMOGRAPHY SCAN (CCTs)

CCTs assess coronary, aortic, and pulmonary arteries, atrial, ventricles, and valvular anatomy, and myocardial perfusion.[22] Fractional flow reserve (CT-FFR) was recently added to the CCTs evaluation. Multidetector computed tomography has excellent accuracy (95%) in dual-energy/spectral analysis in acute myocarditis compared to cardiac magnetic resonance.[23]

CARDIAC MAGNETIC RESONANCE IMAGING (CMR)

CMR supplies reliable diagnostic information in pulmonary and aortic vessels and identifies myocardial ischemic damage versus inflammation. In MINOCA setting supplies reliable size and location information on myocardial infarction and tissue viability. CFR is determined from coronary sinus (CS) flow measurements, assuming that coronary circulation extends from the major epicardial arteries through pre-arterioles, arterioles, and capillaries draining in CS.[24]

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

Both technologies evaluate cardiac perfusion and viability and supply valuable information and prognosis of coronary artery disease. SPECT with technetium-99m labeled tracer and PET with rubidium-82, N-13 ammonia, O-18 water, or F-18 flurpiridanz which is more accurate in terms of myocardial blood flow. This method does not measure blood flow in epicardial coronary arteries and CFR is not allowed. Fluorodeoxyglucose is able to assess myocarditis.[10]

Recommendations

1. Echo, PET, CCTs, or CMR should be performed before patient discharge to confirm MINOCA *(Figure 1)*.
2. In INOCA, the positive ischemic stress test should include CFR determination by echo or CMR and FMD test performed before invasive coronary angiography.

INVASIVE DIAGNOSTIC APPROACH OF MINOCA AND INOCA.

MINOCA

Urgent coronary angiography must be performed if clinical symptoms, ECG changes, cardiac markers or enzymes, and WMA are positive for the diagnosis of myocardial infarction. If no significant obstructive coronary lesion is found, an intravascular image test (IVUS or OCT) will be performed on the proper infarct artery or on multivessel where the culprit lesion has been difficult to determine. Atherosclerotic findings with plaque erosion, plaque fracture; calcified nodule; spontaneous coronary artery dissection (SCAD), or coronary artery spasm (CAS) should not be considered MINOCA[25] nor should Takotsubo syndrome, myocarditis,
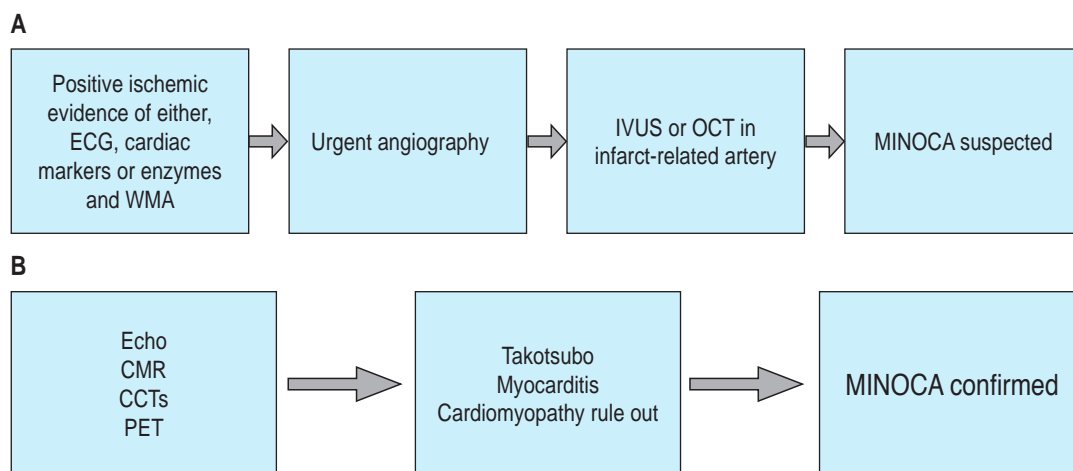
Figure 1: A) MINOCA evaluation. **B)** Predischarge evaluation.
ECG = electrocardiogram. WMA = Wall Motion Abnormalities. IVUS = intravascular ultrasound. OCT = Optical Coherence Tomography. CMR = cardiac magnetic resonance. CCTs = cardiac computed tomography scan.

or cardiomyopathies. Non-invasive studies are needed to confirm the MINOCA diagnosis before patient discharge[26] *(Figure 1)*.

INOCA

Cardiac catheterization and coronary angiography rule out non-obstructive coronary lesions. Then coronary physiology evaluation is performed with hyperemic FFR, CFR, and IMR on the related ischemic territory artery *(Figure 2)*. There be four scenarios:

1. FFR ≤ 0.80 and CFR > 2.0, the diagnosis would be flow-limiting stenosis with preserved microvascular function, and percutaneous coronary intervention (PCI) is indicated.
2. FFR ≤ 0.80 and CFR < 2.0, the diagnosis would be flow-limiting stenosis and Microvascular Dysfunction (MVD), PCI, and medical treatment is indicated.
3. FFR > 0.80 and CFR > 2.0, the diagnosis would be non-flow-limiting stenosis with preserved microvascular function, consider alternative diagnosis plus medical treatment.
4. FFR > 0.80 and CFR < 2.0, the diagnosis would be non-flow-limiting stenosis with microvascular dysfunction. Medical treatment is indicated.[27]

IMR is a microvascular evaluation index whose normal value is < 25 and would be used when CRF is < 2.0 to confirm microvascular angina. CAS with ergonovine provocation test is reserved for non-flow-limiting stenosis diagnosis with preserved microvascular function.[28]

The acetylcholine test is unavailable in Mexico and precludes its use.

Recommendations

1. IVUS or OCT must be performed in MINOCA searching atherosclerotic or calcified complicated lesions as well as SCAD and CAS.
2. Whole cardiac-cycle pressure-wire base adenosine coronary hyperemic physiologic tests such as FFR and CFR must be performed to get specific diagnoses and treatment in INOCA.
3. IMR is a microvascular evaluation index to find microvascular dysfunction.
4. Ergonovine provocation test is reserved for non-flow-limiting stenosis with preserved microvascular function diagnosis.
5. Always measured LVEDP and transaortic valve gradient.

NON-PHARMACOLOGIC TREATMENT

The 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes[29] emphasize the benefits of lifestyle changes in diet, alcohol, smoking, weight loss, physical activity, cardiac rehabilitation, psychosocial/environmental intervention, and sexual counseling as follows:

1. Vegetables 200 g or more per day.
2. Dietary fiber 35-45 g per day, especially whole grains.
3. Unsalted nuts 30 g per day.
4. Fish, especially oily fish, 1-2 servings per week.
5. Limited lean meat.
6. Low-fat dairy products.
7. Liquid vegetable oils.
8. Saturated fats < 10% of total energy intake.
9. Replace saturated with polyunsaturated oils.
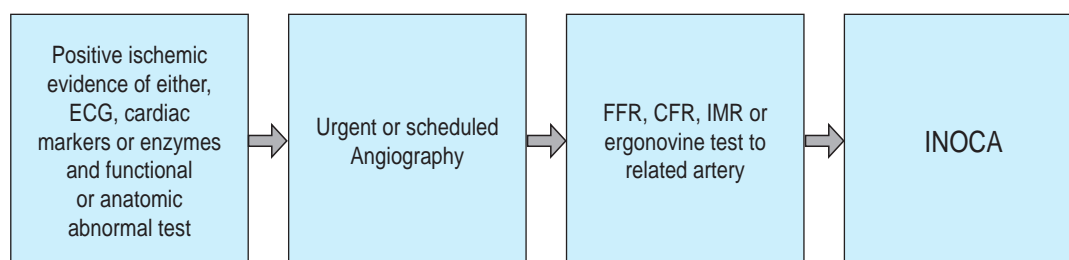
Figure 2: INOCA evaluation.
ECG = electrocardiogram. FFR = fractional flow reserve. CFR = coronary flow reserve. IMR = index of microvascular resistance.

10. Avoid trans-unsaturated fats.
11. Avoiding preprocessed food.
12. Consume ≤ 5-6 g of salt per day.
13. Limit alcohol to ≤ 100 g/week, or < 15 g/day, consider cero alcohol intake.
14. Avoid high-sugar food, especially soft drinks.
15. Quit smoking, considering nicotine replacement, e-cigarette, bupropion, and varenicline.
16. Reduce and/or keep body mass index, to < 25 kg/m^2.
17. Encourage moderate aerobic activity 30-60 min/day, for at least five days/week.
18. Promote exercise-based cardiac rehabilitation.
19. Recognize mental disorders and treat them with psychological and/or pharmacological interventions.
20. Reduce exposure to pollution by limiting polluted air and excessive noise.
21. Recommend air purifiers and face masks.
22. Sexual activity is usually safe.
23. Pharmacological treatment for erectile dysfunction is usually safe.

These recommendations may work with or without significant epicardial coronary stenosis, as they may improve endothelial integrity, plaque stability, and microvascular dysfunction under certain conditions.

Diet

There is experimental evidence that obesity and high fat, high sugar, and low fiber diet (Western diet) may cause unhealthy gut microbiota, higher body weight, and body fat percentage, and endothelial dysfunction due to a reduction in nitric oxide synthase following the increased release of adipose tissue release of interleukin, interferon and, tumor necrosis factor from adipose tissue.[30,31]

Current knowledge provides solid evidence of the interaction between all the non-pharmacological interventions, especially diet, with dysbiosis of the gut microbiota and eubiotics, through various metabolites that act pro and against endothelial hemostasis. The article of Jessica Maiuolo et al. supplies a clear and simplified overview of these concepts, particularly the importance of proper nutrition for healthy gut microbiota, as the benefits of taking prebiotics and probiotics.[32]

The Mediterranean diet contains healthier plant-based nutrients, including oils and whole grains, as well as natural agricultural and marine products with significant amounts of antioxidants, low processed food, simple carbohydrates, and, beef, which create a more stable gut microbiota that leads to local production of short-chain fatty acids, that cannot otherwise be supplied externally and that enter the portal circulation, resulting in improved metabolism and weight.[33] These benefits are accompanied by fewer harmful metabolites, such as trimethylamine N-oxide (TMAO), which is abundant in the Western diet.[34,35] This diet receives attention because of its known cardiovascular benefits, high amounts of nuts and olive oil, low-saturated fat, and low-meat diet, which may improve the endothelium of healthy individuals and those at cardiovascular risk, particularly endothelial function as measured by FMD. Mechanisms involved in this improvement in endothelial function include:[36,37]

↓ Oxidative stress, inflammation, and platelet aggregation.
↓ Cancer-related hormones and growth factors.
↓ Low-density lipoprotein.
↓ Inflammatory markers.
↓ Hyperglycemia-induced endothelial dysfunction.
↑ Nitric oxide bioavailability through more L-arginine.
↑ High-density lipoprotein.
↑ Eubiosis.

Vitamins (A, C, D, and E), carotenoids, polyphenols, flavonoids, selenium, iron, copper, zinc, and manganese, natural antioxidants, may regulate vascular oxidative stress and promote reendothelialization and vascular repair.[38]

Dysbiosis is also associated with overexpression of vasoconstrictor substances (endothelin, thromboxane A2, angiotensin II, etc.) and reactive oxygen species which then from superoxide anion, leading to inflammation, dysfunction, and increased permeability of the endothelium with further leukocyte infiltration and various types of

vascular catastrophes, including endothelial erosion, rupture, and thrombosis, apart from other late complications such as cancer, neurological disorders, etcetera.[39,40]

The link between microbiota health, obesity, and endothelial function is supported by recent experimental transplantation of feces from obese human donors to germ-free mice, which develop glucose intolerance and impaired endothelial function, without gaining weight compared with mice receiving feces from lean human donors. Experimental information also shows protection against atherosclerosis after feces of a healthy microbiota and microbiome transplants.[41-43]

Another important relationship of the microbiota concerns the very low calories ketogenic diet, which can provide benefits if it consists mainly of polyunsaturated oils, predominantly plant rather than animal proteins, complex rather than simple carbohydrates, abundant fiber, and avoidance of artificial sweeteners; more short chain fatty acids, improved diversity of bacteria, Achaea and Eukarya with a propensity for a healthier metabolism, including greater insulin sensitivity, weight loss, and lipid balance, leading to less oxidative stress, less chronic low-intensity inflammation, and better endothelial performance.[44,45] The pre and probiotics undoubtedly enhance these benefits.[46-48]

Sedentariness can also lead to dysbiosis in men and women, and physical activity can lead back to eubiosis.[49,50] Lifestyle conditions such as dietary habits, lack of exercise or physical activity, mental state, and physical environment correspond to the exposome, which influences the epigenetic conditions of the microbiota.[51,52]

Low concentration of ketones, specially β-hydroxybutyrate, and acetoacetate is present in hyperglycemia, during the ketogenic diet, brings several benefits to cardiovascular health, including improved insulin sensitivity and endothelial function, and eventually antioxidant, anti-inflammatory and anti-aging effects:[53-55]

↓ Weight
↓ LDL-cholesterol.
↓ Triglycerides.
↓ HbA1c.

↓ Blood glucose.
↓ Low-intensity chronic inflammation.

↓ Pathological cardiac remodeling.
↓ Mitochondrial oxidative stress.

↑ Ketonemia.
↑ Histone β-hydroxybutyrylation.
↑ Histone hyperacetylation.
↑ Insulin sensitivity.
↑ HDL-cholesterol.
↑ Neuroprotection.

The ketogenic diet has experimental evidence of cardio-protection by increasing tolerance to cardiac ischemia, reducing chronic low-intensity inflammation, decreasing oxidative stress, improving cardiac remodeling after ischemic injury and hypertension, and improving control of obesity, diabetes mellitus, and hypertension.[56-58]

The Mediterranean diet and the very low-calorie ketogenic diet have beneficial effects on gut microbiota that begin on the first day after starting the diet and peak after three months. Nevertheless, the ketogenic diet shows better results in body composition and gut microbiota profile.[59]

Exercise

Physical activity is a key part of treatment, either as primary or secondary prevention, and of rehabilitation programs in high cardiovascular risk and already diagnosed significant coronary atherosclerosis.[60,61] It can provide significant benefits in patients with myocardial ischemia with < 50% coronary stenosis with the following changes:[62,63]

↓ Weight.
↓ Fat tissue.
↓ Triglycerides.
↓ LDL-cholesterol.
↓ HbA1c.
↓ Major adverse events.
↓ All-cause mortality.
↑ HDL-cholesterol.
↑ Workload.
↑ Angina-score improvement.
↑ Depression-score improvement.

- ↑ Mean physical health score.
- ↑ Retinal microvascular health in children and adults.
- ↑ Microvascular function in the elderly's soleus.

Mental disorders

Anxiety and depression cause acute and chronic clinical and experimental coronary microvascular dysfunction, reduced coronary flow reserve, and impaired coronary endothelial function, especially but not exclusively in women.[64-66] Mental stress vasoconstriction results from the degradation of nitric oxide after endothelial nitric oxide synthase is downregulated and inactivated by stress hormones (glucocorticoids and pro-inflammatory cytokines and endothelin-1, amines, adhesion molecules, oxidized LDL particles, and so on), especially during maladaptive hypothalamic-pituitary-adrenal and sympathetic-adrenomedullary signaling pathway;[67,68] dysfunction of endothelial progenitor cells play an important role.[69,70] Stress and depression can lead to and cause endothelial and microvascular dysfunction with has been shown to increase cardiovascular morbidity and mortality. These mental disorders are associated with vicious cycles of vascular dysfunction, smoking, alcoholism, excessive carbohydrate intake, obesity, heart rate variability and arrhythmia, sedentism, and specific vitamin lack.[71-73] There is evidence of benefit after several psychological and psychiatric pharmacological and non-pharmacological interventions.[74-76]

Addictions

The known risk factors included in the metabolic syndrome (diabetes/pre-diabetes, hypertension, obesity, and dyslipidemia), together or separated, cause coronary microvascular disease. Other relevant lifestyle aspects include cigarette smoking, alcoholism, and opioid abuse.

Acute cigarette smoking causes a significant reduction of the coronary flow reserve measured by intracoronary Doppler, positron emission tomography, or transthoracic Doppler-echo of the left anterior descendant coronary artery through direct endothelial damage due to inflammation and oxidative stress.

Alcohol causes microvascular dysfunction through endothelial disorganization, degeneration, edema, perivascular fibrosis, sclerosis, inflammation, and increased capillary density; otherwise, opioids produce direct endothelial damage by nitric oxide counteraction and capillary density reduction. Cessation of these addictions may act on improvements.[77]

PHARMACOLOGIC TREATMENT

If MINOCA[78,79] or INOCA,[80,81] is not confirmed and an ischemic etiology is suspected, the patient can be stabilized with lower medication for a brief time.

Antiplatelet medication

Aspirin (75-300 mg) is an irreversible cyclooxygenase (COX-1) inhibitor in prostaglandin synthesis. COX-1 mediates the production of thromboxane A2 (TxA2) which induces platelet aggregation and vasoconstriction. The low-dose aspirin inhibits the production of TxA2.

- ↑ Vasodilation.
- ↓ Platelet aggregation.

Clopidogrel 75 mg, ticagrelor 90 mg, prasugrel 10 mg, orally and cangrelor 50 mg, intravenous are thienopyridines that inhibit adenosine diphosphate-induce, cause irreversible blockade of the P2Y12 receptor.

- ↓ Platelet aggregation.

Cilostazol 100 mg, inhibits collagen, 5'-adenosine diphosphate, epinephrine, and arachidonic acid, generates vasodilation in smooth muscle cells, and increases nitric oxide availability.

- ↑ Vasodilation.
- ↑ Antiplatelet properties.
- ↑ Anti-proliferative effects.
- ↓ Smooth muscle cell hyperproliferation.
- ↓ Intimal hyperplasia.

Dipyridamole 100 mg inhibits cyclic nucleotide phosphodiesterase, responsible for the degradation of adenosine monophosphate (AMP) to 5-AMP, which increases intra-platelet cyclic AMP reducing platelet aggregation, and blocks the uptake of adenosine by the platelets, increasing cyclic AMP.

↓ Platelet aggregation.
↓ Adenosine uptake.

Glycoprotein IIb/IIIa drugs block membrane glycoprotein IIb/IIIa platelet receptors, inhibiting fibrinogen binding. Indications: acute coronary syndromes (ACS), before and after PCI with or without stenting and stable angina.[82] The role of antiplatelet agents in the MINOCA setting is not well established.[83]

Anticoagulants

Anticoagulation is the first-line treatment for ACS, facilitating PCI and reducing cardiovascular disease complications, morbidity, and mortality. Thrombus is present in most ACS, including erosion, plaque fracture, and SCD. Unfractionated heparin (UFH), enoxaparin, fondaparinux, bivalirudin, and direct inhibitors of factor Xa are commonly used as adjuvants in pharmacologic or mechanical thrombolysis with antiplatelet agents.

↓ Mortality.
↓ Thrombosis cascade.
↓ Reduce the ischemic burden.
↓ Medication-related bleeding.
↓ Platelet activation.

There is no straightforward evidence of benefit for short or long-term use in the context of MINOCA or INOCA.[84,85]

Beta-blockers

There are major differences among beta-blockers. Lipophilic such as metoprolol, propranolol, and timolol have first-pass effects (metabolized in the gut wall and liver). Hydrophilic such as atenolol and esmolol which is absorbed in the gastrointestinal tract and excreted as active metabolites by the kidney.

On the other hand, β_1 selectivity. They had antihypertensive and anti-ischemic actions, decreasing myocardial oxygen consumption, reducing heart rate and cardiac contractility, renin release, and angiotensin II production reduction, and improves left ventricular function. Beta-blocker is indicated in ACS, chronic stable ischemic heart disease, heart failure, arrhythmias, sudden cardiac death prevention, cardiomyopathies, valvular disease, myocardial bridging, hypertension, aortic dissection, vasovagal syncope, as well as secondary prevention, MINOCA, and INOCA.[86]

↓ Blood pressure.
↓ Cardiac output.
↓ Release of renin and production of angiotensin II.
↓ Presynaptic stimuli alfa adrenoceptors.
↓ Central vasomotor activity.
↓ Myocardial oxygen demand.
↓ Myocardial oxidative stress.
↓ Heart rate.
↓ Cardiac apoptosis.
↓ Platelet aggregation.
↓ Vascular smooth muscle cell proliferation.
↓ Cardiac contractility.
↓ Life-threatening arrhythmias.
↓ Mortality, including sudden cardiac death.
↓ Ischemia.
↓ Catecholamine-induced hypokalemia.
↑ Prolongation of diastole.
↑ Baroreflex function.
↑ Myocardial perfusion.
↑ Left ventricular structure and function.
↑ Fatty acids released from adipose tissue.

Calcium channel blockers (CCBs)

This is a heterogeneous group of drugs classified as Phenilalchilaminic (verapamil), dihydropyridines (DHP) amlodipine-like, or benzothiazepine (diltiazem), acts chiefly by vasodilatation and peripheral vascular resistance reduction. Verapamil and diltiazem act on nodal tissue and could be used in supraventricular arrhythmias. As secondary prevention, CCBs are indicated in exertional angina, myocardial ischemia, supraventricular arrhythmias, hypertension, vasospastic angina, INOCA, and postinfarction.[81]

↓ Stroke risk.
↓ Blood pressure.
↓ Voltage-dependent L-type calcium channel.
↑ Smooth muscle dilation.
↓ Inotropism.
↓ Chronotropism.
↓ Coronary spasm.

Angiotensin-converting enzyme inhibitors (ACEi)

These drugs produce vasodilatory effects leading to the increased local formation of bradykinin, the release of nitric oxide, and vasodilator prostaglandins, not observed with Angiotensin Receptor Blockers (ARB). ACEi are indicated in coronary artery disease, heart failure, ACS, and chronic kidney disease, associated or not with diabetes, MINOCA, and INOCA. Significantly reduces major cardiac events follow-up.[78-81]

↓ Adverse cardiac event.
↓ Blood pressure.
↑ Sympathetic-inhibitory effects.

Statins

Also known as 3-hydroxy-3methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors have several pleiotropic effects like anti-inflammatory, antihypertrophic, antifibrotic, and antioxidant properties, improve endothelial dysfunction, neurohormonal activation, and cardiac arrhythmias. Statins are indicated in primary and secondary atherosclerotic cardiovascular disease, coronary artery disease, ACS, vasospastic angina, MINOCA, and INOCA.[78-81]

Nicorandil

It is a vasodilator drug that increases the intracellular concentration of cyclic guanosine monophosphate (GMP). Beneficial effects are driven by the improvement of heart failure and ventricular arrhythmias. Nicorandil is indicated in the treatment of unstable or stable angina, INOCA, and PCI no-reflow phenomenon. It is available in tablets of 10 or 20 mg twice daily but also intravenously or intracoronary.[87]

Ranolazine

Inhibits the late phase of inward sodium channels, reducing intracellular sodium and calcium via the Na-Ca channel, and inhibits fatty acid oxidation, which enhances glucose oxidation, reduces lactic acid production, and improves heart function, does not affect heart rate or blood pressure. Ranolazine is indicated in the treatment of chronic stable angina and could be used in incomplete revascularization after PCI or CABG, INOCA, and as an adjunctive anti-arrhythmic agent in new or chronic atrial fibrillation. It is available in tablets of 500 mg twice a day.[88]

↓ Fatty acid oxidation.
↓ Lactic acid production.
↑ Glucose oxidation.
↑ Ventricular action potential duration.

Ivabradine

Lower heart rate by inhibiting if channels located in the sinoatrial node, without affecting other channels, consequently, does not affect myocardial contractility or vascular tone and reduces myocardial oxygen demand. Ivabradine is indicated in the treatment of heart failure, chronic stable angina, and INOCA. Is available in tablets of 5 and 7.5 mg twice a day.[89]

↓ Chronotropism.
↓ Myocardial oxygen demand.
↑ Diastolic time.
↑ Coronary circulation filling time.

Trimetazidine

It inhibits mitochondrial 3-ketoacyl coenzyme A thiolase, decreasing long-chain fatty acid β-oxidation, and improving mitochondrial metabolism with glucose oxidation stimulation. Its ant-ischemic action modulates cardiac metabolism without hemodynamic functions (coronary flow, contractility, blood pressure, or heart rate), has an anti-inflammatory profile, improves endothelial dysfunction, and limits membrane damage induced by reactive oxygen species. Trimetazidine is indicated for stable

angina, coronary interventions, pre or post-CABG, left ventricular dysfunction, diabetes mellitus, and INOCA. It is available in tablets of 35 or 80 mg twice or once a day.[90]

↓ Fatty acid oxidation.
↓ Glucose oxidation.
= Contractility.
= Blood pressure.
= Heart rate.

Long-acting nitrates

Activated by mitochondrial or cytosolic aldehyde dehydrogenase (ALDH2) into nitric oxide (NO), an endothelium-derived relaxing factor (EDRF), activates guanylate cyclase, increased cyclic guanosine monophosphate (cGMP) and causes vasorelaxation, and prevention of platelet aggregation and adhesion. Dilate venous capacitance vessels and coronary arteries, inducing venous pooling and preload reduction leading to a reduction of left ventricular end-diastolic filling pressure and wall stress, also decreasing right atrial pressure with a redistribution of blood from the central circulation into larger capacitance veins. Nitrate therapy is indicated in acute or chronic heart failure, stable coronary artery disease, acute coronary syndromes, arterial hypertension, and INOCA.[91]

↓ Preload.
↓ Left ventricular stress.
↑ Venous and coronary capacitance.
↑ Ventricular function.

Phosphodiesterase (PDE 5) inhibitors

These drugs are selective inhibitors of phosphodiesterase type 5 which increased cGMP and produces smooth muscle relaxation, and vasodilation, improving blood flow, providing benefits for both vascular and myocardial remodeling, attenuating hypertrophy, fibrosis, and impaired cardiac relaxation. The concomitant use of nitrates and other PDE inhibitors is contraindicated. PDE 5 inhibitor is indicated in erectile dysfunction, pulmonary hypertension, and INOCA.[92]

↑ Inotropic.
↑ Cardiac action potential.
↓ Blood pressure.
↓ Pulmonary arterial pressure.

Recommendation

1. Non-pharmacologic treatment must be the cornerstone in patients with MINOCA/INOCA.
2. Patients should stay under a multidisciplinary therapeutic approach including a cardiologist, nutritionist, psychiatrist, and psychologist.
3. The cardiologist must interact with nutritional advice for goals.
4. Improve lifestyle factors (diet, exercise, weight management, smoking cessation, and coping with stress.
5. Get in goals with hypertension, dyslipidemia, and diabetes.
6. In CAS, calcium channel blockers, long-acting nitrates, cilostazol, dipyridamole, PDE 5 inhibitors, nicorandil, and statins are indicated.
7. In MVD, ACE inhibitors, CCBs, nicorandil, long-acting nitrates, statins, beta-blockers, ivabradine, ranolazine, and trimetazidine, are indicated.
8. In MINOCA patients, statins, ACEi, and beta-blockers are indicated.
9. In INOCA patients, CCBs, long-acting nitrates, beta-blockers, nicorandil, statins, ACEi, PDE 5 inhibitors, trimetazidine, ranolazine, and ivabradine are indicated.

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