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Summary

EDITORIAL

Nocturnal Hypertension

Hipertensión arterial nocturna

JUAN CARLOS PEREIRA REDONDO[1,2]

The transition between office-based and ambulatory blood pressure (BP) recordings, particularly with the use of home and ambulatory blood pressure monitoring (HBPM and ABPM), has allowed greater recognition of nocturnal hypertension (NHTN) and abnormal patterns of nighttime BP lowering.

Since the communication by O'Brien et al., (1) in which hypertensive patients with a lower decrease in nighttime blood pressure (non-dippers) had a more frequent history of stroke, numerous publications and some reviews, such as those of the international database IDACO, (2) have appeared, pointing out the prognostic value of NHTN, both in hypertensive, as well as in diabetic and chronic renal patients. In this meta-analysis, the authors demonstrate that the increased risk of overall mortality and cardiovascular events attributed to NHTN (with every 10-mmHg increment), daytime HTN (with every 10-mmHg increment), nighttime/daytime BP ratio, and the non-dipping status of NHTN, is statistically significant after adjusting for age, sex, body mass index, smoking, alcoholism, cholesterolemia, history of cardiovascular disease, diabetes, and antihypertensive drug treatment. However, when NHTN is adjusted for daytime HTN and vice versa, only NHTN and the non-dipping status are statistically significant.

Subsequently, population-based studies have been published, such as those of Ohasama, (3) Copenhagen, (4) and PAMELA, (5) among others, which also demonstrate that home and 24-h BP monitoring are superior to office BP in determining the risk of all-cause death and cardiovascular death. Thus, systolic BP was superior to diastolic BP, and nocturnal BP was superior to diurnal BP in determining the risk of death and cardiovascular death.

Some of the problems in determining NHTN are sleep quality during measurement (insomnia, nocturia), assessment of actual time in bed, (6) ambient temperature (heat), daytime BP treatment, etc., that hinder reproducibility. (7) This problem is greater in the assessment of nighttime BP lowering relative to daytime BP (dipping, non-dipping, riser).

Isolated systolic nocturnal hypertension (ISNHTN), characterized by a daytime BP less than 135/85 mmHg and a nighttime BP greater than 120/70 mmHg, is a condition that has aroused interest because it is not detected by office BP monitoring or by HBPM. (8) Its prevalence is 6-10% in the general population, higher in South America and Japan than in Europe. Several pathophysiological mechanisms have been implicated in the relationship between ISNHTN and worse cardiovascular prognosis, such as sympathetic activation, altered baroreflex sensitivity or autonomic failure, decreased diurnal sodium excretion, natriuresis due to nocturnal pressure, insulin resistance, impaired endothelial function, and sleep apnea. Patients with ISNHTN tend to be older, male, obese, with diabetes, increased heart rate, and history of cardiovascular disease. (9)

Also, in the case of refractory hypertension, defined as office BP greater than 140/90 mmHg despite treatment with three classes of drugs, including diuretics, or four classes of drugs without control of HTN, the circumstance of presenting NHTN was associated with an increased risk of cardiovascular events for every 10-mmHg increment, after adjusting for daytime BP levels. (10)

The management of NHTN is especially important to prevent cardiovascular events, (especially heart failure), as well as target organ damage, as in chronic kidney disease and cognitive impairment. (11) Nocturnal hypertension involves mechanisms that are the same as those related to the development of heart failure. Therefore, new treatments in heart failure, such

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as sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor blockers, sacubitril-valsartan, etc., are being tested in the treatment of NHTN, (12) as well as in diabetic patients, without signs of heart failure, in which NHTN is associated with the development of diastolic dysfunction. (13)

The present issue of the Argentine Journal of Cardiology presents the study of Perea J et al. (14), in which a prevalence of NHTN of almost 64% was retrospectively observed in a contemporary cohort, with significant role as an independent predictor of adverse cardiovascular events, even when considering for the presence of daytime HTN. The categorization of the severity of NHTN and its statistically significant correlation with the incidence of major cardiovascular events should be highlighted as originality of the study. This finding adds to what we have previously reported in hypertensive patients and in population-based studies.

Conflict of interest

None declared.

(See author conflict of interests form on the web/Additional material).

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ORIGINAL ARTICLE

Nocturnal Hypertension: Analysis According to its Severity

Hipertensión arterial nocturna: análisis según su gravedad

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ABSTRACT

Background: In the diagnosis and follow-up of arterial hypertension (HTN) most practice guidelines recommend ambulatory blood pressure monitoring (ABPM). In this regard, there is increasing evidence supporting the superiority of nocturnal hypertension (NHTN) as a predictor of cardiovascular events. Little is known about the relationship with cardiovascular events according to the severity of NHTN. Furthermore, it is unclear from what nighttime pressure value the risk begins to increase.
Objectives: The aim of this study was to determine whether the presence of NHTN and its severity levels are associated with adverse cardiovascular outcomes during follow-up.
Methods: An observational study was performed analyzing data collected from 24-hour ABPM studies obtained in a high complexity medical center in Buenos Aires. We examined patients' clinical characteristics, laboratory findings, imaging studies and their results during the follow-up period. Our study included ≥18 year-old persons who had been diagnosed with hypertension. We defined NHTN as those cases with blood pressure values ≥120/70 mmHg during the nighttime period.
Results: The final analysis included 981 patients. Among these, 53 % were men, mean age was 59.4 years and NHTN was present in 63.6 % of cases (n=624). Nocturnal HTN was classified into four severity strata for comparison, according to the nighttime systolic blood pressure value: 83-119 mmHg, 120-139 mmHg, 140-159 mmHg and 160-220 mmHg. Major adverse cardiovascular events were recorded in 8 (2.2 %), 17 (4.1 %), 8 (5.6 %) and 7 (11.3 %) subjects, respectively, and this difference between groups was statistically significant (p=0.007). Multivariate Cox regression analysis showed that the presence of NHTN was an independent predictor of adverse cardiovascular events (HR 3.60; 95% CI 1.12-11.5; p=0.033), even when considering the presence of daytime hypertension.
Conclusion: In this contemporary cohort, NHTN and its severity were independently associated with the incidence of adverse cardiovascular events.

Key words: Hypertension - Nocturnal hypertension - Coronary Heart Disease - Ambulatory Blood Pressure Monitoring

RESUMEN

Introducción: En el diagnóstico y seguimiento de la hipertensión arterial (HTA) la mayoría de las guías de práctica recomiendan el monitoreo ambulatorio de la presión arterial (MAPA). En este sentido, existe cada vez más evidencia que respalda la superioridad de la hipertensión arterial nocturna (HTAN) como predictor de eventos cardiovasculares. Se sabe poco sobre la relación con los eventos cardiovasculares según la gravedad de la HTAN. Además, no está claro a partir de qué valor de presión arterial nocturna comienza a aumentar el riesgo.
Objetivos: Conocer si la presencia de HTAN y sus niveles de gravedad se asocian con resultados cardiovasculares adversos durante el seguimiento.
Material y métodos: Estudio observacional. Realizamos un análisis de los datos obtenidos en un centro médico de alta complejidad de Buenos Aires, recopilados a partir de estudios de MAPA de 24 horas. Examinamos las características clínicas de los pacientes, los resultados de laboratorio, los estudios de imagen y sus resultados durante el período de seguimiento. Nuestro estudio incluyó personas de 18 años o más a las que se les había diagnosticado hipertensión. Definimos HTAN como aquellos casos con valores de presión arterial ≥ 120/70 mmHg durante el periodo nocturno.
Resultados: Fueron incluidos 981 pacientes en el análisis final. De ellos, el 53 % eran hombres; la edad media era de 59,4 años. Presentaban HTAN 63,6 % (n=624). Clasificamos la HTAN en cuatro estratos de gravedad para comparar, según el valor de presión arterial sistólica nocturna: 83-119 mmHg, 120-139 mmHg, 140-159 mmHg y 160-220 mmHg. Se registraron eventos adversos cardiovasculares mayores en 8 (2,2 %), 17 (4,1 %), 8 (5,6 %) y 7 (11,3 %) sujetos, respectivamente, y esta diferencia entre grupos fue

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estadísticamente significativa (p=0,007). El análisis multivariado de regresión de Cox demostró que la presencia de HTAN fue un predictor independiente de eventos cardiovasculares adversos (HR 3,60; IC 95% 1,12-11,5; p=0,033), incluso al considerar la presencia de hipertensión arterial diurna.
Conclusión: En esta cohorte contemporánea, la HTAN y su gravedad se asociaron independientemente con la incidencia de eventos cardiovasculares adversos.

Palabras clave: Hipertensión arterial- Hipertensión arterial nocturna - Enfermedad cardiovascular - Monitoreo ambulatorio de presión arterial

INTRODUCTION

The global prevalence of atherosclerotic cardiovascular disease continues to rise due to the increase of risk factors such as obesity, unhealthy lifestyles and population aging. (1,2) Hypertension (HTN) is recognized as one of the most significant risk factors, and has a high worldwide prevalence; therefore, it is crucial to make a correct diagnosis and treatment. (3)

Most international guidelines recommend ambulatory blood pressure monitoring (ABPM), which has become essential for the management of patients with HTN, not only for initial diagnosis but also for follow-up and subsequent control. (4-7) Most studies have shown that 24-hour average blood pressure is a better predictor of cardiovascular events than office blood pressure measurement. (8) In this context we have increasing evidence supporting the superiority of nocturnal hypertension (NHTN) as a predictor of cardiovascular events relative to daytime hypertension, so that ABPM has become essential not only for detection but also for determining its severity. (9,10) There is scarce information about the value of the degree of blood pressure elevation during the nighttime period and its relationship with cardiovascular events and, moreover, from what value of nighttime blood pressure the risk of cardiovascular events begins to increase.

The aim of this study was to find out whether the presence of NHTN and its severity levels are associated with the incidence of cardiovascular adverse events during follow-up.

METHODS

Study design

A retrospective cohort study was conducted including patients who underwent 24-hour blood pressure monitoring for diagnostic confirmation of HTN, or for prognostic purposes, in hypertensive subjects, in a hospital of the Autonomous City of Buenos Aires, Argentina, from March 2017 to December 2022. The composite of adverse cardiovascular events, the so-called major adverse cardiovascular events (MACE) which include cardiovascular death, nonfatal infarction and nonfatal stroke; and hospitalization or visit to the emergency department for heart failure (defined by Framingham criteria), was considered as primary endpoint. Each component of the primary endpoint, in addition to hospitalization for hypertensive urgency/emergency, were considered secondary endpoints.

Study population and definitions

We created our own database, including patients over 18 years of age who underwent pressure monitoring in the Cardiology department.

The variables included in the registry were: a) personal data, gender, age, weight in kg, body mass index (BMI) expressed in kg/m^2 (DuBois formula), medical history and classical cardiovascular risk factors; b) from the pressure monitoring data: study date, percentage of successful readings, 24-h averages, daytime and nighttime averages, pulse pressure, nocturnal pattern of blood pressure behavior (dipper, non-dipper, inverted dipper, or hyper dipper); c) laboratory data: creatinine value prior to the study, creatinine clearance value according to the Cockroft-Gault formula, and values at follow-up; d) echocardiographic data: atrial size, septal thickness, posterior wall thickness, left ventricular ejection fraction (LVEF) by Simpson's method; e) antihypertensive treatment with specification of drugs used, use of statins and aspirin.

Patients with technically unsatisfactory studies, duplicate pressure monitoring reports (the first record was included) and those in whom follow-up data could not be obtained were excluded. Follow-up was performed through the institution's electronic medical record.

Nocturnal HTN was defined according to the criteria of the American Heart Association (AHA) taking as reference a blood pressure value ≥120/70 mmHg during the passive/nighttime period, and a value ≥135/85 mmHg in the active/daytime period, both referred in the follow-up chart. (11) We classified NHTN into four severity strata according to nighttime systolic blood pressure: 83-119 mmHg (normal blood pressure), 120-139 mmHg, 140-159 mmHg and 160-220 mmHg.

Procedures

MEDITECH® pressure gauges (model ABPM 05) were used, with oscillometric method and ±3 mmHg accuracy/2 % of the measured value according to the manufacturer's technical specifications. They were programmed to take measurements every 15 minutes during the active period and every 30 minutes during the passive period, for 24-hour intervals. Data collection analysis and reporting software was provided by the manufacturer. Follow-up was performed by a group of 4 investigators by consulting the institutional electronic medical record; in cases where the data were incomplete or absent, contact and follow-up were made by telephone and closed-ended questions, for a maximum period of 48 months after the index pressure monitoring.

Statistical analysis

Statistical analyses were performed with R Studio, version 1.4.1106 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Qualitative variables are expressed as absolute and relative frequencies. Qualitative variables were compared using the chi-square test or Fisher's exact test, while continuous variables with parametric and nonparametric distribu-

tion were compared using Student's t test and the Mann Whitney U test, respectively. Multiple imputation of the database was performed for the treatment of missing data, which was carried out through the random forest method since most of the variables imputed were categorical. (12) Bivariate and multivariate analyses were performed to identify factors associated with cardiovascular events. Cox regression models were used to search for predictors of events in the long-term follow-up. All variables that in the bivariate analysis presented a p value <0.20 or that were considered clinically important in relation to the response variable were included in the multivariate model. Nested models were compared and chosen according to Akaike's information criterion, ANOVA and concordance index. Kaplan Meier curves and the log-rank test were performed for variables associated with events at follow-up. The association between predictors and the incidence of events was expressed as Hazard Ratio with its 95% confidence interval (95% CI). All tests were two-tailed and statistical significance was established at $p<0.05$.

RESULTS

Baseline population characteristics

Out of a total of 1060 initial subjects, 79 cases were excluded from the analysis (60 did not meet the definition of HTN and 19 did not present follow-up). A total of 981 patients remained as the study population. Fifty-three percent were male, and mean age was 59.8±14.2 years. The baseline characteristics of the population stratified according to nighttime systolic blood pressure are shown in Table 1. NHTN was present in 63.6% of the subjects (n= 624). This group had higher BMI, greater prevalence of male gender, diabetes (DM), and as expected, higher daytime systolic and diastolic blood pressure. In the stratified analysis according to the severity of NHTN, we found a positive gradient with respect to cardiovascular risk factors, that is, the higher the degree of nighttime blood pressure, the higher the BMI and the greater the prevalence of DM, sedentary lifestyle and dyslipidemia. Those with higher nighttime blood pressure values had a more frequent history of atrial fibrillation, obstructive sleep apnea-hypopnea syndrome (OSAHS) and echocardiographic repercussion. Patients with NHTN had a lower use of antihypertensive drugs (76 % vs. 86 %, $p<0.001$). In this group, the most commonly used antihypertensive drugs were angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Events by group

At a median follow-up of 40 (IQR 26-54) months, the main endpoint was present in 130 subjects corresponding to 13.2 % of the total sample, 105 (15.3 %) in the group with NHTN and 25 (8.3 %) in the group without NHTN ($p=0.003$). In the stratified analysis according to the degree of HTN we found differences between groups in the incidence of: a) the primary endpoint: from 7.6 % between 83-119 mmHg to 24.2 % between 160-220 mmHg ($p=0.001$); b) MACE: from 2.2 % between 83-119 mmHg to 11.3 % between 160-220 mmHg ($p=0.007$); c) hospitalization for heart failure: from 1.1 % between 83-119 mmHg to 8.1 % between 160-220 mmHg ($p=0.002$), and d) hospitalization for hypertensive crisis: from 2.5 % between 83-119 mmHg to 4.8 % between 160-220 mmHg, ($p=0.007$). Regarding cardiovascular death, although the proportion was higher in the NHTN group, there were no statistically significant differences: from 2.2 % between 83-119 mmHg to 8.1 % between 160-220 mmHg ($p=0.102$). The probability of event-free survival according to the presence of NHTN, and of the primary endpoint, MACE and hospitalization for heart failure according to the severity of NHTN is shown in Figure 1.

Multivariate analysis: independent predictors of cardiovascular events

We excluded from the multivariate analysis DM, BMI, OSAHS variables and HTN patterns because they presented a p value >0.20 in the bivariate analysis (Table 2). The remaining variables were evaluated in multivariate analysis with the Cox proportional hazards model. Two regression models were fitted and compared with each other. Model 1 included the NHTN strata, age, smoking, left ventricular hypertrophy, and daytime HTN; and model 2 the same variables except for daytime HTN. The latter model showed the best fit (Table 3), including the severity of NHTN variable as an independent predictor of cardiovascular events, with HR (95% CI) 1.30 (0.65 - 2.58), 2.25 (1.02 - 4.94) and 4.18 (1.60 -10.8) for 120-139, 140-159 and 160-220 mmHg strata, respectively. The NHTN behaved as an independent predictor of cardiovascular events (HR 3.60 95% CI 1.12-11.5 $p=0.033$). Age and presence of left ventricular hypertrophy in the echocardiogram also behaved as independent predictors, with HR (95% CI) 1.04 (1.01-1.06) and 2.35 (1.32-4.20), respectively. When adjusted for the presence of daytime HTN, the severity of NHTN remained as an independent predictor of events, so due to the principle of parsimony it was eliminated from the final model. All the adjusted models complied with the proportional hazards assumptions.

DISCUSSION

The main finding of our study is the high prevalence of NHTN and its association with cardiovascular outcomes at the long-term follow-up. We observed that this risk begins in the first severity stratum (120-139 mm Hg) and increases exponentially through each stratum, with the highest risk in the highest severity one (160-220 mm Hg). The severity of NHTN behaved as an independent predictor of adverse cardiovascular outcomes, even in the presence of the daytime HTN variable. Age and left ventricular hypertrophy variables in the echocardiogram were also factors associated with poor outcome.

Hypertension is the main modifiable risk factor,

Tabla 1. Baseline characteristics of the population stratified according to nocturnal systolic blood pressure

	83-119 mmHg	120-139 mmHg	140-159 mmHg	160-220 mmHg	p
n	357	419	143	62	
Male gender, n (%)	186 (52.1)	222 (53.0)	76 (53.1)	38 (61.3)	0.612
Age, mean (SD)	59.73 (13.37)	58.96 (14.65)	61.90 (14.79)	61.61 (14.42)	0.133
BMI, median (IQR)	28 (25-31)	29 (26-32.43)	30 (27-34)	33.16 (29.40-36.80)	<0.001
Diabetes, n (%)	36 (10.1)	68 (16.2)	38 (26.6)	24 (38.7)	<0.001
Dyslipidemia, n (%)	139 (38.9)	131 (31.3)	47 (32.9)	28 (45.2)	0.045
Sedentary lifestyle, n (%)	208 (58.3)	244 (58.2)	83 (58.0)	52 (83.9)	0.001
Smoking, n (%)	87 (24.4)	82 (19.6)	26 (18.2)	14 (22.6)	0.303
History of ACS, n (%)	23 (6.4)	25 (6.0)	9 (6.3)	6 (9.7)	0.743
History of stroke, n (%)	16 (4.5)	21 (5.0)	2 (1.4)	4 (6.5)	0.253
History of CHF, n (%)	5 (1.4)	6 (1.4)	1 (0.7)	2 (3.2)	0.579
History of AF, n (%)	4 (1.1)	16 (3.8)	4 (2.8)	7 (11.3)	<0.001
OSAHS, n (%)	21 (5.9)	34 (8.1)	10 (7.0)	11 (17.7)	0.014
Daytime SBP, mean (SD)	127.95 (10.14)	140.19 (10.34)	153.42 (12.69)	164.37 (15.47)	<0.001
Daytime DBP, mean (SD)	76.31 (9.37)	81.18 (10.83)	86.74 (12.25)	88.24 (12.07)	<0.001
Daytime PP, median ((IQR))	51 (45-57)	58 (52-66)	65 (58-73)	72 (62.25-86.25)	<0.001
Nighttime SBP, mean (SD)	109.48 (7.46)	128.19 (5.65)	147.12 (5.07)	171.52 (10.52)	<0.001
Nighttime DBP, mean (SD)	62.02 (7.34)	70.81 (8.24)	79.77 (9.59)	88.05 (12.85)	<0.001
Nighttime PP, median ((IQR))	47 (42-53)	57 (51-63)	68 (59-74.5)	84.5 (74-91)	<0.001
24 h SBP, mean (SD)	121.78 (9.33)	136.18 (8.61)	150.90 (9.27)	166.24 (12.66)	<0.001
24 h DBP, mean (SD)	71.57 (8.47)	77.69 (9.74)	84.41 (10.64)	88.10 (11.45)	<0.001
24 h PP, median ((IQR))	49 (45- 55)	58 (52-65)	66 (58-73)	74.5 (68-87)	<0.001
LVEF, median ((IQR))	68 (65-70)	69 (64.5-70)	68 (62.5-70)	67.5 [64-70)	0.387
IVS, mm; median ((IQR))	11 (10-12)	11 (10-12)	11.8 (10-12.75)	12 (11- 13)	<0.001
Daytime HTN, n (%)	87 (24.4)	297 (70.9)	134 (93.7)	61 (98.4)	<0.001
Treatment, n (%)	306 (85.7)	310 (74.0)	114 (79.7)	50 (80.6)	0.001
ACEI, n (%)	128 (35.9)	136 (32.5)	50 (35.0)	18 (29.0)	0.631
ARBs, n (%)	129 (36.1)	134 (32.0)	54 (37.8)	23 (37.1)	0.486
Calcium channel blockers, n (%)	92 (25.8)	106 (25.3)	42 (29.4)	16 (25.8)	0.812
Thiazides, n (%)	45 (12.6)	40 (9.5)	21 (14.7)	7 (11.3)	0.331
Aldosterone antagonist, n(%)	10 (2.8)	6 (1.4)	2 (1.4)	2 (3.2)	0.468
Beta-blocker, n (%)	105 (29.4)	88 (21.0)	45 (31.5)	18 (29.0)	0.018
Statins, n (%)	114 (31.9)	108 (25.8)	36 (25.2)	25 (40.3)	0.037
Aspirin, n (%)	66 (18.5)	65 (15.5)	24 (16.8)	7 (11.3)	0.467
CrCl, mean (SD)	106.35 (41.92)	111.92 (51.30)	111.57 (50.20)	111.73 (65.36)	0.417
MACE, n (%)	8 (2.2)	17 (4.1)	8 (5.6)	7 (11.3)	0.007
CV death, n (%)	8 (2.2)	15 (3.6)	7 (4.9)	5 (8.1)	0.102
Primary endpoint, n (%)	27 (7.6)	61 (14.6)	27 (18.9)	15 (24.2)	<0.001
Heart failure, n (%)	4 (1.1)	8 (1.9)	1 (0.7)	5 (8.1)	0.002
Hypertensive crisis, n (%)	9 (2.5)	27 (6.4)	14 (9.8)	3 (4.8)	0.007
Follow-up in months, median (IQR)	41 (28-54)	39 (24-53)	38 (18-49)	37 (18.50-47.75)	0.020

ACEI: angiotensin-converting enzyme inhibitors; ACS: acute coronary syndrome; AF: atrial fibrillation; ARBs: angiotensin II receptor blockers; BMI: body mass index; CrCl: creatinine clearance; CHF: Chronic heart failure; CV: cardiovascular; DBP: Diastolic blood pressure; HTN: hypertension; IQR: interquartile range; IVS: interventricular septum; LVEF, left ventricular ejection fraction; MACE: major adverse cardiovascular events; OSAHS: obstructive sleep apnea and hypopnea syndrome; PP: pulse pressure; SBP: systolic blood pressure; SD: standard deviation

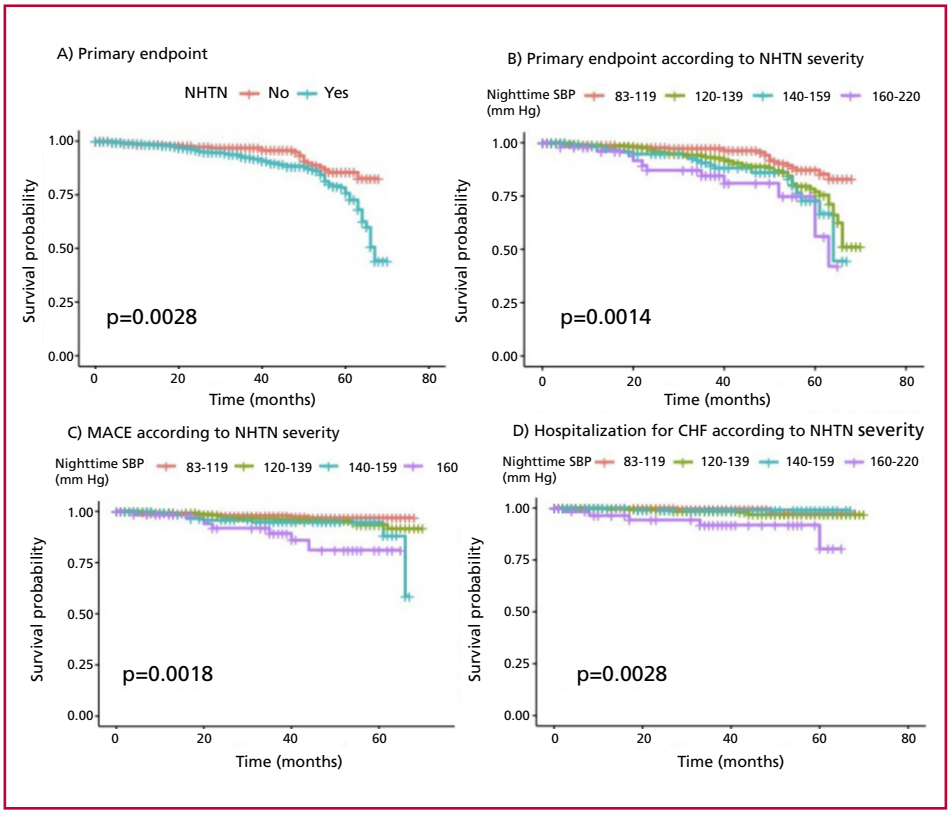

Fig. 1. Event-free survival. A) Primary endpoint according to the presence of nocturnal arterial hypertension (NHTN). B), C) and D) Primary endpoint, MACE and hospitalization for chronic heart failure (CHF) according to NHTN strata

SBP: systolic blood pressure

Table 2. Predictors of cardiovascular events. Bivariate analysis

Variable	b coefficient	HR (95% CI)	p
Diabetes	0.402	1.49 (0.72-3.09)	0.391
OSAHS	0.226	1.25 (0.44-3.49)	0.700
BMI			
Overweight	0.270	1.31 (0.58-2.91)	0.509
Obesity	0.485	1.62 (0.74-3.55)	0.223
NHTN stages			
120-139 mmHg	0.953	2.59 (1.25-5.36)	0.010
140-159 mmHg	0.869	2.38 (0.86-6.58)	0.090
160-220 mmHg	1.066	2.90 (0.99-8.51)	0.051
Age	0.020	1.02 (0.99-1.04)	0.072
LV hypertrophy	0.831	2.29 (1.28-4.12)	0.005
Patterns of HTN			
Attenuated dipper	0.199	1.22 (0.49-3.05)	0.674
Non-dipper	0.661	1.93 (0.87-4.29)	0.101
Inverted dipper	0.893	2.44 (0.97-6.12)	0.052
Hyper dipper	1.351	3.86 (1.68-8.88)	0.001
Smoking	0.981	2.67 (1.51-4.73)	0.001

BMI: body mass index; HR: hazard ratio; LV: left ventricular; NHTN: nocturnal hypertension; OSAHS: obstructive sleep apnea and hypopnea syndrome; 95% CI: 95% confidence interval.

Variable	b coefficient	HR (95% CI)	p
Model 1			
NHTN strata			
120-139 mmHg	1.110	3.03 (1.44-6.37)	0.003
140-159 mmHg	1.306	3.69 (1.36-10)	0.010
160-220 mmHg	1.907	6.73 (2.32-1.95)	<0.001
Age	0.03	1.03 (1-1.05)	0.006
LV hypertrophy	0.80	2.22 (1.24-3.98)	0.006
Daytime HTN	-0.30	0.73 (0.38-1.41)	0.356
Model 2			
NHTN strata			
120-139 mmHg	0.263	1.30 (0.65-2.58)	0.454
140-159 mmHg	0.811	2.25 (1.02-4.94)	0.041
160-220 mmHg	1.431	4.18 (1.60-10.8)	0.003
Age	0.039	1.04 (1.01-1.06)	<0.001
LV hypertrophy	0.858	2.35 (1.32-4.20)	0.003

HR: hazard ratio; HTN: hypertension; LV: left ventricle; NHTN: nocturnal hypertension

Table 3. Predictors of cardiovascular events. Multivariate analysis

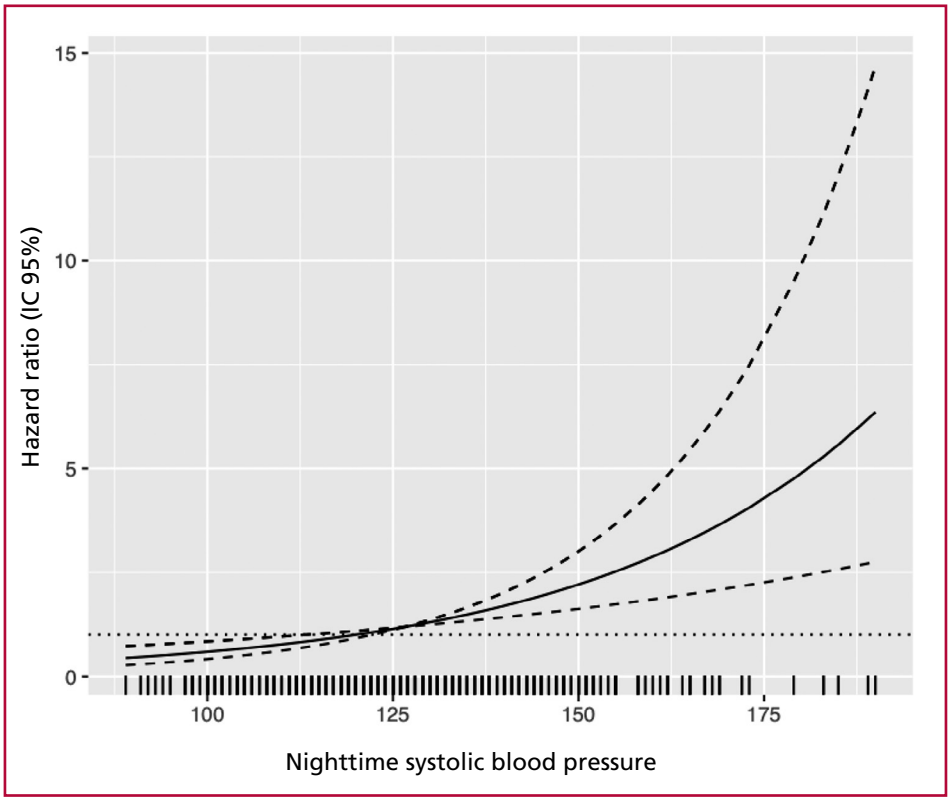

Fig. 2 Continuous association between nighttime systolic blood pressure and risk of cardiovascular events. Solid line represents the Hazard Ratio. Dashed lines represent the 95% confidence intervals. We can observe that the risk starts to increase from 127 mmHg

and it is possible that the prevalence of the NHTN phenotype is underestimated because its diagnosis depends on the request for 24-h pressure monitoring. (13) In our cohort, this prevalence was 69% and we were able to observe that these patients had a greater number of cardiovascular comorbidities and less antihypertensive treatment. In their work, also carried out in Argentina, Salazar et al (14) found a NHTN prevalence of 61%. Individuals with NHTN had greater history of previous cardiovascular disease (4.2% vs. 1.5%, p= 0.007). These authors found no differences in terms of classical cardiovascular risk factors or in relation to antihypertensive treatment. In another study by Yao Du et al. (15) the

reverse dipper or riser pattern was associated with a greater number of comorbidities, including renal dysfunction, overweight and diabetes. In addition to this, they were able to determine that those patients with NHTN presented a 77% higher risk (HR 1.77, 95% CI 1.25-2.50) compared with those without this condition.

Very few previous studies have studied NHTN according to its severity. (16) We were able to prove that the higher the level of nighttime blood pressure, the higher the risk of cardiovascular events. In addition, we were able to determine that this risk begins to increase very early and close to the reference value by which NHTN is defined (127 mmHg) (Figure 2). This is important, since it not only determines a goal to be achieved by antihypertensive treatment, but also reinforces the notion that nighttime blood pressure measurements carry valuable prognostic information.

Hypertension is an important and very frequent comorbidity in patients with a history of heart failure, especially in those with preserved left ventricular ejection fraction. From previous studies we know that more than 50% of patients with heart failure suffer from HTN. (17,18) In their study, Huang et al. in a cohort of patients with a previous diagnosis of heart failure with preserved ejection fraction showed prevalence of HTN in 77% of patients, 40% of which had NHTN. (19) These authors verified that the presence of NHTN is independently associated with rehospitalization for heart failure in the long-term follow-up. In another interesting study carried out by Kidawara et al (20) in patients with diabetes and without previous heart failure, the presence of NHTN behaved as an independent predictor of the progression of left ventricular diastolic dysfunction. In our cohort, as part of an exploratory analysis, we were able to observe a tendency to greater hospitalization for heart failure associated with the presence of NHTN, and that this risk is related to the severity of NHTN.

Our study has some limitations: first and foremost, the retrospective design, which implies biases. Although multivariate regression analysis was performed, we cannot completely rule out the possibility that variables may have altered our results. Secondly, this was a single-center study; however, it was a heterogeneous population with characteristics similar to those of previous studies. Thirdly, as this is a relatively healthy population, we believe that a larger sample size accompanied by a longer follow-up would allow us to determine with greater accuracy the impact of NHTN on cardiovascular events.

In conclusion, in this cohort of patients with HTN the NHTN phenotype and its severity were associated with adverse cardiovascular outcomes at the long-term follow-up.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

Financing

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ORIGINAL ARTICLE

Durability of Bioprosthetic Aortic Valves: Structural Deterioration and Incidence of Events at Long-Term Follow-Up

Durabilidad de prótesis valvulares aórticas biológicas: deterioro estructural e incidencia de eventos en el seguimiento alejado

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ABSTRACT

Background: In the treatment of severe aortic stenosis there has been a shift in the choice of the valve prosthesis type toward the use of biological valves. At present, bioprosthetic valves are used in 80% of aortic valve replacements worldwide. Their main limitation is their reduced long-term durability. No assessment has been yet performed in our setting regarding the durability of bioprosthetic valves and the incidence of long-term events.
Objectives: To evaluate the long-term performance of bioprosthetic aortic valves related to survival and echocardiographic incidence of structural valve deterioration (SVD).
Methods: A retrospective study of 2365 patients undergoing aortic valve replacement with biological prosthesis between January 2003 and December 2023. We analyzed the long-term survival and the incidence of SVD pursuant to changes in the mean transprosthetic gradient (mTPG) according to age (< or ≥60 years) and prosthetic valve size (< or ≥ 23 mm).
Results: Mean age was 73±3.05 years (105 patients <60 years and 2530 patients ≥60 years). A total of 63.4% was male. Of patients, 92% completed a long-term follow-up, mean 5.9±3.2 years. Survival at 5 and 10 years according to age was: in patients <60 years: 98.3 and 91.7% vs. patients ≥60 years: 81.7 and 65.7% (p=0.007), respectively. A total of 1399 (59.7%) patients had an overall echocardiographic follow-up. The values of mTPG at baseline, 5 and 10 years were: a) according to age: in patients <60 years: 16±3 mmHg, 16±6 mmHg and 19±5 mmHg, vs. in patients ≥60 years: 15±5 mmHg, 16±7 mmHg and 18±7 mmHg (p=NS); b) according to prosthesis size: <23 mm: 17±6 mmHg, 19±7mmHg and 22±7 mmHg, vs. ≥23 mm: 15±5 mmHg, 16±6 mmHg and 18±6 mmHg (p= 0.001).
Conclusions: Patients with bioprosthetic valves experienced high long-term survival with some differences according to age group. At follow-up, differences in mTPG (<10 mmHg) were observed in prosthetic valve sizes <23 mm, showing low incidence of severe SVD.

Key words: Aortic valve stenosis - Heart valve prostheses - Structural bioprosthetic valve degeneration

RESUMEN

Introducción: En el tratamiento de la estenosis aórtica grave ha habido un cambio en la elección del tipo de prótesis valvular, con priorización de la utilización de válvulas biológicas. En la actualidad, a nivel mundial, en el 80 % de los recambios valvulares aórticos se utilizan prótesis biológicas, cuya menor durabilidad alejada representa su mayor limitación. No contamos con evaluación reciente en nuestro medio de la durabilidad de las válvulas biológicas y la incidencia de eventos a largo plazo.
Objetivos: Evaluar el comportamiento alejado de las prótesis valvulares aórticas biológicas, respecto de su sobrevida e incidencia ecocardiográfica de deterioro valvular estructural (DVE).
Material y Métodos: Estudio retrospectivo sobre 2365 pacientes operados entre enero de 2003 y diciembre de 2023. Se evaluó la sobrevida alejada y la incidencia de DVE de acuerdo con las modificaciones del gradiente medio transprotésico (GMt) según la edad (dicotomizada en 60 años) y el tamaño de la prótesis utilizada (dicotomizado en 23 mm).
Resultados: La edad promedio fue de 73 ± 3,05 años (105 pacientes < 60 años y 2530 pacientes ≥60 años). Sexo masculino en 63,4 %. Seguimiento alejado en el 92 % de los pacientes, media de 5,9 ± 3,2 años. Sobrevida a 5 y 10 años según edad: en <60 años: 98,3 y 91,7 % vs. ≥60 años: 81,7 y 65,7 % (p=0,007) respectivamente. Seguimiento ecocardiográfico global en 1399 (59,7 %) pacientes. Valores del GMt basal, y a 5 y 10 años: a) según edad: en < 60 años: 16 ±3 mmHg, 16 ± 6 mmHg y 19 ± 5 mmHg, vs. en ≥60 años: 15 ± 5 mmHg, 16 ± 7 mmHg y 18± 7 mmHg (p=NS); b) según tamaño de la prótesis: en <23 mm: 17±6 mmHg, 19±7 mmHg y 22 ± 7 mmHg, vs. en ≥23 mm: 15 ± 5 mmHg, 16± 6 mmHg y 18± 6 mmHg (p= 0,001).

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Conclusiones: Los pacientes con prótesis valvulares biológicas presentaron una elevada sobrevida alejada con diferencias según el grupo etario. Se registraron en el seguimiento diferencias del GMt (<10 mmHg) en las válvulas < 23 mm, demostrando baja incidencia de DVE grave.

Palabras clave: Estenosis de la válvula aórtica - Prótesis valvulares cardiacas - Degeneración estructural de prótesis biológicas

INTRODUCTION

Severe aortic stenosis is the most common primary valve disease, with an increased prevalence in the last few decades due to a higher life expectancy for general population. (1) More than 400 000 aortic valve replacements (AVR) are performed annually worldwide, with important social and economic consequences. It is estimated that in 2050 this procedure will be performed in more than 850 000 patients. (2)

In recent years, there has been a shift in the choice of the prosthesis type, with priority towards the use of biological valves over mechanical valves, even in patients younger than 60. Nowadays, it is estimated that bioprostheses are used in 80% of aortic valve replacements worldwide. (3) This is a consequence of a significant improvement in valve durability and the desire to avoid definitive anticoagulation. (4) There have been improvements in the hemodynamic profile of the prostheses, and changes in the methods of tissue preservation. Although bioprosthetic valves do not require anticoagulation, their shorter long-term durability represents their main limitation, requiring reoperation during the long-term follow-up. We have the latest generation of valve prostheses, but their durability and the incidence of long-term events still remain to be studied. This study aims to evaluate the long-term performance of bioprosthetic aortic valves in relation to survival, the need for reoperation and the echocardiographic incidence of structural valve deterioration (SVD) in a consecutive group of patients undergoing elective and emergency surgery.

METHODS

Between January 2003 and December 2023, 2635 patients underwent bioprosthetic AVR, either electively or urgently, and were prospectively and consecutively entered into a general database. Patients with coronary artery bypass grafting were included but those with pure aortic regurgitation, diagnosis of valve infection, mitral valve compromise, and thoracic aortic surgery were excluded. Preoperative baseline characteristics and intraoperative variables were analyzed in overall population. In patients without coronary artery disease (n=448), AVR was performed by a minimally invasive technique through an upper hemisternotomy in the third or fourth intercostal space with femoral venous drainage by puncture using the Seldinger technique, guided by intraoperative transesophageal echocardiography (TEE). (5) In the analysis of early postoperative results and long-term follow-up, patients were divided according to age (< or ≥60 years) and prosthesis size (< or ≥23 mm). In-hospital mortality was defined as mortality during hospitalization or in the 30-day postoperative period. In-hospital mortality, deep sternal infection (mediastinitis), postoperative acute myocardial infarction (AMI) and postoperative stroke (central neurological deficit lasting more than 72 hours, regardless its confirmation by computed tomography), reoperation for bleeding, renal failure requiring dialysis, and the need for a permanent pacemaker were analyzed. Early postoperative data were obtained from medical records during hospitalization. At long-term follow-up, survival and the presence of events were assessed. The follow-up was carried out by direct communication with patients, their family members, and the general practitioner, as well as by medical records review. The presence of a new stroke and signs of congestive heart failure (CHF) due to prosthetic valve dysfunction were considered reasons for reoperation, and the need for valve replacement was considered to assess the reoperation-free period.

Long-term follow-up data were obtained from cardiology office visits, general practitioner's records, and/or telephone calls. The date of the last visit recorded at follow-up database was defined as evidence of long-term survival according to Kaplan-Meier analysis.

An echocardiographic follow-up was performed. The baseline study was the one conducted within 90 days of surgery, and the long-term follow-up included studies performed 5 and 10 years after surgery. A Phillips Epiq 7 equipment (Philips Medical Systems, Andover, MA) with matrix 5-1 transducer was used. Although many data were obtained from prosthetic function (ejection fraction, outflow tract velocity, effective orifice area, presence of periprosthetic leaks, prosthetic valve regurgitation, and so on), we considered the values of the mean transprosthetic gradient (mTPG) at baseline and at follow-up to be the most representative data of structural valve deterioration (SVD). According to the American Society of Echocardiography (ASE), SVD was defined as possible prosthetic stenosis in the presence of a mean gradient from 20 to 25 mmHg, and as significant prosthetic stenosis in the presence of a mean gradient ≥35 mmHg. (6)

We considered the recommendations of the European Association for Cardiovascular Imaging (EACVI), which considers as possible prosthetic stenosis an increase in mean gradient of 10-19 mmHg and as significant prosthetic stenosis an increase in mean gradient greater than 20 mmHg. (7)

In addition to the long-term survival according to age and the prosthesis size, we analyzed the period free from readmission due to cardiological diseases, the period free from reoperation and the incidence of SVD at long-term follow-up.

This study aimed to evaluate the performance of bioprosthetic valves in relation to long-term survival, the need for readmission and reoperation, and to describe the echocardiographic incidence of SVD according to changes in mTPG at long-term follow-up by age and prosthesis size.

Statistical analysis

Time-to-event analysis was performed according to Kaplan-Meier method for survival, freedom from reoperation and freedom from readmission at 10 years. Differences in time-to-event curves between groups were analyzed by the log-

rank test. Patient characteristics were expressed as mean ± standard deviation, median and interquartile range (IQR) or prevalence (in percentage), as appropriate. Differences between groups were analyzed with Student's t test for continuous variables with normal distribution, with the Mann-Whitney U test for continuous variables with non-normal distribution, and the chi-square test for categorical variables. A value of $p < 0.05$ was considered statistically significant.

The statistical software IBM ® SPSS ® Statistics (version 21) was used.

Ethical considerations

The study was conducted in accordance with national ethical standards (CABA Law 3301) and was approved by the Ethics Committee of our Institution.

RESULTS

A total of 2635 patients were included in the study. The mean age was 73±3.05 years; 105 patients were younger than 60 years, and 2530 patients were 60 years or older. Of them, 63.4% were male. Combined procedures were carried out in 1135 patients (43%). A minimally invasive approach was performed in 16.6%, and in 73% of the cases the prosthesis size was ≥23 mm. The type of implanted prosthesis was pericardial in 509 patients (19.4%) and non-pericardial in 2126 patients (80.6%). Overall in-hospital mortality was 2.9%; the incidence of stroke was low (0.6%) and the need for permanent pacemaker was 2.8%.

In patients with known coronary artery disease who underwent combined procedures, the mean number of grafts was 2.06±0.6. Although the analysis of perioperative complications was not the purpose of this study, they are shown in Table 2.

The long-term follow-up was complete in 92% of patients, with a mean of 5.9±3.2 years. Survival at 5 and 10 years according to age was : in patients <60 years 98.3 and 91.7%, vs. in patients ≥60 years 81.7 and 65.7% (p=0.007), respectively. There were no significant differences in the long-term survival according to the prosthesis size: <23 mm: 67.5% vs. ≥23 mm: 66.2% (p=NS). (Figure 1) The 10-year survival free from readmission for cardiac diseases was low, and without significant differences between groups (94.7% vs. 86.1%, p=NS). The 10-year period freedom from reoperation was greater than 95%, with no statistical differences according to age and the implanted prosthesis size. (Figure 2).

An overall echocardiographic follow-up was performed in 1399 patients (59.7%): at baseline in 845, at 5 years in 473 and at 10 years in 101 patients. The changes in mTPG at 5 and 10 years from baseline were analyzed. This analysis was performed a) according to age: in patients <60 years: 16±3 mmHg, 16±6 mmHg and 19±5 mmHg vs. in patients ≥60 years: 15±5 mmHg, 16±7 mmHg and 18±7 mmHg (p= NS), and b) according to implanted prosthesis size: <23 mm: 17±6 mmHg, 19±7 mmHg and 22±7 mmHg vs. ≥23 mm: 15±5 mmHg, 16±6 mmHg and 18±6 mmHg (p=0.001). (Figure 3)

DISCUSSION

In surgical AVR, bioprosthetic valves are increasingly implanted to the detriment of mechanical valves. (8) Biological tissues are used in most procedures, and currently in percutaneous valve implantations. This tissues have low thrombotic effect, and do not need patient's permanent anticoagulation. However, bioprostheses have disadvantages related to their limited durability due to SVD.

Age (>70 years) has been a limiting factor for the indication of bioprosthetic valves. Recently, the European Society of Cardiology (ESC) guidelines have recommended biological prostheses in patients over 65 years. (9) In contrast, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines consider biological prostheses in patients over 50 years to be reasonable. (10) In the AUTHEARTVISIT study, Traxler et al. assessed surgical valve replacement in young patients (<50 years) and demonstrated that patients with bioprosthetic valves have a higher incidence of reoperations and a shorter reoperation-free period than the group of patients with mechanical valves. (11) This evolutionary damage depends on many factors (age, prosthesis type and size, etc.). In our setting, we have the latest generation of bovine pericardial valves with improved design to ensure better hemodynamics, and with improvements in tissue preservation processes. An example of this is the INSPIRIS RESILIA Aortic Valve (INSPIRIS; Edwards Lifesciences Corporation, Irvine, CA, USA) which combines a new design with new tissue preservation techniques. A recent study of 689 patients who underwent surgery with this type of prosthesis (66.9±11.6 years of age) experienced a very low incidence of SVD at a 7-year echocardiographic follow-up, which was showed by mTPG values lower than 12 mmHg. (12)

SVD usually presents as leaflet calcification resulting in stenosis, but it may also develop as severe valve regurgitation due to leaflet tearing. Definitions and criteria for classifying SVD have changed over time. Dvir et al. have proposed a set of practical and standardized definitions to clinically and echocardiographically assess SVD at long-term follow-up. (13)

This classification is crucial to define the accurate durability of bioprostheses; it is known that relying on the need for reoperation often underestimates the incidence of SVD, since many patients are considered at high-risk for valve reoperation.

Meta-analyses involving porcine and bovine pericardial valves have shown that SVD usually begins 8 years after surgery with a marked increase 10 years after surgery. (14,15) Although the presence of SVD usually includes increased leaflet thickness, leaflet calcification or tissue tearing with stenosis and/or regurgitation detected by computed tomography, changes in mTPG at long-term follow-up from baseline are the strongest indicator of suspected prosthetic damage, whether moderate or severe. (16) The experience

Table 1. Patients' baseline characteristics

Patients		n=2635
Age (years)		73 (68-78)
	≥60 years	95.9%
	<60 years	4.1%
Male		63.4%
Weight (Kg)		79 (65-89)
Height (cm)		169 (155-183)
HTN		70.2%
Smoking		44.9%
DM		21.0%
FMH		10.5%
COPD		6.8%
CKD		5.5%
Previous AMI		10.1%
Previous PCI		12.2%
Stroke		3.5%
Anemia		12.4%
PVD		5.5%
SR		96.0%
Symptoms	Asymptomatic	15.7%
	Angor	27.6%
	Dyspnea	51.7%
	Syncope	5.0%
NYHA FC	≤I	19.5%
	II	35.9%
	III / IV	44.6%
Approach	Mini-invasive	16.6%
	Conventional	83.4%
Prosthesis size	<23 mm	27.0%
	≥23 mm	73.0%
Number of arterial bypass grafts	None	57.3%
	1	18.4%
	2	13.8%
	3 or more	10.5%
Previous cardiac surgery		5.7%
Elective surgery		83.5%
Emergency surgery		16.5%
Clamping time (min)		73 (65-87)
ECC (min)		93 (87- 110)
LVSF	Normal / Mild	91.7%
	Moderate	5.7%
	Severe	2.6%
Extubated in the operating room		10.1%
Postoperative stay (days)		6 (4-7)

AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DLP: dyslipidemia; DM:diabetes mellitus;ECC: extracorporeal circulation; FMH: family medical history; HTN:hypertension; VSF: left ventricular systolic function; NYHA FC: New York Heart Association functional class; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; SR: sinus rhythm. Quantitative variables are expressed as median and interquartile range.

Table 2. Early postoperative results

A. According to age	≥60 years	<60 years	Total	p
n	2530	105	2635	
Death	2.9%	0.0%	2.8%	0.097
Bleeding	4.0%	0.0%	3.8%	0.064
AF	27.2%	7.2%	26.4%	<0.001
PM	2.8%	2.4%	2.8%	0.828
Dialysis	1.9%	0.0%	1.8%	0.206
Stroke	0.6%	0.0%	0.6%	0.474
Prolonged MV	4.0%	0.0%	3.8%	0.064

AF: atrial fibrillation; MV: mechanical ventilation; PM: pacemaker

B. According to prosthesis size	< 23 mm	≥23 mm	Total	p
n	705	1930	2635	
Death	3.1%	2.4%	2.8%	0.070
Bleeding	4.8%	3.5%	3.8%	0.162
AF	29.4%	25.2%	26.4%	0.052
PM	3.0%	2.7%	2.8%	0.649
Dialysis	2.3%	1.6%	1.8%	0.306
Stroke	0.5%	0.6%	0.6%	0.835
Prolonged MV	5.2%	3.3%	3.8%	0.056

AF: atrial fibrillation; MV: mechanical ventilation; PM: pacemaker

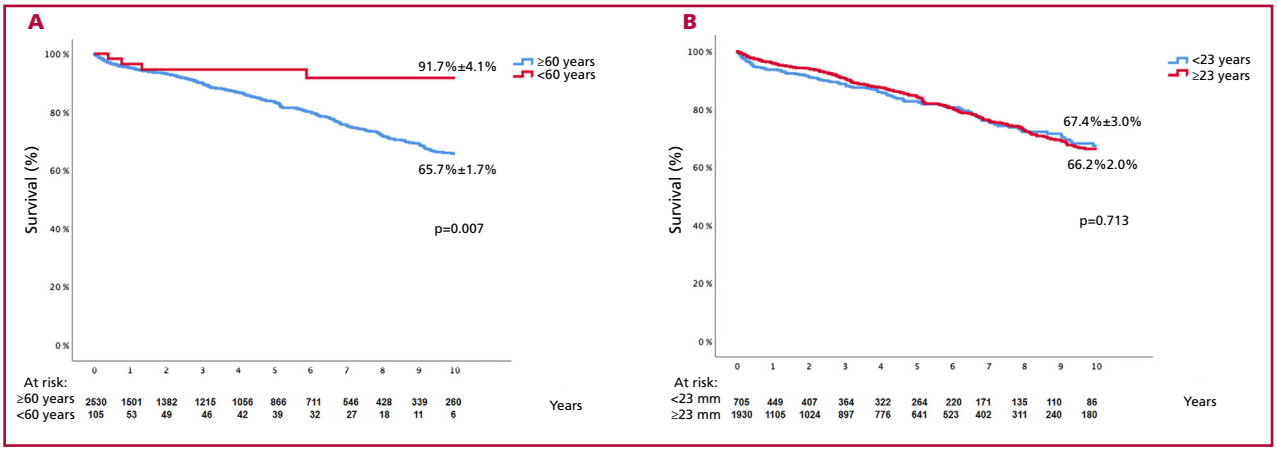

Fig 1. Long-term survival according to age (A) and prosthesis size (B)

published by several surgical groups describes a low incidence of severe SVD at long-term follow-up without a clear direct relationship with age dichotomized at 65 years. (17,18) However, in young patients (<50 years) the incidence of severe SVD is significantly more frequent. (19) In our series, on 1399 echocardiograms evaluated during a 10-year follow-up, the presence of severe SVD has been low and with no statistical differences according to age. There was a significant statistical difference in the mTPG at 5- and 10-year follow-up according to the prosthesis size, although these values were lower than those considered severe (mTPG in <23 mm = 22 mmHg vs. in ≥23 mm = 18 mmHg).

According to most publications, the incidence of severe patient-prosthesis mismatch is low. Patient-prosthesis mismatch could accelerate the development of early SVD. Currently, surgical techniques to enlarge the aortic annulus are used to adjust the size of the aortic valve prosthesis to the patient's body surface area. (20,21)

In this study, prosthetic valve sizes ≥23 mm were

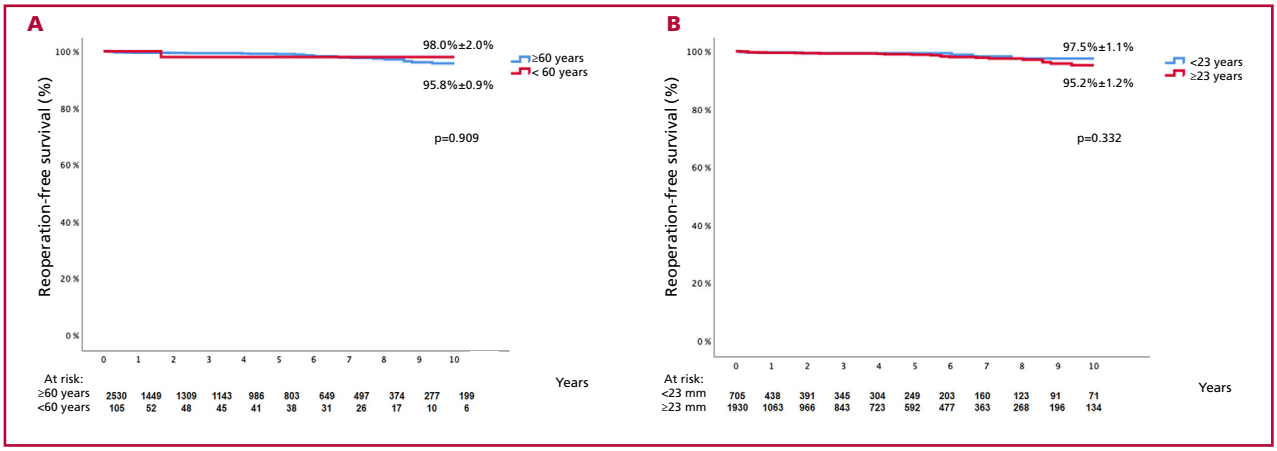

Fig 2. Reoperation-free survival according to age (A) and prosthesis size (B)

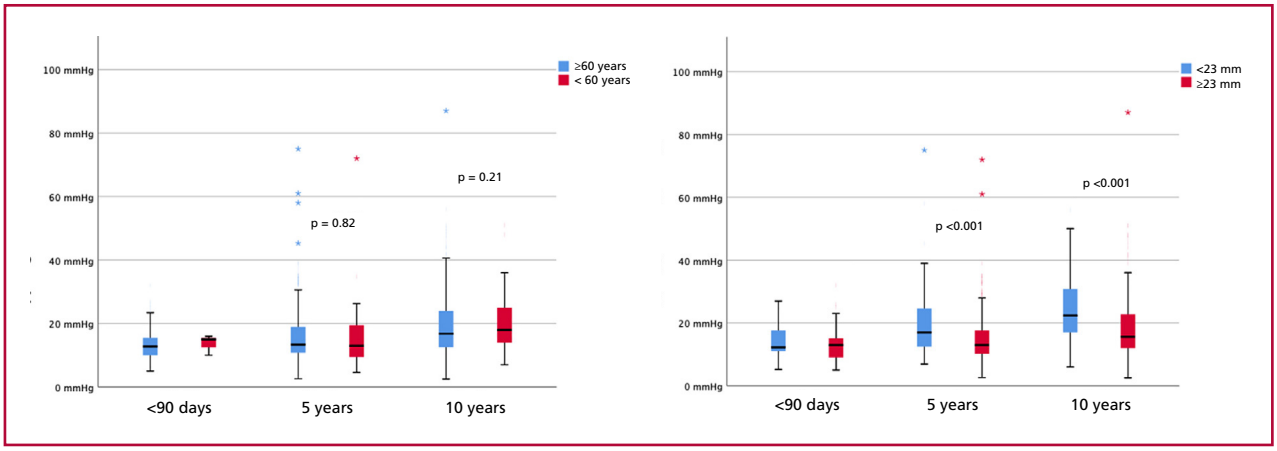

Fig 3. Measurement of mean transprosthetic gradient according to age (A) and prosthesis size (B)

implanted in 73% of patients considering their body surface area.

Limitations

Our study has several limitations: it was a retrospective and single-center analysis. However, it should be noted that all consecutively included patients represent a good sample of the real-world daily practice.

Despite the long study period, 92% of patients were followed-up. The echocardiographic study at long-term follow-up could only be performed in 59% of patients. Many patients underwent their studies sporadically and in other sites, without a clear follow-up protocol. The long-term follow-up of this study took place during the pandemic period showing a marked negative effect as regards collecting evolutionary data. Despite these limitations, it was possible to analyze a non-negligible sample of 1399 echocardiographic studies performed in 10-year period. Only the changes in mTPG over time were important for analysis, and our experience, in terms of incidence and severity of SVD, coincides with that of most of the different groups worldwide

CONCLUSION

Patients with bioprosthetic valves had a high long-term survival with significant differences according to age group. The reoperation-free period was high for all patients. Although there were significant mean changes in mTPG in the group of patients with prosthesis size <23 mm at 5- and 10-year follow-up, these differences were less than 10 mmHg from baseline, demonstrating a low incidence of long-term severe SVD. There were no significant differences in the mTPG values according to age.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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ORIGINAL ARTICLE

Risk of Embolic Events in Patients with Chagasic Cardiomyopathy and Atrial Fibrillation Despite Antithrombotic Therapy: Is Anticoagulation Enough?

Riesgo de eventos embólicos en pacientes con miocardiopatía chagásica y fibrilación auricular a pesar de terapia antitrombótica: ¿es la anticoagulación suficiente?

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ABSTRACT

Background: Chagasic cardiomyopathy (CC) differs from other heart failure causes in multiple aspects, highlighting the risk of systemic embolisms. However, few studies have evaluated the risk of embolic events in anticoagulated patients with CC compared with other cardiomyopathies.
Objective: We aimed to analyze the incidence of systemic embolisms in a cohort of anticoagulated patients diagnosed with atrial fibrillation (AF) with and without CC.
Methods: A retrospective cohort study was carried out at a fourth level hospital in Colombia during the period 2014-2020. All patients diagnosed with cardiomyopathy of any etiology and AF, who were on an anticoagulation regimen were included. The primary outcome was the incidence of embolic events. A survival analysis was performed using adjusted Cox proportional hazard models. A p-value <0.05 was considered significant. All statistical tests were two-tailed.
Results: A total of 149 anticoagulated patients with cardiomyopathy were evaluated (median age: 71 years; women: 30.20%). The cumulative incidence of embolic events was significantly higher in patients with CC (17.50%) compared with those presenting other cardiomyopathies (4.95%), despite that the latter had a significantly higher CHA_2DS_2-VASc score (p=0.013). After multivariate analysis, patients with CC had a significantly higher risk of embolic events regardless of the CHA_2DS_2-VASc score and the type of anticoagulant prescribed (HR 5.65; 95% CI 1.46-21.83; p=0.012).
Conclusions: Chagasic cardiomyopathy was associated with a significantly higher risk of embolic events, despite anticoagulation therapy in both groups. More research is required to understand the origin of the risk observed in order to translate this knowledge into specific indications for anticoagulation in patients with CC.

Key words: Cardiomyopathy - Chagas disease - Embolic events - Oral anticoagulation

RESUMEN

Introducción: La miocardiopatía chagásica (MC) difiere de otras causas de insuficiencia cardíaca en múltiples aspectos, destacándose el riesgo de embolias sistémicas. Sin embargo, pocos estudios han evaluado el riesgo de eventos embólicos en pacientes anticoagulados con MC en comparación con otras miocardiopatías.
Objetivo: Nuestro objetivo fue analizar la incidencia de embolias sistémicas en una cohorte de pacientes anticoagulados con diagnóstico de fibrilación auricular (FA) con y sin MC.
Material y métodos: Se realizó un estudio de cohorte retrospectivo en hospital de cuarto nivel en Colombia durante el periodo 2014-2020. Se incluyeron todos los pacientes con diagnóstico de miocardiopatía de cualquier etiología y FA que estuvieran en régimen de anticoagulación. El resultado primario fue la incidencia de eventos embólicos. Se realizó un análisis de supervivencia mediante modelos de riesgos proporcionales de Cox ajustados. Un valor de p <0,05 se consideró significativo. Todas las pruebas estadísticas fueron de dos colas.

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Resultados: Se evaluaron 149 pacientes anticoagulados con miocardiopatía (mediana de edad: 71 años; mujeres: 30,20 %). La incidencia acumulada de eventos embólicos fue significativamente mayor en los pacientes con MC (17,50%) en comparación con aquellos con otras miocardiopatías (4,95 %), a pesar de que estos últimos tenían una puntuación CHA_2DS_2-VASc significativamente mayor (p=0,013). Tras el análisis multivariado, los pacientes con MC tuvieron un riesgo significativamente mayor de eventos embólicos independientemente de la puntuación CHA_2DS_2-VASc y del tipo de anticoagulante prescrito (HR 5,65; IC 95% 1,46-21,83; p=0,012). **Conclusiones:** La MC se asoció con un riesgo significativamente mayor de eventos embólicos, a pesar del tratamiento anticoagulante en ambos grupos. Se requiere más investigación para comprender el origen de este riesgo observado y traducir este conocimiento en indicaciones específicas de anticoagulación para pacientes con MC.

Palabras clave: Miocardiopatía - Enfermedad de Chagas-Eventos embólicos-Anticoagulación oral

INTRODUCTION

Chagas disease (CD) is endemic in American tropical and subtropical regions and has represented a public health problem in Latin America for decades. However, due to migration, it has become a global economic and health burden. (1) It is estimated that there are six million people infected with T. cruzi in Latin America, 300 000 in the United States, and 42 000 in Europe. (2) Chagas disease attributes a substantial burden to the patient and society regarding direct and indirect costs associated with medical care, early mortality, disability, and negative labor consequences such as loss of productivity due to absenteeism and tardiness. (3)

Chagas disease is known to have two forms: acute and chronic. (4) The acute phase of the disease is usually asymptomatic. After this phase, the patient enters a chronic phase, in which about 60-70% remain in the indeterminate form of the disease, characterized by positive serology for CD, but no evidence of structural cardiomyopathy or heart failure (HF) symptoms. (5) In this context, 30-40% of cases progress to clinical forms of the disease, with the cardiac form being the most frequent and severe manifestation. (6,7) Cardiac involvement is characterized by symptoms of HF, alterations of the conduction system, bradyarrhythmia and tachyarrhythmias, in addition to radiographic and echocardiographic alterations. (8,9) Besides, HF of chagasic origin is associated with higher mortality compared with other etiologies. (10)

During the chronic phase, multiple alterations in the structure and function of the myocardium lead not only to the development of HF symptoms but also to the appearance of prothrombotic conditions such as atrial fibrillation (AF) or even intraventricular clots, which are the product of the slow flow and structural alterations in the endocardium. (11,12) This association has been evidenced in some studies evaluating patients with cardiomyopathy of chagasic origin compared with cardiomyopathies of other etiologies. (13) This differential risk could be explained by some of the characteristics of chagasic cardiomyopathy (CC), such as a higher incidence of AF and apical aneurysms. Consequently, multiple studies have found a high incidence of ischemic stroke in patients with heart failure of chagasic etiology, highlighting the significant risk of embolic events with this condition. However, it is unknown whether there is benefit from anticoagulation in these patients despite not meeting the criteria for receiving anticoagulants by CHA_2DS_2-VASc scoring. Besides, few studies have compared the risk of embolic events exclusively in anticoagulated patients with CC versus other heart failure etiologies. Therefore, the objective of the present study was to evaluate the risk of embolic events and bleeding in anticoagulated patients with and without CC treated in a fourth-level specialized center in Colombia.

METHODS

Study population

A retrospective cohort study was conducted between 2014 and 2020 at the Heart Failure and Anticoagulation Clinic of a fourth-level hospital in Floridablanca, Colombia. The medical records of all patients assessed in the Anticoagulation Clinic were reviewed to assess their eligibility. Patients were included if they met the following criteria: a) age ≥18 years; b) having a diagnosis of cardiomyopathy of any etiology, and c) diagnosis of atrial fibrillation. The diagnosis of cardiomyopathy of other etiologies was based on the clinical records information, including hypertensive, ischaemic, and valvular etiologies in this group. On the other hand, we excluded patients with less than two follow-up appointments at the Anticoagulation Clinic and those with incomplete data in the electronic clinical records. A structured format was developed to extract information, which was collected retrospectively, covering sociodemographic, clinical, and laboratory variables.

Outcomes and main exposure

The outcomes of interest were time to first embolic event (including cerebrovascular events and systemic embolisms such as ischemic stroke, acute myocardial infarction of embolic origin, mesenteric ischemia of embolic origin, and other systemic embolisms of cardiogenic origin) and time to the first bleeding event (including minor or major skin, periodontal, other mucosae, intra-articular and central nervous system bleeding). Cardiomyopathy of chagasic origin was considered as the primary exposure, which was verified by registering a positive result of at least two different tests for Chagas Disease (Enzyme-Linked ImmunoSorbent Assay, haemagglutination-inhibition test, or indirect immunofluorescence test) and the presence of electrocardiographic abnormalities compatible with CC (left anterior fascicular block, right bundle branch block, atrioventricular blocks, ventricular premature beats, atrial fibrillation or flutter, heart rate ≤50 beats/min), or echocardiographic findings suggestive of myocardial involvement.

Statistical analysis

Categorical variables are presented as absolute numbers and proportions. The normality of the continuous variables was evaluated using histograms and the Shapiro-Wilk test. Variables with normal distribution are presented as means with their respective standard deviations and those with non-normal distribution are reported as medians with the corresponding interquartile range (IQR). A bivariate analysis comparing the sociodemographic and clinical characteristics according to the cardiomyopathy etiology was performed using the Chi-Square test, Fisher's exact test, Student´st test and the Mann-Whitney U test. The cumulative incidence of the events of interest was calculated with their respective 95% confidence intervals. Survival analysis was performed using the Kaplan-Meier method and adjusted Cox proportional hazard models. A value of $p < 0.05$ was considered significant. All statistical tests were two-tailed. The analyses were performed using the statistical software STATA version 16.

Ethical considerations

This research was carried out following Resolution No. 08430 of 1993 of the Colombian Ministry of Health, which establishes the scientific, technical, and administrative standards for health research. The research protocol was submitted and approved by the Scientific Technical Committee and Research Ethics Committee of the Hospital.

RESULTS

A total of 149 anticoagulated patients with cardiomyopathy were evaluated (Figure 1). Median age was 71 (63-78) years and 30.20% were women. Median left ventricular ejection fraction was 35% (25-46) and median international normalized ratio (INR), 2.5 (2.2-3.1). Among these patients, 56.38% were treated with direct oral anticoagulants (DOACs); 55.17% had coronary artery disease, 26.21% chronic kidney disease; 28.86% had a Chagas disease diagnosis; 26.21% had history of bleeding, and 19.31% had history of embolic events. In 33.10% of cases, patients had an implanted device (pacemaker, cardioverter defibrillator, and others). Median CHA_2DS_2-VASc score was 4 (3-5) points and the median HAS-BLED score was 2 (2-3) points (Table 1).

Coronary artery disease and chronic kidney disease were more frequent in patients with cardiomyopathy of other etiologies than in patients with CC. Patients with non-chagasic cardiomyopathies had an apparent higher risk of embolisms (higher CHA_2DS_2-VASc score) while patients with Chagas' cardiomyopathy had a greater number of devices implanted (Table 2).

The median follow-up time for embolism was 373

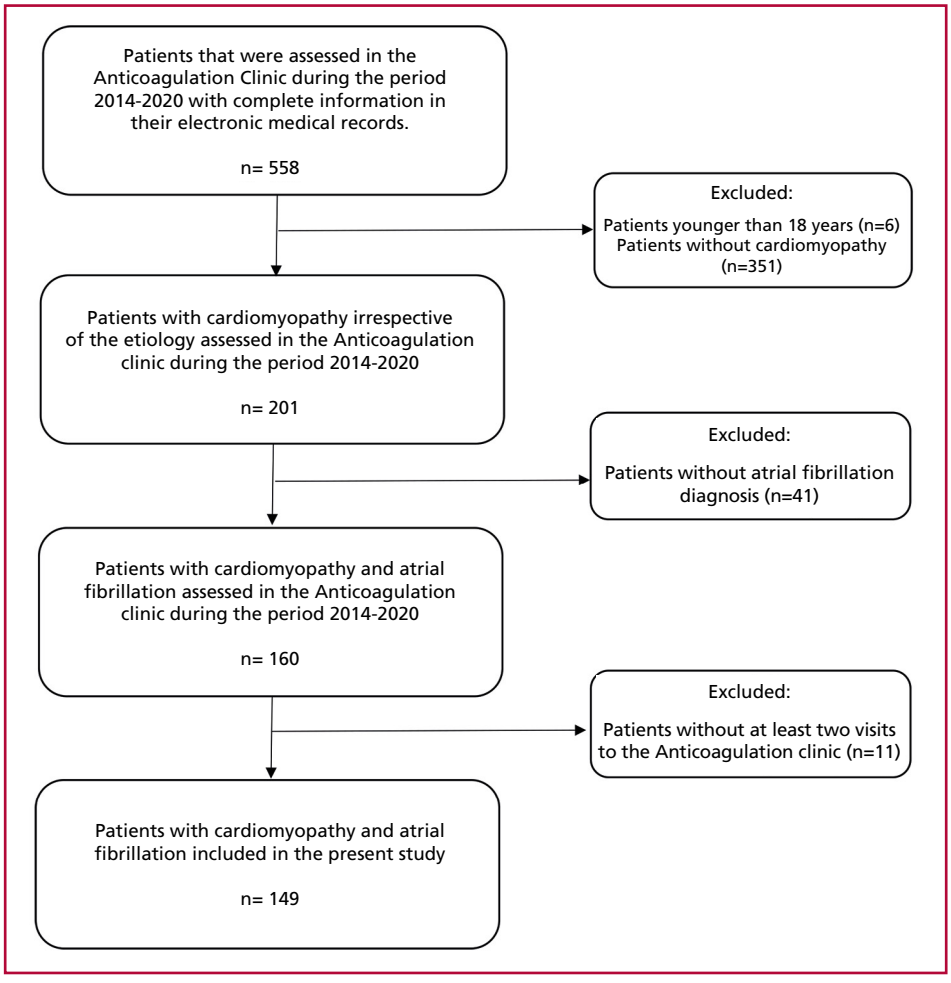

Fig. 1. Flow diagram summarizing the process of patient selection

(128-742) days, with a cumulative incidence of embolic events in the entire cohort of 8.05% (12/149; 95% CI 4.47-14.39%); 16.27% (7/43; 95% CI 7.34 -32.78%) in CC patients and 4.72% (5/106; 95% CI 1.63-11.17%) in other etiologies (p=0.013). Regarding bleeding, median follow-up time was 315 (117-691) days, with a cumulative incidence of 14.09% (21/149; 95% CI 9.19 - 21.28%) for the total cohort; 4.65% (2/43; 95% CI 0.58-16.16%) in CC patients and 17.92% (19/106; 95% CI 11.49-27.29%) in other etiologies (p=0.035).

Chagas disease was significantly associated with the presence of embolic events with a hazard ratio (HR) of 5.65 (95% CI 1.46-21.83; p = 0.012) in a multivariate regression model adjusted for the CHA_2DS_2-VASc score and the type of anticoagulant prescribed (Figure 2), but it was not associated with a higher bleeding risk: HR 0.24 (95% CI 0.05- 1.06; p = 0.059) in a model adjusted for the HAS-BLED score and the type of anticoagulant prescribed (Figure 3). For both models, the proportionality risk assumption was met.

There were no significant differences in embolic events, bleeding, and mortality according to the type of anticoagulant. (Table 3). These results were similar when analyzing only the CC population, but patients

Variable	n= 149
Age (years), median (IQR)	71 (63-78)
Females, n (%)	45 (30.20)
Coronary artery disease, n (%)	80 (55.17)
Chronic kidney disease, n (%)	38 (26.21)
Chagas disease, n (%)	43 (28.86)
History of LV thrombus, n (%)	8 (6.45)
History of bleeding, n (%)	38 (26.21)
History of embolic events, n (%)	28 (19.31)
Implanted devices, n (%)	48 (33.10)
LVEF (%), median (IQR)	35 (25-46)
DOAC use, n (%)	84 (56.38)
Creatinine, mg/dL, median (IQR)	1.0 (0.9-1.2)
INR, median (IQR)	2.5 (2.2-3.1)
CHA_2DS_2-VASc score, median (IQR)	4 (3-5)
HAS-BLED score, median (IQR)	2 (2-3)

DOAC: Direct Oral Anticoagulants; INR: international normalized ratio; IQR: interquartile range; LVEF: Left ventricular ejection fraction.

Table 1. Sociodemographic and clinical characteristics of patients with anticoagulated cardiomyopathy (n = 149).

Tabla 2. Sociodemographic and clinical characteristics according to the cardiomyopathy etiology (n = 149)

Variable	Chagasic Cardiomyopathy (n=43)	Cardiomyopathy of other etiologies (n=106)	p
Age (years), median (IQR)	68 (62-77)	73 (64-78)	0.108
Females, n (%)	15 (34.88)	30 (28.30)	0.428
Coronary artery disease, n (%)	17 (40.48)	63 (61.17)	0.023
Chronic kidney disease, n (%)	6 (14.29)	32 (31.07)	0.037
History of LV thrombus, n (%)	3 (8.11)	5 (5.75)	0.695
History of bleeding, n (%)	12 (28.57)	26 (25.24)	0.679
History of embolic events, n (%)	10 (23.81)	18 (17.48)	0.381
Implanted devices, n (%)	24 (57.14)	24 (23.30)	<0.001
LVEF (%), median (IQR)	35 (23-45)	38 (25-47)	0.510
DOAC use, n (%)	26 (60.47)	58 (54.72)	0.521
Creatinine, mg/dL, median (IQR)	1.0 (0.8-1.2)	1.0 (0.9-1.3)	0.307
INR, median (IQR)	2.4 (2.2-3.1)	2.5 (2.2-3.1)	0.905
CHA_2DS_2-VASc score, median (IQR)	3 (2-4)	4 (3-5)	0.013
HAS-BLED score, median (IQR)	2 (2-3)	3 (2-3)	0.345

DOAC: Direct Oral Anticoagulants; INR: international normalized ratio; IQR: interquartile range; LV: Left ventricular; LVEF: Left ventricular ejection fraction.

treated with warfarin in this group tended to present a higher risk of bleeding.

DISCUSSION

In the present cohort study, a significantly higher risk of embolic events was evidenced in patients with CC, despite receiving anticoagulant therapy and regardless of other clinical factors reflected by the CHA_2DS_2-VASc score and the type of anticoagulant prescribed. On the other hand, there was no significant difference in bleeding risk after adjusting for the HAS-BLED score and the type of anticoagulant received. These findings highlight the differential role of CC compared with other etiologies of heart failure.

Chagasic cardiomyopathy represents a unique model of thromboembolic risk due to its complex pathophysiology, which leads to a series of typical structural and functional alterations of the myocardium. (14) Some of the first evidence of the CC thromboembolic potential was reported in autopsy studies carried out almost 50 years ago, revealing that around 20% of the cases presented multiple cerebral infarcts, half of which were the cause of death. (15-17) Subsequently, several epidemiological studies have observed a significant association between CC and the development of symptomatic cerebrovascular disease, where the meta-analysis by Cardoso et al.¸ which evaluated eight studies that compared the risk of stroke in patients with CC in comparison to other etiologies stands out. This study concluded that patients diagnosed with CC had a risk almost two times higher for this outcome (OR 1.74, 95% CI 1.02-3.00), with a consistent result after sensitivity analysis. (13) Among the studies that compared the risk of cerebrovascular events in patients with CC versus other cardiomyopathy causes, only one corresponded to a cohort study, the majority being cross-sectional or case-control studies. (15,18-24)

Nevertheless, embolic events can occur even in the early stages of the disease, as reported in a cohort of patients with mild CC, in which a rate of 2.7 embolic events per 100 patient-years was estimated, being much higher than that observed in healthy patients. (25,26) However, there seems to be no difference regarding the risk of embolic events in patients in the indeterminate phase of the disease, even though a series of alterations in different coagulation factors have been documented in it, conditions which warrant further study. (25,27)

This observed high embolic risk derives not only from the development of congestive heart failure as a result of the chronic persistence of the parasite in the myocardium but also from the high frequency of severe conduction disorders (notably atrial fibrillation, intraventricular conduction defects, and even atrioventricular blocks), ventricular aneurysms, and mural thrombi, which have been significantly associated with sudden cardiac death and systemic thromboem-

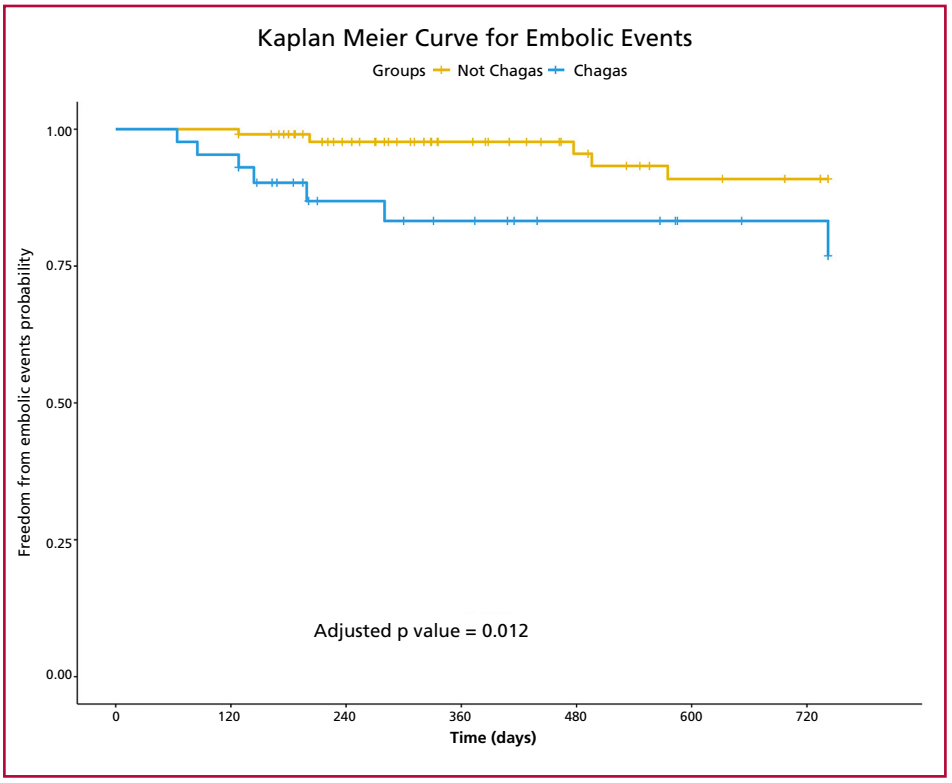

Fig. 2. Freedom from embolic events according to the cardiomyopathy etiology

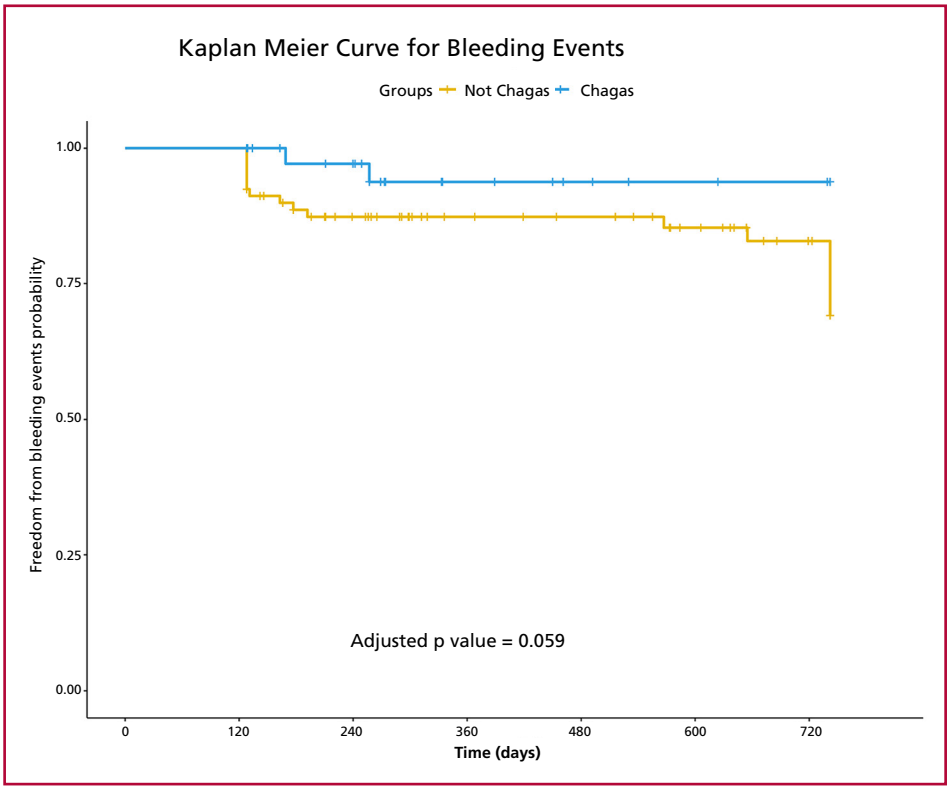

Fig. 3. Freedom from bleeding events according to the cardiomyopathy etiology

Anticoagulant	Embolic events	Bleeding events	Mortality
Warfarin (n= 65)	6 (9.23 %)	12 (18.46%)	2 (3.08%)
DOAC (n=82)	6 (7.31 %)	9 (10.97%)	1 (1.21%)
Total (n=147)	12 (8.16 %)	21 (14.28%)	3 (2.04 %)

Table 3. Outcomes according to the type of prescribed anticoagulant.

bolism in these patients. (2) However, other cardiovascular disorders observed in CC may also increase the risk of thromboembolic events, such as atherothrombosis of the great vessels and small vessel disease, which can be attributed to both typical cardiovascular risk factors and direct damage of T. cruzi to the vascular smooth muscle. (28) This may explain why about 25% of cerebrovascular events in patients with CC are classified as cryptogenic even after conducting additional studies such as echocardiography, 24-hour Holter monitoring, and carotid echo-Doppler. (29)

The present study adds relevant information to the current literature, revealing a significant difference between CC and other cardiomyopathies regarding embolic events incidence despite anticoagulation and after adjusting by relevant covariates. However, even when the potential pathophysiological mechanisms explaining these differences are well-known, there is still very poor awareness of the importance of initiating early prophylaxis in high-risk groups, although they do not fulfill the conventional criteria for anticoagulation used in other cardiomyopathies. (30-32) An important initiative in this aspect is being led by the Instituto de Pesquisa Evandro Chagas and the Fundação Oswaldo Cruz in Brazil. These two entities created the IPEC-FIOCRUZ score, which aims to propose prophylaxis strategies against cardioembolic ischemic stroke in Chagas disease based on clinical risk-benefit, achieving high precision in the identification of high-risk of embolic events groups (area under the ROC curve of this model was 0.90 [95% CI 0.86 - 0.94]). (33) However, the IPEC-FIOCRUZ was validated in a single center using a relatively small sample size, highlighting the need to perform additional studies to obtain an adequate external validation of this score and promote a more widespread use. This will potentially favor optimal anticoagulant prophylaxis among CC patients, further reducing the risk of embolic events in this population. (33)

Finally, not having observed differences in the risk of embolic events when comparing the types of anticoagulants used may reflect the limited statistical power of the present study derived from the relatively small sample. Currently, there is still a debate

in the literature regarding the usefulness of DOAC compared to warfarin for the management of conditions such as intraventricular thrombi and anticoagulation in prosthetic valves. (34,35) There are already studies comparing the types of anticoagulants in these contexts; however, we do not have a record of a study designed to evaluate the benefit of DOAC over warfarin as anticoagulant therapy in the specific context of CD. (36,37) Given their characteristic differences and high cardioembolic risk, it is necessary to carry out research aimed at clarifying both the type of optimal anticoagulant and the particular indications for its use in these patients.

Limitations

We must acknowledge the multiple limitations of the present study, highlighting the small sample size, which may have reduced the probability of identifying significant associations between the variables evaluated. The retrospective nature of the study may influence the quality of the information recorded. Finally, the group of cardiomyopathies of other etiologies represented a heterogeneous population, which may also interfere with the analyses performed. On the other hand, our study has a particular strength derived from the inclusion of patients only with a diagnosis of atrial fibrillation, which allowed us to demonstrate the role of other possible causes of embolism that justify the higher risk observed in the CC group.

CONCLUSION

Chronic CC represents a unique and characteristic myocardial involvement condition, associated with a significantly higher risk of embolic events than other cardiomyopathy etiologies, despite anticoagulation. This result was in accordance with what has been published so far in the scientific literature, with the added value of having evaluated only anticoagulated patients. It is necessary to carry out more studies that allow a clear understanding of the origin of this greater risk observed, in order to translate this knowledge into specific indications for anticoagulation in patients with CC, thus allowing an optimization in its management an improvement in its outcomes.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

Financing

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SCIENTIFIC LETTER

Atrial Tachycardia Ablation of a Right Atrial Appendage Aneurysm

Ablación de taquicardia auricular de aneurisma de la orejuela derecha

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Ectopic atrial tachycardia (AT) is a relatively uncommon form of supraventricular tachycardia involving challenging medical care. Radiofrequency ablation (RFA) therapy has a high long-term success rate. (1,2)

Foci tend to be located in distinct anatomical regions. In the right atrium, these foci are found along the crista terminalis, the tricuspid annulus, the coronary sinus ostium, and the right atrial appendage (RAA). The latter is the most frequent focus in young subjects. (1,3)

RAA aneurysms are rare, and focal AT derived therefrom even more. (4) Fewer than 25 cases have been reported to date, and most of them have required surgical treatment (appendage resection). The best way to achieve a definitive diagnosis consists in using multimodal imaging. (5)

We present the case of a 25-year-old female patient with ectopic AT resulting from RAA aneurysm, refractory to medical treatment, treated with RFA.

The patient experienced sporadic palpitations and dyspnea. Holter ECG showed predominant sinus rhythm, with an average heart rate of 133 beats/minute (range: 86-179), and AT episodes. Laboratory tests and cardiac Doppler ultrasound were normal. She was initially administered ivabradine 5 mg/12 h and propanolol 80 mg/8 h. Due to the lack of response to medical treatment, both RFA and 3D mapping of the right AT were performed, guided by intracardiac echocardiography to reach the base and distal third of the RAA.

After 9 months the patient remained symptomatic and refractory to multiple medical therapies. Holter ECG revealed tachycardia of 177 bpm. A computed angiotomography showed a broad-base RAA with the upper end extending from the right atrium. A new ablation was performed. Using a CARTO 3 3D navigation system and a Pentaray® catheter, the reconstruction and activation mapping of the right atrium, superior vena cava and RAA were achieved. Angiography of the RAA (Figure 1A) showed a lobulated and wide-base RAA with a narrow-base aneurysm of about 3 cm in diameter, moved by heartbeats. Intracardiac echocardiography (Figure 1B) confirmed the anatomy and guided ablation. A precocity mapping was performed from the base of the aneurysm to the inner part, where precocity improved (-45 msec). Using a Smarttouch SF® external irrigated catheter, 5 applications were administered inside the aneurysm but they failed to stop tachycardia. We then proceeded to complete applications with a Freezor™ Xtra catheter (-80°C) for 240 seconds in that area, with no evidence of stopping tachycardia. Finally, we decided to electrically isolate the aneurysm with the RF catheter, and 8 seconds after the last application, AT stopped. (Figure 2). After a 30-minute period of observation, atrial stimulation protocol, and from the interior of the aneurysm, was performed, without tachycardia induction.

At the 3-month post-procedure follow-up, the patient is asymptomatic, and Holter ECG has revealed no new tachycardia occurrences.

In patients with ectopic AT, transcatheter ablation is considered the first-line therapy. Even though there is limited experience with this technique, success rates are 80-90%. In this case, we believe that successful ablation was due to the combined use of 3D mapping, intracardiac echocardiography and angiography, which allowed RF applications together with cryoablation at the site of interest to achieve electrical isolation of the aneurysm and, therefore, AT disappearance.

Ethical considerations

Not applicable.

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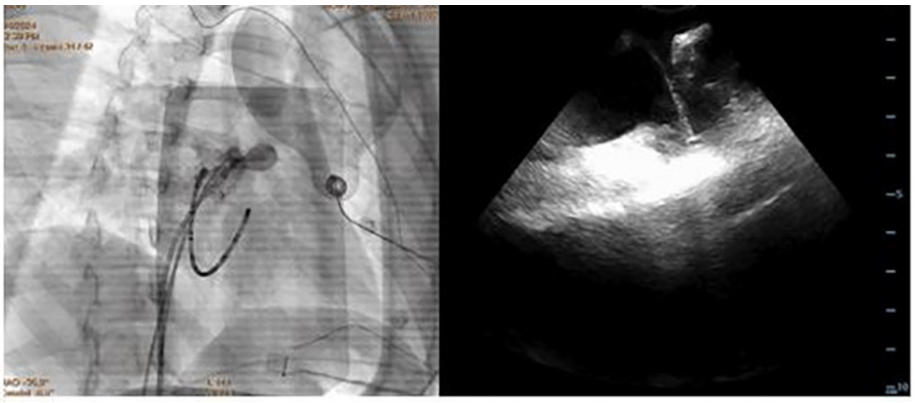

Fig. 1. A. Radioscopy showing right atrial appendage and aneurysm, with an ablation catheter inside.
B. Intracardiac echocardiography from the right atrium displaying right atrial appendage and aneurysm.

Fig. 2. Activation mapping with right atrial appendage isolation which stops atrial tachycardia during applications.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing

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SCIENTIFIC LETTER

Pyoderma Gangrenosum as a Differential Diagnosis of Critical Chronic Lower Limb Ischemia

Pioderma gangrenoso como diagnóstico diferencial de isquemia crónica crítica de miembros inferiores

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Pyoderma gangrenosum is an uncommon ulcerative skin disease, first described 80 years ago, and is classified as neutrophilic dermatosis. (1) Ulcers can occur anywhere on the body, the most common region being the pretibial region. It has no specific serology or histology, and diagnosis is primarily clinical. The ethology is inflammatory and autoimmune (non-infectious). It may occur secondarily to a minor cutaneous (accidental or post-surgical) trauma due to a phenomenon known as pathergy or in association with systemic diseases: inflammatory bowel disease (particularly, ulcerative colitis), and also rheumatoid arthritis, monoclonal gammopathies, or as part of a paraneoplastic syndrome. (2,3)

We present the case of an 87-year-old male patient with a history of arterial hypertension, with a good functional class so far. His disease began 2 months before hospitalization, with low-impact trauma in the anterior region of the right leg. He received antibiotic and analgesic treatment on an outpatient basis, but evolved unfavorably, experiencing painful ulcerative lesions with a necrotic background on the ipsilateral lateral internal and external infrapatellar surface (Figure 1A).

As a result, the patient was hospitalized. Upon admission, he was conscious, and his blood pressure was 130/70 mmHg, his heart rate was irregular reaching 98 beats per minute, temperature was 37.8 °C, and oxygen saturation at room air was 95%. Examination of the right lower limb showed weak positive femoral and popliteal pulse (notably different from contralateral pulse) with good distal foot temperature. Electrocardiogram: atrial fibrillation with moderate ventricular response, and good R wave progression on precordial leads.

Laboratory test: hematocrit 35%, leukocytes: 6300/mm^3, platelets: 450,000/mm^3, erythrocyte sedimentation rate 100 mm/h, with normal hepatic and renal function, as well as acid-base status. Blood cultures: negative.

Arterial Doppler ultrasound evidenced mild calcific irregularities, triphasic flow in deep and superficial femoral, popliteal monophasic flow, tibial-peroneal, anterior and posterior, and foot trunk, with preserved intima-media thickness.

Surgical toilette and a skin biopsy were performed. Antibiotic treatment, intravenous glucocorticoids and opioids were administered for pain, together with low molecular weight heparin anticoagulation. The patient improved and had no fever. Pain was successfully managed. Analgesia was reduced to non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids and oral anticoagulation were rotated: meprednisone 40 mg and rivaroxaban 20 mg per day.

Laboratory immunology tests: antinuclear factor (ANF), anti-DNA, complement, anti-neutrophil cytoplasmic antibodies (ANCA), and anticardiolipin antibodies were all negative. Skin biopsy: marked polymorphonuclear inflammatory infiltrate, with areas arranged as aseptic abscess. Leukocytoclastic reaction was also evident. Please note that skin biopsy in pyoderma gangrenosum is non-specific and indication aims at excluding other causes of ulceration: infectious (bacterial, fungal) or neoplastic processes. (2,3)

Diagnosis of pyoderma gangrenosum led to continued immunosuppressive (first-line) treatment with meprednisone 1 mg/kg, resulting in very good response, progressive healing of the ulcerative lesion and absence of pain (4) (Figure 1B).

Doppler ultrasound is a non-invasive first-line technique used to evaluate the arterial tree and characterize vascular lesions with an accuracy comparable to angiography. The normal (triphasic) flow pattern may be replaced by a monophasic spectral pattern in

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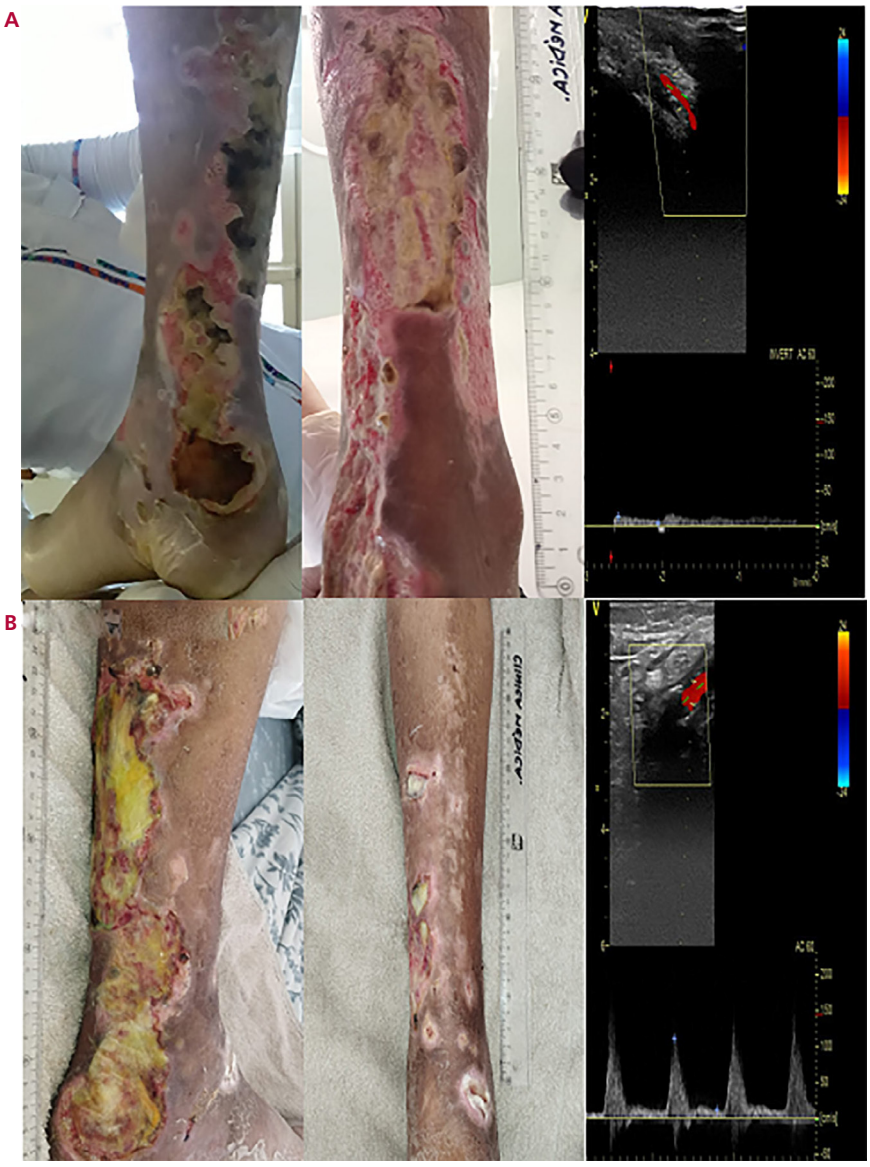

Fig. 1. A. ADMISSION: from left to right: ulcerative lesion upon hospitalization, before and after surgical toilet. Right: Doppler ultrasound with monophasic flow of the anterior tibial artery.
B. POST-TREATMENT: from left to right: granulated and scar tissue after one month of treatment with meprednisone 40 mg/day. Right: Doppler ultrasound with recovered triphasic flow of the anterior tibial artery.

various physiological and pathological conditions. The presence of monophasic flow in arteries without any parietal alterations may be due to the presence of distal vasodilation, which can be physiological due to a hyperdynamic state (exercise), or the presence of vascular lesions in soft tissues leading to distal hyperflow. Arteries that appear normal in ultrasonography, but with an impaired vasomotor tone causing monophasic flow, may be undergoing inflammatory-infectious processes, such as erysipelas or cellulitis. In any case, the most common artery condition is parietal atherosclerosis, with significant sites of stenosis creating distal monophasic flow due to reduced distal artery resistance in response to ischemia. (5,6)

In conclusion, the origin of painful lower limb ulcers along arteries is obstructive and vascular, but we need pyoderma gangrenosum as a differential diagnosis, especially in patients with a history of previous trauma or concurrent autoimmune diseases or neoplasms, since treatment for both pathologies is completely different: revascularization is used for arterial stenotic disease, while immunosuppressive treatment is selected for pyoderma gangrenosum (Table 1).

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing
None.

Table 1. Differential diagnosis: arterial ulcer versus pyoderma gangrenosum

	Arterial ulcer	Pyoderma gangrenosum
Pain	Present	Present
Distal temperature	Cold	Hot
Distal pulses	Absent	Absent
Doppler ultrasound	Distal monophasic waveform	Distal monophasic waveform
Arteriography	Significant lesions	No lesions
Treatment	Revascularization	Glucocorticoids

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Marfan Syndrome with Bilateral Subclavian Artery Aneurysm Associated with Coarctation of the Aorta

Síndrome de Marfan con aneurisma subclavio bilateral asociado a coartación aórtica

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Marfan syndrome is an inherited disease described in children and adults that affects the connective tissue of multiple organs and systems, such as the cardiovascular and musculoskeletal systems, eyes and skin. (1) It involves autosomal dominant inheritance due to a genetic alteration in chromosome 15; prevalence is estimated at 1 in 5000-10 000 newborns, and it affects both sexes equally. (2) Coarctation of the aorta is a highly complex and life-threatening cardiovascular malformation characterized by narrowing of the descending aorta, which in some cases may be a long hypoplastic aortic segment. It is usually located at the ductus arteriosus insertion point, distal to the left subclavian artery. It tends to be associated with anomalies in the aortic arch and results in left ventricular pressure overload. (3)

We present the case of a 51-year-old female patient with a history of arterial hypertension, ischemic heart disease and Marfan syndrome, who presents with increased soft tissue volume in the left anterior thorax. During anamnesis, she denies any pain or any other symptoms.

A computed tomography (CT) of the chest is performed with contrast agent using CT angiography technique, with axial slices, and both sagittal and coronal reconstructions. Aneurysmal dilation of both subclavian arteries is observed in the supraclavicular region (Figures 1 and 2). The left subclavian artery is more prominent, with an 81-mm transverse diameter and a 95-mm longitudinal diameter, and a thrombus on the wall leaving a 41-mm lumen. The contralateral artery has a 57-mm longitudinal diameter and a 36-mm transverse diameter, with absence of thrombi. The ascending aorta is dilated (53-mm), showing coarctation after the left subclavian artery emergency (Figure 2).

In Marfan syndrome, dilated aortic root is the most common cardiovascular occurrence, estimated to affect 60-80% of patients and to cause 90% of deaths. (4)

Aneurysms of the subclavian artery are extremely rare, with an incidence ranging from 0.01% to 3.5% as reported by different authors. It results from infections or degeneration of the *tunica media* of the artery, but it may be part of a clinical spectrum of diseases, including Marfan syndrome. (5) Other causes of subclavian artery aneurysm are thoracic outlet syndrome and trauma secondary to gunshot wound, clavicle fracture or iatrogenic causes. (5,6)

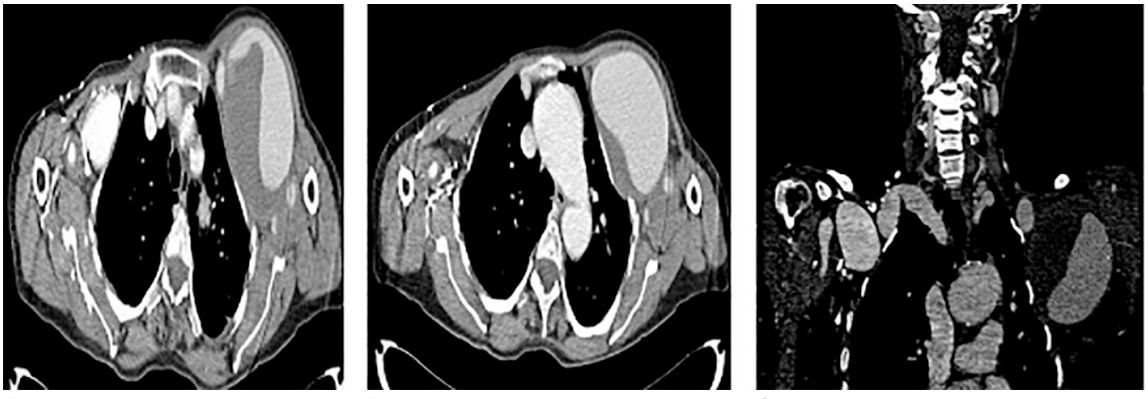

Fig. 1. Computed tomography. A. Axial slice showing both vascular dilations at the subclavian arteries level. B. Axial slice showing aneurysmal dilation of the left subclavian artery, with both dilation and coarctation of the aorta. C. Coronal slice showing aneurysmal dilation of both subclavian arteries, the left one with a thrombus on the wall.

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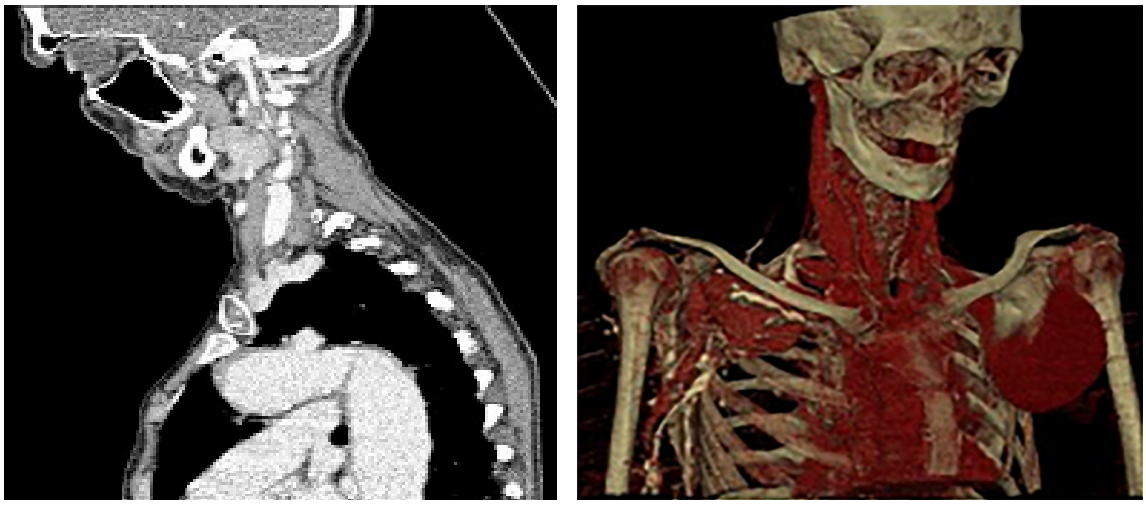

A B

Fig. 2. Computed tomography. A. Sagittal section showing dilation and coarctation of the aorta. B. Volumetric reconstruction showing both aneurysmal dilations of the subclavian arteries

Complications depend on the location, and the most commonly reported are brachial plexus injury or compressed upper extremity vessels possibly leading to edema. Surgical procedures have been reported for treatment, with associated complications in almost one third of cases. (6)

Ethical considerations

Not applicable.

Conflicts of interest

None declared (See authors' conflicts of interest forms on the website).

Financing

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REVIEW ARTICLE

From Observational Studies and Adjustment to Clinical Decision. Part 1

Del estudio observacional y el ajuste a la decisión clínica. Parte 1

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ABSTRACT

In the context of observational studies, the definition of the strength of the association between an exposure variable and an outcome variable, event or endpoint, may be affected by the unequal distribution of covariates among those with and without the specified exposure. In this paper we will review different statistical approaches to the subject matter, from multivariate analysis to adjustment which considers the inverse probability of treatment weighting, and we will apply them to examples taken from the medical literature.

Keywords: Observational studies - Multivariate analysis - Adjustment

RESUMEN

En el contexto de los estudios observacionales, la definición de la fuerza de asociación entre una variable exposición y un resultado, evento o punto final, puede verse alterada por la desigual distribución de covariables entre aquellos que presentan o no la exposición citada. Revisaremos en este escrito diferentes aproximaciones estadísticas al problema en cuestión, desde el análisis multivariado hasta el ajuste que toma en cuenta la inversa de la probabilidad ponderada de tratamiento, y las aplicaremos a ejemplos extraídos de la literatura.

Palabras claves: Estudios observacionales - Análisis multivariado - Ajuste

In recent bibliographic reports the statistical methodology is not the usual one, with terms, tables, and charts that may sometimes be hard to understand, particularly when it comes to making clinical decisions.

Here are some examples.

Trial 1

The aim of this observational study was to compare medical treatment (MT) and percutaneous coronary intervention (PCI) in patients with chronic angina. (1) A total of 9586 patients were included and 1866 were matched in 933 pairs (MT/PCI). The balance between baseline patient characteristics in the paired groups was appropriate. Unadjusted and adjusted hazard ratios (HR) calculated by the Cox model of MT/PCI for the primary endpoint of mortality were 1.50 and 1.49, respectively. (Table 1). The authors conclude that mortality is 49% higher with MT than with PCI.

Table 1. Trial 1. Event rate with medical treatment (MT) and with percutaneous coronary intervention (PCI), and adjusted and unadjusted HR in 933 matched pairs in a model with 20 covariates (modified from reference 1).

n= 9586. Matched pairs (n=933) by propensity score (933 MT/933 PCI).

MT / PCI Result (4 years)	MT % / 4 y	PCI % / 4 y	MT / PCI Adjusted HR	p value	MT / PCI Unadjusted HR	p value
Mortality / infarction	21.6	16.5	1.49	0.002	1.50	0.002

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Trial 2

The aim of this study was to investigate whether prior statin therapy translates into a lower incidence of heart failure in patients hospitalized for acute coronary syndrome. (2) This was a non-randomized observational trial comparing two groups, one with statins and another without statins prior to the acute event. The inverse probability of treatment weighting (IPTW, see explanation below) was used to balance different baseline characteristics and the *standardized difference* to estimate the level of adjustment. Table 2 summarizes the study in terms of the adjustment achieved and the trial outcome expressed as relative risk. The authors conclude that patients with acute coronary syndrome previously treated with statins have a better clinical outcome.

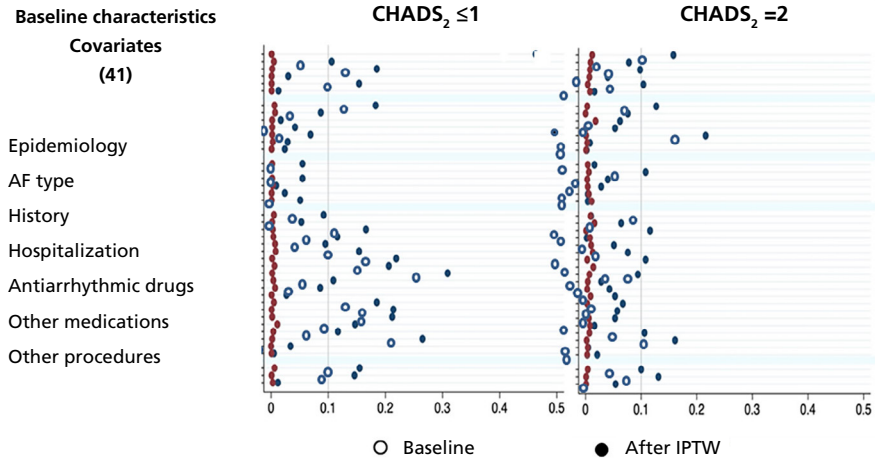
Trial 3

The aim of this observational study was to evaluate the role of oral anticoagulation after atrial fibrillation catheter ablation to prevent systemic thromboembolism and bleeding complications in subgroups according to the $CHADS_2$ score. (3) The authors used different statistical strategies, including IPTW.

	Prior statins Yes n= 1824	Prior statins No n= 12 718	Standardized difference	p
Age (years)	63.2 ± 11.2	61.8 ± 12.2	0.12	
Women	31.2	20.8	0.03	
Cardiovascular risk				
Diabetes	23.2	21.1	0.05	
Hypertension	67.5	61.4	0.13	
Hypercholesterolemia	40.6	36.9	0.08	
Current smoker	42.9	43.5	- 0.01	
Former smoker	13.5	13.5	0.07	
Medical history				
COPD	5.4	5.6	- 0.009	
Kydney disease	5.3	4.3	0.05	
Medication on admission				
Aspirin	19.2	16.6	0.07	
ACEI	35.8	32.6	0.07	
Beta-blockers	23.7	20.1	20.1	
Coronary angiography				
Multiple-vessel disease	43.1	43.8	0.09	
HF on admission	13.4	17.7		<0.0001
RR (95% CI)	0.72 (0.62-0.83)			<0.0001

ACEI: angiotensin-converting enzyme inhibitor; COPD: obstructive pulmonary disease; HF: heart failure; RR: relative risk.

Table 2. Trial 2. The covariates adjusted for IPTW (inverse probability treatment weighting) with the standardized difference after adjustment are shown above. Below, heart failure rates with and without prior statins, and the HR between both groups after IPTW. (Modified from reference 2) Quantitative variables are presented as mean and standard deviation, and qualitative variables as percentages



AF: atrial fibrillation; IPTW: inverse probability treatment weighting

Fig. 1. Trial 3. Standardized difference of more than 40 covariates between groups with and without anticoagulation, before and after adjustment for IPTW in $CHADS_2$ score ≤ 1 and $CHADS_2$ score = 2. The limit was set at 0.10. Confounders were well-balanced after adjustment. The difference was significantly higher in $CHADS_2$ score≤1 before adjustment, indicating that this group was more heterogeneous in terms of confounding variables. (Modified from reference 3)

Figure 1 shows the *standardized difference* in baseline characteristics *before and after adjusting* for IPTW. The acceptance level is <0.10. For the example, the effect of anticoagulation was only considered in the $CHADS_2$ score ≤ 1. The result was expressed as HR by IPTW (primary endpoint), by propensity score matching (PS), and by the Cox proportional hazards model (secondary endpoints).

Table 3 shows the effect of anticoagulation on thromboembolism and major bleeding in $CHADS_2$ score ≤ 1. (The subgroups with $CHADS_2$ score = 2 and $CHADS_2$ score ≥ 3, which were not considered for this methodological analysis, were also analyzed). Figure 2 shows the *incidence* of thromboembolism and major bleeding with and without anticoagulation in the $CHADS_2$ score ≤ 1 subgroup after adjusting for IPTW.

The authors conclude that in $CHADS_2$ score ≤ 1 anticoagulation does not provide any benefit for the prevention of thromboembolism and is associated with higher bleeding rate.

Trial 4

The aim of the investigation was to determine the *risk (prognostic criterion)* of type 2 myocardial infarction compared to type 1. (4) Figure 3 illustrates the *standardized difference before and after adjustment* of several baseline characteristics. The authors highlight that the prognosis for both types of myocardial infarction was similar. However, the detailed analysis in Figure 3 shows differences compared to Figure 1 that could call into question any conclusion about the prognostic value, independent of the type of infarction.

Trial 5

The focus of this investigation differed from the one of the trials mentioned before. (5) The authors wanted to evaluate the natural history of aortic stenosis according to its severity. Although a significant percentage of the sample underwent valve implantation or aortic valve replacement, the aim of the investigators was not to compare the groups with and without intervention, but rather to analyze the spontaneous disease progression. The IPTW methodology was used to adjust for the informative censoring caused by the intervention. Based on the findings presented in Table 4 (adjusted and unadjusted mortality), the authors conclude that the population not intervened represents the natural history of aortic stenosis.

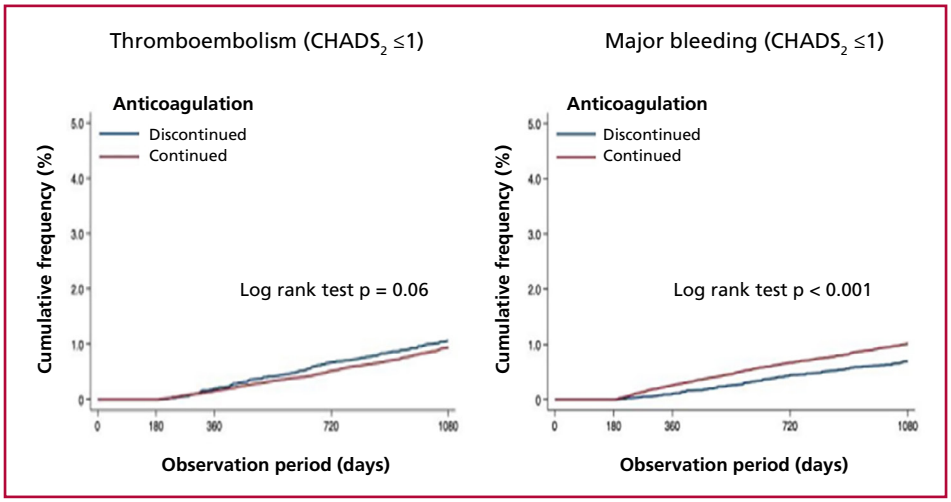


Fig. 2. Trial 3. Incidence of events with and without anticoagulation after atrial fibrillation catheter ablation for the IPTW-adjusted population in the $CHADS_2$ subgroup ≤ 1. There were no differences in the incidence of embolism, but major bleeding was significantly higher (log rank test) in subjects who continued with anticoagulation. (Modified from reference 3)

Table 3. Trial 3. Effect of anticoagulation after atrial fibrillation catheter ablation on thromboembolism and major bleeding in the subgroup with $CHADS_2$ score ≤ 1. The result, expressed in HR and its confidence interval is presented according to three statistical methods. (Modified from reference 3)

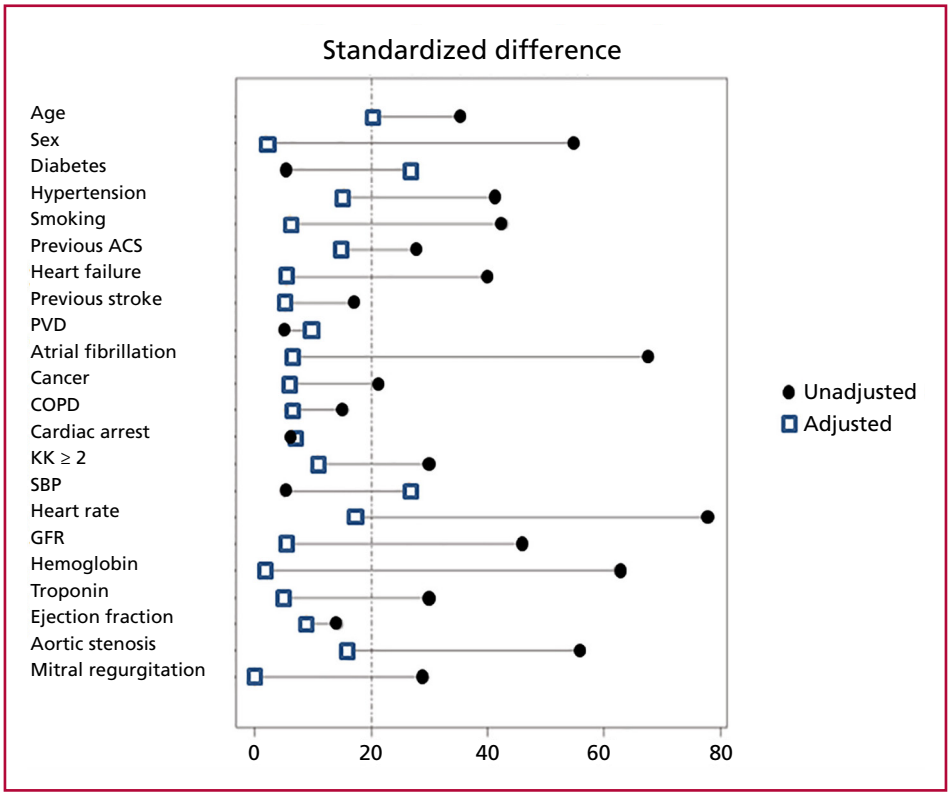
$CHADS_2$ score ≤ 1	HR (95% CI)	p
Thromboembolism		
IPTW	0.86 (0.74-1.01	0.06
Multivariate Cox	0.97 (0.85-1.11)	0.67
PS matching	0.84 (0.71-0.98)	0.03
Major bleeding		
IPTW	1.51 (1.27-1.89)	<0.001
Multivariate Cox	1.57 (1.36-1.82)	<0.001
PS matching	1.50 (1.27-1.78)	<0.001

IPTW: inverse probability treatment weighting; PS: propensity score

Observational studies

The common denominator of the bibliography mentioned can be summarized in the following points:

- design: ***observational study***
- objective: to evaluate the effect of an ***exposure variable*** (intervention or prognostic criterion) on



ACS: acute coronary syndrome; COPD: chronic obstructive pulmonary disease; KK: Killip and Kimball; PVD: peripheral vascular disease; SBP: systolic blood pressure.

Fig. 3. Trial 4. The chart is qualitatively similar to that of Fig. 3. In this case, the adjustment limit was set at 0.20. The differences after adjustment are close to 0.10, which is significantly higher than in the previous example. (Modified from reference 4).

Table 4. Trial 5. Mortality rate in a sample of patients with different grades of severity of aortic stenosis with medical treatment and after adjustment for IPTW. The aim was to adjust for the informative censoring caused by the intervention (valve implantation or replacement). The absence of differences indicates that the medical treatment group is not a selected (biased) population by the intervention. See the explanation in the text. (Modified from reference 5).

Aortic stenosis	Mortality (%/4 years)	
	Unadjusted	Adjusted
No	13.5	13.5
Mild	25.0	25.0
Mild to moderate	29.7	29.7
Moderate	33.5	33.3
Moderate to severe	45.7	42.2
Severe	44.9	42.0

an ***outcome variable*** and estimate the possible association between both variables.

- difficulty: the baseline characteristics of the sample may influence the relationship mentioned above; for this reason, they are often referred to as ***confounding variables*** or simply confounders.
- to affect the association of interest, confounders must be associated with the exposure variable and with the outcome variable.

Perhaps an example will illustrate this point (Figure 4): the outcome variable or study endpoint can be associated with the exposure variable (research objective) but also with a certain number of confounding factors that can influence this association. For example, if an intervention, which can favorably modify the end point, is preferentially indicated for younger patients, this benefit could be attributed to the treatment itself or to the fact that the procedure "selected" young individuals at lower risk. (The example can be extended to a trial investigating the value of a new prognostic criterion). In other words, any imbalance in the prevalence of confounding factors may affect the association that was the research objective.

In randomized (experimental) trials, the indication for intervention is not based on a medical decision but on random allocation. This distributes potential confounding factors uniformly across both groups with and without intervention, so that the exposure/outcome association is "independent" of its effects. However, randomization can sometimes fail, especially if the sample size is small.

The usual procedure to solve the problem is ***multivariate analysis, logistic regression or time-to-event analysis in the Cox proportional hazards model*** (hereafter "Cox model").

This methodology entails the simultaneous analysis of the exposure variable and the selected confounders, which are identified as having either an isolated statistical association or a prior bibliographic contribution (***independent variables***). (Figure 4). This

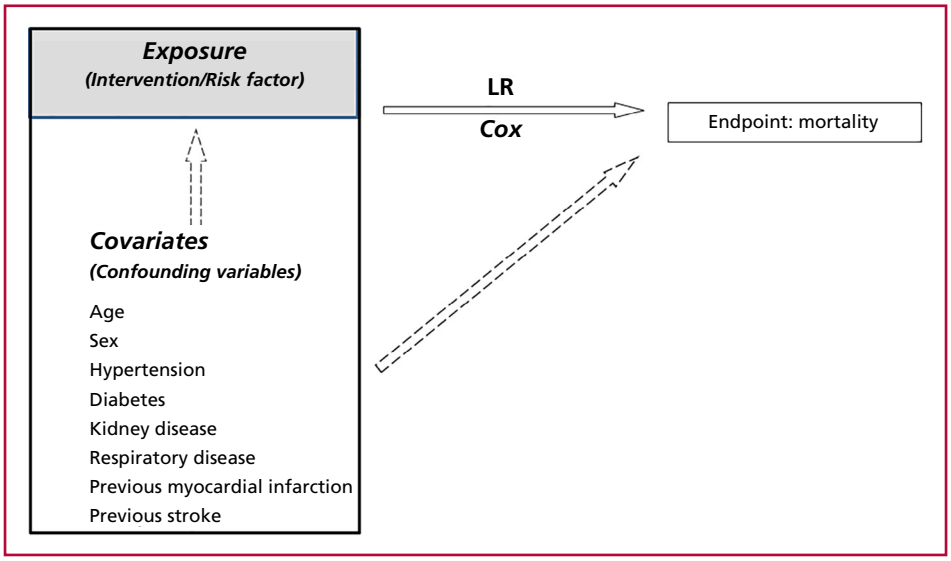


Fig. 4. Multivariate study. Exposure variable (intervention or risk factor, depending on the research objective), and its possible association with the outcome variables (solid arrow). If confounding variables are also associated with the exposure and the outcome variable (dashed arrows), they could attenuate or dilute the exposure/outcome association. The multivariate analysis of the set (box) estimates the "adjusted" association between the exposure and the outcome variable, independently of the confounding variables

Cox: Cox proportional hazards model; LR: logistic regression

procedure is usually referred to as adjustment. If the multivariate analysis determines that the exposure reaches statistical significance, we can conclude that it affects the outcome variable (***dependent variable***) since this association is not conditioned by the confounders.

Multivariate analysis requires a certain proportion between the number of independent variables and the prevalence/incidence of the outcome variable, which in certain circumstances may restrict the applicability of the methodology.

In the second part of this review, we will examine more recent statistical methods used in the statistical analysis of observational studies.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material).

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REVIEW ARTICLE

Analysis of the Latest Clinical Trials of Mechanical Circulatory Support in Cardiogenic Shock and their Potential Role in Modifying Practice Guidelines

Análisis de los últimos ensayos clínicos de soporte circulatorio mecánico en el shock cardiogénico y su potencial rol en modificar las guías de práctica

ELIÁN F. GIORDANINO[1, MTSAC]

ABSTRACT

Cardiogenic shock can complicate the course of ST-segment elevation myocardial infarction in approximately 10% of cases and is associated with high mortality. In this context, practice guidelines recommend the use of mechanical circulatory support devices based on expert opinion or non-randomized studies. Between 2023 and 2024, three randomized clinical trials using ECMO or Impella have been published. The results of these trials and their potential impact on practice guidelines are discussed in the present review.

Key words: Shock, Cardiogenic - Myocardial Infarction - Practice Guideline - Circulatory Support

RESUMEN

El shock cardiogénico puede complicar la evolución del infarto agudo de miocardio con elevación del segmento ST en aproximadamente el 10 % de los casos, y se asocia a elevada mortalidad. Las guías de práctica recomiendan en este contexto el empleo de dispositivos de soporte circulatorio mecánico con base en opinión de expertos o estudios no aleatorizados. Entre 2023 y 2024 se han publicado 3 ensayos clínicos aleatorizados con el empleo de ECMO o Impella, cuyos resultados y posible influencia en las guías de práctica se discuten en la presente revisión.

Palabras claves: Shock cardiogénico - Infarto agudo de miocardio - Guía de práctica clínica - Soporte circulatorio

INTRODUCTION

Cardiogenic shock can occur in approximately 10% of patients with ST-segment elevation myocardial infarction (STEMI) with mortality rates ranging between 40% and 50%. (1) Current clinical practice guidelines recommend the use of short-term mechanical circulatory support devices in patients with cardiogenic shock (recommendation class IIa, with a level of evidence C of the European guidelines, or B-NR of the American guidelines, that is, based on expert opinion or non-randomized studies). (2,3) Yet, after the negative results of the IABP-Shock II trial with intra-aortic balloon pump in infarct-related cardiogenic shock, the use of these devices has increased in recent years, particularly with the advancement in extracorporeal membrane oxygenation (ECMO) implantation techniques. (4,5) Three randomized clinical trials that emerged in 2023 and 2024 are among the most relevant on the use of short-term mechanical circulatory support devices in cardiogenic shock published so far and will likely impact on the indications and the level of evidence in practice guidelines: the ECMO-CS trial, ECLS-Shock trial and the recently published DanGer-Shock trial.

These studies analyze the use of ECMO and Impella in cardiogenic shock, predominantly in the set-

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ting of MI. Briefly, ECMO is a type of mechanical circulatory support that drains blood from the venous system and returns oxygenated blood into the arterial circulation. It can provide complete circulatory and ventilatory support in patients with left ventricular, right ventricular or biventricular heart failure. The Impella device is a catheter-mounted microaxial pump inserted percutaneously that drains blood from the left ventricle and expels it into the ascending aorta, unloading the left ventricle. It is essential to ensure that blood oxygenation is adequate and that right ventricular function is not significantly impaired to guarantee adequate left ventricular filling. This review will address the main aspects of each study and any potential changes in clinical practice that may result from their analysis.

ECMO-CS TRIAL

This multicenter, unblinded, randomized clinical conducted only in the Czech Republic aimed to compare immediate implementation of ECMO versus an initially conservative therapy (allowing downstream use of ECMO) in patients with rapidly deteriorating or severe cardiogenic shock. The primary endpoint was the composite of death from any cause, resuscitated cardiac arrest, and implementation of another mechanical circulatory support device at 30 days. Other secondary endpoints such as death from any cause at 30 days and safety criteria were also evaluated. (6)

Patients with any type of rapidly deteriorating severe cardiogenic shock of the Society for Cardiovascular Angiography and Interventions (SCAI) shock classification stage D-E were included. (7) This implies hemodynamic instability necessitating administration of pressor agents to maintain a mean arterial pressure >50 mm Hg and impaired left ventricle systolic function; or hemodynamic impairment (decreased cardiac index or systolic blood pressure with requirement of norepinephrine and dobutamine) and metabolic impairment (lactate greater than 3 mmol/L or central venous saturation less than 50% in two consecutive values, with no tendency to improve). Hypovolemia (central venous pressure <7 mm Hg or pulmonary capillary wedge pressure <12 mm Hg) should be excluded. In the initial conservative treatment group, downstream use of ECMO was possible in case of further worsening of the hemodynamic status, defined as rise of serum lactate by 3 mmol/L in comparison with the lowest value during the past 24 hours. Patients with shock due to pulmonary embolism or cardiac tamponade, hypertrophic cardiomyopathy, and those with potential contraindications for the use of ECMO (severe peripheral arterial disease precluding arterial cannula insertion, severe bleeding, moderate or severe aortic regurgitation or aortic dissection, among others) were excluded.

From September 2014 to January 2022, 58 patients were included in the initial ECMO group and 59 patients in the conservative group. This indicates that recruitment was relatively slow, likely due to the fact that it was conducted at four centers within a single country. It should be noted that the study population comprised patients with a median age of 66 years [interquartile range, (IQR) 56-70], which is older than the typical age range for this type of mechanical circulatory support in our setting and in much of the world. Most patients were men (73.5%). The primary cause of cardiogenic shock was MI (65% of cases, STEMI, NSTEMI or due to mechanical complications), and 23.1% were due to decompensation of chronic heart failure. Approximately 11 % of the patients had presented cardiac arrest. Median lactate level was 5 mmol/L (IQR 3.2-8.0) and median vasoactive-inotropic score, a measure of the amount of pharmacologic cardiovascular support, was 61 (IQR 30-124); both parameters were relatively high.

There were no significant differences in the primary composite endpoint or in death from any cause at 30 days or resuscitated cardiac arrest. In the early conservative group, 39% of patients required downstream use of ECMO support, with no differences in the endpoints in the intention-to-treat or per protocol analysis. In terms of safety outcomes, the supplementary data showed a non-significant increase in the number of bleeding events in the per protocol analysis (30.9% vs. 13.9%, p = 0.067).

In addition to the aforementioned limitations of the study, another factor to consider is that the sample size was calculated based on a 50% reduction in the primary endpoint. This difference may be excessive and increase the likelihood of a type II error, i.e., a "false negative" result in a relatively small sample. Furthermore, the study was designed to find a difference in the composite primary endpoint, and thus the results of the secondary endpoints should be considered hypothesis-generating. Additionally, the sample size was not sufficient to conduct subgroup analyses.

What key takeaways can we draw from this first clinical trial? It could be argued that the patients were already receiving high doses of pressor agents or inotropic drugs at the time of randomization. This raises the question of what might have happened if an even earlier ECMO strategy had been implemented with lower doses of vasoactive agents. But it is true that the protocol did not require high doses, and that the inclusion criteria permitted the incorporation of patients at substantially lower doses. This may be indicative that they were in fact stage D and E patients according to the SCAI shock classification, for whom pharmacological support had to be rapidly escalated. Furthermore, the protocol allowed for the use of ECMO in the conservative group when the patient did not stabilize rapidly, which occurred in 39% of cases. This suggests that an initial pharmacological treatment plan may be a viable strategy, even in critically ill patients. Yet, it is essential to maintain close monitoring to ensure downstream use of an ECMO strategy if necessary. This approach could prevent the potential

complications associated with the unrestricted use of these devices, which were higher in this study, though they did not reach statistical significance probably due to the relatively small sample size.

ECLS-SHOCK TRIAL

The ECLS-Shock was a multicenter, unblinded, randomized clinical trial conducted in Europe (Germany and Slovenia) which evaluated if the routine early use of ECMO in patients with infarct-related cardiogenic shock reduces death from any cause at 30 days compared to usual treatment. (8) Secondary endpoints included the need for new revascularization, renal replacement therapy, length of intensive care unit stay, time until hemodynamic stabilization or duration of pressor agent therapy and safety endpoints (peripheral ischemic vascular complications, bleeding, stroke or systemic embolism).

The trial included patients with infarct-related cardiogenic shock, defined as hypotension (systolic blood pressure < 90 mm Hg for more than 30 minutes, or requirement of pressor agents to maintain a systolic pressure > 90 mm Hg) with elevated lactate level (> 3mmol/L) and signs of impaired organ perfusion (altered mental status, cold limbs, or urine output < 30 ml/h), that is, cardiogenic shock stage C or higher of the SCAI classification. Patients with shock due to mechanical complications of AMI, cardiac arrest > 45 minutes, severe peripheral arterial disease arterial precluding arterial cannula insertion, shock lasting > 12 hours, or patients > 80 years were excluded. Of the 877 patients screened between June 2019 and November 2022, 417 were included in the final analysis, representing the largest number of patients included in a study of this kind in this clinical setting to date.

The study was well designed. ECMO was initiated during the index coronary angiography (preferably before revascularization). The use of an antegrade arterial femoral sheath was strongly recommended to reduce the risk of lower limb ischemia. Unlike the ECMO-CS trial, details regarding ECMO management in the intensive care unit and predefined criteria for left ventricular unloading and weaning were provided.

Mean age was 63 years (IQR 56-70) and 81.3% were men. Two thirds of the patients presented with STEMI and the left anterior descending artery was the most common culprit vessel (47.6%), while two thirds of the patients had multivessel disease. Although emergency myocardial revascularization surgery was considered, primary coronary intervention was the most common revascularization strategy (96.6% of cases).

As previously mentioned, the study was designed to include critically ill patients, truly in cardiogenic shock, because such patients were thought to be the most likely to benefit from mechanical circulatory support. However, the resulting population was more severely ill than anticipated: 77.7% of patients had experienced cardiac arrest prior to randomization, 86.3% required invasive mechanical ventilation, 95.4% had altered mental status, and the median lactate level was 6.9 mmol/L. Consequently, 48.4% of the patients were in SCAI shock stage D or E and 30-day mortality was 48.4%, higher than the one reported in other studies. (4,9)

Regarding the study results, there were no differences in death from any cause at 30 days in the group treated with early ECMO strategy compared to the control group: 47.8% vs. 4.9%, relative risk (RR) 0.98 (95% CI 0.80-1.19, p = 0.81). In addition, secondary endpoints were similar in both groups. There were also no differences in any of the established subgroups. However, there were significant differences in the safety outcomes. The ECMO group exhibited a higher incidence of moderate or severe bleeding (23.4% vs. 9.6%; RR 2.44, 95% CI 1.50-3.95) and vascular ischemic complications (11% vs. 3.8%; RR 2.86, 95% CI 1.31-6.25).

Some limitations of the study include the lack of blinding, which is difficult to implement in this type of intervention, and the inclusion of centers with both medium and high volumes of ECMO to enhance external validity. This resulted in the participation of many centers that included few patients, and their limited experience could have influenced the results. However, the post hoc analysis did not demonstrate an effect of patient volume in the results. Although 12.5% of patients in the control group crossed over to the ECMO group, there were no differences in the intention-to-treat analysis compared to the per-protocol analysis. However, it is noteworthy that 15.8% of patients in the control group received other type of mechanical circulatory support, mainly the Impella device, which may have attenuated the differences between the groups. Finally, the increase in afterload produced by the use of ECMO in this context can be deleterious, and although criteria for left ventricular unloading were established in the study, it was only used in 5.8% of the patients.

In order to understand the interpretation and impact on current practice of this study, it is essential to contextualize the results and analyze the pathogenesis of infarct-related cardiogenic shock. Given the severity of illness in the ECLS-Shock trial population, it is unlikely that any current treatment, including early ECMO, will have a significant impact compared to the standard treatment: early revascularization. The supplementary material shows that the initial elevated lactate levels return to normal levels and glomerular filtration rate improve in both groups within the first 24-36 hours. Additionally, time until hemodynamic stabilization was relatively short (median 3.1 days) compared to other etiologies of cardiogenic shock, Consequently, the ECMO group required support for a median of 2.7 days. The potential benefit of the circulatory support provided by ECMO may have been partially offset by its higher rate of complications and increased afterload. This calls for a reconsideration of

the current approach to these patients in some situations. In fact, in the publication, presentation at the European Congress of Cardiology 2023 and in several interviews, the authors point out that the routine use of ECMO in this patient population should be reconsidered.

INDIVIDUAL PATIENT DATA META-ANALYSIS OF ECMO IN PATIENTS WITH INFARCT-RELATED CARDIOGENIC SHOCK

After the publication of ECMO-CS trial and ECLS-Shock trial, the two largest randomized clinical trials on the use of ECMO in this context, Zeymer et al. performed an individual patient data meta-analysis including both trials and two smaller studies. (10) Only patients with infarct-related cardiogenic shock were included, (n = 567). Median age was 64 years (IQR 57-71), 81% were men, and 68% were STEMI patients. At the time of randomization, patients presented with a median pH of 7.21 (IQR 7.09-7.31), lactate level of 6.5 mmol/L (IQR 4.1-9.9), and creatinine level of 1.3 mg/dL (IQR 1.1-1.6). Table 1 summarizes the main results of the meta-analysis. The primary outcome was death from any cause at 30 days.

There were no differences in death from any cause at 30 days, but there was a higher rate of associated complications such as moderate to severe bleeding or peripheral ischemic vascular complications. Therefore, this meta-analysis concludes that the early unrestricted use of ECMO in infarct-related cardiogenic shock does not increase survival. Further analysis is required to determine whether mechanical circulatory support with devices that reduce left ventricular afterload can be beneficial. This is partially answered by the DanGer-Shock trial.

DANGER-SHOCK TRIAL

The DanGer-Shock study was a multicenter, unblinded randomized clinical trial conducted in Europe (United Kingdom, Germany and Denmark) which compared routine use of the Impella CP device inpatients with MI-related cardiogenic shock with standard care. (11) The primary endpoint was death from any cause at 180 days. This is an uncommon outcome in contemporary cardiology, as numerous clinical trials are based on composite endpoints that may lack a clear physiological correlation between their components. In addition, analysis strategies such as win-ratio are usually used so that the trials can be considered with a positive outcome. The secondary endpoint included a composite of escalation of treatment to additional mechanical circulatory support, heart transplantation, or death from any cause and number of days alive out of hospital. Additionally, safety endpoints were analyzed and included ischemic vascular complications, bleeding, stroke, and need for renal replacement therapy, among others.

Unlike the ECLS-Shock trial and the ECMO-CS trial, which included STEMI and NSTEMI patients, the DanGer-Shock trial only included patients with STEMI-related cardiogenic shock, defined as hypotension (systolic blood pressure < 100 mm Hg or requiring pressor agents), tissue hypoperfusion (lactate greater than or equal to 2.5 mmol/L) and left ventricular ejection fraction < 45%. Patients with significant right ventricular failure (because, unlike ECMO, the Impella device can assist only one ventricle), with shock due to MI mechanical complications or who remained with altered mental status after out-of-hospital cardiac arrest were excluded. Patients were randomized to Impella vs. standard care before or up to 12 hours after revascularization, depending on when cardiogenic shock was diagnosed. Escalation to mechanical circulatory support was allowed in the control group but not to Impella CP to avoid significant crossover (which was only 1.7%). Like the ECLS-Shock trial, details regarding Impella management in the intensive care unit and predefined criteria for escalation to other mechanical circulatory support devices were provided.

Between January 2013 and July 2023, 179 patients were included in the Impella group and 176 patients in the standard care group. The trial was initially intended to include only centers in Denmark, but because of slow enrollment it was expanded in 2019 to include patients in Germany and in 2021 in the United Kingdom. Thus, most patients were randomized from 2019. The study population had a median age of 67 years and 79.2 % were men. SCAI cardiogenic shock stage C was observed in 55.5 % of the patients and the median lactate level was 4.5 mmol/L (IQR 3.3-

Table 1. Results of the meta-analysis by Zeymer et al. (10)

	ECMO (n=284)	Control (n=283)	Odds Ratio (CI 95%)
Primary outcome			
Death from any cause at 30 days	46 %	48 %	0.93 (0.66–1.29)
Secondary outcomes			
Moderate to severe bleeding at 30 days (BARC 3-5)	25 %	12 %	2.44 (1.55–3.84)
Stroke at 30 days	4 %	3 %	1.41 (0.56–3.57)
Peripheral ischemic vascular complications at 30 days.	11 %	4 %	3.53 (1.70–7.34)

BARC: British Academic Research Consortium; ECMO: extracorporeal membrane oxygenation

7.1). After excluding patients resuscitated from cardiac arrest who remained with a Glasgow Coma Scale < 8, only 20.3 % had presented this event, versus 77. 7 % in the ECMO-CS trial and 11 % in the ECLS-Shock trial. Interestingly, the time from symptom onset to randomization to Impella and control groups was 4.8 hours (IQR 2.4-12.8) and 3.8 hours (IQR 2.2-9.4), respectively, and the time from randomization to placement of the Impella device was 14 minutes (IQR 8-29). Therefore, most patients in the Impella group received mechanical circulatory support within the initial five-hour period following symptom onset.

Regarding outcomes, death from any cause was 45.8% in the Impella group and 58.5% in the standard care group [hazard ratio (HR) 0.74; 95% CI 0.55-0.99; p = 0.04], with an absolute risk reduction of 12.7% and a number needed to treat to prevent one death of only 8. The supplementary material shows that most of the deaths were due to cardiac causes and occurred in within the first 30 days. The subgroup analysis shows the benefit was lower in patients with higher initial systolic blood pressure, something that the authors point out may be due to the fact that these devices are less efficient with high afterload. Additionally, there was a tendency to greater benefit in patients below the median age of 67 years, which is consistent with our context of mechanical circulatory support and with that of other countries. This is evidenced by the recently published Impella registry of the Cardiogenic Shock Working Group, where the average age was 58.6 years. (12) The secondary endpoint also favored the Impella group (52.5% vs. 63.6%; HR 0.72; 95% CI 0.55-0.95). However, the use of these devices was also associated with higher incidence of adverse events, with the composite safety endpoint (major bleeding, limb ischemia, hemolysis, device failure or worsening aortic regurgitation) occurring in 24% of patients in the Impella group and 6.2% in the standard care group (HR 4.74; 95% CI 2.36-9.55). This implies a number needed to harm of 5 patients, reflecting the high complication rate of these devices even in high-volume centers. The Impella group had higher incidence of moderate or severe bleeding (21.8 % vs. 11.9 %; HR 2.06, 95% CI 1.15- 3.66), limb ischemia (5.6 % vs. 1.1 %; HR 5.15, 95% CI 1.11-23.84), renal replacement therapy (41.9 % vs. 26.7 %; HR 1.98, 95% CI 1.27 - 3.09) and sepsis with positive blood culture (11.7 % vs. 4.5 %; HR 2.79, 95% CI 1.20- 6.48)

In addition to the previously mentioned limitations, the study protocol was so meticulous in the management and selection of patients that of the 1211 screened patients, only 355 were randomized. This partially limits the external validity of the study and requires that we interpret the significant reduction in mortality in this study with caution, as it may not be applicable to all cardiogenic shock scenarios. Furthermore, it is important to mention that in the secondary per protocol analysis and not in the intention-to-treat analysis (but without adjusting for multiplicity and excluding patients who received Impella in the control group and those who did not receive it in the Impella group) the benefit in survival was borderline (HR 0.77; 95% CI 0.57 -1.03), perhaps in part because of the smaller number of patients.

These results raise questions about the impact of the DanGer-Shock trial. Few studies that have demonstrated a positive impact on survival in cases of infarct-related cardiogenic shock: the Shock-trial in 1999 with early revascularization, (13) the CULPRIT-SHOCK trial with initial revascularization of the culprit vessel only (14) and now the DanGer-Shock trial with the use of Impella. Only the DanGer-Shock reduced the primary endpoint of death from any cause.

While it is true that there were more adverse events in the Impella group, they do not appear to be significant enough to overshadow the benefit of a 26% reduction in mortality with these devices. It is important to note that the primary endpoint was death from any cause, not just cardiovascular mortality. Patients who were assigned to treatment, despite experiencing more complications, had a greater survival, which is finally the most relevant outcome in the medical treatment approach. In any case, we should bear in mind that in centers with less experience with the Impella device or in a daily scenario outside the rigor of a clinical trial, the increase in the rate of complications could potentially offset the benefit, mainly if associated with other devices. (15)

SUMMARIZING THE EVIDENCE

The ECMO-CS trial, the ECLS-Shock trial, and their meta-analysis represent the most significant studies in the field of ECMO and cardiogenic shock in recent times. The third study, EURO-Shock, was expected to address similar issues but was unfortunately suspended before recruitment was completed due to the COVID-19 pandemic. The study included only 35 patients and did not provide conclusive data. However, it could be included in the aforementioned meta-analysis. (16) These studies demonstrated no benefit in 30-day survival with the early use of ECMO in infarct-related cardiogenic shock and a higher rate of complications when compared to standard care. This does not indicate that ECMO should no longer be used. It is important to note that 39% of patients in the control group of the ECMO-CS trial required subsequent ECMO support (which was a planned aspect of the trial, designed to compare early use of ECMO versus a conservative approach, with the latter allowing for the use of ECMO if necessary). In the ECLS-Shock trial, 12.5% of patients in the control group also required this device, and if we add that 15.8% of the control group required another mechanical circulatory support device, mainly Impella, we see that in both studies approximately 1 out of 3 patients allocated to medical treatment ultimately required the use of ECMO or another device. In other words, there is still a role for ECMO even in infarct-related cardiogenic shock.

However, when viewed from another angle, early use of ECMO was associated with a higher rate of complications without improving survival rates even in critical cases, and 2 out of 3 patients who received medical treatment did not require ECMO. In summary, the evidence does not support the implementation of an early, unrestricted use strategy across all patients. It is possible to initially stabilize patients with pharmacological support, prioritizing early revascularization and, if there is no response, mechanical circulatory support can be considered.

ECMO should not be considered a treatment but a bridge to another strategy and a circulatory support. In parallel, the focus should always be on solving the etiology that led to cardiogenic shock. Myocardial infarction is not an exception, and early revascularization of the culprit vessel is the standard care for cardiogenic shock. Therefore, the use of ECMO support does not provide any actual additional benefit and increases the incidence of complications.

In contrast to the unfavorable outcomes observed in ECMO trials, the DanGer-Shock trial has explored the potential advantages of Impella in cardiogenic shock secondary to STEMI, demonstrating a 26% reduction in death from any cause at 180 days. Unlike the use of ECMO, which increases the afterload, Impella results in left ventricular unloading by driving antegrade blood flow from the ventricle into the aorta. Some small studies or studies in animal models have suggested that this mechanism may have benefits in limiting the extent of infarct size by increasing coronary perfusion, decreasing myocardial oxygen uptake, and activating protective signaling pathways. (17-19) In addition, large registries conducted in Europe and the United States comparing ECMO with Impella in this setting demonstrated a clear advantage for Impella, with lower complication rates and lower in-hospital mortality. (20) Further analysis is required to determine the success of ongoing studies, including REVERSE (NCT03431467), ANCHOR (NCT04184635), and UNLOAD (NCT05577195). These studies will assess the efficacy of an ECMO strategy with left ventricular unloading using Impella or intra-aortic balloon pump and my provide insights into the potential role of these devices in different scenarios.

It is important to consider that Impella has also been associated with complications, so it should not be used unrestrictedly. Indeed, some registries, such as the Cardiogenic Shock Working Group, have demonstrated that the rate of complications increases significantly when associated with the use of other mechanical circulatory support devices. In this context, the benefit seems to be lost, and the use of devices may even be harmful. (12,21) It should be noted that in this registry Impella devices 5.0 and 5.5 were used, which provide higher flow rates than Impella CP. In addition, they provide full circulatory support and not just partial support and do not constitute a ventricular unloading strategy in association with another device. This raises the question if in this population, the use of Impella should be preferred over ECMO and, if used in combination initially, early weaning from ECMO to continue support with high-flow Impella alone may be a viable option.

CONCLUSIONS

These studies require us to reconsider the use of mechanical circulatory support devices in a clinical scenario such as that of infarct-related cardiogenic shock, where mortality remains high. Revascularization of the culprit vessel should be the priority, and it seems reasonable to adopt an initial strategy of pharmacological support, and to resort to ECMO in refractory and selected cases to reduce complications. In the context of STEMI, early use of Impella would contribute to reduce mortality. In addition, in cases where biventricular support is required or if there is concomitant ventilatory failure, ECMO remains the device of choice.

How could these studies modify the guidelines? Probably in the case of infarct-related cardiogenic shock, the early and routine use of ECMO is not recommended (Class III, Level of evidence B, or Class III, Level of evidence B-R according to the guidelines considered). In STEMI-related cardiogenic the use of Impella, if available, should be considered (Class IIa Level of evidence B or Class IIa Level of evidence B-R).

Finally, central expertise and appropriate patient selection to minimize complications and maximize benefits, and thorough treatment of the underlying etiology from the outset remain the cornerstones to ensure successful use of any mechanical circulatory support device.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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LETTER TO THE EDITOR

A Century after Willem Einthoven's Nobel Prize (1860-1927) and the Development of Electrocardiography

A un siglo del Premio Nobel de Willem Einthoven (1860-1927) y el desarrollo de la electrocardiografía

CAMILA AMPUERO ACUÑA[1], ALEJANDRO DONOSO FUENTES[1]

One hundred years after the Nobel Prize in Physiology or Medicine was awarded to Willem Einthoven (1860-1927) for his invention of the string galvanometer, now known as the electrocardiograph, it remains the most commonly used cardiovascular laboratory diagnostic tool for the evaluation of cardiac conduction disorders and ischemic heart disease because it is reliable, noninvasive and inexpensive.

The following is a review of the life of this remarkable Dutch physician and physiologist, and a review of part of the history of the electrocardiograph, which concluded with the definitive establishment of the device and the birth of clinical electrocardiography.

The electrical activity of the human heart was first recorded at the end of the 19th century by the British physiologist August Desiré Waller (1856-1922). During the month of May 1887, at St. Mary's Hospital, in the central London neighborhood of Paddington, he obtained a recording (then called an electrogram) using thoracic surface electrodes and a capillary electrometer, a device previously developed in 1873 by the French physicist Gabriel Lippmann (1845-1921). (1) The tracing was rudimentary and poor in detail, due to the inertia of mercury, and showed only two deflections, ventricular depolarization and repolarization. Waller was not very confident of its usefulness; even much later (1911) he remarked: "*I do not think that electrocardiography will have any practical application in a hospital... It will be used sparingly, or occasionally in the case where a rare abnormality of the cardiac pulse has to be recorded.*" (2)

However, it is widely believed that modern electrocardiography was born with the Dutch physician and physiologist Willem Einthoven (1860-1927) (Figure 1).

Einthoven was born on May 21, 1860 in the city of Semarang, on the island of Java, currently belonging to Indonesia. He was the third of six children of the second marriage of Jacob Einthoven, with Louise Marie Mathilde Caroline de Vogel. When his father died, Willem was only six years old. Four years later, in 1870, he and his family settled in the city of Utrecht, Holland. (3)

At:https://commons.wikimedia.org/wiki/File:Portrait_of_W._(Willem)_Einthoven,_professor_of_Physiology_and_Histology_at_Leiden_University_Icones_332.tiff. Public domain)

Fig. 1. Portrait of Willem Einthoven, professor of physiology and histology at the University of Leiden (1926). Author: Albertus Jan Marinus van Dijk (1892-1967).

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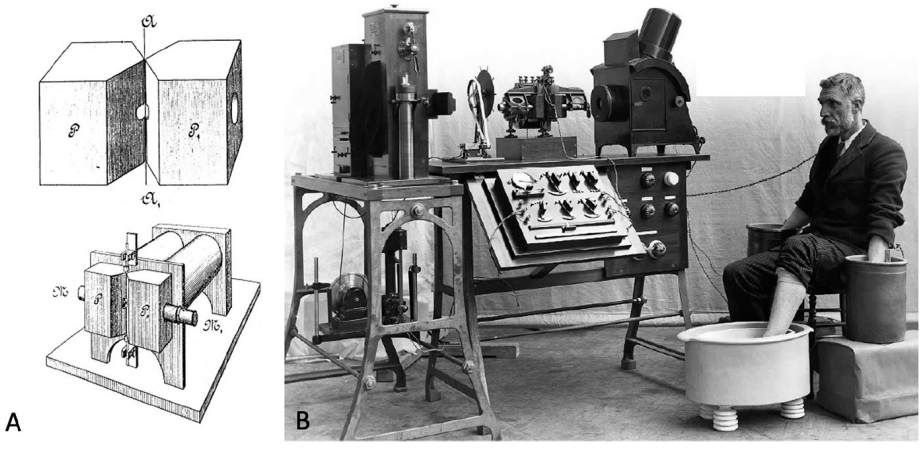
The young Einthoven tried to follow his father's footsteps, and entered the University of Utrecht in 1878 as a medical student. Like his father, he was also financed by the army on the condition that after finishing his studies he would work as a military doctor in the colonies. During his years of study, Einthoven stood out as a great sportsman (gymnast, fencer and rower) and a strong promoter of physical education, as well as being the founder of the Utrecht student rowing club and the Olympic Gymnastics and Fencing Society. He received his medical degree in 1885, and while he was preparing to honor his word and thus return to Java as an ophthalmologist, an unexpected event occurred. Only one year after graduating, the chair of physiology at the prestigious Leiden University, the oldest of the Dutch universities, became vacant. Thanks to the support of his mentor, Dr. Donders, who had persuaded the University Council, he was appointed to the position in February 1886, and held it until his death. Thanks to the salary he began to receive, he was able to pay the guarantee to the army (6000 guilders), and after freeing himself from the commitment to return to Java he was able to devote fully to research. Soon after, he married his first cousin Frédérique Jeanne Louise de Vogel, with whom he had four children. (2,3)

Under Einthoven's direction, the laboratory progressively became a world-renowned reference center. Between 1885 and 1889 Einthoven's research was linked to optics and respiratory physiology, exploring topics such as intrapleural and intrathoracic pressures and the pathophysiology of asthma (he described the role of the vagus nerve). But in 1889 Einthoven attended the International Congress of Physiology held in Basel (Switzerland), where he had the opportunity to witness Waller's new experiments with the capillary electrometer. From then on, his interests were directed towards the electrophysiology of the heart, for which he endeavored to design a device that could measure more precisely and at the same time record cardiac electrical impulses, an interest that accompanied him throughout his life. In this laboratory, at the beginning of the 20th century, always supported by his assistant Van de Woerd (since it is pointed out that he was particularly clumsy in terms of manual dexterity), an essential and everlasting diagnostic tool emerged.

Dissatisfied with the inaccurate recordings he obtained with Lippmann's capillary electrometer, despite having made mathematical corrections and significant improvements, he began work on a new technical solution for a more sensitive galvanometer, an instrument he called the "string galvanometer". Einthoven made his findings known to the scientific world (although he gave credit to Waller's earlier work) in several publications, one of which was published in 1895 as *Ueber die Form des menschlichen Electrocardiograms*. It was here that the term electrocardiogram appeared, but it is noted that Einthoven attributed it to Waller as a mark of respect for his colleague. (4)

In early 1901, he published his preliminary work Un *noveau galvanomètre*, (5) where he described this new instrument in greater detail, comparing the records obtained with those of the capillary electrometer. The string galvanometer, he explained, "*consists of a thin silver-coated quartz filament conducting electric*

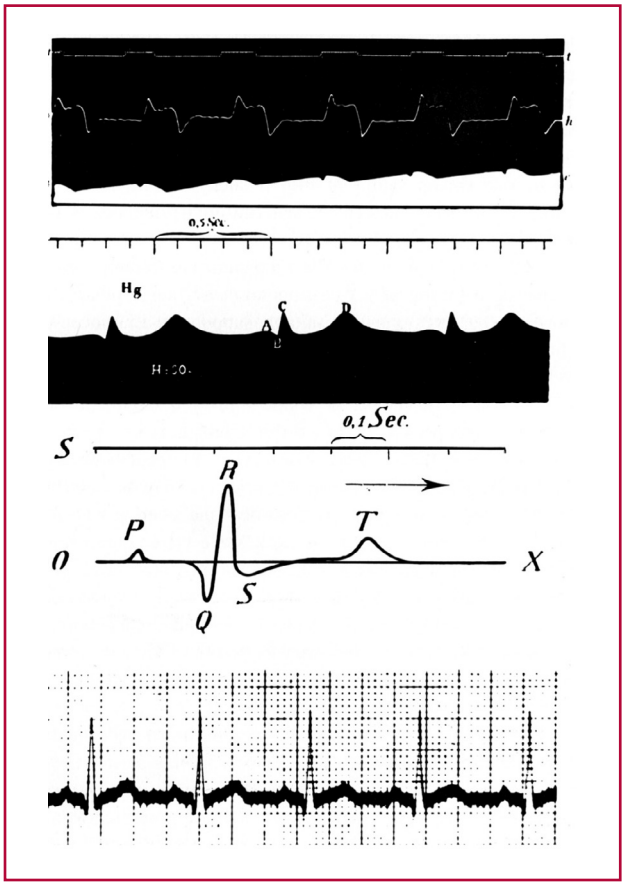


A (At https://commons.wikimedia.org/wiki/File:Einthoven%27s_string_galvanometer.jpg . Public domain)
B (At https://en.wikipedia.org/wiki/Image:Willem_Einthoven_ECG.jpg. Public domain)

Fig. 2. A. Principle of the string galvanometer, according to Einthoven's 1906 article "Le Télécardiogramme" **B.** Electrocardiograph used by Lewis, built by the Cambridge Scientific Instrument Company of London in 1911.

current and stretched like a string in a magnetic field As soon as the current passes through it, the filament moves from its perpendicular equilibrium position to the direction of the lines of magnetic force, revealing a movement which can be observed and photographed by means of a considerable magnification; ... thus being possible to regulate very accurately the sensitivity of the galvanometer within wide limits by tightening or loosening the string" (Figure 2A).

In 1903, he published *Galvanometric recording of the human electrocardiogram, with a review of the capillary electrometer in physiology* thus achieving a great impact on the scientific community, since it was on this occasion that he analyzed the two types of tracings obtained, providing a more detailed description, depending on whether the string galvanometer or the capillary electrometer was used. (Figure 3).



(At https://commons.wikimedia.org/wiki/File:Einthoven_ECG3_(Cardio-Networks_ECGpedia).jpg. Public domain)

Fig. 3. Waves obtained by A.D. Waller (top); waves obtained by Einthoven with his improved capillary electrometer (center); electrocardiographic tracing using the string galvanometer (bottom).

With his new device he recorded five deflections which he named P, Q, R, S and T. Einthoven never explained why he chose this sequence of letters; the reason remains unknown and has given rise to various elucubrations*.

This new galvanometer was easier to use, artifact-free, sensitive and accurate. However, it could not be transported to the hospital. It weighed just over 270 kilograms, took up two pieces, needed a huge water jacket for cooling, and required several people to operate it. In addition, large buckets of saline solution were used as electrodes with the subject immersing his hands and feet in them. On the other hand, it was not easy for patients to leave the hospital. Thus, for clinical use, Einthoven had to think of a method to transmit the electrocardiographic recordings from the hospital to his physiology laboratory in Leiden (where the galvanometer was located) over a distance of about one and a half kilometers. He decided to use the subway wires of the city's telephone network; he called these successful recordings "telecardiograms"; the first of which was made on March 22, 1905 on a "healthy and vigorous man". (6) Unfortunately, the use of this system was not free of charge and had to be financed both by Dr. Einthoven's laboratory and by the hospital's Department of Medicine; but on one occasion, the head of the latter suspended payments and its use was terminated.

However, this did not diminish Dr. Einthoven's enthusiasm, and over time he continued to make various improvements to make it more practical; thus, he proposed to reduce the number of electrodes from Waller's five to three, using the latter to construct an imaginary inverted equilateral triangle, centered on the thorax and with the vertices on both arms and one leg (Einthoven's triangle, as it would be known in the future). (7)

However, like many other great ideas, Einthoven initially encountered no small amount of resistance for the scientific community's recognition of this new diagnostic tool. It should be remembered that Waller himself had not shown much enthusiasm for the nascent electrocardiography (*vide supra*), and that, in fact, he tried to dissuade Einthoven from publishing his ideas. (8)

Despite this Einthoven continued with great conviction to see great diagnostic potential in his instrument ("*A new chapter has been opened in the study of heart disease, which helps suffering humanity*") and made modifications to the device, finally being recognized in two acclaimed articles, one of them published in 1908 (9)** and the other in the Lancet in 1912. (10)

* Einthoven chose for his nomenclature not to use the first letters of the alphabet, but other "intermediate" letters, so that if new waves were identified, an alphabetical order could be followed. This was the case of the U wave described later.

** "Additional considerations on the electrocardiogram". It was in this document, which contained more than 5000 records, that the abbreviation for electrocardiogram was established as EKG (from the German, Elektrokardiogramm). After World War II it was changed to ECG (from the English, electrocardiogram).

In the following decade the clinical application of electrocardiography began to expand, and clinical articles began to appear from all over the world. After 1913, Einthoven made no major contribution to electrocardiography but taught and lectured extensively on the subject. Surprisingly he never published a book based on his work.

This new diagnostic tool was soon manufactured by the Cambridge Scientific Instrument Company, founded by Horace Darwin (1851-1928), the youngest son of Charles Darwin (1809-1882), who was the first to officially market electrocardiographs. One of the first three was given to the British Cardiologist Sir Thomas Lewis (1881-1945) (Figure 2B), who for more than a decade, between 1908 and 1920, corresponded with Einthoven and made important contributions to the understanding of the mechanisms of arrhythmias, being the one who undoubtedly brought the new device to the patient's bedside and definitively endorsed its real usefulness, for which he is considered by many the "father of clinical cardiac electrophysiology". Einthoven formally acknowledged the contributions of Dr. Lewis during the Nobel Prize lecture. (11)

In 1924, Einthoven was awarded the Nobel Prize in Physiology or Medicine "*for his discovery of the mechanism of the electrocardiogram*". After receiving the 40000 dollar prize money, Einthoven sought out one of his first assistants, Van de Woerd, (who had built many of the parts of the new galvanometer) to share the money. When he learned that the latter had already passed away, he persevered with his idea and managed to find two sisters who had survived him and lived in poverty, and gave them half of the sum. During his last years he devoted himself to teaching and lecturing on electrocardiography. He died on September 29, 1927 at the age of 67 from abdominal cancer.

Recently, advances in artificial intelligence (AI) have been employed in the field of electrocardiography, and ECG interpretation algorithms with the ability to process gigantic amounts of data and identify previously unknown patterns have become available. (12) Recent studies show how the use of ECG-AI models can accurately detect reduced left ventricular ejection fraction in asymptomatic patients. Others have pointed out their potential to detect patients with a high probability of atrial fibrillation, and some algorithms have even managed to diagnose the age and sex of patients independently of the clinical data provided.

The true potential of ECG-AI models is beginning to materialize, allowing the ECG to remain a powerful tool in cardiology for years to come, continuing the path initiated by Einthoven.

Einthoven built his work on that of preceding or contemporary physiologists and each of these insights was an important contribution to his ultimate goal. The interval between the initial development of the invention, its clinical establishment and final recognition can be measured in decades. He always proclaimed that science should be placed at the service of mankind. He did not get to see how, a few years after his death, his device became an instrument of universal use.

Ethical considerations

Not applicable .

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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LETTER TO THE EDITOR

Notes on the Electrocardiogram in Childhood and Adolescence

Apuntes sobre el electrocardiograma en la infancia y la adolescencia

SAMUEL SCLAROVSKY[1]

PHYSIOLOGICAL HYPERTROPHIES IN CHILDHOOD

At birth the mammalian ductus arteriosus closes and pulmonary peripheral resistance is reduced. Right ventricular predominance persists for a limited time. Left ventricular predominance appears in rats at 2 weeks, in pigs at 6 weeks (1) and in humans at 12 weeks. (Figure 1) It is amazing to observe small calves and foals in the meadows, which at 4 hours after birth, can run at 40 - 60 km/h. For this to occur, they must have a left ventricle perfectly adapted to survive. Evolution prepares the left ventricle during pregnancy to support intense efforts a few hours after birth.

The newborn has a heart rate of 190 to 200 bpm and a high rate is maintained during childhood, between 80 and 120 bpm. (2) This heart rate is determined by catecholamines. Adrenaline is secreted by 2 sources, one endocrine (the adrenal gland) and one paracrine (the cardiac terminal sympathetic fibers). In the myocytes there are alpha and beta receptors. Exaggerated stimulation of the beta receptors is very harmful to the myocyte. (3) To avoid this effect there is a biological beta-blocker, arrestin. (4) But the effect on alpha receptors (in the myocyte membrane there are 3 types of alpha receptors) stimulates the formation of sarcomeres. (5) Sarcomeres aggregate longitudinally. (5,6) The effect of adrenaline on the alpha receptor determines the growth of sarcomeres and myocyte elongation, which defines the QRS voltage.

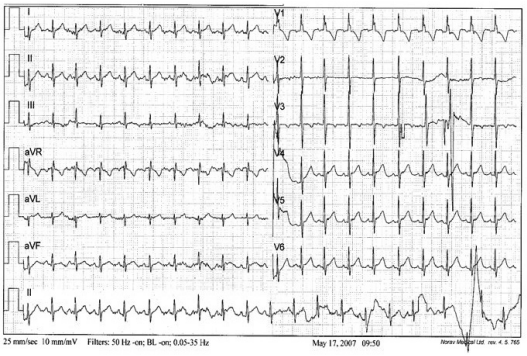

Fig. 1. 3-month-old infant, still with right ventricular predominance. See R wave in V1

But there is another electromechanical system that stimulates physiological hypertrophies. In the endocardium of the left ventricle there are tension receptors, whose distribution in the subendocardium is not homogeneous. (7) It is possible to speculate that the morphology of the child's electrocardiogram varies, depending on the concentration of tension receptors in the endocardium. Higher concentration of tension receptors, plus stimulation of alpha receptors, will induce physiological hypertrophies.

In 30% of cases the electrocardiogram in children is normal (Figure 2) In 70% of cases, during childhood, there is physiological hypertrophy that accompanies body growth. The ECG can record 4 different phenotypes of hypertrophy: 1) apical (Figure 3), which is expressed with dominant R waves in V4 and V5; 2) anteroseptal (Figure 4), which is expressed with dominant R waves in V2 (upper third of the septum), V2 and V3 (upper and middle third of the septum), and V2 to V4 (upper, middle and lower third of the septum); 3) posteroseptal (Figure 5), which is expressed with deep S waves in V2, V3, and V4; and 4) lateral, which is expressed with high R waves in lead I and deep S waves in AVR and V1. In rodents, inhomogeneously distributed endocardial tension receptors have been identified in the septum and lateral apex. (8) It could be suspected that the inhomogeneous distribution of tension receptors is a factor of universal importance in cardiac function in mammalian childhood.

Normal ECG tracing could be due to concentric hypertrophy, homogeneous distribution of tension receptors or a mutation in the hypertrophic cascade. (9) It is important to note that also in 30% of cases adults with systolic overload do not present eccentric hyper-

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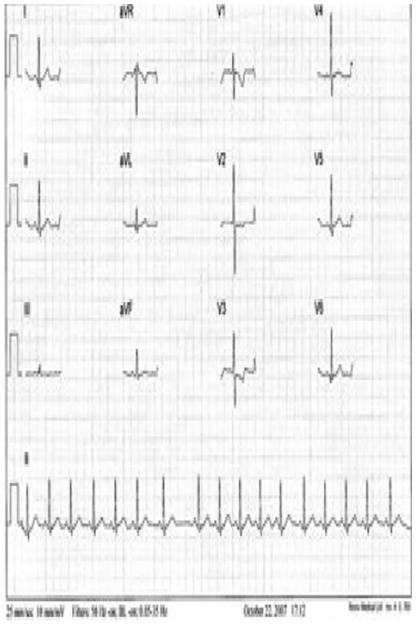


Fig. 2. 6-year-old boy without eccentric physiological hypertrophy, and probably concentric physiological hypertrophy.

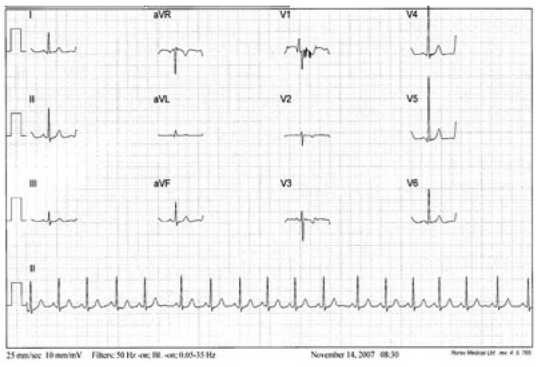


Fig. 3. 9-year-old boy with apical eccentric hypertrophy with high R waves in V4 and V5.

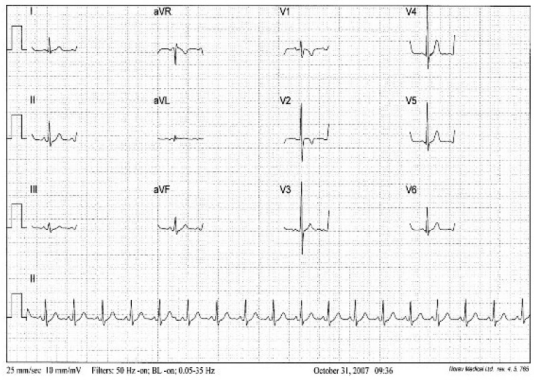


Fig. 4. 9-year-old boy with physiological eccentric anteroseptal hypertrophy, with high R waves in V2, V3 and V4.

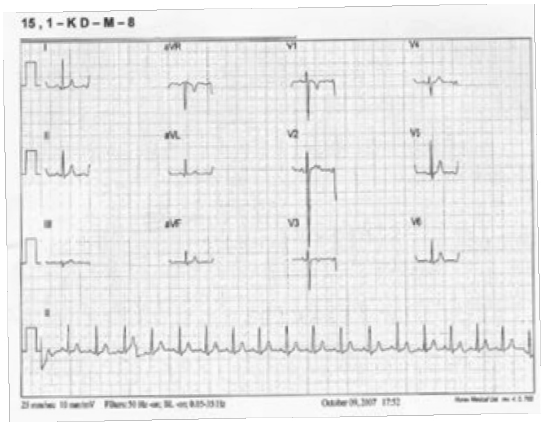


Fig. 5. 5-year-old boy with eccentric posteroseptal hypertrophy, with 40 mm S wave in V2 .

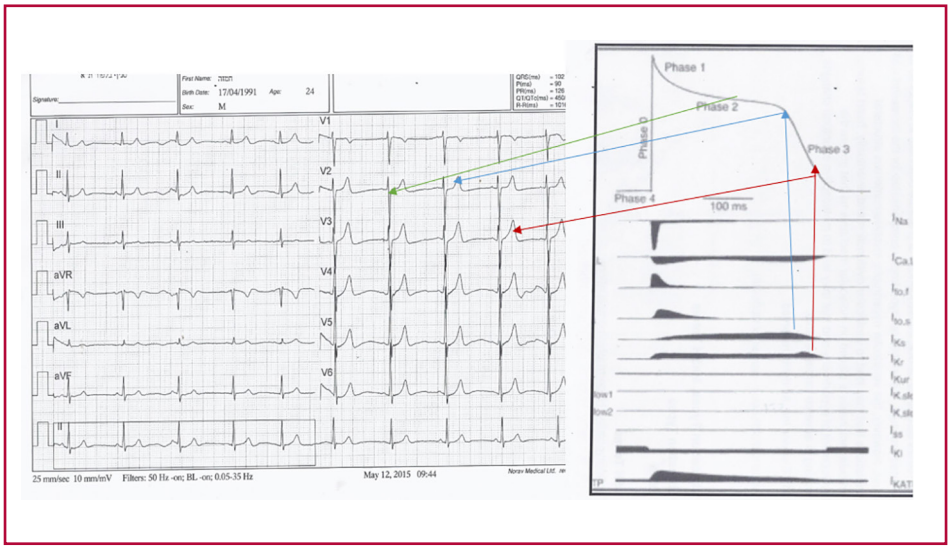
trophy (personal experience). Electrical/mechanical activity induces a feedback reaction. Electrical activity stimulates the Z-line and titin protein to increase tension in the actin-myosin complex. (10)

There is a genetic fetal program in embryonic life, which has a mildly hypoxemic environment. (11) In this context mitochondria use glucose to generate energy. But with birth, the mitochondria begin to use oxygenated fatty acids as energy fuel. The fetal program remains hidden, inactive; but in cases of physiological or pathological hypertrophies it is reactivated. This program prevents the progression of hypertrophies towards dilatation and heart failure. We speculate that in physiological cardiac hypertrophies in children a genetic fetal program may exist as myocardial protection. Interestingly, physiological hypertrophies in children are no longer seen in adolescence.

GENDER HORMONES DETERMINE THE REPOLARIZATION MORPHOLOGY OF THE ELECTROCARDIOGRAM IN ADOLESCENCE

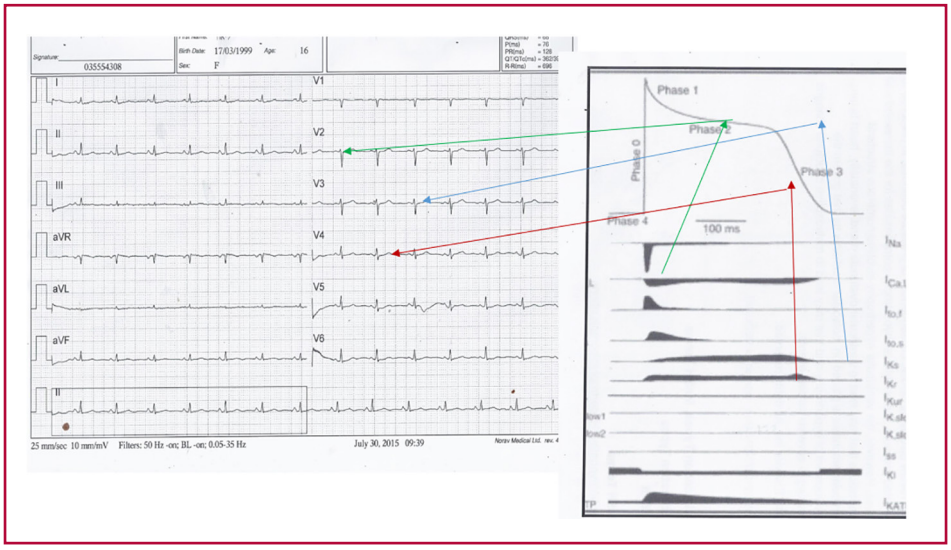
Estrogens control the fast transient outward rectifier potassium current, (12) which forms the downward limb of the T wave, which is slow and elongated compared with this limb in the male gender, and also the slow rectifier potassium current, (13) which forms the

Fig. 6. ECG of a 22-year-old male.



The red arrow points to the fast rectifier potassium current, which acts on phase 3 of the action potential (AP) and forms the short, fast descending limb of the T wave. The blue arrow points to the slow rectifier potassium current, which acts at the junction of phases 2 and 3 of the AP and forms the high, acuminate T wave. The green arrow points to the calcium current that acts in phase 2 of the AP and conditions the short and elevated ST segment on the ECG. From Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev. 2005;85:1205-53. Modified by Sclarovsky S

Fig. 7. ECG of a 16-year-old woman.



The red arrow points to the relationship between the fast rectifier potassium current and phase 3 of the action potential (AP), which conditions the slow and attenuated descending limb of the T wave (with respect to the male T wave). The blue arrow points to the ratio of the slow rectifier potassium current with the junction of phases 2 and 3 of the AP, which forms the peak of the attenuated T wave. The green arrow points to the relationship between the calcium current, phase 2 of the AP, and the long, attenuated ST segment. From Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev. 2005;85:1205-53. Modified by Sclarovsky S

peak of the T wave, which is very low or negative compared with the male high and acuminate T wave.

These hormones also control calcium influx in the phase 2 of the action potential, expressed with an elongated ST segment. (14)

Androgens have a stimulatory effect on potassium (15) and calcium channels, which is expressed by a high and acuminate T-wave peak, a short and fast descending limb, and short and elevated ST segment. (15) The effect of testosterone on the calcium channel influences the ST segment, which is short and elevated usually in V2 and V3. (16) (See Figures 6 and 7)

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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Is There a Place for Rapid-Deployment Valves for Older Intermediate-risk Patients?

¿Hay lugar para las válvulas de rápido implante en pacientes mayores de riesgo intermedio?

IULIA COTI[1], PAUL WERNER[1], DANIEL ZIMPFER[1], MAREK EHRLICH[1]

Transcatheter aortic valve replacement (TAVR) is the treatment of choice in patients older than 75 years of age, irrespective of surgical risk. However, in some health care systems the costs associated with transcatheter valve procedures might be prohibitive and prevent older higher risk patients of receiving treatment for severe aortic stenosis. Compared with conventional valves, rapid-deployment (RD) surgical aortic valve replacement demonstrated better procedural time, cardiopulmonary bypass and cross-clamp times in multiple studies and favored minimally invasive approaches, which were also associated with a reduction in ventilation and intensive care unit (ICU) times, as well as in hospital stay length, and an improved quality of life. (1) Fortunato and colleagues compared the early outcomes of a small group of older intermediate-risk patients receiving either a rapid-deployment valve, RD-V, (n=65) or a conventional surgical aortic valve replacement (n=140). (2) In this retrospective analysis, RD-V demonstrated a trend to lower-in-hospital mortality and was associated with reduced procedural times and improved valve hemodynamics; moreover, minimally invasive approaches were favored. However, a higher number of patients receiving a conventional prosthesis had an indication for urgent treatment or received concomitant procedures, both factors being usually associated with higher early mortality. A recent meta-analysis from Salmasi et al. including almost 10 000 patients (RD-V n=3686 and conventional AVR n=6310) found no significant difference in terms of operative mortality, stroke or bleeding. Despite the reduced operative and length of ICU stay times in the RD-V group, the need for permanent pacemaker implantation and the occurrence of paravalvular regurgitation was higher in this group. (1) Another analysis from the German Registry (GARY) which included more than 16 000 patients who underwent isolated AVR with current generation RD valves (n=1743) or transfemoral TAVR with current generation transcatheter heart valves (n=14 730) revealed higher risk of stroke, need for blood transfusions or postoperative renal replacement therapy in the RD-V group; in-hospital mortality was also higher in this group after propensity score matching compared with the TAVR group. (3)

In the light of present evidence, individualized directed treatment decision is important, especially in situations in which transcatheter valve therapy options are limited, in order to provide optimized medical care with reduced perioperative events in patients requiring aortic valve replacement. As bravely pointed out by Fortunato et al., RD-V represents an important tool in the arsenal of the modern cardiac surgeon, facilitating less-invasive surgical procedures and reducing procedural times while providing optimal hemodynamic performance.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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AUTHORS' REPLY

We gratefully acknowledge the comments on our work of Dr. Marek Ehrlich and the University of Vienna cardiac surgery team. In this article preoperative risk stratification was made using STSprom% to employ universally recognized factors when comparing similar populations considered as "intermediate risk".

In contrast to the study by Salmasi et al., (1) in which a higher percentage of postoperative leaks was observed with rapid implantation prostheses, in our series we did not find this trend (conventional AVR 5% vs. rapid implantation 4.6%). However, we identified what we consider to be the "Achilles heel" of these new prostheses: the need for pacemakers.

In response to this challenge, we have implemented several changes in recent years that have improved this situation and reduced the rate of postprocedural atrioventricular block. These modifications include: 1. No prosthesis oversizing (always opting for the smallest size available), 2. Avoid excessive decalcification, and 3. Carefully select patients, avoiding those with a history of first- or second-degree atrioventricular block and bundle branch block.

Our aim with this article is to present our results with complete honesty. This prosthesis is not intended to replace either transcatheter valves or conventional valves, but, as the Vienna team rightly points out, to act as an additional tool in our practice. Personally, we consider that it has radically changed the way we plan surgeries.

Germán Fortunato

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New Surgical Options for Aortic Stenosis

Nuevas opciones quirúrgicas para la estenosis aórtica

TOMÁS MUSELI[1],

Aortic valve disease treatment has changed radically with the advent of transcatheter aortic valve implantation (TAVI). It is part of the daily practice of our services to have to choose between surgical or hemodynamic treatment of our patients. This decision, based on each particular case, contemplates risk scores, anatomical characteristics, costs and coverage by insurance companies, experience of the center and patient preferences.

Cardiovascular surgery began to offer less invasive approach options and new types of "sutureless" valve prostheses. At present, there are two such valve platforms: the totally sutureless Perceval (Corcym) and the Edwards Intuity rapid deployment valve (Edwards Lifesciences). Both valves, approved by the FDA in 2016, share similar technology to TAVI: Perceval as self-expandable and Intuity as balloon expandable with three points of anchorage to the aortic annulus.

The appeal of the sutureless valve surgical approach and its potential advantages over TAVI are based on the possibility of complete excision of the native valve, decalcification of the aortic annulus, or debridement of potentially infected material. (1) Other advantages of the surgical approach include the possibility of revascularizing complex coronary anatomies unsuitable for angioplasty or reducing surgical times in combined procedures.

Despite the aforementioned theoretical advantages, the debate about the benefits of sutureless valves versus conventional aortic valve replacement (cAVR) or TAVI still persists. The published data come mostly from retrospective observational studies and are inconclusive regarding mortality benefits with the less invasive surgical modality. (2-4)

In their article Rapid deployment valves versus conventional valves in aortic valve replacement in intermediate-risk patients (Rev Argent Cardiol 2024; 92: 198-204) , Fortunato et al. compared a retrospective cohort of patients with severe aortic stenosis who underwent conventional AVR vs. rapid deployment

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valve replacement (RD-V) with Intuity valve. (5) The results replicate, to a large extent, those published internationally: RD-V has a higher proportion of mini-invasive approach, shorter surgical times (cardiopulmonary bypass and aortic clamping), a better hemodynamic profile and a trend towards greater pacemaker implantation with respect to TAVI.

The indication for sutureless surgical techniques seems to be reserved for those patients who are in a gray zone between conventional AVR and TAVI. Certain anatomical features, such as the relationship of the annulus to the coronary ostia, or the need for a combined procedure, given by complex coronary artery disease or multivalvular involvement, could determine a possible benefit of less invasive surgical techniques. (1)

The publication of Hospital Italiano de Buenos Aires outcomes with RD-V in intermediate-risk patients is a valuable contribution to local cardiology. There is still lack of information on the long-term behavior of these valves, their impact on the conduction system, as well as cost-effectiveness studies, so necessary for decision making in our setting.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

(See authors' conflict of interests forms on the web).

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AUTHORS' REPLY

Thank you very much, Dr. Museli, for your valuable comments and feedback on our work.

In relation to indications, I would like to highlight the advantages that rapid-deployment prostheses (RD-V) offer in small aortic annuli. Since we started using them, we have observed a radical decrease in the need to enlarge the aortic annulus. This not only avoids prosthesis-patient mismatch, but also mitigates the negative effects associated with annulus enlargement, such as longer aortic clamp time, prolonged extracorporeal circulation, increased surgical complexity, and risk of bleeding.

The long-term follow-up of these valves is still under development. As mentioned in our article, the system is based on Carpentier-Edwards Perimount valves. Bourguignon et al. (1) showed, at 15 years, freedom from reoperation due to structural damage of 82.7±2.9% in patients over 60 years of age, and 98.1±0.8% in patients over 70 years of age. Truly excellent results for a bioprosthetic aortic valve.

Recently, the TRANSFORM study by Malaisrie et al. was published. (2) This prospective multicenter nonrandomized study showed 95.5% and 96.1% freedom from all types of reintervention for RD-V in isolated or combined aortic valve replacement at 7 years, respectively. As Dr. Museli mentions, longer term results remain to be demonstrated.

Germán Fortunato

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Cardiologic Involvement in an Experimental Model of Reperfused Ischemic Stroke

Compromiso cardiológico en un modelo experimental de accidente cerebrovascular isquémico reperfundido

FERNANDO J. VERDUGO[1, 2]

Patients with ischemic stroke (IS) have a high incidence of cardiological complications, including myocardial injury, acute coronary syndrome, left ventricular dysfunction, electrocardiographic abnormalities, arrhythmias and sudden death. (1) Although these complications are mostly transient, they are associated with worse short-term prognosis. (1) It is important to implement experimental models of IS that reproduce cardiac complications to better understand the underlying pathophysiological mechanisms and to evaluate the potential impact of therapies.

In the Argentine Journal of Cardiology, Barbieri et al. report the implementation of a cerebral ischemia and reperfusion (I/R) model in FVB mice, showing significant neurological and histological deficit of the right hemisphere (with insular territory involvement) and, concomitantly, electrocardiographic and echocardiographic alterations. (2)

Mice subjected to I/R were evaluated electrocardiographically at baseline, at 60-minute ischemia and at 24-hour reperfusion, showing relevant repolarization alterations: prolongation of the QT interval in ischemia, prolongation of the QT interval in reperfusion with respect to ischemia, and prolongation of the T wave peak-to-end interval (TPEI) only in reperfusion. (2) The observations of the experimental model are interesting if we consider the clinical background. QT interval prolongation is observed in 20-65% of patients with IS, and its highest incidence occurs in patients with insular IS or severe neurological damage. (1,3) A prospective study of patients with IS, excluding those with heart disease, reported QT and TPEI prolongation during the first 24 hours of IS, with decreases at 72 hours. (3) In patients with IS, mortality triples in the presence of prolonged QT versus normal QT interval. (1) TPEI prolongation is associated with a higher risk of torsade de pointes in patients with acquired prolonged QT. (4)

Echocardiography was performed 24 hours post-surgery in the I/R group and in a sham group, and statistically significant differences were observed in left ventricular ejection fraction (LVEF) and shortening fraction (SF). (2) Mild systolic dysfunction secondary to I/R is assumed, although LVEF and SF values in the I/R group were similar to those reported as normal for healthy FVB mice, (5) and the sham group evidenced higher averages, suggesting a hyperdynamic state. It would have been useful to compare these parameters of systolic function at baseline to establish causality. QT prolongation is a criterion in clinical scores of Takotsubo syndrome, so it would be relevant to investigate whether the mice subjected to I/R presented segmental motility disorders indicative of this condition, although assessment in mice by echocardiography may be technically challenging.

The experimental model implemented by Barbieri et al. is noteworthy for the study of repolarization alterations secondary to IS. It would be interesting to evaluate the presence of repolarization abnormalities in IS generated in other territories, as well as their association with biomarkers mentioned in their discussion. From the clinical point of view, it seems relevant to determine whether the temporal pattern of QT and TPEI changes are replicated in humans with right IS undergoing reperfusion therapy and whether these observations would modify routine practice

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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AUTHORS' REPLY

First of all, we express our gratitude to Dr. Fernando J. Verdugo for his critical reading and thorough analysis of the results presented in our article "Modifications in left ventricular function and electrocardiogram in mice due to cerebral ischemia and reperfusion", recently published in the Argentine Journal of Cardiology. (1) We also appreciate his dedication in preparing a commentary that enriches and enhances the value of our research. His reflection on the importance of having well-defined preclinical experimental models, which allow a deeper understanding of the mechanisms underlying cardiac complications that worsen prognosis in stroke patients, has fully captured the essence of our work.

Having established this experimental model and obtained relevant results, our aim is to further extend the study of the various mechanisms of cardiac damage in the context of cerebral ischemia and reperfusion. In this sense, Dr. Verdugo's suggestions are valuable to strengthen the importance of our current working hypotheses, especially with regard to the regionality of cardiac injury, cerebral anatomical topography and its relationship with cardiovascular damage, and the use of biomarkers, among other aspects.

We do not agree with Dr. Verdugo's statement that mice in the sham group present echocardiographic data suggesting a hyperdynamic state. Previous studies in conscious mice have shown that the left ventricular ejection fraction under normal conditions ranges from 80% to 85%. (2) At the same time, these values can be differentially reduced depending on the type of anesthesia used during the study. (2) In our case, the sham group showed an ejection fraction of 74.3±0.9%, (1) a value lower than that of a conscious animal, (2) but consistent with what is observed in mice anesthetized with the same type and dose of anesthesia used in our study. (2) Although some papers have reported lower values, (3) and others even higher, (4, 5) than those we present, most have shown similar values. (2, 6) A comparable pattern was observed in the left ventricular shortening fraction. (7)

Therefore, although it is important to take into account the reference values reported by other authors, it is essential to compare the results obtained in the group with the study variable intervention versus their own sham group. This approach minimizes the possibility of introducing methodological errors derived from potential differences in the control of variables such as temperature, type, dose and form of administration of anesthesia, duration of the study, strain, age and sex of the animals, operator experience and type of equipment used, among other factors.

Among Dr. Verdugo's comments, a particularly relevant aspect that enriches the discussion and exchange of ideas is the consideration of the use of control and sham groups. Previous studies in anesthetized mice, but not subjected to surgery, have shown that the values of ventricular function assessed by echocardiography are similar to those we found in our mice subjected to sham surgery. (2, 6) Moreover, in previous investigations performed in our laboratory with control mice without surgery, or sham mice with long evolution, we obtained results comparable to those of the sham group in the current study. (8, 9) Therefore, we lack sufficient biological arguments to ethically justify the sacrifice of animals in order to create an additional control group. In fact, such a protocol would have a very low probability of being approved by our Institutional Committee for the Care and Use of Laboratory Animals, since it would not meet the ethical standards for reducing the use of animals in scientific research.

On the other hand, the aim of our study was not to evaluate the impact of surgery on cardiac function. On the contrary, although our own previous evidence suggests that this does not occur, (9) any alteration that the surgical intervention could generate in the heart would represent a confounding variable, introducing possible biases in the interpretation of the results on the impact of cerebral ischemia on cardiac function. This becomes particularly relevant given that these are acute protocols in which a carotid artery is manipulated and occluded. For this reason, we consider the use of a sham group rather than a control group to be essential.

In summary, methodological, scientific and ethical reasons support the decision to use a sham group and not to include a control group without surgery.

Again, we stress the relevance of these points and sincerely thank Dr. Verdugo for taking the time to write this reader's letter, which contributes to the exchange of ideas and enriches the scientific discussion.

Ignacio P. Barbieri,
Verena B Franco Riveros,
Bruno Buchholz

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Response in Cardiac Resynchronization Therapy: is it Still Uncertain?

Respuesta en la terapia de resincronización cardíaca: ¿continúa siendo incierta?

DANIELA M. RUBIRA[1], ALEJANDRA FERRO[1], FEDERICO SALAZAR[2]

Cardiac resynchronization therapy (CRT) is an electrical treatment that was initially applied as the last therapeutic option for patients with advanced heart failure (HF) associated with left bundle branch block (LBBB). (1)

It is an effective treatment if adequately directed. However, translating consensus guidelines into "real-world" practice is often incomplete. Cardiac resynchronization therapy is underutilized and there is great heterogeneity in its implementation and response; therefore, unequivocally estimating the actual benefit of its use remains a major challenge. (2)

The definition of response to CRT varies across clinical trials. There are two main definitions: the echocardiographic and the functional response. The former is defined as a reduction in left ventricular (LV) end-systolic volume greater than or equal to 15% or an improvement in LV ejection fraction greater than or equal to 5%. Functional response refers to an improvement of at least one dyspnea class category in the NYHA classification. (3) In a study by Nakai et al. in 260 patients, response to CRT at 6 months after implantation was evaluated based on each definition, and the relationship between response and clinical outcomes was investigated. Non-responder status was associated with higher all-cause mortality. (4)

This difference in the response to a widely validated therapy was analyzed in an extensive study by María E. Santillán et al. (5) in 343 patients with heart failure and CRT. These two responses were analyzed, using clinical and echocardiographic parameters, and a predominant positive response to CRT was identified at 24-month follow-up for the first time in Argentina, with statistical significance in terms of hospitalization events, cardiac transplantation and appropriate therapies, and at the limit of significance for all-cause death. In this model, the presence of LBBB and longer QRS duration, as well as a non-ischemic etiology, stand out among the possible positive predictors. Contrary to what was presented in other trials, female sex predominated in the group of non-responders.

The similarity in the standard medical treatment of both groups and the lower incidence of adverse events among responders highlights indirectly the importance of electromechanical synchronization, and reverse remodeling as the main detectable phenomenon in daily clinical practice.

The contribution of the present work, by identifying factors related to suboptimal response to CRT and the waiting times required for its detection, encour-

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ages us to a wider and more targeted implementation of this type of therapeutic tool.

Although this is a retrospective analysis and sensitive to unidentified potential confounders, this study, like many others, highlights the importance of not delaying the indication of CRT in a substantial group of patients with an unfavorable prognosis who are left to standard medical treatment alone.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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AUTHORS' REPLY

Cardiac resynchronization therapy (CRT) is indicated in patients with heart failure (HF) and QRS >120ms, who despite receiving optimal medical treatment persist in functional class II-IV and left ventricular ejection fraction < 35%. (1) It is an effective treatment, which has been shown to improve the long-term prognosis of this subgroup of patients. However, there is a percentage, varying between 20-40% depending on the study analyzed, that does not respond to therapy.

Over time, factors related to the lack of response have been identified and there are clear guidelines for effective therapy, among which we can highlight: 1) correct indication of the device; 2) placement of the catheter in the coronary sinus, lateral branch; 3) avoid pacing in areas of necrosis or use of quadripolar catheters to bypass the eschar using different pacing vectors; 4) programming of the optimal AV and V-V intervals to obtain the best VTI; 5) biventricular pacing > 95-97%.

Taking all these criteria into account, our division has created a work system to maintain strict follow-up of all patients with CRT. Six-monthly check-ups are performed, including clinical and electrocardiographic evaluation and device control, including follow-up with remote monitoring of selected patients.

This has allowed us to perform a broad analysis of the response according to clinical and echocardiographic parameters, identifying that the number of responding patients in our population has been high compared to other published series, and that the response has an effect on the reduction of moderate/severe functional mitral regurgitation (2) and also on the reduction of total mortality, appropriate therapies, cardiac transplantation and hospitalization for HF. (3)

Thanks to these results, we emphasize the importance of a timely indication for CRT in selected patients, as well as the importance of a strict control and follow-up that allows us to identify potential predictors of non-response and worse long-term prognosis.

María Eugenia Santillán

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Between Joy and Horror...

Entre la alegría y el espanto...

The activity generated by the Areas and Councils of our SAC is wonderful. I would like to mention only some of them, since it would be impossible (and I apologize) to mention in this letter the enormous work done by all our members.

After the success of the Imaging Congress, the First Argentine Congress on Prevention, Cardiometabolism and Hypertension was held during the first week of June, with more than 800 participants and an excellent scientific program. During the North Suburban Area, Bahía Blanca and San Luis Conferences, we signed an academic and scientific collaboration agreement with the National University of Villa Mercedes and Ramón Carrillo Hospital of San Luis. Six residents of our biennial course, selected by the best average grades, belonging to different provinces of our country, are currently engaged in rotations at medical centers in Buenos Aires. Additionally, in September, a young cardiologist will undertake a two-week rotation at Mount Sinai Hospital. Another will participate in an agreement between the Argentine Chapter of the ACC and the New York Chapter, which we share with the ACC. All of this is made possible by funding from the SAC.

We have launched a new logo and branding manual that has refreshed our image across all media, increasing our visibility. Our new website is more dynamic and user-friendly, offering a more comprehensive virtual experience of our SAC, thanks to the efforts of the Instructional Resources Area (ARI) over several months.

In addition, we have launched our SAC Educational Institute, which will plan and synchronize all our educational activities, with the aim of providing and ensuring quality education to our members, colleagues and all health professionals. Webinars, courses, face-to-face and virtual conferences complement all scientific activities.

The Consensus Statement on Cardiogenic Shock, the Latin-Shock registry, the first Latin American registry on cardiogenic shock in acute myocardial infarction with the participation of several Latin American countries, and two position papers on Hypertensive Emergencies in the Elderly and Stress Management were published. Our younger cardiologists will be participating in the Young Corner of the European Congress, where they will have the opportunity to exchange experiences and knowledge with colleagues from around the world.

Our Argentine Journal of Cardiology is 90 years old. We are working hard to become an indexed journal next year (and we are very confident that we will achieve this goal).

Our 50th Argentine Congress of Cardiology is fast approaching. This event that will unite us all and has a history that will serve as an inspiration for continuous improvement. his is an opportunity to acknowledge the contributions of those who have played a leading role in the writing of our history and of profound respect for those who preceded us and built our current SAC. The presidents of our sister societies in Latin America, the European Society of Cardiology, the ACC and the AHA will share this moment with us. Furthermore, we are honored to announce that Dr. Valentín Fuster will be delivering the opening lecture.

We are very excited about all of this... but we also have some concerns....

We are concerned about a health care system that is underfunded, fragmented and unequal.

We are concerned about the arbitrary cuts to university funding, given that 80% of our cardiologists are trained in public universities.

We are concerned because 80% of our residents and 60% of our cardiologists, with an average of 7 years of specialization after the residency program, are considering emigration. Similarly, 40% of specialists are considering leaving medicine because of the state of the health care system.

We are concerned that 52% of cardiologists have insecure employment and 82% are dissatisfied with their remuneration in relation to their workload.

We are concerned that 76% of cardiologists have observed a decrease in the frequency of their patients attending outpatient clinics for monitoring visits.

We are concerned that 75% of cardiologists and physicians in other specialties are experiencing burnout, whether professional or job-related.

We patients and physicians are in bad shape.

Fifty-six scientific societies and all of cardiology united (societies, associations, and colleges are seeking to be included in discussions regarding the reorganization of the healthcare system and the negotiation of reimbursement for our work. It is a difficult

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task when there are interlocutors who hear but are not listening, or who only defend their sectorial interests. However, we are committed to pursuing this objective and will continue to do so. We will have a prime-time slot at our Congress to address these issues, and we invite you to participate and commit to changing this reality.

Finally, I encourage you to continue to nurture our spirit in the face of adversity. Resilience is the antidote to depression, and the only way to change is to want to change, for which we must all unite for the common good. All the work you do from SAC is an example of that. Thank you all.

Víctor Mauro MTSAC,
President of the Argentine Society of Cardiology