IMPACT OF PULMONARY VEIN ISOLATION ON LEFT ATRIAL CONTRACTILE FUNCTION IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION: A PROSPECTIVE COHORT ANALYSIS USING STRAIN ECHOCARDIOGRAPHY

IMPACTO DEL AISLAMIENTO DE VENAS PULMONARES EN LA FUNCIÓN CONTRÁCTIL AURICULAR IZQUIERDA EN PACIENTES CON FIBRILACIÓN AURICULAR PAROXÍSTICA: ANÁLISIS DE UNA COHORTE PROSPECTIVA MEDIANTE ECOCARDIOGRAFÍA POR *STRAIN*

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RESUMEN

Objetivo: Investigar la función contráctil de la aurícula izquierda (AI) en pacientes con FA paroxística utilizando ecocardiografía con *strain* antes y después del aislamiento de las venas pulmonares (AVP) y comparar con controles pareados por edad y sexo. **Métodos:** Se realizó un estudio de cohorte prospectivo en el Instituto Nacional de Cardiología Ignacio Chávez de mayo de 2021 a noviembre de 2022. Pacientes con FA paroxística se sometieron a ecocardiografía transtorácica (ETT) para evaluar la deformación global de la AI y las fases de reservorio, conducto y contracción de la AI antes y después del AVP. Los parámetros ecocardiográficos se compararon antes y después del AVP, y con los controles pareados. **Resultados:** Se analizaron 15 sujetos con FA paroxística y 15 controles pareados. Después del AVP, los sujetos mostraron mejoras significativas en strain global y strain en fase de reservorio de la AI. En comparación con los controles, se observaron diferencias ecocardiográficas significativas antes del AVP, pero no después del AVP. **Conclusión:** El AVP puede mejorar los parámetros de deformación de la AI en pacientes con FA paroxística, alineándolos con controles pareados. Esto sugiere el potencial efecto restaurador del AVP en la función auricular. Se justifica una investigación adicional para validar estas observaciones.

Palabras clave: Fibrilación auricular paroxística, strain auricular izquierdo, aislamiento de venas pulmonares

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ABSTRACT

Objetive Assess left atrial (LA) contractile function in patients with paroxysmal (AF) using strain echocardiography before and after pulmonary vein isolation (PVI) and compare them with matched controls. Methods A prospective cohort study was conducted at the National Institute of Cardiology Ignacio Chavez from May 2021 to November 2022. Patients with paroxysmal AF underwent transthoracic echocardiography (TTE) assessing LA global strain and strain in the LA reservoir, conduit, and contraction phases strains before and after PVI. Echocardiographic parameters were compared prior to and after PVI, and against matched controls. Results 15 subjects with paroxysmal AF and 15 matched controls were analyzed. Post-PVI, subjects showed significant improvements in LA global and reservoir phase strains. Compared to controls, significant echocardiographic differences were noted pre-PVI, but not post-PVI. Conclusion PVI may enhance LA strain parameters in paroxysmal AF patients, aligning them with matched controls. This suggests PVI's potential restorative effect on atrial function. Further research is warranted to validate these observations.

Key words: Paroxysmal atrial fibrillation, Left atrial strain, Pulmonary vein Isolation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting around 1-2 % of the entire world population[1]. It has been associated with a significant risk of stroke, heart failure, and mortality. Therefore, accurate AF diagnosis and risk stratification are crucial for appropriately managing and preventing adverse outcomes. Strain echocardiography is a non-invasive imaging technique that has shown increasing clinical significance in assessing left atrial (LA) function in relation to AF[2]. By measuring myocardial deformation, strain echocardiography provides valuable information about the contractile function and deformation of the cardiac chambers, including the atria and ventricles.

Several studies have demonstrated the utility of strain echocardiography in evaluating patients with AF. Strain echocardiography can identify early signs of myocardial dysfunction, especially in AF[3]. For example, Lee et al. demonstrated that although LVEF was comparable between patients with and without AF, the former had impaired left ventricular (LV) global longitudinal strain (GLS)[4]. Moreover, a study by Yoon et al. found that patients with paroxysmal AF have decreased LA reservoir function and increased stiffness compared to control subjects[5]. These findings indicate that strain echocardiography could be helpful in detecting subclinical myocardial dysfunction in patients with AF.

Furthermore, strain echocardiography may be an important predictor of outcomes in patients with AF. For

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instance, global LA strain improves stroke risk prediction over conventional echocardiographic parameters[6]. Moreover, strain echocardiography may even be useful in assessing the risk of developing AF as shown that impaired LV-GLS may predict the development of AF even in the absence of structural heart disease[7].

Nevertheless, the changes in LA strain following atrial fibrillation treatment have not been fully elucidated. Therefore, this study sought to evaluate the contractile function of the LA in sinus rhythm measured by the LA strain to evaluate myocardial deformation in patients with paroxysmal AF before and after pulmonary vein isolation (PVI). Additionally, LA volume and LV function parameters were also assessed. Furthermore, these measurements were compared between subjects and matched controls. We hypothesize that significant differences will be observed in subjects before and after the intervention and that these measurements will resemble those of matched controls after PVI.

Materials and Methods

We conducted a prospective, experimental, and analytical study at a single center that included patients who attended the Electrophysiology Department of the National Institute of Cardiology Ignacio Chavez between May 2021 and November 2022. We enrolled patients diagnosed with paroxysmal AF through non-probabilistic sampling who agreed to undergo transthoracic echocardiography (TTE) to measure atrial strain before and after PVI. This study was approved by the Human Research Ethics Committee of the National Institute of Cardiology Ignacio Chavez, and all patients provided informed consent before the TTE and PVI. We adhered to the STROBE guidelines for conducting retrospective cohort studies (Table S1)[8].

Inclusion, exclusion, and elimination criteria

The inclusion criteria consisted of the following: patients of both sexes aged 18 years and older, have an electrocardiographic diagnosis of paroxysmal AF and be scheduled for PVI in the following three months. Patients were excluded if they had any valvular heart stenosis, moderate or severe aortic or mitral regurgitation, severe pulmonary or tricuspid regurgitation, valvular heart surgery or intervention, significant mitral annular calcification (≥5 mm), ventricular paced rhythm, LV assist devices, left bundle branch block, or those with AF that were not in sinus rhythm at the time of the TTE. Patients with incomplete information that did not allow for all variables to be included in the analysis, patients who did not attend the follow-up echocardiographic assessment, those with inadequate acquisition of an echocardiographic window, and those who withdrew their informed consent were eliminated from the study.

Recruitment of Matched Controls

Matched controls were actively sought and invited to the Department of Nuclear Cardiology to perform a TTE. The potential

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control candidates were briefed about the protocol and the nature of their participation. Those who willingly decided to participate in the study provided their written informed consent. The controls were diligently matched based on sex, age and BMI to ensure comparability with the primary patient group. In our bid to eliminate potential confounders, controls with any known rhythm disturbances or discernible cardiac pathology of significance were excluded from the study. A 1:1 ratio of subjects and controls was chosen to avoid overmatching and for logistical simplification as it is a standard practice and was deemed enough for statistical analysis.

Clinical Characteristics and Comorbidities

For both the subjects and matched controls, detailed information about their clinical characteristics (including sex, age, NYHA functional class, and smoking status) and any associated comorbidities were collected by direct interrogatory. Additionally, patient's height and weight were recorded. An experienced Cardiologist trained medical professionals to conduct these interviews and recorded these measurements to ensure accuracy and thoroughness. Participants were encouraged to provide comprehensive details, and any ambiguities or uncertainties were clarified immediately.

Diagnosis and Ablation of Paroxysmal AF

Paroxysmal AF was diagnosed through 24-hour Holter and was defined as an arrhythmic episode showing a typical pattern of irregular RR intervals and no discernible, distinct P waves lasting at least 30 seconds, in line with the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[9].

The electroanatomic mapping CARTO®3 system (Biosense Webster, Diamond Bar, CA) was used to reconstruct the LA. A trans-septal puncture was performed under fluoroscopy with subsequent radiofrequency ablation using a ThermoCool® catheter (Biosense Webster, Diamond Bar, CA, USA), applied circumferentially to the pulmonary veins, guided by the ablation index or impedance drop.

Transthoracic echocardiographic study

We performed a conventional TTE with subjects in left lateral decubitus using a Siemens Acuson SC 2000 (Mountain View, CA, United States). Measurements were obtained in the apical four-chamber view using a 4V1 Acuson transducer. Measurements of chambers, systolic and diastolic function, and strain were measured following recommendations of the American Society of Echocardiography[10].

TTE was performed one day before the procedure and 90 days (up to 1 year) after PVI. A comparative analysis was then conducted on the following variables: LA global strain (LAGS), reservoir phase (LASr), conduit phase (LAScd), and contraction phase (LASct) LA strain, as well as 3D LV ejection fraction (LVEF) and LA volume indexed by body surface area (LAVI).

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Statistical Analysis

Descriptive Statistics

The frequency distribution of categorical variables was reported as frequencies and percentages. Continuous variables are presented as mean (standard deviation) or median (interquartile range) based on their normal distribution assessed by visual inspection of histograms or the Shapiro–Wilk test and homogeneity of variances evaluated by the Levene test, respectively. Student's t test or Mann–Whitney U-tests were conducted to evaluate differences of continuous variables between subjects and controls. When relevant, χ^2 and Fisher's exact test were carried out for categorical variables.

Comparison of Echocardiographic Parameters Before and After PVI in Subjects with Paroxysmal AF and with Matched Controls

To evaluate differences between echocardiographic parameters (LAGS, LASr, LAScd, LASct, LAVI, and LVEF) in subjects with paroxysmal AF before and after PVI, paired Student's t-test or paired Wilcoxon tests were performed depending on the distribution and the homogeneity of variances of the respective variables. Moreover, the same variables were compared between the controls and the subjects (both before and after PVI), with Student's t-tests or Wilcoxon tests accordingly. A p-value of < 0.05 was considered statistically significant for all tests. All statistical analyses were performed using the R software (version 4.3.1).

Results

Study Population and Clinical Characteristics

From May 2021 through November 2022, 1419, patients attended the Electrophysiology Department, of which only 1319 did not meet the inclusion criteria and 1 met an exclusion criteria. In total, 28 patients with paroxysmal AF were examined for eligibility, however, 14 patients were lost in follow-up. Therefore, 15 subjects with 15 matched controls were included in the analysis (Figure 1). The median time between the pre-PVI TTE and post-PVI TTE was of 124 days (IQR: 98-150 days).

The average age of the subjects was 55 ± 14 years, with 67% being male. For controls, the average age was 54 ± 11 years, with 60% being male. Most subjects had a NYHA functional class of I (73% of subjects and 87% of controls). The matched controls displayed similar clinical characteristics and comorbidities compared to the subjects. The detailed distribution of these characteristics and comorbidities are presented in Table 1.

Echocardiographic Parameters Before and After PVI

Detailed echocardiographic characteristics of patients before and after PVI are presented in Table 2 and Figure 2. In summary, the subjects had an improvement in functional and structural parameters, as evidenced by the echocardiographic variables. However, only LAGS and LASr had a statistically significant improvement (LAGS from 41.81% (±16.27) to 49.14% (±20.50) and

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LASr from 41.51% (±16.08) to 48.92% (±20.49)).

Comparison with Matched Controls

Detailed echocardiographic parameters of controls can be consulted on Table S2. The echocardiographic parameters of controls were as follows: LVEF of 59.45 (±3.02)%, LAVI measured at 19.80 (±6.81) ml, LAGS of 57.67 (±9.34)%, LASr of 57.46 (±9.42)%, LASct of 26.41 (±6.92)%, and LAScd of 31.05 (±8.69)%.

The observed differences between controls and subjects before PVI in LAVI, LAGS, LASr, LASct, and LAScd and between controls were statistically significant (Figure 3). On the contrary, no statistically significant differences were found between control and study subjects after PVI.

Discussion

The role of non-invasive techniques, notably strain echocardiography, has emerged as a pivotal method in analyzing the intricate interactions between atrial function and clinical consequences of AF. However, the gap in understanding the evolution of these mechanics post-intervention, particularly post-PVI, remained conspicuous. This study sought to bridge this gap, lending insights into the transformation of LA contractile function after PVI.

In our cohort, we observed a significant improvement in LAGS and LASr post-PVI. This indicates the PVI's effect in improving LA contractile function in our patient population[11]. Interestingly, the observed improvement brings the post-PVI parameters closer to the matched control group, suggesting a possible partial reversal of atrial dysfunction following treatment.

A surprisingly striking difference of our study with the published literature was the lack of significant improvement in LAVI. Previous studies have observed a significant reduction in atrial volume[12]. This supports the theory of "reverse remodeling," which may contribute to the maintenance of sinus rhythm, thereby preventing the progression of atrial fibrosis[13,14]. Although we observed a decrease in LAVI before and after PVI, it did not reach statistical significance. This may be due to the sample size of our study or due to an extreme value of 95.72 ml of a subject who had a paradoxical increase in size after the PVI. Nevertheless, a decreasing trend was observed in subjects during the follow-up, only partially contradicting what has been observed in the literature.

In contrast, the lack of significant difference in the conduit (LAScd) and contraction (LASct) phases before and after PVI is intriguing. This could be attributed to the nature of AF in our patient group—paroxysmal AF. Previous research has indicated a proportional relationship between the degree of AF and its duration[15–17]. Given that the atrial strain relies on factors like preload and LV function, normal parameters in these areas might explain the lack of observed decrease in strain on these phases[18].

A significant facet of our study lies in further enhancing the potential application

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of LA strain in predicting recurrence post-PVI. Prior studies have indicated that patients prone to AF recurrence post-PVI exhibited lower LA strain prior to the procedure[19–21]. Whilst our study was focused on the dynamics of atrial strain before and after PVI, our findings enrich our understanding of these parameters and highlight the need to clarify the potential role of continuous follow-ups using strain echocardiography post-PVI to assess the risk of AF recurrences.

Limitations

This study suffered from several limitations. First, one of the principal limitations was the sample size. Although significant changes were remarked between LAGS and LASr, with 15 subjects completing the study, the power to detect other subtle changes in atrial function was reduced. The non-significant differences observed between subjects before and after PVI may further clarify with a greater sample size. Having matched controls moderately countered this limitation, as significant differences between the controls and subjects were only observed before PVI. This suggests mechanical function improved in subjects after PVI since the differences with the matched controls were no longer present on the follow-up TTE. Moreover, the attrition rate of the initial patient group led to the exclusion of several patients from the final analysis, potentially introducing bias.

Secondly, the median follow-up duration post-PVI was short. Longer follow-up durations might provide deeper insights into the sustainability of observed improvements in LA function. Additionally, only patients with paroxysmal AF were included. Therefore, the results might not apply to patients with persistent or long-standing AF.

Finally, although inter-vendor variability was eliminated by performing the TTE in a single equipment, strain echocardiography depends on image quality and operator proficiency, adding a layer of unpredicted variability to our results.

Future research should involve multicenter trials with larger patient cohorts to validate these findings and broaden their generalizability. Studies with extended follow-up durations can discern the long-term impacts of PVI on LA function and might reveal changes not evident in the short term. Comparing PVI outcomes with other AF interventions using strain echocardiography would be insightful. Embracing newer echocardiographic technologies or integrating multi-modality imaging can offer more holistic insights into atrial function.

Conclusion

Using strain echocardiography, our study ventured into the understudied field of LA function post-PVI in Mexican patients with AF. These findings, particularly the significant improvement in specific echocardiographic parameters, underscore PVI's potential in rhythm restoration and reverting some of the atrial mechanical dysfunctions associated with AF. On the other hand, it also highlights the potential utility of strain echocardiography in characterizing AF. However, the endeavor to fully comprehend this complex interplay is

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ongoing. With the insights gleaned and acknowledging the study's limitations, we can direct future research to refine our understanding further and, ultimately, patient care in the context of AF.

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TABLES

Table 1. Clinical characteristics and comorbidities between subjects and controls

Characteristic	**Control**, N = 15	**Subjects**, N = 15	**p-value**
Male Sex (%)	9 (60%)	10 (67%)	0.7
Age (years)	54 ± 11	55 ± 14	0.7
Body Mass Index (kg/m2)	27.1 ± 4.1	27.5 ± 5.2	>0.9
Obesity (%)	4 (27%)	5 (33%)	>0.9
Hypertension (%)	4 (27%)	5 (33%)	>0.9
Type 2 Diabetes (%)	2 (13%)	1 (6.7%)	>0.9
Dyslipidemia (%)	2 (13%)	1 (6.7%)	>0.9
Smoker (%)	2 (13%)	5 (33%)	0.4
Hyperuricemia (%)	1 (6.7%)	1 (6.7%)	>0.9
NYHA Functional Class (%)			0.7
I	13 (87%)	11 (73%)	
II	2 (13%)	3 (20%)	
III	0 (0%)	1 (6.7%)	

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Table 2. Selected Echocardiographic Parameters of Subjects Before and After Pulmonary Vein Isolation.

Characteristic	**Pre-PVI**, N = 15	**Post-PVI**, N = 15	**p-value**
LVEF (%)	61.24 (±6.95)	60.48 (±8.62)	0.7
LAVI (ml)	32.17 (±19.75)	26.99 (±19.85)	0.2
LAGS (%)	41.81 (±16.27)	49.14 (±20.50)	**0.048**
LASr (%)	41.51 (±16.08)	48.92 (±20.49)	**0.048**
LASct (%)	17.51 (±8.51)	21.24 (±9.88)	0.2
LAScd (%)	23.86 (±10.19)	27.69 (±15.29)	0.12

Abbreviations. LAGS: Left Atrial Global Strain; LASr: Left Atrial Reservoir Strain; LASct: Left Atrial Contractile Strain; LAScd: Left Atrial Conduct Strain; LAVI: Left Atrial Indexed Volume; LVEF: Left Ventricular Ejection Fraction.

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