A novel, non-invasive, integral imaging assessment in atrial fibrillation by cardiac tomography

Un nuevo método no invasivo en la valoración integral de la fibrilación auricular por tomografía cardíaca

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Abstract

Objective: The objective of the study was to analyze the clinical utility and feasibility of the multidetector cardiac tomography (MDCT) in multi-parametric imaging assessment in atrial fibrillation (AF) patients. **Materials and methods:** This was a prospective case-control study in 84 subjects (54 AF subjects and 30 healthy subjects). Left atrial appendage (LAA) morphology was classified as: cactus, chicken wing, wind sock, and cauliflower. Intra-cardiac thrombus, stroke history, and CHA₂DS₂-VASC scale were compared to cardiac MDCT atrial imaging assessment. **Results:** Left atrial ejection fraction (LAEF) and LAA ejection fraction (LAAEF) were lower in AF subjects ($p < 0.001$), left atrial volume index (LAVI) was higher in AF subjects ($p < 0.001$). An inverse correlation between LAEF and LAVI was found ($r = -0.38$, $p < 0.001$). Cauliflower LAA morphology frequency was higher in AF subjects, whereas cactus LAA morphology frequency was higher in controls. Cauliflower LAA morphology was associated with thrombus presence ($p < 0.01$) as well as a higher CHA₂DS₂-VASC score. Flow velocity was lower in AF subject compared to controls ($p < 0.001$). **Conclusion:** MDCT is a novel, non-invasive, worldwide available method for an integral assessment in AF. Our results could improve precision, clinical utility, and risk stratification analysis in AF. Our proposal is to include this new method into the global cardiovascular and thrombotic risk assessment in AF patients.

Key words: Multidetector cardiac tomography. Atrial fibrillation. Atrial function. Left atrial appendage. Flow velocity.

Resumen

Objetivo: Analizar la utilidad clínica y la viabilidad de la tomografía cardíaca multidetector (TCMD) en la valoración de pacientes con fibrilación auricular (FA). **Material y métodos:** Estudio prospectivo de casos y controles en 84 sujetos (54 con FA y 30 controles). La morfología de la orejuela izquierda (OI) se clasificó en cactus, ala de pollo, manga de viento y coliflor. La presencia de trombo en la OI, el antecedente de accidente cerebrovascular y la escala CHA₂DS₂-VASC se compararon

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con parámetros obtenidos por TCMD. **Resultados:** La fracción de expulsión de la aurícula izquierda (FEAI) y la fracción de expulsión de la orejuela izquierda (FEOI) fueron más bajas en los individuos con FA ($p < 0.001$). El volumen indexado de la aurícula izquierda (VIAI) fue mayor en los pacientes con FA ($p < 0.001$). Se observó una correlación inversa entre la FEAI y el VIAI ($r = -0.38$, $p < 0.001$). La morfología tipo coliflor fue la más frecuente en enfermos con FA, mientras que la de tipo cactus predominó en los controles. La de tipo coliflor fue la más relacionada con presencia de trombos ($p < 0.01$), así como una calificación CHA₂DS₂-VASc alta. La velocidad de flujo fue menor en los pacientes con FA ($p < 0.001$). **Conclusión:** La TCMD es un método novedoso y no invasivo para una valoración integral en la FA. Los resultados de este estudio podrían mejorar la precisión, la utilidad clínica y el análisis de estratificación del riesgo en la FA. Los autores proponen incluir este nuevo método en la valoración integral del riesgo tromboembólico en pacientes con FA.

Palabras clave: Tomografía cardíaca multidetector. Fibrilación auricular. Función auricular. Orejuela izquierda. Velocidad de flujo

Introduction

Atrial fibrillation (AF) is the most common adult cardiac arrhythmia in clinical practice. At present, a global incidence of 1-2% is estimated in the general population, nearly 33.5 million people¹. Around one out of every 5 strokes is due to AF; they are almost always serious and cause long-term disability or death².

The CHA₂DS₂-VASc classification is a tool that is widely used to assess the risk of suffering an embolic episode, and it is essential to identify those patients who benefit from anticoagulant treatment³. Transthoracic echocardiogram constitutes a useful tool and is undoubtedly the basic evaluation technique in with patients AF; however, it has limited capacity for the detection of thrombi in the left atrium (LA) and left atrial appendage (LAA)⁴. Transesophageal echocardiogram (TEE) is the imaging modality most widely used in patients with AF before pulmonary vein ablation procedures or in LAA percutaneous closure⁵. Recently, Nucifora et al. have proposed three-dimensional echocardiography for the assessment of LAA morphology⁶.

Cardiac magnetic resonance imaging (MRI) is an alternative non-invasive imaging modality in cases where TEE is not feasible, but its high cost and low availability difficult its use⁷.

Current advances in cardiac multidetector computed tomography (MDCT) allow high spatial and temporal resolution, with three-dimensional images that enable non-invasive quantitative and multiparametric assessment of the LA and appendage. There are already comparative studies between TEE and MDCT in the identification of intracavitary thrombi, where MDCT showed better diagnostic accuracy. However, no comparison has been made of these two methods in patients with AF⁸. Left atrial volume index (LAVI) and left atrial ejection fraction (LAEF) have already been assessed with MDCT in patients with coronary artery

disease⁹ and in the healthy population¹⁰. Burrell et al. found an increase in LAVI in patients with AF in relation to a control group ($p < 0.001$). In addition, they pointed out that, in the presence of AF, there is LAA contractility and function decrease that manifests itself as a decrease in LAA flow and dilatation velocities¹¹. Mügge et al. demonstrated that there is a correlation between LAA ejection fraction (LAAEF) decrease and thrombus formation on TEE in patients with AF¹². Di Biase et al. classified LAA morphology in four categories: "chicken wing," which is the most common in the healthy population (48%), followed by "cactus" (30%), "windsock" (19%), and "cauliflower" (3%)¹³. Bosi et al. demonstrated, in anatomical models *in vitro*, that LAA morphology is related to blood flow hemodynamics and suggested that the lower the flow velocity, the higher the possibility of thrombotic episodes. These specialists found that the "cauliflower" morphology has the lowest flow velocity and that the "windsock" type is related to a higher flow velocity¹⁴.

At present, the most widely used method to quantify LAA flow velocity is TEE, although this method is invasive and entails certain complications. Yasuoka et al. conducted a study where they correlated TEE- and MDCT-obtained LAA flow velocity and found a good correlation between both methods¹⁵. A recent meta-analysis that included 19 studies with 2,955 patients showed a sensitivity of 96%, specificity of 92%, and a robust negative predictive value of MDCT for the detection thrombi (96-100%)¹⁶. Wu et al. proposed that patients without evidence of thrombi on MDCT do not require TEE for confirmation¹⁷. Furthermore, MDCT has recently been shown to be superior to transthoracic and transesophageal echocardiography for the assessment of LA size, an important predictor of AF recurrence¹⁸.

MDCT enables full assessment in patients with AF; so far, there are no studies simultaneously evaluating LAEF, LAAEF, LA volume index and LAA, LAA morphology, LAA flow velocity, and presence of thrombus

Figure 1. Multidetector computed tomography cardiac parameters. **A:** Left atrial (LA) volume index. **B:** Left atrial appendage (LAA) flow velocity in a patient of the control group. **C:** LAA thrombus three-dimensional reconstruction. **D:** LAA thrombus (arrow). **E:** LAA flow velocity in a patient of the atrial fibrillation group. **F:** LA aneurysm three-dimensional reconstruction. Three-dimensional reconstruction of LAA different types of morphology: 1) cauliflower, 2) windsock, 3) cactus, and 4) chicken wing.

in LAA by MDCT. This multiparametric assessment offers more information to the doctor for optimizing treatment and allows thromboembolism risk re-stratification in patients with AF, which could modify these patients' quality of life and prognosis. This study will open new horizons in the research related to this topic, since medical publications are scarce and it is foreseeable that it will serve as a reference for future research.

Materials and Methods

This was a prospective study carried out between March 1, 2018, and April 1, 2019, at Hospital General "Dr. Miguel Silva" in the city of Morelia, Michoacán, Mexico. The study received approval from the ethics committee with registration number Conbioética-16-CEI-004-20161212, and included a total of 84 patients. Out of them, 54 had been diagnosed with AF and 30 constituted the control group. The latter group was made up of patients who underwent MDCT for clinical suspicion of ischemic heart disease and did not suffer from AF; these controls had some risk factor (high blood pressure (HBP), diabetes mellitus (DM), dyslipidemia, smoking, alcoholism, or obesity).

Both groups were matched by age and gender. All patients were evaluated using the CHA₂DS₂-VASc scale to calculate thromboembolic risk. Weight and height were included to calculate body mass index (BMI), as well as other clinical variables such as smoking, alcoholism, HBP, DM, dyslipidemia, and a history of cerebrovascular event or transient ischemic attack

(CVE/TIA). Patients with valvular heart disease, cardiomyopathies, congenital diseases, autoimmune diseases, kidney failure, or allergy to contrast medium were excluded from the study. All patients underwent MDCT to obtain the images described by Gweon et al.¹⁹ Thirty-two and 64-slice CT scanners (General Electric) were used and contrast medium (Iopamiron® 370) was administered. Beta-blocker with metoprolol was orally administered before the test with the purpose to achieve a heart rate of 60 beats/min. LA and LAA three-dimensional structures were reconstructed with the volume rendering processing technique to assess LA and LAA volume index and expulsion fraction. LA and LAA flow velocity and volume variables were calculated, as well as the presence of thrombi. LAA morphology was evaluated in multiplanar reconstructions and classified by two cardiac imaging experts, who were blinded to patient clinical data.

A cardiovascular imaging specialist performed the analysis of the obtained images using a GE workstation (CardiolQ Express, version 8; General Electric Medical Systems). To determine LAA flow velocity, a two-dimensional image of said structure was obtained and, subsequently, two different points were determined in the LAA (distal and proximal) (Fig. 1B and E); the proximal point was obtained at the center of the LAA orifice, while the distal point was the 7/8 point of a straight line drawn from the flexion point of LAA posterior wall to LAA most anterior distal point. Once both these values were obtained, the ratio of the distal point to the proximal point was calculated, and the result was a ratio in Hounsfield units. Yasuoka previously described and

approved this method¹⁵, LAA morphology was evaluated according to the Di Biase classification¹³, and LAA volume index was calculated based on the LAA maximum and minimum volumes that were determined with the volume rendering processing technique. LAAEF was calculated with the following formula: $EF = (V_{max} - V_{min})/V_{max}$, based on the Boucebci method²⁰.

Statistical analysis

A one-way analysis of variance or Kruskal–Wallis H-test with Dunn *post hoc* was used for continuous variables, such as age, weight, body mass index, and all radiological quantitative characteristics grouped by type of LAA, both in the AF group and in controls; statistical contrast of averages was applied between AF and controls and, within the AF group, between both AF subgroups (paroxysmal vs. permanent), with one- and two-tailed Student's t-test, respectively; the linear correlation coefficient product of Pearson's moment was analyzed for both groups together with LAA flow velocity with respect to the other quantitative variables, and the Chi-square test or Fisher's exact F test were applied for the contrast of frequencies in 2 × 2 Latin square; in all cases, the statistically significant likelihood of alpha error was < 0.05, according to the Sigmaplot 12.5 (CR) 2003-2013 program.

Results

Eighty-four individuals were analyzed, 54 of them with AF: 21 (38.9%) with paroxysmal AF and 33 (61.1%) with permanent AF. Mean age in the AF group was 67 ± 14 years and 55.6% corresponded to males. Table 1 describes both groups' clinical characteristics. An inverse correlation was found between LAEF and age ($r = -0.43$, $p < 0.001$), as well as with LAAEF ($r = -0.33$, $p < 0.001$).

Cauliflower-type morphology was the most common in the AF group (33.3%), while cactus type predominated in the controls (37%). In the LAVI and LAEF analysis, significant differences were found between both groups ($p < 0.001$), and differences with LAAEF and LAA flow velocity were also documented between cases and controls ($p < 0.001$).

The parameters evaluated by MDCT are presented in table 2. LAA flow velocity was lower in the AF group with regard to the control group (0.34 ± 0.16 cm/s vs. 0.87 ± 0.08 cm/s) ($p < 0.001$). In patients with AF, LAA flow velocity was slower in those who had an LAA thrombus, but no statistical difference was found with

Table 1. Control and atrial fibrillation groups clinical characteristics

	Control group (n = 30)	AF group (n = 54)	p
Age (years)	54.83 ± 15	67.43 ± 14	< 0.001
Male gender	53.3%	55.6%	N/S
BMI	27.9 ± 5	28 ± 5	N/S
High blood pressure	43.3%	46.3%	N/S
Dyslipidemia	23.3%	24.1%	N/S
Diabetes mellitus	6.7%	25.9%	< 0.001
Smoking	36.7%	31.5%	N/S
Alcoholism	23.3%	22.2%	N/S
History of CVE/TIA	0%	33.3%	< 0.001
Anticoagulation	0%	42.6%	< 0.001
Antiplatelet aggregation	0%	53.7%	< 0.001
Type of AF Paroxysmal AF Permanent AF		38.9% 61.1%	
CHADS2 scale		1.7 ± 1.2	
CHA2DS2-VASc scale		2.8 ± 1.7	

BMI: Body Mass Index; CVE: cerebrovascular episode; TIA: transient ischemic attack; AF: atrial fibrillation.

regard to those who did not suffer thrombus (0.32 ± 0.14 vs. 0.35 ± 0.17 cm/s; $p = \text{NS}$) (Fig. 2).

The AF group analysis found that LAVI was higher in patients who had LAA thrombus in comparison with those who did not (82 ± 32.7 vs. 48.3 ± 14.9 ml/m², respectively; $p < 0.001$). LAEF was lower in those who showed LAA thrombus versus individuals who did not (14.1 ± 7.9 vs. $23.6 \pm 11.8\%$; $p < 0.001$); the same results were obtained for LAAEF (11.6 ± 6.2 vs. $18.2 \pm 9\%$; $p = 0.002$) (Fig. 3).

Some important differences in LAA morphology were identified in the AF group; the cauliflower-type morphology was the most common in patients in whom LAA thrombus was detected ($p \leq 0.01$); subsequently, the cauliflower-type morphology was compared with forms other than this in patients with LAA thrombus, and 5.9 versus 7.4% ($p < 0.001$); OR, 4.7; and 95% CI, 1.7-12.4, respectively, were observed. The windsock-type morphology was associated with absence of thrombus ($p < 0.05$) (Fig. 4). A high versus low to moderate CHA₂DS₂-VASc score was compared regarding the

Figure 2. A: Left atrial appendage (LAA) flow velocity in subjects with atrial fibrillation (AF) in comparison with controls. B: LAA flow velocity in patients with AF with and without thrombus. AF group versus control group ($p < 0.01$; Student's t-test).

Table 2. Variables on cardiac multidetector computed tomography

	Control group (n = 30)	AF group (n = 54)	p
Calcium score (AU)	10.8 ± 24	59.26 ± 142	N/S
LAVI (mL/m ²)	40.3 ± 9	67.3 ± 27.4	< 0.001
LA Vol _{max} (mL)	75.2 ± 20	116.4 ± 49	< 0.001
LA Vol _{min} (mL)	53.4 ± 19.3	96.6 ± 42.8	< 0.001
LAEF (%)	29.8 ± 12.5	16.2 ± 7.7	< 0.001
LAA Vol _{max} (mL)	10.8 ± 4.4	12.6 ± 5.7	N/S
LAA Vol _{min} (mL)	8.5 ± 3.7	11 ± 5.4	< 0.001
LAAEF (%)	21.1 ± 9	13.87 ± 7.7	< 0.001
LAAEFV (HU ratio) >	0.72 ± 0.20	0.34 ± 0.16	< 0.001
LAA morphology			N/S
Cauliflower	20.0%	33.3%	
Windsock	26.7%	27.8%	
Chicken wing	16.7%	16.7%	
Cactus	37%	22.2%	
Thrombus (%)	0%	42.5%	< 0.001

LAVI, left atrial volume index; LA Vol_{max}: left atrial maximum volume; LA Vol_{min}: left atrial minimum volume; LAEF: left atrial ejection fraction; LAA Vol_{max}: left atrial appendage maximum volume; LAA Vol_{min}: left atrial appendage minimum volume; LAAEF: left atrial appendage ejection fraction; LAAEFV: left atrial appendage flow velocity.

presence of LAA thrombus, with thrombus being found in 16.7 versus 9.3% ($p = 0.056$); OR, 2.4; 95% CI, 0.93-6.2, respectively.

In the AF group, 23 patients (42.6%) received anticoagulant treatment. Of these individuals, 10 (43.5%) had LAA thrombus, while among those who were not anticoagulated, 13 (41.9%) had LAA thrombus ($p < 0.01$).

Discussion

At present, TTE and TEE are the most commonly used imaging modalities for risk stratification assessment in patients with AF; however, the latter is an invasive method that entails potential risks²⁰. TEE is considered the reference standard² for thrombi identification in AF. MDCT is a non-invasive method that allows multi-parametric assessment in patients with AF; however, its role is not well defined, as there are few studies about it and, to date, no publication has comprehensively evaluated patients with AF using MDCT. In this study population, a total of 84 patients were included, and AF patients mean age was 67 years versus 55 years in the control group. Despite not having the same sample number for both groups, this parameter was significant ($p < 0.001$) and agrees with publications where AF average age is around the seventh decade of life. This is important, because there is an increase in AF as age advances²¹. Baseline characteristics between both groups of this study population (smoking, alcoholism, HBP, and dyslipidemia) showed no significant differences.

As for the treatment of patients with AF, only 42.6% (23 patients) were identified to be on anticoagulant

Figure 3. Differences between left atrial volume index and left atrial and left atrial appendage ejection fractions in patients with and without thrombus (Student's t-test).

Figure 4. Comparison between left atrial appendage different morphology types and the CHA₂DS₂-VASc scale.

treatment, while 53.7% (29 patients) were taking platelet aggregation inhibitors. This probably was due to

the fact that a large percentage of these patients attended the outpatient cardiology clinic for the 1st time,

where diagnosis was established and treatment was started. LA dilation is a marker of adverse cardiovascular events, such as stroke, heart failure, or even death. Pavón et al. mention that LAVI should be a systematic measure of atrial growth assessment due to its high sensitivity and specificity. In addition, it reflects an elevation of left ventricular filling pressure and is therefore an important predictor of poor prognosis in patients with AF²². In this study, the authors found that LAVI was markedly higher in the AF population with regard to the control group, even though controls also recorded altered LAVI values ($40.3 \pm 9 \text{ ml/m}^2$; $p < 0.001$). This is important, since AF causes atrial growth *per se*, which favors an increase in filling pressure and thereby a self-perpetuating cycle of arrhythmia is established. Consequently, restoring sinus rhythm prevents and reverses atrial dilatation in these patients, by normalizing filling pressures and cardiac output, which improves patient prognosis²². As for LAA morphology, no significant differences between both groups were identified in this study, probably due to the small size of the sample. However, the “cauliflower” morphology was observed to be the most closely related to the presence of LAA thrombi. The “windsock” and “chicken wing” types were found to be the least associated with the presence of thrombi. These results are consistent with those of Bosi et al., who found that “cauliflower”-type LAA had a lower flow velocity than the rest of morphologies and, although this is a study in anatomical models, it provides an important analysis on thrombogenesis pathophysiology in LAA¹⁴. In patients with AF, a marked decrease in LAA flow velocity was identified versus controls ($p < 0.001$). This can be explained by the anatomical differences of each appendage (angles of the main lobes relative to the ostium, number of trabeculations, and number of lobes). The “chicken wing” shape reveals an obtuse angle that allows higher flow velocity (faster emptying); some studies have described that it is the least related to the presence of thrombi. “Cauliflower”-type LAAs have an acute angle with regard to the ostium, which makes its emptying difficult and, therefore, this shape is most times associated with thrombi formation²³. As for LA and LAAEF in the general population, an inverse correlation has been demonstrated (the older the age, the lower the ejection fraction); Handke et al.²⁴ found similar results. In this study, ejection fraction was observed to be lower in the AF group in comparison with controls ($p < 0.001$) and, within the AF group, ejection fraction was lower when there were LAA thrombi ($p < 0.001$); this can

considered a poorer prognosis criterion in this group of patients. Another analyzed clinical variable was the CHA₂DS₂-VASc scale assessment, where a high value was identified to predominate in the population with AF, and the type that was associated with this parameter was that of “cauliflower.” Furthermore, in the AF group, 18 patients had a history of a vascular event (CVE or TIA). In in this subgroup of patients, the “cauliflower” type predominated over the others, which once again supports the theory that this atrial appendage morphology is the most thrombogenic.

The main limitation of the study is the same that has been faced by most authors who have published on this subject, that is, sample size. Nevertheless, in this preliminary investigation, the authors recorded significant results. One of the advantages for the performance of this study was the integration of a multidisciplinary team made up by clinical cardiologists, cardiovascular imaging specialists, and radiologists.

At present, TEE is carried to rule out the presence of thrombi in LAA before invasive AF procedures for therapeutic purposes, such as LAA occlusion or ablation of the pulmonary veins; however, it is important mentioning that this method is invasive and there is risk of potential complications with the procedure, in addition to a higher cost in comparison with MDCT²⁰. MDCT is a non-invasive method that is currently used. Some disadvantages of this method in relation to the others include costs, use of contrast medium and exposure to radiation. Nevertheless, MDCT has in its favor a better spatial and temporary resolution in comparison with other methods, which is important in this study for the correct determination of atrial appendage morphology. Moreover, with the new CT scanners, the radiation dose is increasingly lower (3-8 mSv)²⁵.

This study shows that patients with AF may require, along with a clinical evaluation with the CHA₂DS₂-VASc scale, electrocardiogram, Holter monitoring and echocardiogram, plus a MDTC, since it is possible for information such as LAA morphology, atrial function, and LAA parameters to be obtained, as well as flow velocity, which appear to play an important role in LAA thrombogenesis. After these parameters are obtained through this method, selecting the most convenient treatment for each patient is possible, which results in an important and novel application, and selection of patients that are suitable for LAA occlusion.

This study descriptively details the findings with regard to MDCT, and determining its sensitivity, specificity, and false and negative positive rate was not possible given that it was not compared with the current

reference standard, that is, TEE. It is important for these methods to be compared in future investigations and these parameters to be determined, since publications on this subject are scarce.

Conclusions

MDCT is a non-invasive method that allows a comprehensive, useful, and accurate assessment for thromboembolic risk re-stratification in patients with AF, and provides relevant information to make decisions in the treatment and prognosis of patients with AF. This protocol should be implemented in the approach to the study of patients with AF.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures that were followed adhered to the ethical standards of the responsible committee for experimentation in human beings and were in agreement with the World Medical Association and the Declaration of Helsinki.

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

Right to privacy and informed consent. The authors have obtained informed consent from the patients or subjects referred to in the article. This document is in the possession of the corresponding author.

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