Long-term effectiveness of the Cox-maze III procedure and its relationship with left atrial postoperative size

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Abstract

Introduction: The Cox-maze III procedure is designed to eliminate atrial fibrillation (AF). **Objective:** To determine the relationship of left atrial (LA) postoperative size after undergoing the Cox-maze III procedure. **Method:** From July 2012 to April 2016, 50 patients with primary mitral valve disease and concomitant AF were operated on. A "cut-and-sew" cox-maze III procedure with a full biatrial lesion pattern was used. AF preoperative duration was 3.5 ± 2.1 years. **Results:** There was no operative mortality. Freedom from AF was 92%, 88% and 73.7% at three months and at one and 3 years, respectively. A direct relationship was found between LA postoperative size and the probability of Cox-maze failure when LA is > 6.5 cm at one year (relative risk [RR] = 10.5; 95% confidence interval [CI]: 4.30-26.67, $p < 0.0001$) and at 3 years (RR = 27.1; 95% CI: 3.87-189.86, $p = 0.0009$). LA size decreased from 7.1 ± 0.5 cm to 6.2 ± 0.5 cm ($p < 0.0001$). **Conclusions:** The Cox-maze III procedure is efficacious for eliminating mitral valve disease-associated AF when LA postoperative size is ≤ 6.5 cm.

KEY WORDS: Atrium. Arrhythmia. Atrial fibrillation. Maze procedure. Mitral valve.

Efectividad del procedimiento de Cox-maze III a largo plazo y su relación con el tamaño posoperatorio de la aurícula izquierda

Resumen

Introducción: El procedimiento de Cox-maze III está diseñado para eliminar la fibrilación auricular. **Objetivo:** Determinar la relación del tamaño posoperatorio de aurículas izquierdas en las que se realizó procedimiento de Cox-maze III. **Método:** De julio de 2012 a abril de 2016 se operó a 50 pacientes con enfermedad mitral primaria y fibrilación auricular concomitante. Se utilizó Cox-maze III mediante "corte y sutura" biatrial completo. La duración preoperatoria de la fibrilación auricular fue de 3.5 ± 2.1 años. **Resultados:** No hubo mortalidad operatoria. La ausencia de fibrilación auricular fue de 92, 88 y 73.7 % a tres meses, uno y tres años. Se encontró relación directa entre el tamaño posoperatorio de la aurícula izquierda y la probabilidad de falla del Cox-maze cuando la aurícula izquierda fue > 6.5 cm a un año (RR = 10.5, IC 95 % = 4.30-26.67, $p < 0.0001$) y a tres años (RR = 27.1, IC 95 % = 3.87-189.86, $p = 0.0009$). El tamaño de la aurícula izquierda disminuyó de 7.1 ± 0.5 cm a 6.2 ± 0.5 cm ($p < 0.0001$). **Conclusiones:** El Cox-maze III es eficaz para eliminar la fibrilación auricular asociada con enfermedad mitral cuando el tamaño posoperatorio de la aurícula izquierda es ≤ 6.5 cm.

PALABRAS CLAVE: Aurícula. Arritmia. Fibrilación auricular. Procedimiento de maze. Válvula mitral.

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Introduction

The Cox-maze procedure has been designed to eliminate atrial fibrillation (AF) or flutter. It is based on the concept of creating a “maze” or path for the electrical impulse, from the sinus node until reaching the atrio-ventricular node, crossing the entire atrial myocardium.¹ With time, surgical incisions to create the maze were replaced by ablation lines using alternative energy; bipolar radiofrequency and cryoablation are the only techniques of unquestionable efficacy to achieve definitive transmural lesions on atrial tissue.² As a general rule, the more complete the maze lesion pattern (the higher the number of incisions or ablation lines), the higher the success rate for freedom from AF.³

Cox-maze complexity has been rated at 9.5 and its adaptability at 0.5, both on a 0-to-10 scale, which means that although it is a safe (operative mortality < 1 %) and effective operation (> 90 %), it has had little impact on total number of treated patients.¹ Therefore, Cox-maze is currently mainly performed with the easier, faster and safer IV modality.⁴ However, Cox-maze III continues to be superior to Cox-maze IV for AF or any other atrial tachyarrhythmia.⁵

The purpose of this article is to present long-term results of the Cox-maze III procedure using the “cut-and-sew” technique to eliminate AF in a series of patients with concomitant rheumatic mitral valve disease. At the same time, the relationship between AF recurrence after Cox-maze and left atrium (LA) post-operative size has been determined.

Method

Ambispective study, where all patients operated in a hospital center are analyzed. The study period was comprised between July 2012 and April 2016. Fifty patients were operated, who concomitantly underwent primary mitral surgery and a Cox-maze III procedure. All patients signed the respective informed consent form prior to surgery. Preoperative demographic characteristics are shown in Table 1.

Data were collected from medical records and patient assessment in the outpatient clinic at different study time-points. Follow-up duration was 4.37 ± 1.1 years (range 2.6 to 6.4 years).

Success was defined according to the criteria described in the Heart Rhythm Society clinical guidelines as sinus rhythm without the use of class I/III antiarrhythmic medications or catheter ablations,⁶

Table 1. Preoperative demographic variables in 50 patients who underwent Cox-maze III (cut-and-sew)

Variable	Median $\pm$ SD	
Age (years)	56.5 $\pm$ 8.3	
Preoperative AF duration (years)	3.5 $\pm$ 2.1	
Preoperative AF size (cm)*	7.1 $\pm$ 0.5	
Preoperative stroke	6 (12 %)	
Tricuspid regurgitation grade	1.4 $\pm$ 1.2	
Pulmonary artery systolic pressure (mmHg)	53.8 $\pm$ 14	
Left ventricular ejection fraction (%)	50.1 $\pm$ 5.4	
	n	%
Gender (female)	34	68
Etiology		
Rheumatic	44	88
Degenerative	06	12
Type of mitral lesion		
Double mitral lesion (stenosis and regurgitation)	44	88
Pure mitral regurgitation	6	12
Other simultaneous diagnoses		
Severe tricuspid regurgitation	6	
Double tricuspid lesion	1	
Double aortic lesion	1	
Ischemic heart disease	1	
Concomitant AF	50	100

*Longest diameter measured by transthoracic echocardiography.
SD = standard deviation, AF = atrial fibrillation.

identified by 12-lead standard electrocardiogram in the office. Only if there was any evidence of AF or any other cardiac arrhythmia, the patient was referred for 24-hour Holter electrocardiographic monitoring. Thus, follow-up for heart rate data was available in 100 % of eligible patients at three and six months post-surgery, in 94 % at one year, in 90 % at two years, in 81.2 % at three years, in 88.9 % at four years and in 81.3 % at five years. There were five patients lost to follow-up, reported as censored, and four late deaths not related to the primary procedure. All these patients were excluded from the study. In this study, quality of life or LA transport function were not investigated due to lack of data in the collection from medical records.

All patients underwent a classic Cox-maze III procedure with standard “cut-and-sew” method, following a full biauricular lesion pattern. In all, the surgery was performed as part of a mitral procedure in a comprehensive way through the classic open heart surgery

approach by longitudinal sternotomy and under cardiopulmonary bypass. All 50 patients were operated using the Mexican modification for the Cox-maze III procedure, described by García-Villarreal,⁷ or any of its variants for cases of difficult access to the LA.⁸ It is important noting that, since 2015, we modified the lesion pattern on the right atrium:⁹ only one counter-lesion is used on the tricuspid ring in the position that corresponds to two o'clock in the hands of the clock, while another T-incision is made from the transverse incision in the right atrium, 1.5 to 2.5 cm outside the right atrioventricular groove and it is prolonged until reaching the tip of the right appendage. In no case was there any cryoablation lesion used on the external face of the coronary sinus on the line of the mitral isthmus, given that this alternative energy source was not available. In all cases, complete resection of the left appendage was performed, by sectioning at its base 1.5 cm above the outer surface of the heart. Resection was performed outside the heart and 3/0 polypropylene continuous double suture was used to close the stump.^{7,8}

Medication

FROM SURGERY UNTIL FIRST THREE MONTHS

Basically, amiodarone or metoprolol, warfarin, furosemide and spironolactone were used. Unless there was any formal contraindication, in all cases was amiodarone started: first, immediately before aortic de-clamping under cardiopulmonary bypass, a 300 mg bolus was intravenously administered, diluted and slowly for several minutes, followed by a 24-hour 900 mg intravenous infusion. At its conclusion, 200 mg were orally administered every eight hours for three days, then 200 mg orally every 12 hours for three days and, finally, 200 mg in a single dose per day during the first three months after surgery.

In patients with allergy or intolerance to amiodarone, metoprolol was orally administered at a rate of 100 mg every 12 hours. In case of hypotension or excessive bradycardia, the dose was reduced to 50 mg every 12 hours. This regimen was maintained for the first three months after surgery. As for anticoagulant, 1000 IU per hour of intravenous unfractionated heparin was initiated. Subsequently, once the thoracic drainage tubes were removed, heparin was replaced by warfarin, with INR ranges between 2.0 and 3.5 for at least four months after surgery. In addition, given

that in all cases was the left appendage resected, double diuretic therapy based on 20 mg of intravenous furosemide was administered every six to eight hours in the immediate postoperative period, then shifting to 40 mg orally every 24 hours in combination with 25 mg of oral spironolactone every 12 hours. This regimen was maintained for the first month, with spironolactone then being discontinued and furosemide being maintained for the first three postoperative months.

AFTER THE THIRD POSTOPERATIVE MONTH

After the first examination to corroborate heart rate by 24-hour Holter monitoring or electrocardiogram in the office at the end of the third postoperative month, if the patient was free of AF or any other atrial tachyarrhythmia, the antiarrhythmic drug was discontinued, with only warfarin being maintained. At the fourth postoperative month, a 12-lead standard electrocardiogram was performed to corroborate the absence of AF or flutter. If the patient remained free of AF or flutter, warfarin was then discontinued, in the absence of any other formal indication for its use (mechanical prosthesis, giant LA). Furosemide was usually discontinued after the four postoperative month. Cardioversion therapy was not systematically included during the first three months because it is not common having this resource systematically.

Statistical analysis

Continuous data are presented as the mean $\pm$ standard deviation and categorical data, as percentage frequencies. A p-value < 0.05 obtained by a two-tailed test was considered to be statistically significant. Data analysis was carried out with the Xlstat program (Addinsoft SARL) for Microsoft Excel®. For the univariate analysis, Student's t-test was used, and for continuous variables, Mann-Whitney's U-test; for categorical variables, Fisher's exact test was used.

Results

There was no operative mortality. Four late deaths were reported during long-term follow-up, out of which two were accidental, one pneumonia and one due to end-stage heart failure. The incidence of definitive pacemaker placement was one single case (2 %). Intraoperative variables are presented in Table 2.

Table 2. Intraoperative variables in 50 patients who underwent Cox-maze III (cut-and-sew)

Variable	Median±SD	
Intensive care unit stay (days)	2.9 ± 0.7	
In-hospital stay (days)	9.3 ± 1.9	
Cardiopulmonary bypass time (minutes)	142.6 ± 21.2	
Aortic clamping time (minutes)	116.8 ± 19.2	
	n	%
Full biauricular maze pattern	50	100
Type of mitral procedure		
Mitral biological prosthesis	43	86
27 mm	10	
29 mm	23	
31 mm	10	
Mitral mechanical prosthesis	3	6
27 mm	2	
29 mm	1	
Mitral valve repair	4	8
Quadrangular resection + annuloplasty with ring	3	
Chordae replacement + annuloplasty with ring	1	
Type of secondary concomitant procedure		
Tricuspid valve repair with ring	6	
Coronary artery bypass graft	1	
Aortic biological prosthesis	1	
Reoperation for bleeding	2	4
Operative mortality	0	0
Thrombi in left atrium	6	12
Thrombi in left appendage	14	28
Left appendage morphology		
Cactus	21	42
Chicken wing	17	34
Windsock	7	14
Cauliflower	5	10

Heart rate analysis progressively in time, as well as its linear trends are represented in Figure 1. In the early stage, during the hospital stay phase, 16 patients (32 %) had some type of supraventricular rhythm disorder different from normal sinus rhythm. Out of them, only two (4 % of total) remained with AF during follow-up, one (2 %) remained with complete heart block and two more (4 %) remained in junctional rhythm. The rest returned to sinus rhythm 8.1 ± 1.7 days after surgery. In the long-term follow-up, freedom from AF was present in 92, 90, 88, 86 and 73.7 % at three and six months and at one, two and three years, respectively. At five years, the probability to continue with normal sinus rhythm was 70 %. In no case was cryoablation applied on the coronary sinus due to lack of such resource during the period comprised by this study.

Table 3. Relative risk for atrial fibrillation after Cox-maze, according to left atrial size

Study period (years)	Left atrial size (cm)	Relative risk	95% CI	p
3 months	≤ 6.5	0.116	0.0083-1.61	0.1088
	> 6.5	7.667	3.630-16.16	< 0.0001*
1 year	≤ 6.5	0.093	0.0065-1.30	0.0797
	> 6.5	10.500	4.130-26.67	< 0.0001*
3 years	≤ 6.5	0.1292	0.020-0.8089	0.0288
	> 6.5	27.125	3.87-189.86	0.0009*
5 years	≤ 6.5	0.500	0.125-1.999	0.3270
	> 6.5	12.000	0.634-226.99	0.0976

*p < 0.001

Eliminating the four cases of late mortality and five more that were lost to follow-up, at the last and most recent cutoff point of this study, with a median of 4.21 years (range, 2.65 to 6.24 years), follow-up was fully complied with in 41 cases (82 %), out of which 30 (73.1 %) were AF-free in normal sinus rhythm and 12 cases (24.4 %) continued taking some type of antiarrhythmic medication.

When the relationship of postoperative LA size and the possibility of developing AF within a variable period of time was analyzed, we found that the critical value from which that possibility alarmingly rose for all time cutoffs was 6.5 cm for LA longest diameter obtained by transthoracic echocardiography (Fig. 2). Relative risk was 7.6 (95 % CI = 3.630-16.16, p < 0.0001) for three months, 10.5 (95 % CI = 4.130-26.67, p < 0.0001) for one year, 27.1 (95 % CI = 3.87-189.86, p = 0.0009) for three years and 12 (95 % CI = 0.634-226.99, p = 0.0976) for five years (Table 3). This indicates a clear tendency towards AF recurrence when postoperative LA diameter is > 6.5 cm. Regarding LA preoperative and postoperative size, the association between the two independent means (7.1 ± 0.5 versus 6.2 ± 0.5 cm) indicates that a p-value < 0.0001 is statistically significant.

No patient had embolism at any time during follow-up.

Discussion

As for conversion to sinus rhythm with the Cox-maze III procedure, Cox et al.¹⁰ described an effectiveness rate higher than 90 % in the long term. In a

Figure 1. Heart rate after Cox-maze III. Black bars represent cases free from fibrillation or any atrial tachyarrhythmia; the weave-pattern bars, atrial fibrillation. The vertical axis indicates the percentage of cases involved.

Figure 2. Heart rate after the Cox-maze III procedure, according to left atrial size. The solid line represents the cases free from atrial fibrillation with a postoperative left atrial diameter > 6.5 cm. The discontinuous line represents the cases free from atrial fibrillation with a postoperative left atrial size > 6.5 cm.

meta-analysis, Chen et al.¹¹ reported a rate of sinus rhythm recovery of 74.6 % versus 18.4 % at five years ($p < 0.0001$) in favor of using the Cox-maze procedure. In our series, we found that 92, 90, 88, 86 and 73.7 % patients were free from AF at three and six months, one year, two years and three years respectively, with a probability trend line of up to 70 % at five years. Even the results of 88 % show be above the minimum

recommended standard of 70 % for freedom from AF after Cox-Maze at one year of follow-up²

As noted by García-Villarreal¹³ and by Ad,¹² the success of the Cox-maze procedure to eliminate AF largely depends on the correct application of the original concept concerning the full biatrial lesion pattern. As a general rule, the more complete the Cox-Maze lesion pattern, the higher the success rate to eliminate

AF.³ We applied the original Cox-Maze III incision pattern in its full biauricular modality to all 50 cases of the series.

We have found that there is a direct relationship between the appearance of AF in the postoperative period and LA postoperative size > 6.5 cm in its longest diameter, measured by transthoracic echocardiography. When the size is > 6.5 cm, the relative risk for developing AF is 7.6 and 10.5 at three months and one year, with a p-value < 0.0001 for both cases. This fact is closely related to the argument of the “critical mass” necessary to develop AF. There is a direct relationship between the amount of “continuous” atrial tissue available for fibrillation and the possibility to develop AF.¹³

The Cox-maze III procedure carried out using the “cut-and-sew” technique has the particularity of exerting a reductive effect on both atria total size, mainly on LA. When preoperative and postoperative LA sizes were compared in all 50 patients, there was a significant reduction in LA final size (7.1 ± 0.5 versus 6.2 ± 0.5 cm, $p < 0.0001$) in the immediate postoperative period (from the transoperative period to postoperative day 10).

Until this report, no study had focused specifically on LA postoperative size as a risk factor for developing AF after the Cox-Maze procedure. We found that the inflection point is 6.5 cm.

Left atrial reduction¹⁴ has been proposed under the premise of critical mass elimination and decrease.¹³ Due to the large diversity of techniques to perform left atrial reduction, currently there is only weak evidence in favor of left atrial reduction added to the Cox-Maze procedure in patients with large LA. In no case did we perform left atrial reduction in this series of patients undergoing a Cox-Maze III procedure by “cut-and-sew”. It is probable that the set of multiple suture lines on the LA may have an additive reductive effect on this anatomical structure’s final size. In our series, the relationship between LA preoperative and postoperative size (7.1 ± 0.5 versus 6.2 ± 0.5 cm) had a p-value < 0.0001. We have only observed the reductive effect in cases of Cox-Maze III with “cut-and-sew”.

Since we never had that resource, we did not use cryoablation on the external face of the coronary sinus at its intersection with Cox-maze mitral line. Cox et al.¹⁵ have described that the lack of cryoablation application in this specific area can cause 15 to 20 % failure after Cox-maze. It is highly likely that the lack of cryoablation use in our cases might explain the recurrence rate of about 24 % at five years.

In conclusion, we can claim that the Cox-maze III procedure by means of “cut-and-sew” is highly effective to eliminate AF in patients with concomitant mitral disease, especially when LA postoperative size is ≤ 6.5 cm in diameter.

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