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Mid-term results of cardiac autotransplantation as method to treat permanent atrial fibrillation and mitral disease☆

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Abstract

Objectives: The results of current surgical options for the treatment of permanent atrial fibrillation (AF) associated with mitral surgery are widely different, particularly in very enlarged left atria. The aim of this study was to assess the mid-term efficacy of cardiac autotransplantation for this goal, through a consistent reduction of left atrium volume and a complete isolation of the pulmonary veins. **Methods**: From April 2000 to September 2002, 30 patients (male/female 5/25) underwent cardiac autotransplantation for the treatment of mitral valve disease and concomitant permanent AF (>1 year). Surgical technique of bicaval heart transplantation was modified maintaining the connection of inferior vena cava in all but three cases. Twenty-eight patients had mitral valve replacement and two had mitral valve repair. Associated procedures were: aortic valve replacement (6 cases), tricuspid valve repair (2 cases), coronary re-vascularization (2 cases) and right atrium volume reduction (4 cases). **Results**: No hospital death occurred; 1 patient died 3 months post-operatively for pneumonia. At a mean follow-up of 21.1 ± 7.7 months (range 6–35), 26 patients (89.7%) were in sinus rhythm and 3 (10.3%) in AF. Santa Cruz Score was 0 in 3 patients, 2 in 2 patients and 4 in the remaining 24 patients (82.7%). Mean left atrial diameter and volume decreased from 65.1 ± 16.4 mm (range 50–130 mm) to 49.9 ± 8.4 mm (range 37–78) ($P < 0.001$) and from 118.3 ± 68.4 ml (range 60–426) to 69.4 ± 34.1 ml (range 31–226) ($P = 0.001$), respectively, after the operation. **Conclusions**: Cardiac autotransplantation is a safe and effective option for the treatment of permanent AF in patients with mitral valve disease and severe dilation of left atrium.

Keywords: Permanent atrial fibrillation; Mitral valve disease; Left atrial volume reduction; Cardiac autotransplantation

1. Introduction

Atrial fibrillation (AF) is present in approximately 79% of patients with mitral valve disease [1] and most remain in AF following mitral valve surgery with no combined AF ablation surgery [2].

The Cox maze procedure, designed to treat and prevent chronic and paroxysmal AF and flutter, has been demonstrated to be effective by several studies. Recently, other alternative approaches, including cryothermy, radiofrequency, microwave, ultrasound and laser surgery, have been introduced in the clinical practice with the goal to treat AF respecting the same anatomo-physiological principles of the Cox procedure.

The presence of a large LA represents the major determinant of the low rate efficacy of linear ablation procedures [3,4].

This study shows our experience with cardiac autotransplantation for the treatment of permanent AF during mitral surgery, in patients with very enlarged left atrium.

2. Materials and methods

From April 2000 to September 2002, 30 patients with indication to mitral surgery have been treated with cardiac autotransplantation for the presence of concomitant permanent AF lasting for more than 1 year and a left atrial diameter greater than 50 mm.

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The clinical and echocardiographic characteristics of the patients are listed in Table 1.

Detection of permanent AF [5] was assessed by using the patient's history and previous electrocardiograms (ECG), and failure of pre-operative cardioversion (4 cases) or the decision to leave the patient in AF (26 cases) was documented.

Post-operative ECG examination was repeated every 6 months.

In order to assess the presence of tachi-brady arrhythmias and to calculate heart rate variability (HRV), Holter examination was performed at least 7 months post-operatively in patients without AF. The following time domain values were considered: SD of successive N–N (normal-to-normal) intervals (SDNN), the square root of the mean squared differences of successive R–R intervals (rMSSD), the number of interval differences of successive N–N intervals greater than 50 ms (NN50) and their relative day/night variations. Moreover, during deep breathing and mental test (parasympathetic and sympathetic stimulation, respectively), spectral analysis (frequency domain) by fast Fourier transform was calculated; the following values were considered: low frequency (LF), high frequency (HF), their ratio (L/H ratio) and the total power (T_{pow}). All the results of the treated patients were compared with those of a group of 12 normal volunteers matched for age.

In order to obtain homogeneous and consistent echocardiographic data, all the pre- and post-operative echocardiographic studies were performed by the same echocardiographer using a Sequoia 512 (Acuson Co., Mountain View, CA, USA) equipped with 2.5–3.5 MHz transducers. The pre-operative examinations were performed 0–7 days before surgery; the post-operative echocardiograms were performed at least 6 months after the operation.

Table 1
Clinical and echocardiographic data

Age (years)	61.7 ± 8.8 (45–78)
Male/female	5/25
NYHA class	3.1 ± 0.7 (2–4)
Embolic antecedent	5 (16.7%)
Previous mitral operation	6 (20%)
Etiology	
Rheumatic	28 (93.3%)
Degenerative	2 (6.7%)
AF duration (years)	6.7 ± 6.3 (1–25)
AF duration >10 years (*n*)	13 (43.3%)
EF (%)	59.8 ± 6.4 (42–70)
LVEDD (mm)	53.1 ± 7.7 (42–72)
LA superoinferior diameter (mm)	65.1 ± 16.4 (50–130)
LA volume (ml)	18.3 ± 68.4 (60–426)
Mitral valve lesions	
Stenosis	9 (30%)
Incompetence	6 (20%)
Mixed lesion	14 (46.7%)
Mitralic prosthesis dysfunction	1 (3.3%)
Associated valve lesions	
Aortic disease	6
Tricuspid disease	5

NYHA, New York Heart Association; AF, atrial fibrillation; EF, ejection fraction; LVEDD, left ventricle end diastolic diameter; LA, left atrium.

Echocardiogram examinations were used for sizing atrial dimensions and assessing atrial contractility.

The superoinferior diameter ($D1$), measured on B-mode in the four-chamber apical view, from the mitral valve plane towards the pulmonary veins, was considered as the left atrial diameter. The lateromedial ($D2$) and anteroposterior ($D3$) left atrial diameters were also measured to enable calculation of the left atrial volume by the formula: $(D1 \times D2 \times D3 \times 0.53)/1000$.

Post-operative atrial contractility was assessed with pulse-doppler, in four-chamber apical view, considering effective restoration of the atrial transport function when transvalvular peak A wave was ≥ 20 cm/s.

Results of atrial contraction function were expressed in terms of Santa Cruz Score (SCS) [6].

2.1. Surgery

All the operations were accomplished through a median sternotomy, standard aortic and direct bicaval cannulation and normothermic cardiopulmonary bypass. After aortic cross-clamping, myocardial protection was obtained through retrograde cold blood cardioplegia with warm reperfusion (26 cases) or continuous normothermic retrograde blood perfusion and beating heart (four cases).

In three patients, the Wythenshawe bicaval heart transplantation technique [7] was used, and in 27 patients the connection of the inferior vena cava was maintained, according to the 'modified autotransplantation' technique previously described by us [8]. A reduction of left atrial cavity was obtained by excising the left atrial appendage and redundant atrial wall, and by longitudinally plicating the posterior left atrial wall between the orifices of right and left pulmonary veins with an everting double running suture. Thus, the LA posterior wall is reduced to a very small surface, electrically and functionally silent, since totally isolated from the remaining left atrium. In four patients with severe dilation of the right atrium, a reduction of this cavity was obtained by excising the right appendage and a large part of the free wall [8].

2.2. Protocol of post-operative treatment

Amiodarone administration (5 mg/kg by slow administration of an intravenous bolus and an infusion of 10 mg/kg per 24 h) was started intraoperatively only in case of unstable SR with AF episodes and a need of internal cardioversion.

Early (in-hospital) post-operative atrial arrhythmias were treated with amiodarone (5 mg/kg by slow administration of

an intravenous bolus and an infusion of 10 mg/kg per 24 h), which was combined with external cardioversion if necessary. In these patients, amiodarone oral therapy (200 mg/day) was continued after discharge of the patient and withdrawn after 3 months.

All patients were treated with spirolactone 100 mg daily during their hospital stay.

Oral anticoagulation treatment was suspended after the third month in patients without a mechanical prosthesis and with echocardiographic evidence of effective biatrial contraction.

All patients were assessed for rhythm and atrial contractility at hospital discharge and every 6 months thereafter by means of electrocardiography and echocardiography.

After patient discharge, new AF or atrial flutter episodes were treated with antiarrhythmic medications and/or external cardioversion. No more than two external cardioversion was taken into account during the first 6 months after surgery. After 6 months the presence of AF or flutter was defined as permanent AF [9].

2.3. Statistics

Values of continuous variables are expressed as mean ± SD; comparisons between pre- and post-operative data were established with the paired Student's *t*-test (two-tailed).

In HRV analysis, continuous variables are expressed as mean ± SE; comparisons with control group were established with non-parametric Mann–Whitney *U*-test.

3. Results

3.1. Operative findings and clinical follow-up

All patients underwent mitral valve surgery alone or in association with other procedures. Two patients underwent mitral valve repair consisting of a posterior leaflet quadrangular resection and posterior annular ring implantation. Twenty-two patients underwent isolated mitral valve replacement with biological (seven cases) or mechanical (15 cases) prosthesis, and six patients had a double mitro-aortic valve replacement with mechanical prostheses.

Associate procedures were: CABG (2 cases), De Vega tricuspid annuloplasty (2 cases) and right atrial volume reduction (4 cases).

Mean cardiopulmonary bypass and aortic cross-clamp times were 162 ± 31 and 107 ± 22 min, respectively; by using the continuous blood perfusion, the mean total myocardial anoxic ischemic time was 73 ± 32 min.

The post-operative complications were: one case of re-operation for bleeding, one case of acute renal insufficiency successfully treated with continuous venovenous hemofiltration, and one case of prolonged mechanical ventilation (72 h) for acute respiratory failure. The mean length of hospital stay was 9.1 ± 4.4 days (range 5–23 days). No hospital death occurred in this series.

The mean follow-up interval was 21.1 ± 7.7 months (range 6–35), and during this time one patient (3.3%) died for a bilateral pneumonia occurred 3 months after the hospital discharge. The mean New York Heart Association functional class of the 29 survivors was 1.4 ± 0.6, and no thromboembolic episode has been recorded so far.

3.2. Cardiac rhythm and atrial function

At the end of the operation 23 patients (76.7%) recovered SR (4 required internal cardioversion and amiodarone infusion for intraoperative AF recurrence), 6 patients (20%) presented a regular atrial rhythm (RAR) and 1 patient (3.3%) remained with AF.

During the hospital stay 11 patients (36.7%) presented recurrence of AF (9 patients) or atrial flutter (2 patients) successfully treated with amiodarone infusion alone in 2 cases or with combined external cardioversion in 7 cases; in 2 patients the treatment was ineffective.

Cardiac rhythm of each patient, observed at different time intervals after surgery, is reported in Table 2. At discharge, 90% of patients presented a regular rhythm (25 cases sinusal and 2 cases atrial rhythm). At 6 and 12 months of follow-up, the percentage of patients with SR was 86.2% (25 out of 29 survived patients) and 88.8% (24 out of 27 patients), respectively.

During the follow-up, five patients (after a previous ineffective pharmacological cardioversion) had nine external cardioversions for recurrence of AF (five during the first 6 months, two between 6 and 12 months and two between 12 and 18 months); in two patients, a recurrence of AF during the first 6 months of follow-up was successfully treated with pharmacological cardioversion; one patient had two episodes of atrial tachiarrhythmia, at 6 and 12 months of follow-up, both successfully treated with medical therapy (beta-blockers); one patient had a double-chamber pacemaker implantation for a sick sinus syndrome occurred 12 months after surgery.

In seven patients (24.1%) a stable sinus rhythm is maintained with the chronic use of antiarrhythmic medications.

At hospital discharge the SCS was 0 for three patients, 2 for six patients, 3 for one patient, and 4 for 20 patients (66.7%).

During the follow-up, one patient with score 2 died, two patients moved from score 2 to score 4, and the patient with score 3 moved to score 4.

At the last control of each patient (mean follow-up 21.1 ± 7.7 months; range 6–35), the SCS was 0 for three patients, 2 for three patients, and 4 for 23 patients (79.3%).

No prosthesis dysfunction or mitral valvuloplasty failure was found at the last echocardiographic evaluation.

The mean post-operative left atrial diameter and volume were 49.9 ± 8.4 mm (range 37–78 mm) and 69.4 ± 34.1 ml

Table 2
Cardiac rhythm of each patient at different time intervals after surgery

Patient #	Discharge	6 months	12 months	18 months	24 months	30 months
1	RAR	AF	AF	AF	AF	AF
2	SR	SR	SR	SR	SR	SR
3	SR	SR	SR	SR	SR	SR
4	SR	SR	SR	SR	SR	SR
5	SR	SR	SR	SR	SR	SR
6	SR	SR	SR	SR	SR	
7	SR	Exitus				
8	SR	SR	SR	SR	SR	
9	AF	SR	SR	AF	SR	
10	AF	AF	AF	AF	AF	
11	SR	SR	SR	SR	SR	
12	RAR	SR	SR	SR	SR	
13	SR	SR	SR	SR	SR	
14	SR	SR	SR	SR	SR	
15	SR	AF	SR	SR	SR	
16	AF	SR	SR	SR		
17	SR	SR	SR	SR		
18	SR	SR	SR	SR		
19	SR	SR	SR	SR		
20	SR	AF	AF	AF		
21	SR	SR	SR	SR		
22	SR	SR	SR	SR		
23	SR	SR	SR			
24	SR	SR	SR			
25	SR	SR	SR			
26	SR	SR	SR			
27	SR	SR	SR			
28	SR	SR	SR			
29	SR	SR				
30	SR	SR				

RAR, regular atrial rhythm (not sinusal); SR, sinus rhythm; AF, atrial fibrillation.

(range 31–226 ml), respectively. The reduction in the mean left atrial diameter was statistically significant when compared with the mean pre-operative value of 65.1 ± 16.4 mm ($P < 0.001$). Similarly, the reduction in mean left atrial volume was statistically significant when compared with the pre-operative value of 118.3 ± 68.4 ml ($P = 0.001$).

Holter test was performed in 15 patients with a mean follow-up of 27.6 ± 8.5 months (range 7–38 months). No significant ventricular or supraventricular arrhythmias were found and all the patients were in SR but one with regular non-sinus atrial rhythm. The statistically different values in the study population versus the control group are shown in Table 3.

4. Discussion

AF is a complex arrhythmia of incompletely understood multifactorial pathogenesis [10,11] and the best treatment is still not well defined. Multiple circuit re-entry has been the most worldwidely accepted pathogenetic mechanism of AF and the Cox maze procedure was exactly designed in order to prevent the propagation of multiple re-entrant wavelets by means of a compartmentalization of the atria with linear lesions [12].

Similarly, the pathogenesis of AF associated with long-lasting mitral valve disease is not completely known and the best treatment, even if evolving rapidly, is still in its infancy [13].

Experimental observations in a canine model suggest that increases in atrial size and pressure cause an increase in atrial refractoriness and dispersion of atrial effective refractory periods, which slow conduction velocity and increase AF inducibility [14,15]. These triggers could be considered peculiar of AF associated with chronic mitral disease. Thus, the reduction of left atrial mass and volume together with the reduction of the left atrial wall stress should be comprised in procedures adopted for a complete removal of AF causes.

Autotransplantation for treatment of AF in mitral valve surgery, proposed by R.J. Batista (personal communication—*IX Scientific Forum, 2–5 December 1999, Belo Horizonte, Brazil*), in its theoretical assumption, satisfies the obtaining of the above-mentioned goals: it is possible to reduce the wall stress into the LA by (a) reducing the atrial pressure with the mitral valve repair or replacement and (b) in real terms reducing the left atrial size.

Table 3
Heart rate variability analysis

	Control (12 pts)	Treated (15 pts)	*P*
Time domain			
HR max (bpm)	120.5 ± 6.1	100.1 ± 4.2	<0.01
HR average (bpm)	75.7 ± 2.9	68.7 ± 1.7	<0.05
SDNN (ms)	144.2 ± 12.4	105.5 ± 8.5	<0.05
SDNN night (ms)	108.0 ± 8.3	66.3 ± 11.0	<0.01
Frequency domain			
Mental stress			
ln T_{pow}	7.46 ± 0.27	5.72 ± 0.53	<0.05
ln LF	6.63 ± 0.29	4.80 ± 0.69	<0.05
L/H ratio	6.0 ± 0.8	1.6 ± 0.2	<0.01
Deep breathing			
ln Tpow	7.35 ± 0.36	5.82 ± 0.45	<0.05
ln HF	6.54 ± 0.39	3.88 ± 0.64	<0.01

HR, heart rate; SDNN, SD of successive NN (normal-to-normal) interval; T_{pow}, total power; LF, low frequency; HF, high frequency; L/H, low/high frequency ratio. All data are expressed as mean ± SE. The value of Tpow, LF and HF have been transformed in logarithmic scale.

From the technical point of view, autotransplantation, despite its apparent complexity, has the advantage to gain a comfortable access to the left atrium, allowing a relatively short mitral procedure time. Furthermore, the problem of the ischemic time length is overwhelmed by the possibility to perform retrograde continuous blood perfusion during the entire procedure time ('beating heart') [16] or at least during the re-implantation time. For these reasons autotransplantation technique appears to be comparable with the Cox maze procedure in terms of reproducibility.

The results of our series in terms of stable AF conversion (89.7%) and normal atrial function re-establishment (SCS 4 = 82.7%) at 21.1 ± 7.7 months of mean follow-up, are comparable with the reported results of the maze procedure [4,17], and superior to those of other surgical ablation techniques [18,19].

According to the suggestions proposed by Gillinov et al. [9], the data of our series are described with a longitudinal analysis method (Table 2) which is the most precise way to allow the comprehension of the phenomenon of effective and stable SR restoration and to compare different series and procedures.

The need for antiarrhythmic medications and subsequent interventions to restore/maintain SR, even at long interval time post-operatively, shows the importance of protocols for strict and periodic clinical controls.

The incidence of early sinus node dysfunction in our series is similar to that reported by others [20]. Two cases of atrial rhythm at discharge were recorded and only one patient underwent a pacemaker implantation post-operatively.

Mid-term results of our series appear favourable, considering that the mean pre-operative values of LA diameter and volume in our patients are significantly higher than that reported in other series [19], and that with maze-type procedures the rate of success falls below 60%, when the pre-operative LA diameter exceeds 70 mm and can fall to 0%, when it exceeds 87 mm [4].

The important and statistically significant post-operative reduction of LA diameter and volume is certainly due to the autotransplantation technique, more than to the treatment of mitral disease per se.

A considerable gap between the percentage of SR recovery and normal atrial function detection with the Cox maze or maze-type procedures has been reported [19,21]. Moreover, some authors [22] state that atrial systolic function is lost with the maze operation. Our data suggest that autotransplantation allows a normal atrial contractility to develop pari passu with SR and a stable LA volume.

Discordant results are reported about the effectiveness of the Cox maze on the prevention of late thromboembolic events [13,23]. The absence of thromboembolisms at intermediate-term follow-up in our series is encouraging and could be explained by the higher percentage of patients with SR who recovered a normal atrial contractility, even in the presence of an electrically silent and non-contracting small surface of posterior LA wall.

The autotransplantation technique can be considered an isolated left atrial procedure with a low incidence (two cases) of post-operative atrial flutter. In our series, only in four cases of a very large right atrium, a surgical reduction of the right atrial cavity combined with an excision of the right appendage was performed, with the aim to reduce the incidence of supraventricular tachyarrhythmias in the post-operative course.

As regarding the possible role of autonomic tone as trigger of AF, our analysis of HRV (Table 3) shows that patients treated with autotransplantation have a reduction of both sympathetic and vagal drive and there are no signs of re-innervation. This issue has been debated in the field of heart transplantation with contrasting conclusions [24,25]. A longer follow-up is necessary to assess the behavior of autotransplanted hearts and the possible influence of denervation/reinnervation on the onset of AF.

In conclusion, the autotransplantation procedure is effective in obtaining a stable SR and normal atrial function recovery in the mid-term, particularly in patients with very large left atrium, in whom the real reduction of LA cavity is a fundamental part of the treatment. A longer follow-up is necessary to confirm the stability of these results.

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Appendix A. Conference discussion

Dr L. Bockeria (*Moscow, Russia*): It might bring a long discussion, but we know that atrial fibrillation is an in-heart pathology but not outside. When you do this autotransplantation you definitely cut the possibility to cure the atrial fibrillation by means we know for today. How can you explain this?

Dr Troise: Excuse me?

Dr Bockeria: For example, the maze procedure is an in-heart procedure, and when you do this type of surgery you don't affect the process which is inside the heart.

Dr Troise: I think that autotransplantation can be classified as an isolated left atrial procedure. The basic concept is that we know that in this kind of very large left atria,as we are talking about, the main goal is to reduce the left atria. So the difference with the maze procedure is that autotransplantation is an isolated left atrial procedure,with a complete isolation, transmural, because surgical, isolation of the pulmonary veins and reducing, at the same time, the left atrial volume.

Dr F. Mohr (*Leipzig, Germany*): On the other hand, you completely disconnect the major part of the left atrium, and the question is whether contractility is in a simultaneous mode to the right side or not. That is what you do with the autotransplantation.

Dr Troise: We noted that, in the time, it's possible to have a restoration of left atrial function even at one year after the operation. There is a sort of remodeling in these atria. The posterior wall with the pulmonary veins ostia, which is left intact, is a very small portion of posterior wall, and it is plicated just to reduce the diameter. The contraction, it is interesting, regards the anterior part of the left atrium, with the mitral valve, connected with the right side.

Dr J. Melo (*Carnaxide, Portugal*): I think this is a very interesting surgical model for our understanding, and in my view there is another alternative to explain some of the very good results. You are denervating the heart. The ventral cardiac plexus is being completely sectioned. So my question is, do you have any evidence on your late follow-up that your sinus rhythm patients are denervated regarding Holter monitoring, tilting test, several tests that can be done?

Dr Troise: We are studying this problem. And you know that some people say that there is an influence of the autonomic nervous system

as a trigger for atrial fibrillation. So we studied the effect of this on 15 of our patients with stable sinus rhythm and with a follow-up of 25 months from surgery with the heart rate variability analysis and with parasympathetic and sympathetic stimulation, and we compared this group of patients with a number of 15 normal volunteers matched for age.

Up to now we found that there is a reducing of sympathetic and vagal drive in the autotransplanted patients but, up to now, there are no clear signs of reinnervation. It should be nice to consider this operation as a model just to evaluate the influence of denervation and/or reinnervation on the maintenance of sinus rhythm.