SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

THE COX MAZE III PROCEDURE: PARALLEL NORMALIZATION OF SINUS NODE DYSFUNCTION, IMPROVEMENT OF ATRIAL FUNCTION, AND RECOVERY OF THE CARDIAC AUTONOMIC NERVOUS SYSTEM

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Objective: The Cox maze III procedure includes isolation of the pulmonary veins and multiple incisions in both atria in what corresponds to partial autotransplantation and partial denervation of the heart. The aim of this prospective longitudinal study was to identify physiologic effects of reinnervation on changes in heart rate at rest and in response to various stimulations and on atrial function after the Cox maze III procedure. **Patients and methods:** Power spectral analysis of heart rate variability, exercise testing, 24-hour Holter monitoring, electrocardiography, and transthoracic and transesophageal echocardiography were performed in 30 adult patients after the combined Cox maze III procedure and mitral valve surgery (maze group). They were prospectively followed up at 1, 3, 6, and 12 months after the operation. The results were compared with those of 15 heart transplant recipients (transplant group) and normal probands (healthy adults, n = 12). **Results:** The physiologic effects of denervation with no differences in cardiac autonomic activity between the groups were seen early after the operation. Later, evidence of autonomic reinnervation was observed only in the maze group but not in the transplant group. Inappropriate heart rate responses during physical exercise were clearly evident in both groups after 1 and 3 months, with progressive improvement seen between 6 and 12 months only in the maze group. Left atrial function after the Cox maze procedure improved parallel to the recovery of sinus node function. **Conclusion:** Progressive improvement of sinus node function and atrial contractions with significant functional normalization 1 year after the Cox maze procedure corresponded to functional reinnervation and recovery of the autonomic nervous system. (J Thorac Cardiovasc Surg 1999;118:287-96)

The Cox maze procedure,^{1,2} the technique of choice for the management of atrial fibrillation, includes isolation of the pulmonary veins and multiple incisions in both atria^{3,4} in what corresponds to partial autotransplantation and partial denervation of both the parasympathetic and sympathetic systems of the heart. In con-

trast, the transplanted heart is completely denervated and, therefore, without efferent parasympathetic or sympathetic innervation. The aim of this prospective longitudinal study was to identify physiologic effects of reinnervation on changes in heart rate at rest and in response to various stimulations, to evaluate the

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mechanical activity of the left atrium and its effect on left ventricular function after the Cox maze procedure, and to compare them with the results in heart transplant recipients and normal healthy subjects.

Patients and methods

Maze group. Thirty consecutive adult patients underwent a combination of the Cox maze procedure and mitral valve repair ($n = 8$) or replacement ($n = 22$). The group comprised 24 women and 6 men with ages varying from 27 to 72 years (average 61 years). All patients had chronic sustained atrial fibrillation before the operation. Duration of documented arrhythmia ranged from 0.5 to 12 years with a mean of 5.5 years. The mean left ventricular ejection fraction assessed by ventriculography and echocardiography was 50% ranging from 35% to 80%. The Cox maze procedure was offered in conjunction with mitral valve surgery to all patients who were scheduled for elective mitral valve surgery for 2 of the authors (R.H and M.P.). The exclusion criteria for combined Cox maze procedure and mitral valve surgery were as follows: left ventricular function less than 30%, concomitant significant coronary artery disease necessitating coronary artery bypass, acute valve endocarditis, calcification of the left atrium, extensive calcification of the mitral valve anulus necessitating annular decalcification, redo surgery, a giant left atrium, and unwillingness of the patients to undergo the procedure. Our policy has been that a giant left atrium poses a contraindication for the Cox maze procedure. In such situations the alternative is the "mini-maze" procedure on the right side of the heart combined with plication of a giant left atrium and long-term anticoagulation.

Operative technique of the Cox maze procedure. In brief, operations were carried out through a median sternotomy with separate caval cannulation, total cardiopulmonary bypass, and mild systemic hypothermia (32°C). Cardioplegic arrest was afforded by aortic root infusion of crystalloid cardioplegic solution (Cardioplegin), followed by infusion of cold hydroxyethylene starch solution and topical cooling. Myocardial protection was maintained by repeated infusion of cold hydroxyethylene starch solution every 20 minutes thereafter. The second modification of the maze technique, the Cox maze III procedure,⁴ was applied with some minor modifications in all patients. Our preliminary experience with this technique applied in patients with chronic atrial fibrillation and organic heart disease has been published elsewhere.⁵

Postoperative management of the patients undergoing the maze operation. No operative death occurred in the series of patients undergoing the maze operation. Only 2 patients required positive inotropic medication after the operation, and all but 2 were extubated on the first postoperative day. Temporary wires were used for temporary pacing if necessary, to monitor the rhythm or to overdrive the atrium.

In the early postoperative period, patients with junctional rhythm were treated with continuous intravenous administration of orciprenaline sulfate (Alupent). During the hospitalization, patients with atrial fibrillation were treated with

digoxin in combination with verapamil or digoxin in combination with sotalolol. After discharge from the hospital, the same regimen of antiarrhythmic agents was given in patients with episodes of postoperative supraventricular tachyarrhythmias. The dosage was tapered if the rhythm became stable. However, 5 patients who had used antiarrhythmic medications for a long time before the operation continued to take the drugs intermittently or continuously during the follow-up period for different nonmedical reasons. A stable regular atrial rhythm was not found in 15 (50%), 6 (20%), 3 (10%), and 0 (0%) patients in the early postoperative period and at 3, 6, and 12 months, respectively. The patients were told to discontinue cardiovascular medications a week before postoperative studies, especially drugs that could have substantial effects on chronotropic response and heart rate variability, such as β -blockers, except angiotensin-converting enzyme inhibitors. The patients were maintained without these drugs during the examinations. All examinations were performed with the subjects having an empty stomach (no intake of food or drinks, and especially no caffeine use, on the day of the examination). All patients were put on a regimen of long-term anticoagulation with phenprocoumon (Marcumar) after initial heparin therapy during the first few postoperative days.

Heart transplant recipients. Fifteen heart transplant recipients with the mean age of 36.5 years (range, 19-52 years) were prospectively followed up and underwent the same exercise protocol at the same follow-up time points after orthotopic heart transplantation as the patients in the maze group. The heart transplant recipients were selected for examination by chance (formally randomized). Because this group of patients was obviously younger than those in the maze group, there was no intention to match the patients by age. All these patients were in sinus rhythm during follow-up studies. All operations were performed according to the standard technique of Lower and Shumway.^{6,7} This technique includes the use of conventional cardiopulmonary bypass, with resection of the diseased heart at the level of both atria, leaving behind the atrial posterior walls and the stumps of aorta and pulmonary artery.⁸ The donor hearts were arrested with 2000 or 3000 mL of cold Bretschneider cardioplegic solution. The donor heart was explanted by transecting both caval veins and the 4 pulmonary veins after dividing the ascending aorta and the pulmonary artery, preserving the sinus node, its artery, and the sinoatrial pathways. A dual-chambered telemetric pacemaker was routinely implanted for postoperative monitoring of acute rejection through measurements of the intramyocardial electrogram amplitude.⁹ Immunosuppression was induced by triple-drug therapy (cyclosporine [INN: ciclosporin], azathioprine, and prednisone). Endomyocardial biopsies were not routinely performed. Acute rejection was monitored noninvasively by telemetric—day-by-day—intramyocardial electrocardiography, echocardiographic examinations, and, if indicated, occasionally by endomyocardial biopsy.⁹ Episodes of acute rejection were treated by high-dose steroids alone or in combination with rabbit antithymocyte globulin or murine monoclonal T3-cell antibodies (OKT3).

Healthy adults. Twelve healthy sedentary persons (patients referred to the electrocardiography laboratory for an exercise stress test and some volunteers from hospital staff) underwent the same examination protocol. None of them had evidence of any disease, none was being treated with any medication, and all were in sinus rhythm. The mean age of the group was 44 years (range, 22-63 years).

Echocardiographic studies. All patients underwent transthoracic and transesophageal echocardiography with complete M-mode and 2-dimensional echocardiography, including pulsed-wave, tissue Doppler, and color imaging echocardiography. All echocardiographic studies were performed by the same echocardiographer (H.S.). An Aloka SSD-2200 Vario View echocardiographic machine (Aloka Co, Ltd, Tokyo, Japan) with a multifrequency 2.5 to 7.5 MHz probe was used. Left ventricular diastolic and systolic dimensions were measured in the parasternal long-axis view. All measurements of the left atrial dimensions were taken at end-diastole. Noninvasive estimation of the extent of left atrial contraction was performed by analysis of pulsed Doppler echocardiography of transmitral blood flow velocity, pulsed tissue Doppler echocardiography, and by automatic boundary detection (the latter performed in only 7 patients [data not shown]). Phonocardiography, apexocardiography, and electrocardiography were traced simultaneously with the echocardiographic examination. The sample volume for transmitral flow velocity pattern was placed in the left side of the heart above the mitral valve, and the best recording of the transmitral flow was carefully searched. Peak velocity of the early (E) and atrial (A) filling waves, the relation of the height of the A and E waves of the transmitral flow (A/E ratio), and the duration of atrial contraction were determined. Tissue Doppler echocardiographic analyses were measured on the posteroinferior wall of the left atrium about 1 cm from the mitral anulus.

Exercise testing and power spectral analysis. The cardiac autonomic nervous system conveys information that reaches the sinus node in the heart through efferent vagal and sympathetic pathways. Two clinically applicable methods for assessment of the cardiac autonomic control value were applied, namely, time or frequency measurements of heart rate variability. Time domain analysis, which is a statistical analysis of the fluctuations in heart rate, is defined in terms of standard deviation or variance of the mean sinus R-R intervals over time. Study of time domain heart rate variability in human beings shows that fluctuations in sinus rate are mediated solely by efferent vagal activity. Frequency domain, so-called power spectral analysis, decomposes the sinus R-R interval signal into its frequency components and quantifies it in terms of "power." Power spectrum analysis provides the suggestive evidence that heart rate variability reflects oscillations in sympathovagal balance: high frequency is considered to reflect the vagal activity on the cardiac autonomic system, and the ratio between the low frequency and high frequency is considered to reflect the cardiac sympathetic activity. Power spectral analysis of heart rate variability assessed by head-up tilt test (0° and 60°), exercise testing, 24-hour Holter

monitoring, and standard electrocardiography was used to assess dysfunction of the autonomic nervous system, ability of the sinus node to accelerate in response to internal physiologic chronotropic stimuli, and heart rate variability. Electrocardiographic documentation was continuously registered with a 2-channel ambulatory recorder in the supine and 60° head-up tilt position for 10 minutes each. The last 512 consecutive heartbeats in each position were processed by the maximal entropy method. Low-frequency and high-frequency components, as well as low-frequency/high frequency ratio, were calculated.⁵ Power of both low-frequency and high-frequency components was expressed in absolute units (ms²). The ergometer bicycle study started at 25-watt workload (150 kpm/min), increasing by 25 watts every 3 minutes until peak exercise was reached as defined by development of fatigue and/or dyspnea.⁵ The measurement of heart rate during exercise is closely associated with age, resting heart rate, and functional capacity. A traditional measure of heart rate response is percentage of age-predicted maximum heart rate achieved. An alternative method is a measurement of a heart rate reserve used at peak exercise, by which the key confounders of the heart rate response to exercise (age, resting heart rate, functional capacity) are effectively taken into account. A heart rate reserve (HRR) was calculated according to the method of Wilkoff and Miller¹⁰; HRR used at peak exercise was determined as follows: $HRR \text{ used at peak exercise} = (\text{Peak heart rate} - \text{Resting heart rate}) / (220 - \text{Age} - \text{Resting heart rate})$.

Statistical analysis. All data are reported as mean $\pm$ standard deviation. Data were analyzed with the use of an unpaired or paired *t* test, as appropriate. Multiple comparisons within a group over time were made by use of univariate repeated measures analysis of variance and the Scheffé test; the Kruskal-Wallis test was used for data that were not normally distributed.

Results

Heart rate at rest and exercise. Heart rate at rest was lower in the maze group than in the transplant recipients but higher than in normal subjects (maze group 74 ± 6 beats/min vs heart transplant group 108 ± 6 beats/min at 12 months, $P = .005$). Serial exercise studies found lower resting heart rates and higher maximal exercise heart rates over time in the maze group, whereas resting heart rates and peak heart rates were unchanged in the heart transplant recipients (maze group, $P = .02$; heart transplant recipients, $P = .51$). Inappropriate heart rate responses during physical exercise were clearly evident after the maze procedure during the first 6 months, and normalization of its physiologic functions can be seen at 12 months (Fig 1). The heart rate reserve was abnormally low in both groups at 3 and 6 months (Fig 2). At 12 months, the heart rate reserve in the maze group improved in contrast to that of the heart transplant recipients (maze

Fig 1. Postoperative increase in heart rate during exercise in 30 patients with the maze procedure, in 15 heart transplant recipients, and in 12 normal probands.

Fig 2. A heart rate reserve used at peak exercise in 30 patients with the maze procedure, in 15 heart transplant recipients, and in 12 normal probands. The calculations were determined according to the method of Wilkoff and Miller,¹⁰ by which the key confounders of the heart rate response to exercise (age, resting heart rate, functional capacity) are effectively taken into account. A heart rate reserve used at peak exercise was determined as follows: Heart rate reserve used at peak exercise = (Peak heart rate – Resting heart rate)/(220 – Age – Resting heart rate).

group vs heart transplant group, $P = .01$; maze group vs healthy adult group, $P = .08$) (Fig 2). Thus the heart rate response to exercise of the maze group was pathologically low from 1 through 6 months, and values were normal 12 months after the operation. When compared with those of the healthy group and heart transplant recipients, the heart rates 1 to 6 months after the maze procedure corresponded with those of the heart transplant recipients (which remained depressed throughout the study period from 1 to 12 months after transplantation); at 12 months they approached those of the healthy subjects.

Power spectral analysis of heart rate variability. Early after the operation, both the maze and heart trans-

plant groups exhibited the physiologic effects of denervation. No differences in cardiac autonomic activity were noted between the 2 groups, as demonstrated by very low values in power spectral analysis of heart rate variability, inhibited cardiac autonomic activity, and no response after sympathetic stress with nonmeasurable values for the heart transplant group and minimal values for the maze group (maze group at 3 months: low-frequency power, high-frequency power, and low-frequency/high-frequency ratio at 0°, $15 \pm 5 \text{ ms}^2$, $43 \pm 10 \text{ ms}^2$, and 0.35 ± 0.03 ; at 60°, $2 \pm 1 \text{ ms}^2$, $22 \pm 7 \text{ ms}^2$, and 0.09 ± 0.02 , respectively) (Table I). During the follow-up period, the maze group but not the heart transplant group demonstrated evidence of autonomic reinnerva-

Table I. Type of heart rate variability measurements

Type of HRV measurements	Definition	Autonomic correlate
Time domain (ms)	Standard deviation of normal (non-VPC) R-R intervals Energy in heart period power spectrum between:	Vagal tone
Frequency domain		
LF (ms ²)	0.004-0.15 Hz	Vagal and sympathetic tone
HF (ms ²)	0.15-0.40 Hz	Vagal tone
LF/HF ratio	Ratio of LF to HF power	

HRV, Heart rate variability; LF and HF, low-frequency and high-frequency components; LF/HF, low-frequency/high frequency ratio; VPC, ventricular premature complex.

tion with documented recovery of cardiac autonomic activity to sympathetic stress at 1 year in the maze group (maze group low-frequency power, high-frequency power, and low-frequency/high-frequency ratio: at 0°, $206 \pm 123 \text{ ms}^2$, $403 \pm 79 \text{ ms}^2$, and 0.51 ± 0.05 ; at 60°, $10 \pm 4 \text{ ms}^2$, $26 \pm 7 \text{ ms}^2$, and 0.37 ± 0.03 , respectively) (maze group at 3 months vs maze group at 12 months for 0°, $P = .001$, $.001$, and $.05$, respectively); however, it was still lower than that of the healthy adults (low-frequency power, high-frequency power, and low-frequency/high-frequency ratio: at 0°, $490 \pm 154 \text{ ms}^2$, $310 \pm 104 \text{ ms}^2$, and 1.6 ± 0.1 ; at 60°, $447 \pm 120 \text{ ms}^2$, $79 \pm 23 \text{ ms}^2$, and 5.7 ± 0.7 , respectively) (maze group vs healthy adults for 0°, $P = .02$, $.05$, and $.002$, respectively) (Fig 3).

Left atrial and left ventricular dimensions in patients undergoing the Cox maze III procedure. The preoperative left atrial dimensions ranged from 76 to 38 mm with a mean $55 \pm 8 \text{ mm}$. Three months after the Cox maze procedure, the left atrial diameter was smaller than it had been before the operation (mean $49 \pm 6 \text{ mm}$; $P = .01$). Left atrial size remained larger in patients with larger preoperative left atria than in patients with normal or near-normal preoperative dimensions. In the late study period, left atrial dimensions decreased in general for the group but not in 6 patients (mean diameter of the left atrium at 12 months, $46 \pm 4 \text{ mm}$) (left atrial diameter at 3 months vs 12 months, $P = .02$; preoperative vs 12 months, $P = .01$). Left ventricular diastolic diameter was reduced from preoperative, $55 \pm 8 \text{ mm}$ to $48 \pm 3 \text{ mm}$ ($P = .01$) at 1 year after the Cox maze procedure, and fractional shortening remained unchanged ($32.6\% \pm 5\%$ preoperatively vs $29\% \pm 8\%$ postoperatively; $P = .6$).

Echocardiographic studies of left atrial mechanical function. The evidence of Doppler-recorded A waves could be seen immediately after the Cox maze procedure in 26 patients. Six and 12 months after the operation, an A wave could not be recorded in 2 patients despite obvious sinus rhythm on the electrocardiogram. However, the absence of detection of the A

wave could not rule out left atrial contraction, because in these 2 patients without detectable A waves, transesophageal examination with automated boundary echocardiography proved some degree of atrial contraction. All patients with detectable A waves showed an increase of Doppler A wave signals over the following months. One year after the operation, there were no differences between the maze group ($0.49 \pm 0.13 \text{ m/s}$), heart transplant recipients ($0.65 \pm 0.6 \text{ m/s}$), and healthy adults ($0.52 \pm 0.25 \text{ m/s}$) (maze group vs healthy adults, $P = .9$; maze group vs heart transplant group, $P = .7$). Tissue Doppler measurements (Fig 4) confirmed atrial mechanical function during the follow-up period with a nonsignificant difference between the groups at 12 months; the mean diastolic velocity of left atrial myocardium at the end of the study was $5 \pm 2 \text{ cm/s}$ for the maze group, $7.4 \pm 2 \text{ cm/s}$ for the heart transplant recipients, and $8.2 \pm 2 \text{ cm/s}$ for the healthy adults (maze group vs healthy adults, $P = .6$; maze group vs heart transplant group, $P = .7$). At the same time, the duration of the waves was $85 \pm 18 \text{ ms}$, $115 \pm 20 \text{ ms}$, and $90 \pm 12 \text{ ms}$ for the maze group, heart transplant recipients, and control subjects, respectively (maze group vs healthy adults, $P = .8$; maze vs heart transplant group, $P = .7$).

Discussion

Our study clearly showed that progressive improvement of sinus node function and atrial contractions after the Cox maze procedure corresponded to functional recovery of the autonomic nervous system. Development of functional reinnervation was clearly evident after partial heart denervation in patients with the Cox maze III procedure with functional normalization 1 year after the operation. In contrast, completely denervated hearts demonstrated a lack of physiologic effects of reinnervation during the first postoperative year.

Similarities between the Cox maze procedure and heart transplantation. Sinus node dysfunction after the maze procedure corresponds at least partly to the denervation of the donor heart in heart transplant recip-

Fig 3. Power spectrum analysis showed inhibited cardiac autonomic activity during the first postoperative months both after the Cox maze procedure and after heart transplantation. Evidence of late autonomic reinnervation was found only in the maze group, but it was still lower than that of the healthy probands. *LF/HF*, Low-frequency/high-frequency ratio.

ients. The maze procedure includes isolation of the pulmonary veins and multiple incisions in both the atria in what corresponds to partial autotransplantation of the heart and, therefore, to partial denervation of both parasympathetic and sympathetic systems. Mechanisms of denervation and reinnervation might be the main factors that generated sinus node dysfunction after the maze procedure and orthotopic heart transplantation. Except for some additional possible causes, such as allograft rejection or use of immunosuppressive medication, the main difference between the 2 groups is the extent of surgical denervation of the heart. According to experimental studies, denervation of the heart causes changes in heart rate and pacemaker location, atrioventricular conduction time, and contractile response. Basal heart rate after transplantation may be influenced by many factors, including sinus node dysfunction and autonomic neural reinnervation.¹¹⁻¹³ Sympathetic neurally mediated changes in heart rate that normally occur during exercise, Valsalva maneuver, and orthostasis have been reported to be absent in patients after heart transplantation.^{14,15} As after heart transplantation, the physiologic effects of denervation in changes in heart rate are clearly exhibited early after the maze procedure; however, the physiologic effects of reinnervation in response to different stimulations are evident earlier after the maze procedure than after heart transplantation, should they appear. The intensity of sinus node dysfunction after the maze procedure in our patients was less evident than in heart transplant recipients, and its duration was shorter. These abnormalities resolved

over time, suggestive of faster and more complete reinnervation after partial denervation of the heart after the maze procedure than after complete denervation performed according to standard techniques of orthotopic heart transplantation. Limited sympathetic and occasionally parasympathetic reinnervation occurs within the first months after cardiac transplantation in animal models, with regrowth of sympathetic nerves along coronary blood vessels and over the anastomoses between the donor heart and recipient atria and great vessels.^{16,17} In human beings, sympathetic reinnervation may occur after orthotopic cardiac transplantation, but it could not be detected during the first 5 months after transplantation.^{12,18} It frequently takes place in the absence of parasympathetic reinnervation.¹² However, anatomic studies of transplanted hearts in human beings rarely demonstrated nerve fibers, which have been interpreted as postganglionic parasympathetic neurons of the ganglia transplanted with the heart.¹⁹ Reinnervation may be a regionally heterogeneous process, and its magnitude varies substantially among subjects. Its specific effects can also be heterogeneous, with differences in different regions.^{20,21} This inhomogeneity of parasympathetic innervation in the atria could lead to regional differences in repolarization and conductive velocity, with different changes in heart rate and contractility in different patients. Consequently, the sinus node may normally be less reinnervated than the rest of the heart with consecutive dysfunction late after transplantation.^{11,13}

Heart rate variability. Determination of the variability of the heart rate is one of the most extensively used clinical approaches for assessing the autonomic nervous system. The high-frequency band, which is in the 0.15- to 0.4-Hz range, is thought to represent the parasympathetic component of the autonomic nervous system. Low frequency, which is in the 0.04- to 0.15-Hz range, is mediated by both the parasympathetic and sympathetic nervous systems,²² although some questioned the hypothesis that low-frequency spectral power reflects sympathetic tone.²³ We found that both the low and high components were significantly attenuated after both the Cox maze procedure and orthotopic heart transplantation in comparison with values in the normal subjects. The early findings presented the physiologic effects of heart denervation with no differences in cardiac autonomic activity between the 2 groups. It should be emphasized that abnormal postoperative heart rate variability is not a specific feature of these types of operations. It can also be found after other types of heart procedures. After coronary artery bypass grafting, high-frequency power decreased to

Fig 4. Assessment of mechanical function of the left atrium using tissue pulsed Doppler echocardiography. **A**, Two-dimensional (long-axis view) tissue Doppler echocardiogram showing activity of the left atrium (arrow). **B**, Corresponding simultaneous tracing of phonocardiogram, apexocardiogram, and electrocardiogram showing atrial contraction. *LA pw*, Left atrial posterior wall.

one third of the preoperative level and low-frequency power to one seventh of the preoperative level.²⁴ However, these values are still higher than observed values in our patients. Unfortunately, because of preoperative chronic atrial fibrillation in patients undergoing the Cox maze procedure, we were unable to determine the preoperative values of heart rate variability and only have postoperative evaluations. An important observation of our study is the evidence of cardiac reinnervation and recovery of autonomic neural activity later after the Cox maze procedure but not after heart transplantation.

Left atrial dimensions after the Cox maze procedure. There are 3 main causes attributable to the reduction of the atrial dimensions after the Cox maze procedure, namely, establishment of stable sinus rhythm, surgical technique of the Cox maze procedure, and therapy of organic mitral valve disease. The Cox maze procedure causes some degree of surgical reduction of the left atrial dimensions per se. After stable sinus rhythm had been established, further reduction of the left atrium was noted. This change was similar to the reduction of the left atrium after cardioversion of atrial

fibrillation by direct-current countershock,^{25,26} which causes a significant decrease of the left atrial dimension after 1 month²⁵ and 20% reduction of the left atrial volume after 6 months.²⁶ In our patients with organic mitral valve disease, surgery also has a favorable influence on left atrial dimensions. However, on the basis of our data, it is not possible to determine the influence of the Cox maze procedure alone on the reduction of the left atrial diameter. In the present study, we have not compared the results of the Cox maze procedure combined with surgery for organic mitral valve disease and that of mitral valve surgery in patients with a preoperative stable sinus rhythm.

Left atrial function after the Cox maze procedure. Only a few studies have dealt with the postoperative mechanical function of the left atrium after the Cox maze procedure,²⁷⁻³⁰ which shows some degree of restoration of active atrial contraction in most patients. All of them used transthoracic echocardiography to determine atrial function. In all studies the patients were examined at different time points after the operation and without serial follow-up examinations. Also, according to the different time points of surgery,

patients in these studies underwent different modifications of the Cox maze procedure. Furthermore, in some patients the maze procedure was performed alone for atrial fibrillation without concomitant mitral valve surgery, and some of them had had only intermittent atrial fibrillation. In contrast to other studies, we performed serial transesophageal echocardiographic examinations of the same patients throughout the study period of 12 months, and all of them underwent the second modification of the maze procedure, the Cox maze III procedure.⁴

Limitations of the study. A major problem of the study with regard to physiologic effects of possible reinnervation in patients with the Cox maze procedure is the difficulty in obtaining a suitable control group of patients. However, in this specific situation, in which we observed the patients for several months after the Cox maze procedure, a control group per se was actually not necessary because the maze group was used as its own control group: the same group of patients was compared at the different time points, and these comparisons showed the important changes over time. Using this model, we were able to demonstrate normalization of the sinus node function and probably reinnervation of a partially denervated heart after the Cox maze procedure.

A second limitation of our study was that the studied groups were not strictly matched by age or sex. However, despite this difference, we showed that changes in heart rate were not affected by age or sex but only by the type of surgical procedure. Furthermore, our patients were not randomized for operations for mitral valve disease with and without the concomitant Cox maze procedure.

One possible limitation is measurement of echocardiographic left atrial dimensions and estimation of left atrial contraction, which are complicated by technical factors and may limit the accuracy of the measurements. Asymmetric atrial enlargement of the left atrium can occur, and the exact determination of the left atria can be biased. Although echocardiography can identify postoperative atrial contractions, there are several factors that may make it difficult to obtain echocardiographic determinations of real qualitative and quantitative atrial function after the operation. Furthermore, atrial contraction can be influenced by many factors.²⁷

Finally, a significant limitation of this study was the small group of patients studied. The maze group comprised only 30 patients and the heart transplantation group, 15 patients. Because of the small number of patients and the fact that the patients had been selected for the maze procedure, the maze group of patients cannot be

considered as a representative group of the general population with chronic atrial fibrillation. Thus this study should be considered only as an observational study.

In conclusion, the Cox maze procedure effectively establishes sinus rhythm, normalizes sinus node function, and improves or in some instances completely restores left atrial function. It is a time-dependent process that lasts several months after the procedure.

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Discussion

Dr James L. Cox (*Washington, DC*). This is without question the finest example of scientific evaluation of the maze procedure since it was first reported in 1991. The authors have applied state-of-the-art analysis to detect and quantitate in many cases cardiac innervation and denervation, sinus node function, and atrial transport function. They established not only one control group, the heart transplant recipients, but

also a second control group of normal patients. Their end points were evaluated in all patients at appropriate intervals up to a year after the operation. Therefore the format of this study was excellent.

It is at this point in most discussions, particularly those concerning the maze procedure, that the discussant begins to focus in on the glaring deficiencies of the paper presented and the presenter begins to sweat. However, I must say that I could find no such deficiencies in this work to criticize. The authors were honest to point out that this is a selected group of patients and the findings cannot therefore be applied to all. It is a rather small group of patients. However, the importance of this study is not only in its design but also in the importance to those of us interested in this field and to the millions of patients who have atrial fibrillation. Many of the deficiencies of our own follow-up in our own series of patients have been corrected by this study. I am delighted to learn, for example, that the partial denervation that we have always suspected to occur as a result of the maze procedure is a temporary phenomenon. That has not been shown before. In addition, the authors confirm that both the sinus node function and atrial contraction continue to improve for up to a year. These findings, which I think are well established by this study, confirm our less sophisticated clinical observations that virtually all of these patients eventually become essentially normal after the operation.

I have one question only: In our own series of patients, we found a substantial variation regarding left atrial transport function between the findings in transthoracic and transesophageal echocardiograms. Did you find a similar disparity? I believe you mentioned that you did both transthoracic and transesophageal echocardiograms. We found a 10% to 15% variability, in that the transthoracic echoes in several patients have shown good function in the right atrium and no apparent function in the left atrium at 6 months. We then performed an immediate transesophageal echocardiogram, which confirmed the presence of excellent function by a transesophageal echocardiogram in the left atrium.

Dr Pasic. Dr Cox, thank you very much for your comments. We also had seen some variations between transthoracic and transesophageal echocardiographic results. We believe that some of these differences were patient-dependent, with variable echocardiographic conditions, as well as being due to different angles of transthoracic and transesophageal echocardiographic view. We considered transesophageal echocardiography with its different possibilities as an optimal method for assessment of mechanical function of the left atrium. Furthermore, pulsed Doppler echocardiographic quantification of blood flow across the mitral valve and therefore the left atrial systolic function can be influenced by several factors. The relationship between the height of the Doppler-recorded A (atrial) wave and that of the E (early) wave of the transmitral flow can be used to express the contribution of atrial contraction to left ventricular filling. However, the height of the A wave is dependent on the pressure gradient across the mitral valve at end-diastole. An important problem of our study was that the pressure gradi-

ents across the mitral valve in our patients were heterogeneous, because some patients underwent mitral valve replacement with mechanical prostheses, some with biologic prostheses, and some had mitral valve reconstruction. Patients with mitral valve replacement had a significantly smaller A to E wave because of a higher-than-normal transmitral E wave caused by relative stenosis or increased impedance across the prosthetic mitral valve compared with that of the native valve.

Furthermore, it is also possible that atrial function may be present but not detectable. The absence of detection of the A wave cannot rule out left atrial contraction. In 2 of our patients, the A wave could not be detected, but other transesophageal examinations with automated boundary echocardiography showed atrial contraction. Lack of a concomitant increase in the A wave or a reduced A/E ratio may suggest attenuation or absence of physiologic compensation resulting from extensive arteriotomies and cardiac denervation.

Dr Hartzell V. Schaff. I have 3 questions. Did you document that atrial contraction in the patients with the Cox maze procedure was really a sinus mechanism? Often there will be other sites of atrial depolarization early after the maze procedure.

Second, would you speculate on the outcome of patients who had only the left-sided incisions? Some surgeons might argue that in patients with mitral valve disease, atrial fibrillation might be ablated by just doing the left-sided incisions, and therefore you might avoid trauma to the area of the sinoatrial node.

Finally, some surgeons might question the wisdom of performing the maze procedure in patients who are receiving a mechanical valve; another protocol is ligation of the left atrial appendage, replacement of the valve with a mechanical prosthesis, and acceptance of long-term anticoagulation. Do you have any comparisons of outcome of these patients with parallel patients who did not have the maze procedure and simply had anticoagulation and ligation of the left atrial appendage?

Dr Pasic. Thank you very much for your comments. Your question about postoperative sinus node function and identification of the P wave, especially early after the Cox maze procedure, is an important one. We learned from the surface mapping performed early after the Cox maze procedure that pacemaker activity with a consecutive P wave may occur not only from the sinus node but also from any other ectopic site located in parts of the atria, the coronary sinus, the atrioventricular nodal area, the His bundle, or the bundle branches. Such sites may take over the pacing function from the sinus node because of modulation of normal pacemaker activity by postoperative neurohumoral autonomic influences and depressed activity of the sinus node. Therefore, early after the operation it is better to consider the rhythm as an atrial rhythm rather than a sinus node rhythm.

Regarding your second question, we started to perform the Cox maze III procedure in selected patients at the beginning of 1995. Our plan was to analyze the postoperative results of a group of patients having a uniform procedure. After excellent initial results, we have continued to perform the original Cox maze III procedure. We consider that the complete maze III procedure is more advantageous than only the left-sided maze procedure.

Your final question concerned our philosophy on performing the maze procedure in a patient receiving a mechanical valve who will require long-term anticoagulation. Although patients with mechanical heart valves should receive anticoagulation because of the increased thrombogenicity of the prostheses, the risk of thromboembolism is still present in some patients with atrial fibrillation. Theoretically, reversion of atrial enlargement by surgically decreasing the atrial dimensions, restoring sinus rhythm, and improving mechanical function of the left atrium after the Cox maze procedure might further reduce the incidence of thromboembolism. Proof of this hypothesis will require a longer follow-up.