Current perspective

Total correction of tetralogy of Fallot: late clinical follow-up

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Key words:
Arrhythmias;
Cardiac surgery;
Sudden cardiac death.

Forty-five years after the first repair of tetralogy of Fallot we have sufficient data to describe the post-surgical history of these patients in terms of survival, quality of life and delayed complications. The long-term results of surgical repair during infancy and childhood are good in terms of health assessment and exercise capacity. However arrhythmias and right ventricular dysfunction secondary to ventriculotomy and residual pulmonary regurgitation characterize the delayed follow-up. The identification of the clinical parameters which are predictive of premature ventricular dysfunction and electrical instability is a primary aim of clinical follow-up.

(Ital Heart J 2002; 3 (1): 24-27)

This study was supported by the Research Project of the Veneto Region (Italy), "Registry of operated patients with CHD. Clinical follow-up".

Received October 8, 2001; revision received November 27, 2001; accepted December 5, 2001.

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The first successful repair for tetralogy of Fallot was performed by Lillehei on August 31st, 1954[1]. Forty-seven years later the patient leads a normal life. A total of 10 patients were operated upon in this initial clinical series. There were 5 hospital and 3 delayed deaths: 1 patient died suddenly at home 13 years later; the second with a residual ventricular septal defect and pulmonary stenosis died during reoperation 10 years later when a large coronary artery in an anomalous location and hidden within adhesions was transected; the third late death occurred 17 years after operation when the patient hit a tree while driving home from a party[2]. Forty-five years after this initial series do we have data on patients operated upon for tetralogy of Fallot, which have modified medical and surgical strategies such as the timing and technique of surgery, the reduction of sequelae and the prevention of side effects? Perioperative death has been significantly reduced and is now less than 1% in high level cardiac surgery centers[3]. The surgical damage of the atrioventricular node or the common His bundle is prehistory. Actuarial 10, 20, 30 and 36-year survival rates of 490 patients who survived the first year after surgical repair were 97, 94, 89 and 85% respectively[4]. In terms of health assessment and exercise capacity, the long-term results of surgical repair during infancy and childhood are good: 82% of long-term survivors described their health as "excellent" or "good", and 79% had an almost normal exercise capacity of more than 80% of the predicted value[5,6]. Obviously, a good health assessment is an important determinant for the quality of life. We did not however find a correlation between a "good" or "excellent" health assessment and the absence of symptoms (decreased exercise capacity) or the occurrence of sequelae (right ventricular dysfunction, ventricular or supraventricular arrhythmia). This confirms that personal health assessment is an uncorrected indicator of the patient's objective clinical condition, and that during follow-up, invasive and non-invasive examinations have to be programmed.

If the long-term results of surgical repair were to be based on the presence of a normal cardiac anatomy or electrophysiology, the score would not be good: consequent to pulmonary and tricuspid incompetence, 60% of patients had substantial dilation of the right ventricle 5 years after operation and 90% after 15 years. At long-term follow-up 75% of patients had a ventricular or supraventricular arrhythmia as diagnosed at 24-hour ECG[7]. The relatively low prevalence of an elevated right ventricular systolic pressure reported in studies inclusive of a long-term follow-up (7-8%) is due to reoperations and to the more frequent use of a transannular patch. In the past, a high ventricular pressure was correlated with ventricular arrhythmias and with sudden death.

Clinical follow-up

Stratification of arrhythmic risk. In the last 15 years, follow-up of populations with a satisfactory surgical result has shown that electrical instability may result from anatomical modifications following surgery or from mechanical events such as ventricular dilation and stretching[8]. In these patients, particularly those operated upon late (> 5 years of age), abnormal fibrous tissue was found at different sites in the right and left ventricles. Fibrous fatty substitution characterizes the area around the scar, the residual effect of ventriculotomy. All these lesions might provide substrates for local abnormalities in ventricular depolarization and repolarization[9]. With regard to the ECG findings, the accuracy of signal-averaged ECG to non-invasively record abnormalities in ventricular depolarization is high, and the value of this method in predicting the risk of severe arrhythmias has been documented in patients with arrhythmogenic right ventricular cardiomyopathy, who have similar structural abnormalities in their myocardial walls. We found a statistically significant difference between the amplified ECG parameters of patients operated upon for tetralogy of Fallot with minor ventricular arrhythmias and those with severe arrhythmias; however the presence of complete right bundle branch block reduces the clinical significance of the occurrence of late potentials in these patients[10,11].

A QRS complex of > 180 ms, suggested by Gatzoulis et al.[12] as a strong predictive parameter of ventricular tachycardia because of a correlation between the duration of the QRS complex and the end-diastolic volume of the right ventricle, has had, in our experience, a low clinical significance, in the presence of complete right block. In fact, we were unable to distinguish the increased duration of the QRS complex secondary to surgical damage of the conduction tissue from that due to right ventricular dilation. Rather than the absolute value of the QRS complex duration, simultaneously occurring modifications in the duration of the QRS complex and in the end-diastolic volume of the right ventricle during post-surgical follow-up assume a more predictive significance. Because QT dispersion has been deemed to reflect inhomogeneous ventricular repolarization, we first described the clinical significance of spatial and temporal QT dispersion as independent predictive factors of ventricular instability in patients operated upon for total correction of tetralogy of Fallot by ventriculotomy with a cut-off of 80 and 65 ms respectively. QT dispersion was unrelated to the presence of right bundle branch block and to functional conditions of the right and left ventricles, in particular ventricular dilation. It is probably related to particular myocardial substrates secondary to ventriculotomy. Indeed, patients with uncorrected tetralogy of Fallot and patients undergoing correction through a transatrial approach showed significantly lower QT dispersion values than those in whom correction involved ventriculotomy.

In our series, at uni- and multivariate analysis, QT dispersion and the end-diastolic volume of the right ventricle were the parameters distinguishing between patients with and without ventricular tachycardia[13].

On the basis of the degrees of QT dispersion and of the end-diastolic volume of the right ventricle we can calculate the probabilities for sustained ventricular tachycardia or ventricular fibrillation.

Role of the adrenergic nervous system. Effort increases the likelihood of sudden death, suggesting a role of the adrenergic nervous system, such as in patients with long QT syndrome, myocardial ischemia and arrhythmogenic right ventricular cardiomyopathy. In these patients a myocardial adrenergic derangement has been demonstrated by means of 123-metaiodobenzylguanidine (MIBG) scintigraphy. We studied the autonomic nervous system of 22 patients operated upon for total correction of tetralogy of Fallot by MIBG scintigraphy and by heart rate variability analysis. In our study, heart rate variability and MIBG analysis showed significant abnormalities of the adrenergic nervous system, particularly in patients with repetitive ventricular arrhythmias. Heart rate variability data revealed a reduction in parasympathetic activity with consequent sympathetic dominance of the sinus node[14].

By means of MIBG-SPECT we demonstrated the presence of significant sympathetic innervation defects, particularly in the group at higher risk of ventricular tachycardia. Adrenergic fiber variability was more evident in patients with the highest ventricular end-diastolic volumes and the lowest ejection fraction of the right ventricle.

Right ventricular dysfunction and pulmonary valve incompetence. Finally, right ventricular dysfunction appears to be the most important factor of the post-surgical history, because it conditions ventricular electrical instability and, in the long term, progressive heart failure. Several recent reports correlate pulmonary insufficiency with right ventricular dilation and with a reduced capacity for exercise. Long-term follow-up data reveal that in more than 75% of cases, the indication to re-operation is pulmonary regurgitation. Homograft insertion for pulmonary regurgitation after repair of tetralogy of Fallot improves cardiorespiratory exercise performance in terms of an increased anaerobic threshold and oxygen uptake[15]. Nevertheless, in 70 patients operated upon for total correction who underwent delayed pulmonary valve replacement, after 4.7 years of follow-up, the incidence of ventricular tachycardia diminished from 22 to 9% ($p < 0.001$) and that of atrial flutter/fibrillation decreased from 17 to 12% ($p = 0.32$). This was the case even if right ventricular dilation decreased to 37% compared with preoperative 71%; QRS duration and QT dispersion remained unchanged[16].

After pulmonary valve replacement, no significant change in the heart rate response during exercise was

found. This suggests that the impaired chronotropic response occurring afterwards cannot be attributed to pulmonary regurgitation *per se* or to the decreased preload of the left ventricle, but to sinus node dysfunction, to impaired function of the autonomic nervous system, to a compensatory increase in the diastolic filling time or to the presence of conduction disturbances. Thus, the inadequate increase in stroke volume and cardiac output after exercise can be attributed to numerous factors including right ventricular fibrosis and scarring, a noncontractile ventricular septal or right outflow tract patch and an impaired coronary blood supply, particularly in patients who were much older at the initial tetralogy of Fallot repair. In addition, physical deconditioning is an important determinant of exercise performance. A recent study by the Toronto group[17] demonstrated the lack of a significant improvement in the contractility and dimensions of the right ventricle following pulmonary valve implantation in an adult cohort of patients. This was especially true for patients who underwent pulmonary valve replacement at a median age of 13 years and in patients with a preoperative right ventricular ejection fraction < 40%. The potential for contractile recovery and the capability of the right ventricle to undergo remodeling after pulmonary valve replacement may diminish over time.

Redington's group[18] has suggested that in patients operated upon for tetralogy of Fallot, a reduced right ventricular compliance, as indicated by diastolic forward flow in the pulmonary artery after atrial contraction, may later protect against the detrimental effects of pulmonary valve incompetence after repair (restrictive physiology). This effect was denied by Helbing and de Roos[19] who studied right ventricular diastolic function by means of magnetic resonance velocity mapping. Right ventricular outflow tract stenosis, pulmonary artery branch stenosis or a residual ventricular septal defect are additional lesions that may be present in patients in whom pulmonary incompetence is poorly tolerated. However, the associated lesions do not modify the length of the time interval from initial repair to pulmonary valve replacement (mean interval 13 vs 10 years) or the age at pulmonary valve replacement (mean value 19 years).

Treatment of arrhythmias and prevention of sudden death. In the middle of the '80s, Garson et al.[20] proposed an aggressive program aimed at the abolition of ventricular extrasystoles by means of antiarrhythmics. The concept that suppression of asymptomatic ventricular arrhythmias necessarily reduces the risk of sudden death was rejected by the results of the Cardiac Arrhythmia Suppression Trial (CAST)[21]. In particular, for patients operated upon for total correction of tetralogy of Fallot by ventriculotomy, the prognostic significance of ventricular arrhythmias was determined by Cullen et al.[22], who confirmed that patients with ventricular extrasystoles or nonsustained ventricular tachycardia are not at high risk of sudden death: furthermore the risk may actually be increased by the administration of potentially proarrhythmic drugs. Moreover, the consequences of chronic use and side effects also have to be taken into consideration. Nowadays, the prevention of sudden death by antiarrhythmics should be restricted to patients with complex ventricular arrhythmias or sustained ventricular tachycardia, in the absence of severe symptoms or residual hemodynamic substrates amenable to surgical reintervention such as residual pulmonary stenosis or pulmonary valve incompetence. The cardioverter-defibrillator should be implanted in patients with severe right ventricular dysfunction who have been resuscitated after ventricular fibrillation or who have had episodes of syncope with rapid sustained ventricular tachycardia in spite of chronic use of amiodarone or amiodarone plus beta-blockers. In the series of Therrien et al.[16], 15 patients with recurrent monomorphic ventricular tachycardia underwent concomitant intraoperative mapping and ventricular cryoablation at the time of pulmonary implant; none of them had recurrent ventricular tachycardia after surgery. The same results were observed in 6 patients with preoperative recurrent episodes of atrial flutter/fibrillation in whom no tachyarrhythmias were recorded after cryoablation performed during replacement of the pulmonary valve. On the contrary, more than 70% of patients in whom cryoablation was not performed during pulmonary valve replacement continued to suffer from recurrent tachyarrhythmias after surgery. Percutaneous transcatheter radiofrequency ablation seems to be effective[23,24] in the presence of macroreentry usually located near the ventriculotomy scar in the infundibular area. More than one circuit can exist in the same patient and the ablation might produce a new substrate for repetitive arrhythmias.

Final considerations

Current surgical policy, aimed at early complete surgical correction, results in considerable transannular patch rates which induce residual pulmonary regurgitation and an increased percentage of stenosis of the pulmonary arteries[25]. Thus the optimism for minor electromechanical complications during delayed follow-up might necessitate re-evaluation.

In the future, clinical follow-up will include measures aimed at avoiding these disadvantages by means of appropriate surgery (homograft, monocuspid patch, others) or timely interventional catheterization techniques. However, the final fate of these procedures remains unknown. Thus, the primary aim is primitive preservation of the pulmonary valve and of its annulus.

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