Baština Akademije nauka i umjetnosti Bosne i Hercegovine

Perspectives in Paediatric Cardiology: Perspektive u pedjatrijskoj kardiologiji

Mesihović Dinarević, Senka

2012

Akademija nauka i umjetnosti Bosne i Hercegovine

https://bastina.anubih.ba/items/ff7d5ad2-af81-4f1b-8490-552285003fe6

Preuzeto s Baštine Akademije nauka i umjetnosti Bosne i Hercegovine

https://bastina.anubih.ba/

ADULT PATIENTS WITH FALLOT'S TETRALOGY: NATURAL HISTORY, LATE OUTCOME AFTER OPERATION AND RV- LV INTERACTION

Jochen Weil

Abstract

Tetralogy of Fallot (TOF) is the most frequent cyanotic congenital heart disease. According to a recent prospective study on the prevalence of congenital heart diseases in Germany, 2.5% of all neonates suffer from TOF [1].

Without treatment this frequent occurring CHD has a high morbidity and mortality. Surgical treatment has improved this grim outlook dramatically.

In the following, the rate of survival and morbidity of the natural and unnatural history will be summarized.

Natural history

The degree of central cyanosis in patients with TOF depends on the severity of the RVOTO. In early infancy the cyanosis might be less significant, but with increasing age the RVOTO becomes more severe and the patient more cyanotic.

Before the era of palliative or corrective surgery the mortality and morbidity of unoperated patients was high.

In 1978 E.G. *Bertranou and coworkers* [2] analysed all published autopsy cases of patients with TOF who died without surgical treatment to determine the life expectancy of such patients. These data were compared with a study of patients living in Denmark in 1949 [3]. The rates of survival according to these two sources were remarkably similar. According to these data 75% of patients with TOF and pulmonary stenosis were alive at age 1 year, 60% at 3 years and 30% at age 10 years (Figure 1).

In the subset of patients with TOF and pulmonary atresia the survival rates were lower than in patients with pulmonary stenosis indicating that only 66% of patients were alive at age 6 months, 50% at 1 year, 33% at 2 years and 8% at age 18.

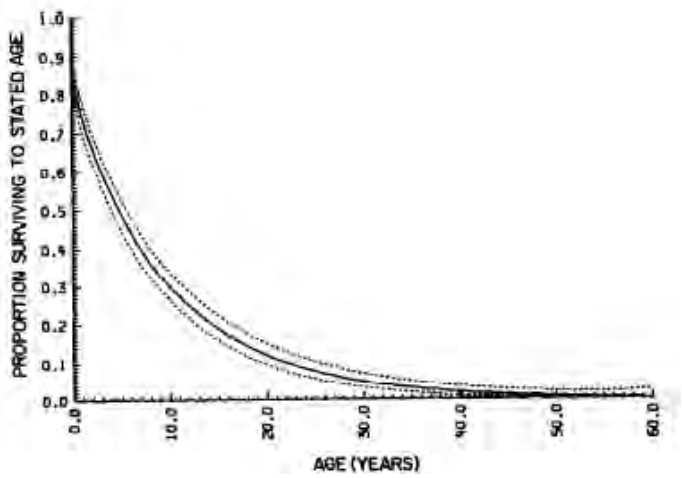

Figure 1: Life expectancy of persons with Tetralogy of Fallot without pulmonary atresia (After Bertranou et al. (1978) Life expectancy without surgery in Tetralogy of Fallot. Am J Cardiol 42(3):458-66, with permission)

These data were comparable to other publications. *M. Samanek* [4] studied the probability of survival in non operated children with CHD in Bohemia. For the patients with TOF, the actuarial survival rate at 1 year was 64%, at 5 years 49%, at 10 years 23% and only 4% at 15 years. *M. Campbell* [5] found the mean age at death in Fallot's Tetralogy of 8, 9 years.

There are several case reports on individuals with non treated TOF and unusual longevity such as the report on the American composer Mr. Henry Gilbert who died 8 days following left hemiplegia within a few months of his 60th birthday [6].

Morbidity in adult survivors of TOF without surgery is high. The chronic hypoxemia results in exercise of intolerance and excessive erythrocytosis with an increased risk of thrombosis. Cerebral abscesses are frequent since infectious agents can easily reach the brain via right to left shunting on ventricular level. The risk of thrombosis and brain abscess is increased in the presence of iron deficiency due to the impaired rheology.

Death occurs frequently secondary to RV failure due to long standing RV pressure load and secondary to endocarditis or to arrhythmia.

Patients with repaired TOF

The introduction of surgical repair of TOF has dramatically improved the survival and decreased the morbidity in these patients.

There are a number of issues which are important to consider for the long-term care of adult patients surviving surgical repair of TOF.

The following issues are dealt in this chapter:

– Survival
– Reoperations
– Changes of left heart

The issues of pulmonary valve regurgitations with requirement of pulmonary valve replacement, arrhythmia and sudden death are covered in the respective chapters.

Long-term survival after repair

It is obvious that the era in which a patient was operated would influence the outcome, as well the age in which the patient underwent the repair.

Kirklin and co-worker [7] reported a hospital mortality of 50% in 1955 and 15% in 1960. Nowadays the hospital mortality will be <5% in patients after repair in most centres [8].

There are several recent publications reporting an excellent survival over 3 decades after successful operation or primary repair.

Murphy and co-workers [9] reviewed the records of all patients who underwent complete surgical repair of TOF at the Mayo Clinic (USA) between 1955 and 1960 and survived the immediate (30 days) postoperative period. The overall 32 years actuarial survival rate among 163 patients was 86% as compared with an expected rate of 96% in a control population matched for age and sex (Figure 2).

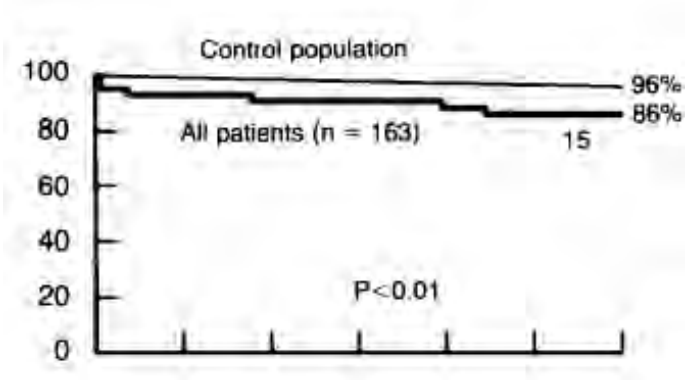

Figure 2: Long-term survival of patients with complete repair of Tetralogy of Fallot who survived the immediate postoperative period.

This panel shows the actuarial survival rate up to 32 years after surgery for all patient groups combined and the expected survival rate in an age- and sex-matched control population. (After Murphy et al. (1993) Long-term outcome in patients undergoing surgical repair of Tetralogy of Fallot. Engl J Med 329:593–599, with permission)

The survival rates among patients less than 12 years of age ranged between 90 and 93% which was slightly less than the expected rates. Among patients 12 years old or older at the time of surgery the survival rate was only 76% as compared with an expected rate of 93%. Primary palliation with a Blalock-Taussig shunt before repair was not associated with a reduced long-term survival nor was the need for a transannular patch at the time of surgery. A systolic RV-LV pressure ratio of 0.5 and more was predictive of a higher mortality during the first 20 years after surgery (92% versus 88% after 20 years).

Most patients had a good functional status with 77% in New York Heart Association (NYHA) functional class I, 17% in class II and 6% in class III at the late follow-up examination. Late sudden cardiac death occurred in 10 patients.

This study provides evidence that the rate of long-term survival – even in the earliest era of open heart surgery – is excellent, but remains lower than in the general population. The actuarial survival rate was 90% of the expected survival rate. The late functional status was also excellent. The occurrence of late sudden cardiac death accounted for approximately half of all late deaths.

Similar good long-term results were reported by *Nollert and co-workers* [10] in 490 patients who were operated from 1958 to 1977 and survived the first year after surgical repair. They found actuarial 10–, 20–, 30– and 36 years survival rates of 97%, 94%, 89% and 85% respectively. The most common cause of death was sudden cardiac death (n=13) followed by congestive heart failure (n=6).

It is important to realize that the mortality increased 25 years after surgery from 0.24% to 0.94% per year which emphasizes the need for close life-long follow-up examinations (Figure 3).

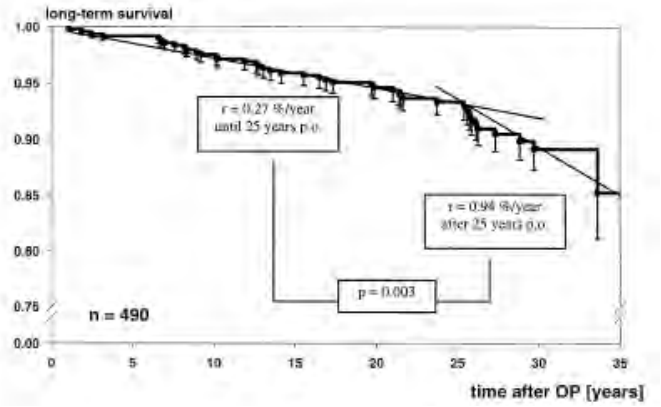

Figure 3: Long-term survival after correction of TOF. All patients who died within the first year after correction were excluded for calculation of long-term survival. The curve shows two different phases that are distinct. The early, low first phase lasts 25 years; thereafter, the risk increases significantly. Mortality risk (r) per year, as a linearized number, is calculated for each phase. Note the break in the y axis. OP = operation; p.o. =

postoperatively. (After Nollert et al. (1997) Long-Term Survival in Patients with Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year after Surgical Repair. JACC Vol. 30, No. 5:1374–83, with permission)

In the Single centre 50 years' experience with surgical management of Tetralogy of Fallot, *Lindberg and co-workers* [8] reported the long-term outcome in 570 patients showing that there was no difference in security from death or reoperation following primary repair versus primary palliation (Figure 4). This finding was in agreement with the previous publications by *Nollert and co-workers* [10].

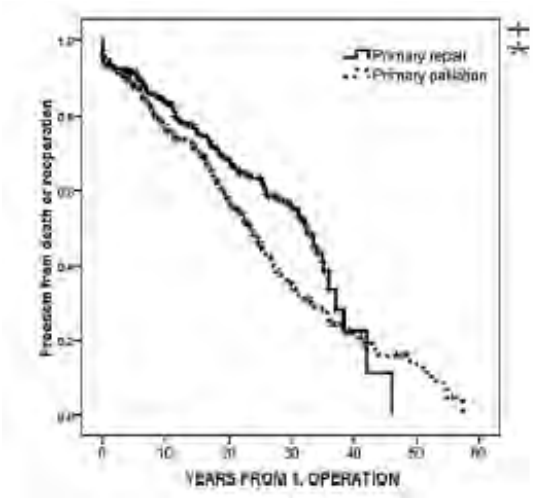

Figure 4: Long-time follow-up after different approaches in surgical treatment, primary repair or primary palliative surgery. (After Lindberg et al. (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

Furthermore it was shown that there was no difference in long-term survival between patient with and without transannular patch [8, 11,].

Reoperations

The long-term survival of patients after repair for TOF is excellent; these patients however continue to be at risk for long-term morbidity. With increasing length of follow-up from the time of primary surgery, problems will occur such as

– stenosis of the RVOT
– pulmonary valve regurgitation
– branch pulmonary arteries
– regurgitation of tricuspid valve

These problems may be well tolerated for the early years after operation, but with longer period of long-term follow-up there is an increased risk for ventricular and supraventricular arrhythmia, heart failure and sudden cardiac death.

Reoperations are required in about 10–30% of patients with TOF during long-term follow-up [9, 12, 13, 14].

The group from the Toronto Congenital Cardiac Centre for Adults reviewed its experience with reoperation in adults who got their primary repair at a mean age of 13.3 years [12]. Out of a total of 330 patients with repaired TOF over 18 years of age, 60 consecutive patients underwent reoperation between 1975 and 1997. Mean age at reoperation was 33.3 years and the mean follow-up after reoperation was 5 years.

The most common indication for reoperation was complications of the RVOT in 75% of patients. Severe pulmonary valve regurgitation (38%) and conduit failure (22%) were the most frequent problems of the RVOT. Less frequent indications were a significant leak after patch closure of the VSD and severe tricuspid valve regurgitation.

A bioprosthetic valve to reconstruct the RVOT was used in 42 out 60 patients. The number of reoperations increased in the recent years. Within the last 6 years (1990–1996) 72% of all reoperations were performed (Figure 5).

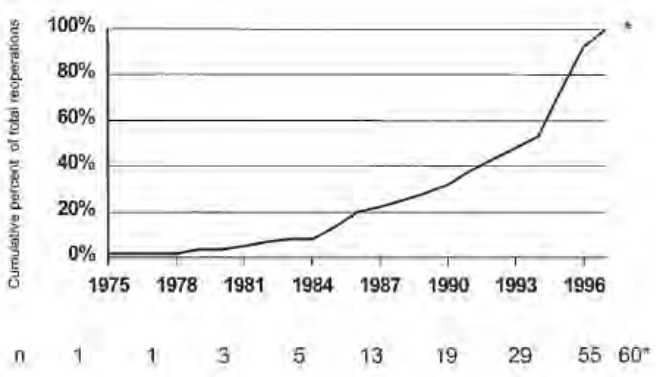

Figure 5: Cumulative percent of reoperations from 1975 until March 1997. There is a marked increase of reoperations in recent years. N indicates numbers of reoperations. Asterisk denotes March 31, 1997 (After Oechslin et al. (1999) Reoperation in adults with repair of Tetralogy of Fallot: indications and outcomes. J Thorac Cardiovasc Surg 118(2):245–51, with permission)

There was no perioperative mortality. The most recent follow-up examinations revealed excellent results after reoperation: 93% of the patients were in NYHA classification I or II. Actuarial 10-year survival reached 92% (Figure 6).

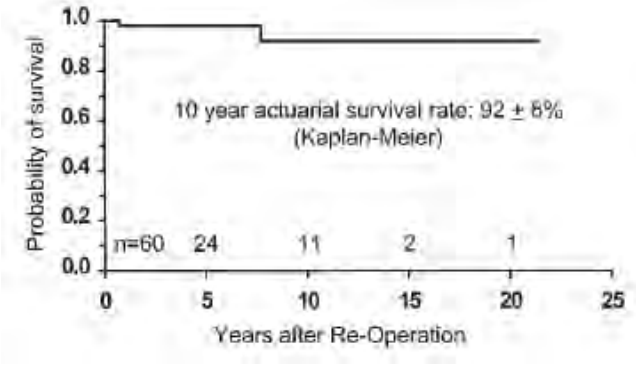

Figure 6: Kaplan-Meier actuarial survival analysis for patients after reoperation. N represents the number of patients entering each time interval. (After Oechslin et al. (1999) Reoperation in adults with repair of Tetralogy of Fallot: indications and outcomes. J Thorac Cardiovasc Surg 118(2):245–51, with permission)

In an earlier retrospective study from the Mayo Clinic (USA), a reoperation rate was found in 10% (16 patients) of 163 survivors who had their repair between 1955 and 1960 [9]. At that time the principal reasons for late reoperations were residual ventricular septal defects (10 patients) and false aneurysm of the pulmonary outflow tract (3 patients). Only 2 out of 16 patients requiring reoperations got a valve replacement for severe pulmonary valve insufficiency.

The use of a transannular patch does not influence the long-term survival, but increases the risk of reoperation due to severe pulmonary valve regurgitation.

Lindberg and co-workers [8] showed that the freedom from reoperation was significantly reduced in patients repaired with a transannular patch compared to patients without (Figure 7). These authors did not find an influence of previous palliation, transatrial or transventricular repair on the rate of survival or reoperations.

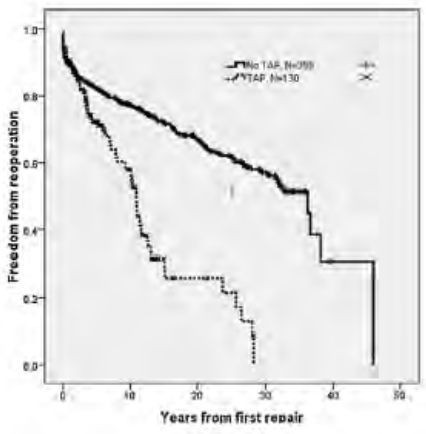

Figure 7: The influence of repair crossing the pulmonary annulus upon freedom from reoperation following surgery for Tetralogy of Fallot (After Lindberg et al. (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

Similar results were published by *Park and co-workers* [13]. They found a rate of reoperation or intervention in 31.7% (224 patients) out of 734 patients. The most common causes for reoperation or re-intervention were pulmonary valve regurgitation in 109 patients and branch pulmonary artery stenosis in 127 patients. It could be shown that preservation of the pulmonary annulus can reduce the reoperation rate.

Interestingly the rate of reoperations seems not to be changed over the last decades. The frequency of reoperations did not differ significantly during five decades from 1959–2009 according to the publications by *Lindberg and co-workers* [8] (Figure 8).

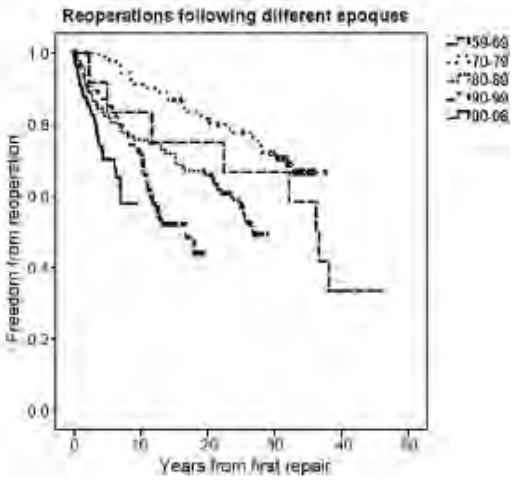

Figure 8: Survival and frequency of reoperations during the five different decennials following surgery for Tetralogy of Fallot (After Lindberg et al (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

It is anticipated that the rate and the mode of reoperations will change in the present time or in the future.

Nowadays intraoperative echocardiography is performed in most centres. With the help of this intraoperative monitoring of the surgical results, a residual ventricular septal defect, significant tricuspid valve regurgitation or a severe RVOTO are detected and treated immediately. These lesions should require less frequent reoperation than decades ago.

Furthermore many reoperations can be replaced by non-surgical treatment in the catheterization laboratory. The most common morbidity in the long-term outlook is the problem with the RVOT and the pulmonary arteries.

Stenosis of branch pulmonary arteries can be now treated in most patients with balloon dilatation and/or implantation of stents. Re-stenosis or insufficiency of an

RV to pulmonary artery conduit are amenable to percutaneous pulmonary valve replacement.

Right-left ventricular interaction

Despite an excellent long-term survival after repair of TOF many patients will show a significant morbidity. This morbidity will increase with time after repair and is thought to be caused mainly by problems of the right heart such as stenosis and insufficiency of pulmonary valve with consecutive RV pressure and volume load. These changes lead to a reduced RV function with decreased exercise tolerances and functional status as well as atrial and ventricular arrhythmia and sudden death.

Over the last years it has become obvious that the changes of the right heart after repair for TOF will affect the morphology and performance of the left heart.

Broberg and co-workers studied the LV function with echocardiography in 511 adult patients with a mean age of 37.2 years. All patients had a successful repair of TOF performed at a median age of 6 years. In this large cross-sectional study LV systolic dysfunction was found in 20.9% of patients with TOF. LV dysfunction was defined as a LVEF < 55% showing increased LV diameter, decreased fractional LV shortening and a reduced myocardial performance index. A moderately (EF 35–44%) and severely (EF < 35%) reduced LV function was found in 5.2% and 1.1% respectively out of the 20.9% of patients with LV dysfunction (Figure 9).

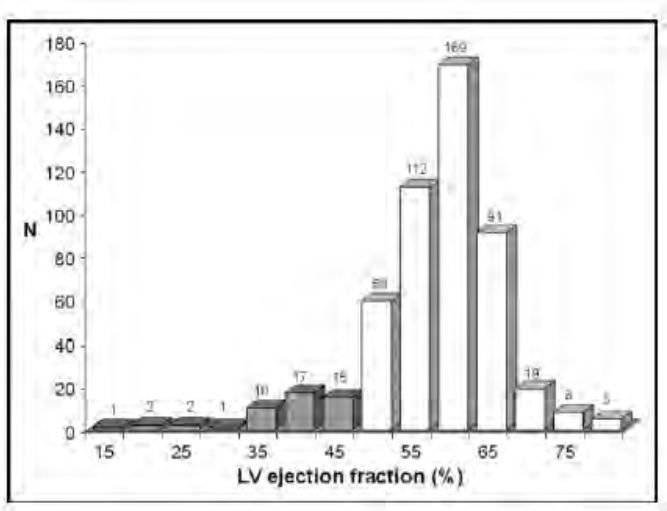

Figure 9: Histogram of estimated left ventricular ejection fraction displays the lower limit of each category (x-axis labels) and decreased ejection fraction (gray bars).
From Broberg.

There was a strong association between a reduced RV function and LV dysfunction. Most patients with normal LV function had normal RV function (67%) In patients

with moderate-severe LV-dysfunction only 28% had a normal right ventricle, whereas 44% had a moderate to severe RV dysfunction. (Figure 10).

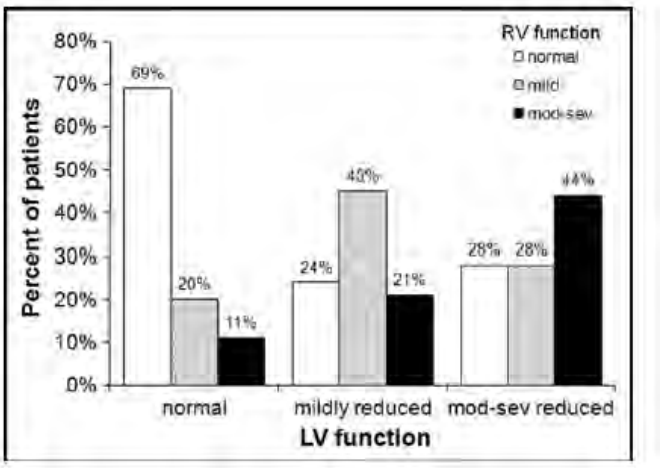

Figure 10: Histogram of estimated left ventricular function were more likely to have normal left ventricular function. In contrast, moderate-severe (mod-sev) right ventricular dysfunction was more prevalent in patients with moderately to severely decreased left ventricular dysfunction (p <0.001, chi-square test).

From Broberg

Interestingly there was no relation between the severity of pulmonary regurgitation and LV function. This is in accordance with a study by *Geva et al.* who did not find a correlation between the degree of pulmonary valve regurgitation and impaired clinical status.

A strong association, however, could be found between LV dysfunction and arrhythmia. Patients with LV dysfunction showed a wider QRS duration and had more often previous arrhythmia or implantation of a pacemaker and cardioverter-defibrillator, respectively.

The assumption that reduced LV function results in an increased risk of arrhythmia was supported by a retrospective survey of implanted cardioverter-defibrillator discharges in patients with TOF (*Khairy P, circulation Lit 15 and 16 bei Broberg).*In this study the strongest independent predictor for appropriate shock was an increased LV end-diastolic pressure, more than RV dysfunction, QRS duration or syncope.

There is further evidence that there is a close relationship between reduced RV and LV dysfunction suggesting an unfavourable ventricular-ventricular interaction in patients with repaired TOF. *Geva and co-workers* studied 100 consecutive patients with a median age of 21 years after repair. They correlated the clinical functional class of these patients with the ejection fraction of RV and LV determined by cardiac MRT. They found that a low LV ejection fraction – more than an RV dysfunction

– was to the strongest independent factor associated with impaired clinical status. The combination of lower LV EF (< 40%) and older age at TOF repair had a high sensitivity and specificity for being in NYHA functional class > III.

Furthermore a significant correlation was found between RV and LV ejection fraction in these patients (Figure 10). This finding confirmed the results of a previous publication in adults after TOF repair which showed an adverse right-to-left ventricular interaction in patients with RVOT aneurysm or akinesia (*Davlouros*)

All these data underline the necessity not only to focus on RV mechanics and its interaction with pulmonary valve regurgitation, but also on concomitant dysfunction of the LV. The mechanism that links RV dysfunction to a decrease in LV function is not clearly understood. Possible causes for LV dysfunction could be chronic hypoxemia, altered mechanics of IVS due to patch closure of VSD and volume loading of RV, damage of coronary arteries during repair or altered electro-mechanical interactions due to a long QRS duration.

Another cause for ventricular dysfunction could be ventricular fibrosis. *Babu-Narayan et al.* examined the extent of fibrosis in RV and LV detected by late gadolinium enhancement (LGE) using cardiovascular MRT in 92 adult patients with repaired TOF. Besides marked fibrosis in different parts of the RV, they found LGE in the LV (53%) not only at the apex consistent with apical vent insertion (49%), but also in the inferior or lateral wall consistent with infarction (5%) or in other areas (8%).

References

1. Lindinger A, Schwedler G, Hense HW. Prevalence of Congenital Heart Defects in Newborns in Germany. Results of the First Registration Year of the PAN Study (July 206 to June 2007). Klin Padiatr 2010;222: 321–326.
2. Bertranou EG, Blackstone EH, Hazelrig JB, Turner ME, Kirklin JW. Life expectancy without surgery in Tetralogy of Fallot. Am J Cardiol 1978;42(3):458–66
3. Rygg IH, Olesen K, Boesen I. The life history of Tetralogy of Fallot. Dan Med Bull 1971;18(SupplI):25–30
4. Samánek M. Children with congenital heart disease: probability of natural survival. Pediatr Cardiol 1992;13(3):152–15
5. Campbell M. Natural history of cyanotic malformations and comparison of all common cardiac malformations. Br Heart J 1972;34(1):3–8
6. White PD, Sprague H. The Tetralogy of Fallot. Report of a case in a noted musician who lived until his 60th year. JAMA 1929;92:787–91
7. Kirklin JW, Wallace RB, McGoon DC. Early and late results after intracardiac repair of Tetralogy of Fallot: 5–year review of 337 patients. Ann Surg 1965;162:578–89
8. Lindberg HL, Saatvedt K, Seem E, Hoel T, Birkeland S. Single-center 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 2011;40;538–542
9. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, McGoon DC, Kirklin JW, Danielson GK. Long-term outcome in patients undergoing surgical repair of Tetralogy of Fallot. Engl J Med 1993;329:593–599

10. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichard T. (1997) Long-Term Survival in Patients With Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year After Surgical Repair. JACC Vol. 30, No. 5:1374–83
11. Bacha EA, Scheule AM, Zurakowski D, Erickson LC, Hung J, Lang P, Mayer JE Jr, del Nido PJ, Jonas RA. Long-term results after early primary repair of Tetralogy of Fallot. J Thorac Cardiovasc Surg 2001;122:154–161
12. Oechslin EN, Harrison DA, Harris L, Downar E, Webb GD, Siu SS, Williams WG. Reoperation in adults with repair of Tetralogy of Fallot: indications and outcomes. J Thorac Cardiovasc Surg 1999;118(2):245–51
13. Park CS, Lee JR, Lim HG, Kim WH, Kim YJ. The long-term result of total repair for Tetralogy of Fallot. Eur J Cardiothorac Surg 2010;38(3):311–7
14. Gerling C, Rukosujew A, Kehl HG, Tjan TD, Hoffmeier A, Vogt J, Scheld HH, Krasemann T. Do the age of patients with Tetralogy of Fallot at the time of surgery and the applied surgical technique influence the reoperation rate? Herz 2009;34(2):155–60