Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation

Folkert J. Meijboom, MD, PhD,^a Jolien W. Roos-Hesselink, MD, PhD,^a Jackie S. McGhie,^a Silja E. C. Spitaels, MD, PhD,^a Ron T. van Domburg, MS, PhD,^a Lisbeth M. W. J. Utens, PhD,^c Maarten L. Simoons, MD, PhD,^a and Ad J. J. C. Bogers, MD, PhD^b

The GUCH team at Erasmus MC

Earn CME credits at <http://cme.ctsnetjournals.org>

From the Departments of Cardiology^a and Cardio-Thoracic Surgery^b of the Thoraxcentre and the Department of Child Psychiatry,^c Sophia Children's Hospital, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

The Netherlands Heart Foundation, research grant No. 99.033, financially supported the study.

Received for publication April 24, 2007; revisions received June 18, 2007; accepted for publication July 5, 2007.

Address for reprints: Folkert J. Meijboom, MD, PhD, Erasmus MC, Thoraxcentre, Room BA 300, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands (E-mail: w.tomasouw@erasmusmc.nl).

J Thorac Cardiovasc Surg 2008;135:50-5

0022-5223/\$34.00

Copyright © 2008 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2007.07.030

Objective: The aim of the study was to assess the long-term results of a selective policy toward pulmonary valve replacement in adult patients with repaired tetralogy of Fallot and severe pulmonary regurgitation.

Methods: Sixty-seven patients with tetralogy of Fallot were followed up from 15 ± 3 years until 27 ± 3 years after surgery.

Results: Twenty-two patients had mild-to-moderate pulmonary regurgitation. No significant changes occurred in the follow-up period. Of 45 patients with severe pulmonary regurgitation and severe right ventricular dilatation, 28 (62%) remained free of symptoms and did not undergo pulmonary valve replacement. No changes in right ventricular size or exercise capacity were found. In 3 (11%) of 28 patients, QRS duration increased to more than 180 ms. Seventeen patients had symptoms and underwent pulmonary valve replacement: 9 (54%) of 17 patients improved clinically and echocardiographically, and QRS duration shortened postoperatively. Right ventricular dimensions did not regress despite pulmonary valve replacement in 8 patients.

Conclusion: Refraining from pulmonary valve replacement in asymptomatic patients led to no measurable deterioration in 25 (89%) of 28 patients. Referring symptomatic patients for pulmonary valve replacement led to an improvement in 9 (53%) of 17 patients. In 11 (24%) of 45, a selective approach led to questionable or unsatisfactory results.

Surgical correction of tetralogy of Fallot consists of closure of the ventricular septal defect and relief of the right ventricular (RV) outflow tract obstruction. A longitudinal incision from the RV outflow tract across the pulmonary annulus into the main pulmonary artery, closed with a transannular patch, was used liberally in the 1970s and 1980s, because the most important factor associated with poor survival and ventricular arrhythmias was identified as elevated RV pressure persisting after surgery.¹⁻³ The unavoidable consequence of this approach is pulmonary regurgitation (PR). PR, even if it is severe, is tolerated remarkably well in childhood, but in adolescence and adulthood RV dysfunction develops in some patients.^{4,5} Presenting symptoms are signs of venous congestion, deterioration of exercise capacity,⁶ or arrhythmias, both ventricular⁷⁻⁹ and supraventricular.^{10,11} Pulmonary valve replacement (PVR) for symptomatic patients has been the treatment of choice for years.¹²⁻¹⁶ In 2000, Therrien and associates¹⁷ reported that RV

Abbreviations and Acronyms

ECG	= electrocardiogram
PR	= pulmonary regurgitation
PVR	= pulmonary valve replacement
RV	= right ventricular
TR	= tricuspid regurgitation

function sometimes did not recover after valve replacement, especially if RV ejection fraction was substantially decreased. Because decline in RV ejection fraction, and the coinciding increase of RV dimensions, is thought to be a gradual process, an intervention earlier in the process was advocated.¹⁸ In recent years, many have reported low surgical risks and good short-term results of this policy,¹⁹⁻²⁷ but no long-term results are yet known. When these results become available, they should be compared with long-term follow-up data of the alternative, more selective approach to help to determine the optimal timing of PVR.²⁸ This study presents the outcome of a selective approach in a single-institution, longitudinal, ultra-long-term follow-up study of a cohort of patients with tetralogy of Fallot with varying degrees of PR and RV dilatation, with emphasis on how patients fared with severe PR and severe RV dilatation who were not operated on.

Patients and Methods

A total of 77 patients with tetralogy of Fallot, who underwent intracardiac surgical repair in our institution between 1968 and 1980 at a mean age of 4.7 ± 3.4 years, participated in a follow-up study in 1990, 15 ± 3 years after surgery.¹⁰ Since then, all were followed up at regular intervals at our institutional outpatient clinic. In 2001, they were invited to participate in a second follow-up study. Those who responded positively underwent an extensive cardiologic and psychologic examination in 2001 and 2002. The results of the psychologic study were presented separately.²⁹ The study was approved by the local ethical review board.

Definition of Subgroups of the Study Population

Patients who participated in the second follow-up study were divided in 3 groups. Group 1 consisted of patients with mild-to-moderate PR on the basis of the 1990 echocardiogram. Group 2 comprised patients with severe PR in 1990 who did not undergo PVR. Group 3 consisted of patients with severe PR in 1990 who underwent PVR before 2002.

Types of Measurements

In 2002, all participants underwent the same set of investigations as in 1990: medical history, physical examination, 12-lead electrocardiogram (ECG), 24-hour ambulatory ECG, echocardiographic examination, and a bicycle exercise test. In the group with PVR, the indication for PVR was retrieved. All patients underwent an extensive psychologic examination, which is reported separately.²⁹

Echocardiographic measurements and definitions. PR and tricuspid regurgitation (TR) were assessed by color Doppler and

were classified as absent to light, moderate, or severe. Maximal flow velocity over the pulmonary valve was measured with continuous-wave Doppler. RV dimensions at the level of the RV outlet were measured by M-mode in the standard parasternal long-axis view. RV dimensions at the inlet level were measured in the apical 4-chamber view just above the tips of the tricuspid valve, from the interventricular septum to the lateral wall.³⁰ Two persons measured, independently from each other, all echocardiographic parameters from both the 1990 and the 2002 study. Patients who were in sinus rhythm in 1990 and who had ventricular pacing in 2002 were excluded from comparative measurements of RV dimensions.

ECG measurements. The maximum width of the QRS complex was measured in the lead with the longest QRS duration, usually V₁. Patients with a ventricular pacemaker rhythm were excluded from the QRS analyses.

Exercise test. Maximal exercise capacity was assessed with bicycle ergometry with stepwise increments of 20 W/min until exhaustion. Tests were assumed to be maximal if the impression was that the patient had exercised maximally and if greater than 80% of the targeted maximal heart rate was reached.³¹ Test results were excluded if the maximal heart rate was less than 80%. The results are presented as relative to the predicted value for age, sex, and body length, standardized for the Dutch population (M. L. Simoons,³² Computer Assisted Interpretation of Exercise ECGs. PhD thesis, Rotterdam, The Netherlands, 1976). Patients who were in sinus rhythm in 1990 and who had ventricular pacing in 2002 were excluded from comparative measurements of exercise capacity.

Definitions of Outcomes

The outcome was called satisfactory if the aims of the treatment were met: measurable improvement (in terms of ECG, exercise test, and echocardiographic measurements) in case of PVR and no signs of deterioration (in terms of ECG, exercise test, and echocardiographic measurements) in the group of patients who were treated conservatively. The outcome was defined as unsatisfactory if the treatment aims were not met: no improvement after PVR or deterioration in the group of patients with conservative treatment. Significant increase of echocardiographic measurements, QRS duration greater than 180 ms, or decreased exercise capacity relative to the test in 1990 were graded as unsatisfactory outcomes.

Statistical Analysis

Time-related data are presented as mean values with standard deviation. A Fisher exact test was used for comparison of dichotomized variables. A Student *t* test was used for comparison of 2 sets of continuous variables.

Results: Study Participation and Subgroup Analysis

Since 1990, all patients were checked regularly at our outpatient clinic, with intervals between visits ranging from 1 to 3 years. Visits included history, physical examination, 12-lead ECG, and occasionally echocardiography. Sixty-seven patients, 87% of the patients who had participated in the 1990 study, had an extensive cardiologic evaluation in 2002, 26 ± 3 years after surgery. The mean age was 30 ± 5 years. Group 1, with mild-to-moderate PR, comprised 22

TABLE 1. Age at operation, surgical data, and duration of follow-up

	Mild-to-moderate PR	Severe PR	
		No PVR	With PVR
No. of patients	22	28	17
Surgical data			
Age at operation (y)	5.3 ± 3.3	3.5 ± 2.5	4.2 ± 3.4
Prior palliation: n (%)	4 (18%)	8 (30%)	9 (50%)
Transannular patch: n (%)	2 (9%)	20 (74%)	14 (78%)
Cold cardioplegia: n (%)	7 (32%)	13 (48%)	9 (50%)
Follow-up			
Age in 2002 (y)	30.9 ± 5.7	27.7 ± 4.7	27.6 ± 5.8
Years after surgery	25.4 ± 2.8	23.9 ± 2.6	23.3 ± 2.7
Years after PVR			6.4 ± 4.4

PR, Pulmonary regurgitation; PVR, pulmonary valve replacement.

patients. Group 2, severe PR in 1990 and not having undergone PVR, consisted of 28 patients. Group 3 comprised 17 patients with PVR 18.6 ± 5.4 years after surgical correction. In Table 1 the most important differences between the subgroups are shown. Table 2 summarizes the changes in time of echocardiographic parameters, QRS duration, and results of the exercise test.

Mild-to-moderate PR (n = 22). None of the 22 patients had symptoms: no arrhythmia and no decrease in exercise capacity. None of these patients used medication and none had signs of venous congestion.

ECHOCARDIOGRAPHIC RESULTS. The degree of regurgitation and the RV dimensions, both at the inflow and at the outflow tract level, had not changed significantly in 12 years. None of the patients in this group had more than mild TR.

ECG. All patients were in sinus rhythm. None of the patients had a QRS duration of 180 ms or more.

EXERCISE TEST. In 22 of 22 patients (100%), a conservative treatment had led to a satisfactory outcome (Table 2).

Severe PR; no PVR (n = 28). Twenty-six (93%) patients reported no symptoms between 1990 and 2002. Two patients had had one period of atrial fibrillation, for which direct-current cardioversion was performed; they remained asymptomatic afterward, without medication. In 2002, nobody used cardiac medication. None of these patients had signs of venous congestion.

ECHOCARDIOGRAPHIC ANALYSIS. The relevant echocardiographic parameters of this group and the changes over time are presented in Table 2. One patient had moderate TR; in 27 patients the TR was not more than mild.

ECG. All 28 patients were in sinus rhythm in 1990 and in 2002. In Table 2, the change in QRS duration between in 1990 and 2002 is shown. There was a statistically significant increase in QRS duration in the whole group of patients; the number of patients with a QRS duration of more than 180 ms increased from 2 to 3.

TABLE 2. Changes in echocardiographic parameters, ECG, and exercise capacity between 1990 and 2002

	15 y after surgery	26 y after surgery	P value
Mild/moderate PR (n = 22)			
Echocardiography (n = 22)			
RVOT diastole (mm)	27 ± 5	26 ± 8	.7
RVOT systole (mm)	23 ± 6	22 ± 6	.6
RV inlet diastole (mm)	49 ± 7	50 ± 6	.6
RV systole (mm)	37 ± 6	38 ± 5	.5
PA Vmax (m/s)	1.9 ± 0.8	2.3 ± 0.9	<.01
ECG (n = 22)			
Mean QRS duration (ms)	106 ± 27	117 ± 25	<.001
QRS > 180 ms (No of patients)	0	0	
Exercise test (n = 22)			
% of predicted	91 ± 13	92 ± 16	.6
Severe PR; no PVR (n = 28)			
Echocardiography (n = 28)			
RVOT diastole (mm)	39 ± 8	39 ± 8	.95
RVOT systole (mm)	32 ± 8	33 ± 8	.69
RV inlet diastole (mm)	52 ± 9	54 ± 10	.18
RV inlet systole (mm)	41 ± 8	43 ± 7	.46
PA Vmax (m/s)	1.8 ± 0.8	1.9 ± 1.0	.16
ECG (n = 28)			
Mean QRS duration (ms)	123 ± 27	145 ± 29	<.0001
QRS > 180 ms (No. of patients)	2	3	
Exercise test (n = 28)			
% of predicted	78.0 ± 19	82 ± 14	.32
PVR (n = 17)			
Echocardiography (n = 13)			
RVOT diastole (mm)	40 ± 8	32 ± 7	<.001
RVOT systole (mm)	35 ± 7	27 ± 7	<.001
RV inlet diastole (mm)	53 ± 8	52 ± 8	.61
RV inlet systole (mm)	42 ± 8	42 ± 8	.90
PA Vmax (m/s)	2.1 ± 0.9	2.4 ± 0.8	.20
ECG (n = 13)			
Mean QRS duration (ms)	125 ± 25	150 ± 31	<.001
QRS > 180 ms (No. of patients)	1	4	
Exercise test (n = 13)			
% of predicted	71 ± 19	76 ± 15	.29

ECG, Electrocardiographic; N, number of patients in group or participating in test; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; PA, pulmonary artery; Vmax, maximal flow velocity measured with Doppler; % of predicted, relative to the predicted value based on sex, age, and body length of the normal Dutch population.

EXERCISE TEST. In Table 2 results of the exercise tests in 1990 and 2002 are shown. The exercise capacity in this group is significantly worse than that in the group with mild-to-moderate PR ($P < .01$). Neither in 1990 nor in 2002 was there a significant difference in exercise capacity be-

tween the group with severe PR who did receive a homograft and the group that did not.

The 3 patients with a QRS duration of more than 180 ms were graded as having an unsatisfactory outcome; the outcome in 25 (89%) of 28 patients was regarded as satisfactory.

PVR ($n = 17$). Of the 45 patients with severe PR and severe RV dilatation in 1990, 17 (38%) had symptoms that had prompted PVR. Nine patients had a worsened exercise capacity, without signs of clinical or echocardiographic deterioration. Of these, 2 patients had atrial fibrillation. Three patients had the combination of a decrease in exercise capacity and an increase in central venous pressure. Three other patients had elevated central venous pressure without symptoms. Two patients had recurrent episodes of ventricular tachycardia.

In terms of baseline conditions (age at operation, use of transannular patch, use of cold cardioplegia, and duration of follow-up) and data from the 1990 study, there were no significant differences between patients who had symptoms and patients who did not.

The mean interval between primary surgical correction and PVR was 18.6 ± 5.4 years. The mean follow-up after PVR was 6.4 ± 4.4 years. Four patients received a pacemaker: 2 patients with advanced atrioventricular block and 2 patients with atrial fibrillation and an unstable ventricular rhythm. One of the 2 patients with ventricular tachycardias received an implantable cardioverter-defibrillator. None of these patients died and the postoperative course was uneventful in all. The venous congestion disappeared in all patients. Seven of 9 patients who were operated on because of progressively diminished exercise capacity reported an improved exercise capacity after valve replacement. Decreased exercise capacity persisted after surgery in 2 patients; both had an RV inlet diameter measured with echocardiography that had become larger postoperatively.

ECHOCARDIOGRAPHIC RESULTS. In Table 2 the changes of RV dimensions between 1990 and 2002 are shown. Four patients with a pacemaker were excluded from comparative measurements. In all patients the RVOT dimensions had decreased substantially. The mean diameter of the RV inlet diameter of the patients as a group did not change significantly, but in 9 of 13 the RV inlet diameter diminished significantly compared with preoperatively, with a mean decrease of $14\% \pm 4\%$. In 2 patients the RV inlet diameter did not change; 2 other patients showed an increase of RV inlet diameter, with an increment of 14% and 39%, respectively.

PR was absent or mild in 16 patients and severe in 1 patient.

In terms of baseline variables—age at operation, prior palliation, use of transannular patch, and cold cardioplegia—and the conditions measured after 15 years of follow-up, the

patients who did not show a decrease in size of the RV at the inlet level were not significantly different from the group of patients who were operated on and improved in terms of both inlet and RV outflow tract diameter.

ECG. In 2002, 13 patients had sinus rhythm and 4 had a pacemaker rhythm. Of these, 2 had atrial fibrillation. The QRS duration had increased substantially before PVR, from 132 ± 28 ms in 1990 to 166 ± 30 ms on the last ECG before valve replacement ($P = .000$). In 2002, 4 patients with pacemaker rhythm were excluded from comparison. From the remaining 13 patients, 10 (77%) showed a significantly shorter QRS duration than just before valve replacement, with a mean value of 144 ± 26 ms ($P < .01$). Three patients had a persisting broad QRS complex with duration of 180 ms or more, but no further prolongation.

EXERCISE TEST. The 9 patients with a decrease in diameter of both RV inlet and RV outflow tract showed an increased exercise capacity, from $72\% \pm 25\%$ in 1990 to $81\% \pm 22\%$ in 2002 ($P < .05$). The 4 patients with an unchanged or increased RV inlet diameter showed no significant change in exercise capacity, from $77\% \pm 4\%$ in 1990 to $73\% \pm 3\%$ in 2001 ($P = .4$). The 4 patients with pacemaker rhythm were excluded from comparison.

In 9 (53%) patients with a significant reduction of the RV at both the inlet and outlet levels, who also showed shortening of the QRS duration and improvement of the exercise capacity, the outcome was graded as satisfactory. The 8 other patients, including the 4 patients with pacemaker implantation, were graded as having an unsatisfactory outcome.

Discussion

For the duration of the follow-up, refraining from PVR has led to a satisfactory outcome in all patients with no more than moderate PR and in 89% of the asymptomatic patients with severe PR and severe RV dilatation. In only 11% of the asymptomatic patients with severe PR was the outcome graded as unsatisfactory on the basis of a QRS duration of more than 180 ms. In light of the evidence about the risks of sudden death and ventricular tachycardia in patients with a QRS duration greater than 180 ms^{8,33-36} and the studies, including ours, that QRS duration can shorten after PVR,³⁷ the decision not to replace the pulmonary valve is questionable for these patients. Has the policy of delaying PVR until after the onset of symptoms led to a good outcome? The symptoms that prompted PVR disappeared in 15 (88%) of 17 patients. In all surgically treated patients there was a significant reduction in dimensions of the RVOT, but this cannot be attributed to abolishment of PR alone. It also reflects the effects of surgical remodeling of the RV outflow tract: excision of the often aneurysmatically dilated transannular patch³⁸ and reduction of the RV outflow tract to a size that enables anastomosis with the homograft. Dimension at

the level of the RV inlet, without being touched by the surgeon and without surgical scars, probably is a better measure of improvement of the RV after PVR. This was diminished in 9 of 17 patients. These 9 patients also showed a significant reduction of QRS duration and an improvement of exercise capacity; they were graded as having a satisfactory outcome. In 4 patients, the RV inlet diameter did not diminish and in 4 other patients the ECG and RV echocardiographic measurements before and after PVR were not comparable because of a pacemaker insertion at the time of PVR. We conclude that the outcome was unsatisfactory in these 8 (47%) of 17 surgically treated patients. This seems to confirm the report of Therrien and associates¹⁷ that the condition of some patients does not improve after PVR. Possibly, these patients might have benefited from earlier PVR.

Summarizing, we can conclude that the selective policy toward PVR has led to an unsatisfactory or uncertain result in 11 (24%) of 45 patients but to a satisfactory outcome in 34 (76%) of 45 patients.

Inasmuch as the patients whose condition did not improve after PVR could not be identified beforehand with the diagnostic tools that are currently available in clinical practice, early PVR for all patients with severe PR and RV dilatation can be considered, hoping that early PVR will reduce the percentage of patients who will not improve after the procedure. If the presence of severe PR and severe RV dilatation would have been indications to replace the pulmonary valve in our study population in 1990, approximately half of these patients (20-25 patients) would probably have had re-replacement by now, because of the mean survival of homografts or porcine valves used for this indication.³⁹ That would have meant 45 PVRs in 45 patients in 1990 and probably a total of 60 to 70 PVRs by now, instead of the 17 valve replacements in this study. The treatment options seem to be either overtreatment of a large proportion of the patients (ie, early valve replacement in all patients) or undertreatment in a much smaller, but still considerable proportion of patients by referring only symptomatic patients.

Supported by good ultra-long-term survival of patients with tetralogy of Fallot after surgical repair reported by follow-up studies done before the era in which early PVR became fashionable,^{39,40} we think that for patients like those described in this study, a selective approach should still be considered a serious treatment option as an alternative for early PVR. The most important drawback of this study, although describing one of the longest durations of follow-up of a consecutive series of patients reported so far, is that the duration of follow-up is still too short to assess the effect of long-standing (lifelong) volume overload on the RV. This remains to be established, and only when these data become available will we learn more about the optimal timing of PVR.

This study represents our clinical practice: if there are signs that might be attributed to worsening of RV function—symptoms, development of venous congestion, significant increase of QRS duration, or increase of RV size measured with echocardiography or magnetic resonance imaging—we refer the patient for PVR. History taking and a good physical examination, maybe undervalued in the high-technology environment that cardiology is nowadays, are still very important. If the patient has severe PR and a substantially dilated RV, but is entirely stable in all respects, we discuss the treatment options with the patient, do not advise PVR, but advise regular follow-up with echocardiography and/or magnetic resonance imaging every year. If, during follow-up, deterioration occurs, we advise PVR. New treatment options, such as percutaneous PVR, will probably become available in the coming years for our patients with very wide RVOTs. Whether these will change not only the execution of PVR but also its indication remains to be established.

Mild-to-moderate PR in combination with mild-to-moderate RV dilatation is tolerated extremely well long term after surgical correction of tetralogy of Fallot in childhood. There is no tendency toward increase of degree of PR, and RV size does not increase in time. The exercise capacity is nearly normal, the QRS complex is still narrow, despite a statistically significant increase in duration in 12 years, and no arrhythmias are reported or detected. On the basis of these data, there seems to be no indication to consider PVR for these patients.

Limitations of the Study

Apart from the duration of follow-up which is still not long enough to give a lifelong perspective for these patients, the small number of patients and the fact that RV dimensions were not assessed by magnetic resonance imaging are the most important limitations of the study. Magnetic resonance imaging, the tool for assessment of global RV function nowadays, was not available in 1990, and we chose to use echocardiography for longitudinal follow-up with every patient as his or her own control.

Conclusions

In this ultra-long-term follow-up study of patients with long-standing, severe PR and RV dilatation after surgical repair of tetralogy of Fallot in childhood, the policy of refraining from PVR in asymptomatic patients and doing a PVR only in symptomatic patients led to a good outcome in a large majority of patients. This policy is different from the recently much-advocated early PVR. Outcomes like those from this study can be used as benchmark when the long-term result of early PVR become available in the coming years.

We offer special thanks to Ms Willeke van der Bent, research assistant, who was responsible for the database management of the study and for the preparation of the manuscript and tables.

References

- Garson A, Nihill MR, McNamara DG, Cooley DA. Status of the adult and adolescent after repair of tetralogy of Fallot. *Circulation*. 1979; 59:1232-40.
- Fuster V, McGoon DC, Kennedy MA, Ritter DG, Kirklin JW. Long-term evaluation (12-22 years) of open-heart surgery for tetralogy of Fallot. *Am J Cardiol*. 1980;46:635-42.
- Katz NM, Blackstone EH, Kirklin JW, Pacifico AD, Barger LM Jr. Late survival and symptoms after repair of tetralogy of Fallot. *Circulation*. 1982;65:403-10.
- Bove EL, Byrum CJ, Thomas FD, Kavey RE, Sondheimer HM, Blackman MS, et al. The influence of pulmonary insufficiency on ventricular function following repair of tetralogy of Fallot: evaluation using radionuclide ventriculography. *J Thorac Cardiovasc Surg*. 1983; 85:691-6.
- Bouzias B, Kilner PJ, Gatzoulis MA. Pulmonary regurgitation: not a benign lesion. *Eur Heart J*. 2005;26:433-9.
- Carvalho JS, Shinebourne EA, Bust C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J*. 1992; 67:470-3.
- Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechano-electrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231-7.
- Marie PY, Marcon F, Brunotte F, Briancon S, Danchin N, Worms AM, et al. Right ventricular overload and induced sustained ventricular tachycardia in operatively "repaired" tetralogy of Fallot. *Am J Cardiol*. 1992;69:785-9.
- Harrison DA, Harris L, Siu SC, MacLoughlin CJ, Connelly MS, Webb GD, et al. Sustained ventricular tachycardia in adult patients late after repair of tetralogy of Fallot. *J Am Coll Cardiol*. 1997;30:1368-73.
- Meijboom FJ, Szatmari A, Utens EMWJ, Deckers JW, Roelandt JRTC, Bos E, et al. Cardiac status and health-related quality of life long term after surgical repair of tetralogy of Fallot in infancy and childhood. *J Thorac Cardiovasc Surg*. 1995;110:883-91.
- Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels SEC. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. *Circulation*. 1995; 91:2214-9.
- Misbach GA, Turley K, Ebert PA. Pulmonary valve replacement for regurgitation after repair of tetralogy of Fallot. *Ann Thorac Surg*. 1983;36:684-91.
- Yemets IM, Williams WG, Webb GD, Harrison DA, McLaughlin PR, Trusler GA, et al. Pulmonary valve replacement late after repair of tetralogy of Fallot. *Ann Thorac Surg*. 1997;64:526-30.
- Bove EL, Kavey RE, Byrum CJ, Sondheimer HM, Blackman MS, Thomas FD. Improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency or stenosis. *J Thorac Cardiovasc Surg*. 1985;90:50-5.
- Oechslin EN, Harrison DA, Harris L, Downar E, Wegg GD, Siu SS, et al. Reoperation in adults with repair of tetralogy of Fallot: indications and outcomes. *J Thorac Cardiovasc Surg*. 1999;118:245-51.
- Discigil B, Dearani JA, Puga FJ, Schaff HV, Hagler DJ, Warnes CA, et al. Late pulmonary valve replacement after repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2001;121:344-51.
- Therrien J, Siu S, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? *J Am Coll Cardiol*. 2000;36:1670-5.
- Therrien J, Dore A, Gersony W, Iserin L, Liberthson R, Meijboom F, et al. for the Canadian Cardiovascular Society. CCS Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease. Part I. *Can J Cardiol*. 2001;17:940-59.
- Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults with tetralogy of Fallot. *Am J Cardiol*. 2005;95:779-82.
- Lim C, Lee JY, Kim WH, Kim SC, Song JY, Kim SJ, et al. Early replacement of pulmonary valve after repair of tetralogy: is it really beneficial? *Eur J Cardiothorac Surg*. 2004;25:728-34.
- Buechel ER, Dave HH, Kellenberger CJ, Dodge-Khatami A, Pretre R, Berger F, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. *Eur Heart J*. 2005;26:2721-7.
- Warner KG, O'Brien PK, Rhodes J, Kaur A, Robinson DA, Payne DD. Expanding the indications for pulmonary valve replacement after repair of tetralogy of Fallot. *Ann Thorac Surg*. 2003;76:1066-71.
- Graham TP. Management of pulmonary regurgitation after tetralogy of Fallot repair. *Curr Cardiol Rep*. 2002;4:63-7.
- Yemets IM, Williams WG, Webb GD, Harrison DA, McLaughlin PR, Trusler GA, et al. Pulmonary valve replacement later after repair of tetralogy of Fallot. *Ann Thorac Surg*. 1997;64:526-30.
- Vliegen HW, van Straten A, de Roos A, Roest AA, Schoof PH, Zwinderman AH, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of Fallot. *Circulation*. 2002;106:1703-7.
- Eyskens B, Reybrouck T, Bogaert J, Dymarkowsky S, Daenen W, Dumoulin M, et al. Homograft insertion for pulmonary regurgitation after repair of tetralogy of Fallot improves cardiorespiratory exercise performance. *Am J Cardiol*. 2000;85:221-5.
- Oechslin EN, Harrison DA, Harris L, Downar E, Webb GD, Siu SS, et al. Reoperation in adults with repair of tetralogy of Fallot: indications and outcomes. *J Thorac Cardiovasc Surg*. 1999;118:245-51.
- van der Wall E, Mulder BJM. Pulmonary valve replacement in patients with tetralogy of Fallot and pulmonary regurgitation: early surgery similar to optimal timing of surgery? *Eur Heart J*. 2005;26:2614-5.
- van Rijen EHM, Utens EMWJ, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JRTC, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J*. 2003;24:673-83.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. *J Am Soc Echocardiogr*. 2005;12:1440-63.
- Ellestad MH. Stress testing. Principles and practice. 5th ed. Oxford: Oxford University Press; 2003.
- Simoons ML. Inspannings electrocardiografie. De betekenis van patiëntselectie voor de interpretatie van het inspanningsonderzoek. *Ned Tijdschr Geneesk*. 1977;121:830-2.
- Abd El Rahman MY, Abul-Khaliq H, Vogel M, Alexi-Meskishvili V, Gutberlet M, Lange PE. Relation between right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair. *Heart*. 2000;84:416-20.
- Book WM, Parks WJ, Hopkins KL, Hurst JW. Electrocardiographic predictors of right ventricular volume measured by magnetic resonance imaging late after total repair of tetralogy of Fallot. *Clin Cardiol*. 1999;22:740-6.
- Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden death in repaired tetralogy of Fallot: a multi-centre study. *Lancet*. 2000;356:975-81.
- Oosterhof T, Vliegen HW, Meijboom FJ, Zwinderman AH, Bouma B, Mulder BJ. Long-term effect of pulmonary valve replacement on QRS duration in patients with corrected tetralogy of Fallot. *Heart*. 2007;93: 506-9. Epub 2006 Oct 25.
- Davilouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left interaction. *J Am Coll Cardiol*. 2002;40:2044-52.
- Oosterhof T, Meijboom FJ, Vliegen HW, Hazekamp MG, Zwinderman AH, Bouma B, et al. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. *Eur Heart J*. 2006;12:1478-84.
- Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med*. 1993;329:593-9.
- Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. 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. *J Am Coll Cardiol*. 1997;30:1374-83.