Late correction of tetralogy of Fallot in children

Heinisch Paul P.a, Guarino Laetitiaa, Hutter Damiana, Bartkevics Marisb, Erdoes Gaborb, Eberle Balthasarb, Royo Carlosd, Rhissass Jaafara, Pfammatter Jean-Pierreb, Carrel Thierryd, Kadner Alexanderd

a Centre for Congenital Heart Disease, Department of Cardiovascular Surgery, Inselspital, Bern University Hospital, University of Bern, Switzerland
b Centre for Congenital Heart Disease, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland
c Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
d Terre des hommes, NGO, Lausanne, Switzerland

Introduction

Usually, surgical correction of Tetralogy of Fallot (ToF) is performed during infancy. The majority of paediatric cardiac centres aim to achieve total correction by the age of nine months [1–3]. According to recent analysis of the Society of Thoracic Surgeons’ congenital database, the perioperative mortality rate lies at 1.3% [4]. Early repair of ToF has many advantages: it reduces the duration of hypoxaemia and its negative sequelae, such as the development of cyanotic nephropathy, preserves myocardial function, allows early normalisation of pulmonary flow, which in turn stimulates angiogenesis in the pulmonary vascular bed and supports lung growth [5]. In addition, chronic hypoxaemia, especially during the first year of life, may result in cognitive and developmental delay.

ABBREVIATIONS:

BMI body mass index
BT Blalock Taussig
CHD congenital heart disease
ICU intensive care unit
CBT cardiopulmonary bypass time
CPB cardiopulmonary bypass
ICD implantable cardioverter defibrillator
LBBB left bundle branch block
MACCE major adverse cardiac and cerebrovascular events
MI myocardial infarction
MS median sternotomy
NIRS cerebral near-infrared spectroscopy
PS pulmonary stenosis
PV pulmonary valve
REDCap research electronic data capture
RV right ventricle
RV-PA conduit right ventricle to pulmonary artery conduit
RVOT right ventricle outflow tract
SD standard deviation
TAP transannular patch
TOE transoesophageal-echocardiography
ToF tetralogy of Fallot
URL upper reference limit

Summary

AIM OF STUDY: To report our experience of late correction after infancy in patients with tetralogy of Fallot (ToF).

METHODS: Observational single-centre retrospective analysis of the surgical techniques and perioperative development of patients from developing countries undergoing total surgical correction of ToF after infancy, between 1 November 2011 and 30 November 2016. Variables are presented as numbers with percentages or as mean ± standard deviation. Due to the setting of the humanitarian programme, clinical and echocardiographic follow-up procedures could be conducted for only one month postoperatively.

RESULTS: Twenty-five children (mean age: 70.8 ± 42 months, range 23-163; 44% female) underwent total surgical correction of ToF. Two patients (0.8%) initially received a Blalock-Taussig shunt and underwent subsequent correction 24 and 108 months later, respectively. Preoperative mean right ventricular/pulmonary artery (RV/PA) gradient was 84 ± 32 mm Hg, with a Nakata index of 164 ± 71 mm²/m². Major aortopulmonary collateral arteries (MAPCAs) were observed in eight children (32%), six (26%) of whom underwent transcatheter closure before surgery. 24 children (96%) underwent a valve-sparing pulmonary valve repair and one patient received a transannular patch (TAP). There were no cases which saw major adverse cardiac and cerebrovascular events (MACCE). Mean duration of mechanical ventilation was 28 ± 19.6 hours (range 7-76). Pre-discharge echocardiography demonstrated a mean RV/PA gradient of 25 ± 5.7 mm Hg, with left ventricular ejection fraction >60% in all cases. Overall length of hospital stay was 11.7 ± 4.5 days. There were no in-hospital mortality cases.

CONCLUSIONS: Late surgical correction of ToF can be safely performed and produce highly satisfying early postoperative results comparable to those of classic “timely” correction. A valve-sparing technique can be applied in the majority of children.

Keywords: tetralogy of Fallot, congenital cardiac surgery, perioperative outcome, late correction
Due to the concomitant unrestrictive ventricular septal defect and the stenosis of the right ventricle outflow tract (RVOT), the right ventricle is chronically exposed to systemic (or suprasystemic) pressure, resulting in right ventricular hypertrophy with subsequent fibrosis, right ventricular dysfunction and cardiac arrhythmias. Finally, early repair decreases the psychosocial impact of the disease on the child and family [2, 3, 6–8].

Contrary to practice in developed countries, patients in developing countries usually do not receive timely repair intervention. Less than 50% of the population in these countries has access to health care facilities and for many children suffering from ToF, the likelihood of receiving corrective surgery is extremely low [9]. Many of these children are diagnosed very late due to limited paediatric medicine infrastructure and a lack of specialised medical centres. Furthermore, in regions with a low socioeconomic status, the majority of the population does not have health insurance, this is particularly the case for children. Thus therapy, diagnosis and intervention in particular, are beyond the reach of the average patient in these countries. Furthermore, when medical centres do perform an (often limited) number of corrective surgeries in children affected by ToF, these operations are rarely performed during infancy. Often, the affected patients and their families have to live with the afore-mentioned negative sequelae for years. A humanitarian programme, established by the centre for congenital heart disease at the Inselspital Bern, has been providing correcting congenital cardiac surgery for children from developing countries for several years now. In the context of this programme, late corrections of tetralogy of Fallot (ToF) have been performed. Due to limited data on late total repair, we investigated the surgical techniques, perioperative development and short-term outcomes following late corrective surgery for ToF in children. This information may be of interest to programmes offering treatment to older children in developing nations or in industrialised countries as part of humanitarian programmes.

### Methods

#### Patient selection and data collection

An observational retrospective single-centre study was conducted using perioperative patient data retrieved from clinical reports. All patients over the age of one year undergoing corrective surgery for ToF at our centre between 1 November 2011 and 30 November 2016 were included. An observational design following the STROBE statement was used [10]. The Research Electronic Data Capture (REDCap) system was used to record all data in a standardised database.

Patient characteristics, procedural data and outcomes are shown in tables 1-3. All statistical calculations were performed using Stata 12 (College Station, Texas). Parameters are presented as numbers with percentage or as mean ± standard deviation.

#### Definition of major adverse cardiac and cerebrovascular events

Major adverse cardiac and cerebrovascular events (MACCE) were defined as sudden cardiac death, myocardial infarction (MI), cardiac arrhythmias needing intervention in the form of permanent pacemaker implantation, neurological complications or renal failure requiring replacement therapy. Myocardial infarction was defined according to the 2012 Third Universal Definition of Myocardial Infarction by the European Society of Cardiology Guidelines as elevation of cardiac high-sensitive troponin (hs-TnT) >10 x 99th percentile URL in patients with normal baseline hs-TnT levels. In addition, the following were considered indicative of MI [11]:

- new pathological Q-waves
- new left bundle branch block (LBBB)
- angiographically documented new native coronary artery occlusion

### Table 1: Preoperative demographics.

| Parameter                              | Mean/% | SD   | Range  |
|----------------------------------------|--------|------|--------|
| Number of patients                     | 25     |      |        |
| Male (%)                               | 56%    |      |        |
| Female (%)                             | 44%    |      |        |
| Age (months, mean)                     | 70.8   | ±42  | 23–163 |
| Weight (kg, mean)                      | 17.7   | ±10.2| 9.0–63.9|
| Height (cm, mean)                      | 107    | ±23  | 77–167 |
| BMI (kg/m², mean)                      | 14.6   | ±1.9 | 10.9–19.3|
| CT index, mean                         | 0.6    | ±0.1 |        |
| Peripheral O₂ saturation, (%)          | 84     | ±12.2| 55–99  |

#### Preoperative echocardiography

| Parameter                              | Mean/% | SD   | Range  |
|----------------------------------------|--------|------|--------|
| Presence of ASD (%)                   | 18 (70%)|      |        |
| Aberrant coronary artery (%)           | 7 (40%)|      |        |
| RV/PA gradient (mm Hg)                | 84.3   | ±31.6| 40–180 |
| PV diameter (mm)                       | 11.6   | ±2.9 | 8–18   |
| PV Z score                            | −1.9   | ±1.6 |        |
| LPA diameter (mm)                      | 8.7    | ±2.4 | 5–13   |
| LPA Z score                           | −0.05  | ±1.27| −2.49–2.37|
| RPA diameter (mm)                      | 8.1    | ±2.8 | 4–14   |
| RPA Z score                           | −1.32  | ±1.41| −3.74–1.30|
| Nakata index                           | 163.6  | ±70.5| 66–321 |

BMI = body mass index; ASD = atrial septal defect; LPA = left pulmonary artery; PA = pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; RV = right ventricle

Parameters are presented as percentages or as mean ± standard deviation and range.
imaging evidence of new loss of viable myocardium
– new regional wall motion abnormality.

Anaesthesia and surgical technique

Patients received general anaesthesia with endotracheal intubation after induction with sevoflurane, sufentanil and rocuronium. Intraoperative monitoring employed American Society of Anesthesiologists (ASA) standard monitoring tools, as well as invasive monitoring of arterial blood pressure and central venous pressure, nasopharyngeal temperature and urine output. Additionally, transoesophageal echocardiography (TOE) and cerebral near-infrared spectroscopy (NIRS) were used in all cases.

All patients underwent median sternotomy and standard aortic and bi-caval cannulation. Cardiopulmonary bypass (CPB) was conducted in a state of mild hypothermia. The aorta was cross-clamped and antegrade cardioplegia was administered, using a low-dose (1.5 ml/kg), single-shot crystalloid solution (Cardioplexol™, Bichsel, Switzerland) [12]. In case of significant backflow from major aortopulmonary collateral arteries (MAPCA), moderate hypothermia was induced and the flow reduced accordingly. In children with modified Blalock-Taussig (BT) shunt, shunt takedown was performed at the time of the ToF correction.

Closure of the ventricular septal defect (VSD) was performed either using a transatrial approach or through a right ventricular outflow tract (RVOT) incision in case of a RVOT enlargement by patch plasty.

For pulmonary valve management, a valve-sparing approach was preferred, applying commissurotomy and shaving of the leaflets in the majority of patients. Thus, the drawbacks related to RVPA conduits, such as multiple re-interventions and an elevated risk of endocarditis, could be avoided. This is of particular interest for children from developing countries. The transvalvular pressure gradient between RV and PA was always invasively assessed following weaning from CPB.

Postoperative management

Postoperative management was performed according to standard operating procedures for ToF. Patients were discharged from hospital and transferred to a specialised paediatric care centre operated by the non-governmental organization Terre des Hommes. From there, the children ultimately returned to their country of origin. Follow-up procedures included clinical examination and echocardiography by board-certified paediatric cardiologists. Due to the setting of the humanitarian programme, clinical and echocardiographic follow-up could be conducted for only one month postoperatively, before the patients returned to their country of origin.

Results

Demographics

A series of 25 children (44% female) underwent total correction of ToF as part of this study. Their mean age was 70.8 ± 42 months and their mean weight was 17.7 ± 10.2 kg (range 9–53.9), with a BMI of 14.6 ± 1.9 kg/m² (range 10.9–19.3). Preoperative oxygen saturation was 84 ± 83.9.

| Table 2: Intraoperative data and surgical procedures. | Mean/% | SD / n | Range |
|-------------------------------------------------------|--------|--------|-------|
| Perfusion                                              |        |        |       |
| Cardiopulmonary bypass time (min)                      | 93.0   | ±22    | 35–140|
| Aortic cross-clamp time (min)                          | 56.0   | ±15    | 21–93 |
| Core temperature nadir (°C)                            | 30.6   | ±2.1   | 25–32 |
| Surgical technique                                     |        |        |       |
| Valve-sparing approach                                 | 96%    |        | 24    |
| Transannular patch plasty                              | 4%     |        | 1     |
| Concomitant procedures                                 |        |        |       |
| Subvalvular patch plasty                               | 72%    |        | 18    |
| Supravalvular patch plasty                             | 72%    |        | 18    |
| RVOT enlargement                                       | 100%   |        | 25    |
| Valvulotomy                                            | 63%    |        | 16    |
| VSD patch closure                                      | 100%   |        | 25    |
| ASD direct closure                                     | 72%    |        | 18    |

ASD = atrial septal defect; RVOT = right ventricular outflow tract; VSD = ventricular septal defect Parameters are presented as percentages or as mean ± standard deviation and range.

| Table 3: Postoperative characteristics.                | Mean/% | SD  | Range |
|-------------------------------------------------------|--------|-----|-------|
| ICU                                                   |        |     |       |
| Mechanical ventilation (hours)                        | 28.7   | ±19.6| 7–76  |
| ICU stay (days)                                       | 4.8    | ±2.35| 2–10  |
| Postoperative O₂ saturation                           | 1.0    | ±0.01| 0.95–1|
| Hospital stay (days)                                  | 11.7   | ±4.54| 4–25  |
| Mortality                                             | 0%     |     |       |
| MACCE                                                 |        |     |       |
| Sudden cardiac death (%)                              | 0%     |     |       |
| Myocardial infarction (%)                             | 0%     |     |       |
| Cardiac arrhythmias needing intervention (%)           | 0%     |     |       |
| Neurological complications (%)                        | 0%     |     |       |
| Renal failure requiring RRT (%)                       | 0%     |     |       |
| Adverse outcomes                                      |        |     |       |
| Budd-Chiari syndrome (%)                              | 4%     |     |       |
| Endocarditis (%)                                      | 4%     |     |       |

OR = operating room; ICU = intensive care unit; MACCE = major adverse cardiac and cerebrovascular events, RRT = renal replacement therapy Parameters are presented as percentages or as mean ± standard deviation and range.
12.2%. The calculated Nakata index was 164 ± 71 mm²/m². MAPCAs were observed in eight cases (32%) and in six of these (26%), patients underwent preoperative interventional closure. Additional preoperative demographics are summarised in table 1.

Operative data
In all patients (n = 24) a valve-sparing approach was initially performed, using commissurotomy and leaflet shaving. Subvalvular patch plasty was performed in 72% (n = 18) and supravalvular patch plasty in 72% (n = 18), while a transannular patch plasty (TAP) was performed in one patient. VSD patch closure using xenopericardium tissue was performed in all patients. All patients underwent RVOT enlargement by subvalvular extensive resection of hypertrophic myocardial tissue.

Mean total CPB time was 93 ± 22 min (range 35–140), with a mean aortic cross-clamp time of 56 ± 15 min (range 21–93). The mean temperature on CPB was 30.6 ± 2.1°C. It had been necessary to lower the temperature to less than 30°C in seven patients (28%) to manage non-coronary collateral flow from significant MAPCA vessels.

Following CPB weaning, the intraoperative RV-to-PA gradient was invasively measured by direct needle transduction and demonstrated a transvalvular gradient of 34.6 ± 14.8 mm Hg. Intraoperative characteristics are summarised in table 2.

Postoperative course
Postoperative data are summarised in table 3. Mechanical ventilation lasted 28.7 ± 19.6 hours (range 7–76). Length of high-dependency unit (ICU, IMC) stay was 4.8 ± 2.4 days (range 2–10) and total length of hospital stay was 11.7 ± 4.5 days (range 4–25). There was no occurrence of MACCE. There was no in-hospital mortality.

Budd-Chiari syndrome occurred in a 27-month-old girl after surgery, requiring longer ICU care (10 days) and consequent discharge from hospital after 25 days. Surgical reintervention was necessary in two cases. In the first case, the patient underwent reoperation due to significant residual RVOT stenosis. In the second case, the patient was referred for treatment due to endocarditis of the PV three weeks after corrective surgery, necessitating implantation of a right ventricle-to-pulmonary artery (RV-PA) conduit (20mm Contegra® Medtronic, USA). The remaining postoperative development of both patients was uneventful thereafter.

Follow-up echocardiography for all patients one month postoperatively demonstrated a residual mean gradient over the RVOT of 25 ± 5.7 mm Hg, normal biventricular function in all cases and oxygen saturation of 98% (range 95–100%).

A residual pulmonary valve stenosis (PS) was trivial in 48% (n = 12) and moderate in 16% (n = 4). A moderate residual subvalvular PS was observed in 12% (n = 3). A trivial residual supravalvular PS was noticed in 20% (n = 5) and moderate in 8% (n = 2). Pulmonary valve insufficiency was trivial in 44% (n = 11) and moderate in 8% (n = 2) of patients.

Discussion
Correction of ToF is part of the standard spectrum of congenital cardiac surgery. In recent decades, excellent results have been reported, with low morbidity and mortality rates. There is general consensus that the recommended patient age for correction is during infancy, with most patients undergoing surgery between six and nine months of age [1–3]. The current correction strategy emphasises a valve-sparing approach. This often creates a mild residual stenosis due to the hypoplastic pulmonary valve together with a mild insufficiency as a result of valvular commissurotomy, but has the advantage of preserving the pulmonary annulus, while enlargement of the hypoplastic pulmonary artery and of the RVOT is possible through patch plasty. Several groups advocate a strategy which preserves the pulmonary annulus. This would also maximize the preservation of valve function over the long term, even if the effect of these strategies on the long-term function of the right ventricle and pulmonary valve remain unknown [4, 13, 14].

This study reports the results obtained in a small number of ToF-affected children who were operated on at a mean age of 71 months. This is older than usually reported [15]. The oldest patients who benefitted from total ToF correction (without a previous BT shunt) were even older than 10 years of age. The mean BMI was 14.6 ± 1.9 kg/m² (range 10.9–19.3) and the mean weight was 17.7 ± 10.2 kg (range 9–53.9). These were associated with chronic malnutrition, hypoxia and growth retardation [7]. Malnutrition is common in children with congenital heart disease (CHD) and studies from developed countries have documented normalisation of somatic growth when corrective surgery for CHD is performed early [16]. It is also known that 25% of children have persistent malnutrition even after corrective intervention, especially if the correction is performed late [16].

Other characteristics included the higher percentage (32%) of MAPCAs in the paediatric population with ToF compared to the international average (2%) [17]. This finding can be explained by the response to the chronically decreased pulmonary blood flow and cyanosis [8, 17]. This is well-recognised, since the percentage of MAPCAs in untreated adults is between 13% and 25%, but unlikely to occur at all in patients who received correction before six months of age [8, 17]. In addition, MAPCAs can result in a number of complications, including gross enlargement and erosion of the bronchi, massive haemoptysis, postoperative pulmonary oedema and prolongation of postoperative mechanical ventilation and ICU stay [17]. In this study, 26% of the treated children underwent transcatheter closure just prior to surgical correction to avoid complications. By following this strategy, it was possible to successfully manage intraoperative collateral vessels and postoperative therapy. A more frequent occurrence of coronary abnormality was found compared to the international average for patients with ToF [18].

Regarding mortality after ToF correction, the Society of Thoracic Surgeons Database reports a rate of 7.5% at discharge after palliation with a BT shunt, 0.9% after a total repair with a previous palliation and 1.3% following correction without a previous shunt [4]. However, the patients
in our study were significantly older than the international mean age at total repair surgery.

Benbrik compared patients from developing countries (mean age of 57.6 ± 38 months) who underwent total correction of ToF, with a control population from an industrialised country (mean age: 8.3 ± 9.1 months) who underwent timely complete repair of ToF. He reported a mortality rate of 4.2%, with no difference between the groups [15]. Another study by Raj reported a 2% mortality rate after late total correction of ToF [19]. In our study population there was no perioperative mortality. This confirms that even late repair of ToF can be accomplished with a low mortality rate.

Another important point to note when evaluating repair strategies, is the management of the pulmonary valve. It is well recognized that a total repair of ToF, even if associated with a certain degree of pulmonary stenosis, should aim to preserve the native pulmonary valve [4, 13]. Stewart reported on a pulmonary valve-sparing approach for the repair of tetralogy of Fallot [14]. The group identified significant markers for success, including a measured pulmonary annulus z score of negative 4 or greater and the existence of a tricuspid pulmonary valve [20]. In our study group, the mean preoperative pulmonary annulus z score was −1.9 ± 1.6, and a tricuspid pulmonary valve was found in in 24 patients (96%), all of whom were operated on with a pulmonary valve-sparing approach.

The valve-sparing procedure may preserve the integrity of the pulmonary valve. Conversely, liberal application of a transannular patch increases the incidence of pulmonary regurgitation, persistent RV hypertension and chronic RV volume loading. In addition, a short-term benefit of the valve-sparing procedure is the shorter duration of mechanical ventilation compared with patients who receive a transannular patch (TAP) [14].

Benbrik performed a TAP in 35% of patients, with the same percentage in both developing-country and control groups [15]. Raj et al. found that a native valve could be preserved in only 30% of their patients [19]. In some cases, a valve-sparing approach might be impossible due to a highly hypoplastic PV. However, both studies also reported a percentage of TAP among patients who underwent “timely” correction. We were able to perform a valve-sparing correction in 24 patients (96%) by applying the above-listed techniques in the majority of our patients. However, this might have been made possible by favourable characteristics of our patients. Further follow-up is mandatory in order to demonstrate whether the valve-sparing strategy is advantageous when mid- to long-term PV and RV development and function are considered in this patient population [21].

As stated above, the duration of mechanical ventilation is shorter when patients are subjected to a valve-sparing procedure than when they undergo TAP placement [14]. In our cohort, the ICU stay was 4.8 ± 2.4 days within a total hospital length of stay (LOS) of 11.7 ± 4.5 d. The mean duration of mechanical ventilation was 28.7 ± 19.6 h. At the beginning of our work as part of the humanitarian programme, we were cautious with early extubation due to the limited experience with these specific patients. Subsequently, ventilation time was reduced, even leading to fast-track extubation in selected patients.

The length of time of mechanical ventilation varies among published studies. Hirsch et al. reported an average duration of 163.2 hours of mechanical ventilation after a complete repair of ToF in neonates [22]. Benbrik et al., while comparing patients from developing and industrialised countries, observed a mechanical ventilation duration of 48 ± 89h (developing) vs 67 ± 97 h (industrialised), with an ICU stay of 93 ± 81h (vs172 ± 329h) and a total length of stay of 11 ± 6d vs 15 ± 15 d. They concluded that older patients tended to experience shorter durations of mechanical ventilation, stays in the ICU and stays in hospital [15].

Raj reported mechanical ventilation lasting 34 ± 28h and ICU LOS of 6.86 ± 6.32d as part of a total hospital LOS of 11.8 ± 6d [19]. Our late-repair cohort does well in comparison with these data, with a mean duration of mechanical ventilation of 29 hours, an average ICU stay of 4.8 days and a mean hospital stay of 11.7 days. From the literature and our own experience, there appeared to be no need for prolonged ventilation or extended length of stay in older ToF patients. We therefore established postoperative fast-track protocols during the later stages of our collaboration.

The only exception was our patient with Budd Chiari syndrome, who required prolonged ICU and hospital stays. The outcome after total repair of ToF is determined by several factors, the most important of which appears to be postoperative RV function [23]. Due to advanced RV hypertrophy in late repair candidates, restrictive RV dysfunction may be present [15]. Even today, conclusive information is lacking on the optimal surgical strategy for primary repair, with the aims being the preservation of RV function, reduction of arrhythmogenicity and optimisation of functional status [24]. After ToF repair, biventricular systolic function is usually normal, but RV diastolic function may be impaired to the extent that it requires close surveillance [24, 25]. At this stage in our study, we only have echocardiography data on early postoperative RV systolic and diastolic function, which was good in all patients. Long-term follow-up is needed, with echocardiographic assessment of the RV.

Late correction of ToF can be safely performed in older children with excellent early postoperative results and low mortality and morbidity comparable to results reported for timely correction in infants. A valve-sparing correction should be considered for those patients. Follow-up investigation of the development of right ventricular and pulmonary valve dysfunction is urgently needed and is currently under way.

This study has several limitations. It is a retrospective single-centre observational analysis, therefore cause and effect are hard to establish. Selection bias is possible, since most of these children have survived early infancy without surgical palliation, correction or even appropriate medical management, which indicates less severe ToF pathology. Furthermore, our cohort size was small, obviating robust conclusions on outcomes like perioperative mortality. Follow-up and cardiac function assessment were carried out using echocardiography only. MRI studies would have been preferable but financial restrictions on this humanitarian programme meant that this was not possible.
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