Università di Pisa

Facoltà di Medicina e Chirurgia
Corso di laurea in Medicina e chirurgia

Fondazione Toscana "Gabriele Monasterio"

Ospedale del cuore G. Pasquinucci
U.O.C. Cardiochirurgia pediatrica e del congenito adulto
Resp. Dr. Bruno Murzi

Tesi di Laurea

Right ventricular outflow tract reconstruction using a valved biological conduit (Hancock conduit) late after tetralogy of Fallot surgical repair

RELATORE
Chiar.mo Dott. Bruno Murzi

CANDIDATO
Daniele Dallimonti Perini

Anno Accademico 2014–1015

To my Father

Abstract

OBJECTIVES: The most appropriate strategy in the management of right ventricular outflow tract (RVOT) reconstruction in patients with tetralogy of Fallot early repair and late failure of right ventricle to pulmonary artery continuity is still debated. This study addresses this issue by evaluating retrospectively 12 years experience in this kind of reconstruction, focusing exclusively on the performance of Hancock® conduits.

METHODS: Data from 32 patients with an early repaired Tetralogy of Fallot, 23 males and 9 females, who underwent 34 RVOT reconstruction (2 were reinterventions) with Hancock® conduit at Fondazione Toscana "G. Monasterio" Pediatric Cardiac Surgery department, Massa, Italy between February 2003 and May 2015 were retrospectively reviwed. *Median age* was $17,6 \pm 11,32$ years (range 13 months to 41 years and 8 months), *mean BSA* $1,4 \pm 0,54 m^2$ (0,34 m^2 minimum and 2,12 m^2 most), *mean height* $148,1 \pm 33,6$ cm (range 61 cm to 195 cm) and *mean weight* $49,5 \pm 26,35$ Kg (range 6,9 Kg to 96 Kg). The RV-PA peak gradient, RV mean pressure and pulmonary regurgitation were measured before and after the surgical conduit implantation and on follow-up, in addition RV end-diastolic volume index was measured, when feasible, before and after Hancock® implantation.

RESULTS: The early 30 days mortality was 6,25% and not related to conduit failure. Complete follow-up was feasible in 27 patients and the mean duration was $31,6 \pm 34,42$ months. The observed RV-PA peak gradient means were $60,4 \pm 30,06$ mmHg preoperatively, $29,1 \pm 11,48$ mmHg postoperatively and $45,3 \pm 26,02$ mmHg on the last follow-up; RV mean pressures were $53,3 \pm 27,73$ mmHg preoperatively $41,6 \pm 12,71$ mmHg postoperatively and $53,6 \pm 18,8$ mmHg on the last follow-up; RV end-diastolic volume index means were $218,3 \pm 57,94 ml/m^2$ before surgery and $126,1 \pm 14,49 ml/m^2$ after surgery. Conduit failure was observed in 5 patients in which the the mean *freedom from conduit failure* was $70,56 \pm 15,02$ months (mean age at failure $6,86 \pm 1,78$ years), in 4 of them percutaneous intervention were attempted (2 ballooning and 2 melody), 2 successful.

DISCUSSION: From our series the Hancock® conduit can be actually considered as a valuable solution for RVOT reconstruction in already operated patients with ToF, considering good RV pressures and gradients values even after up to 9 years of follow up.

Contents

Glossary

AC Allograft Conduit. 34, 36–38

ASD Atrial Septal Defect. 1, 21

AV Atrio-Ventricular. 17, 51

BJVC Bovine Jugular Vein Conduit. 36–39

BSA Body Surface Area. 44

CHD Congenital Heart Disease. 3, 5, 7, 27, 36, 59

CMR Cardiac Magnetic Resonance. 10, 11, 23, 41, 42, 46, 50

CPB Cardiopulmonary Bypass. 16, 19, 48

CT Computed Tomography. 10, 11

EDV End-Diastolic Volume. 41

ESV End-Sistolic Volume. 41

HDE Humanitarian Device Exemption. 37, 39

ICU Intensive Care Unit. 30

JET Juctional Ectopic Tachycardia. 19, 21, 22

LV Left Ventricle. 19, 21, 22, 42, 46

LVEDVi Left Ventricle End-Diastolic Volume index. 24

MAPCA Major Aorto-Pulmonary Collateral Artery. 3, 5

MBTS Modified Blalock-Taussig Shunt. 14

MRI Magnetic Resonance. 10, 11

PA Pulmonary Artery. 40

PDA Patent Ductus Arteriosus. 3, 7

PFO Patent Forame Ovale. 17

PGE1 Prostaglandine E1. 11

PI Pulmonary Insufficiency. 13, 20, 23, 29, 40, 41, 45, 46, 57

PTFE Polytetrafluoroethylene. 29–31, 50

PVR Pulmonary Valve Replacement. 23, 24

PVres Pulmonary Vascular Resistance. 29

Ross-AVR Ross Aortic Valve Replacement procedure. 36, 38

RV Right Ventricle. 11, 13, 16, 19–24, 27–30, 39, 41, 42, 45, 46, 50, 53

RV-PA Right Ventricle-to-Pulmonary Artery. 27, 39, 40, 48, 57

RVEDVi Right Ventricle End-Diastolic Volume index. 23, 46, 50, 53, 54, 58

RVESVi Right Ventricle End-Sistolic Volume index. 24

RVH Right Ventricular Hypertrophy. 7, 8, 12, 36

RVOT Right Ventricle Outflow Tract. 3, 8, 9, 14, 16, 21, 24, 27–31, 36, 38, 40–44, 46, 50–53

SCD Sudden Cardiac Death. 13, 21–23

SVT Sopra-Ventricular Tachycardia. 22

ToF Tetralogy of Fallot. 3, 5–9, 11–13, 15, 17, 19, 20, 22–24, 28, 30, 31, 44, 46, 59

TR Tricuspid Regurgitation. 46

TV Tricuspid Valve. 29

US Ultrasound. 10, 11

VSD Ventricle Septal Defect. 2, 3, 7, 8, 13, 14, 17, 20, 21, 28, 31, 45, 46, 50

VT Ventricular Tachycardia. 23

Chapter 1

Tetralogy of Fallot†

† "Robert D. Stewart, Constantine Mavroudis, and Carl L. Backer"
Tetralogy of Fallot – Pediatric Cardiac Surgery
Fourth Edition, Ed.: Wiley-Blackwell

1.1 Definition, Morphology and Nomenclature

`Consensus definition of International Working Group for Mapping and Coding of Nomenclatures for Pediatric and Congenital Cardiac disease:`

> *Tetralogy of Fallot is defined as a group of malformations with biventricular atrioventricular alignments or connections characterized by anterosuperior deviation of the conal or outlet septum or its fibrous remnant, narrowing or atresia of the pulmonary outflow, a ventricular septal defect of the malalignment type, and biventricular origin of the aorta. Hearts with tetralogy of Fallot will always have a ventricular septal defect, narrowing or atresia of the pulmonary outflow, and aortic override; hearts with tetralogy of Fallot will most often have right ventricular hypertrophy.*(Beland, Franklin, Jacobs, & *et al.*, 2004)

The first syndrome description is from Niels Stentons' published report, dated back 1671 (Steno, 1671). Yet, we commonly refer to *"A. L. E. Fallot"* as first original syndrome definition, which included the term "tetralogie" referring to the four anatomical cornerstones' syndrome he pointed out from autopsy specimens: *pulmonary artery stenosis, ventricle septal defect, rightward deviation of the aorta's origin* and *hypertrophy of the right ventricle* (Fallot, 1888), as described by Figure 1.1. Not uncommonly it's also named *Pentalogy of Fallot* for frequent recurrence of Atrial Septal Defect (ASD) (Abbott & Dawson, 1924), but the most recent actual consensus definition is the one above.

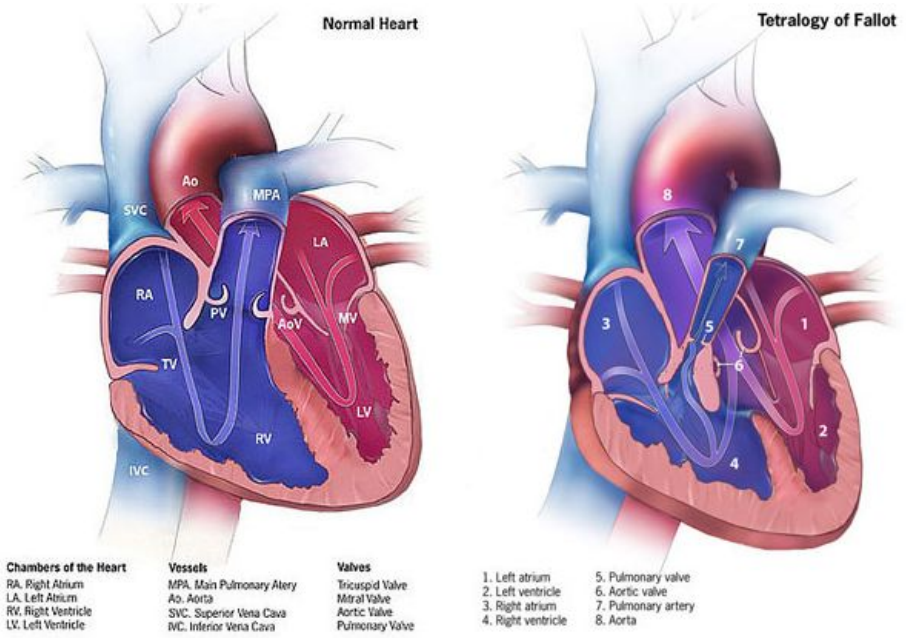


Figure 1.1: Comparison between a normal heart and an heart with Tetralogy of Fallot [Reproduced from CDC *web site: http://www.cdc.gov/ncbddd/heartdefects/tetralogyoffallot.html*]

Nowadays It's widely accepted that the four pathologic features origin secondarily to a common pathway of altered cardiac development, rather than representing four "coincidence" errors of morphogenesis. It's mainly involved, as stated by Anderson et al.(Becker et al., 1975; Howell et al., 1990), the *subpulmonary infindibulum hypoplasia and narrowing*, which may even appear variable in length. They suggested *the anterocephalad deviation of the infundibular septum relative to septomarginal trabeculation* as key feature for this event, however this was not a completely satisfactory unifying hypothesis. A more suitable one does involves anterocephalad deviation of the outlet septum (muscular or fibrous), but also requires abnormal relation of the septum to septoparietal trabeculations, producing subpulmonary obstruction (Anderson & Weinberg, 2005). Anterocephalad malalignment and deviation of the infundibular septum, relative to the limbs of septomarginal trabeculation, determine the *Ventricle Septal Defect (VSD)*, which is large, physiologically non restrictive, located di-

rectly under aortic valve orifice and has three common morphological variants.

Deviation of outlet septum determine also varying degrees of *Right Ventricle Outflow Tract (RVOT) obstruction*, defined as os infundibulum, which is related to the hypoplasia of ventricular infudibulum and prominent septoparietal trabeculations that undergo progressive hypertrophy postnatally. Moreover pulmonary valve morphology is usually abnormal, with thickened and immobile leaflets, commissural fusion with or without tethering of leaflets to pulmonary artery wall and bicuspid in more than half of the cases (Altrichter, Olson, Edwards, & et al., 1989).

Other anatomical variants are the presence of one or more *additional VSD* (5%) anteriorly on muscular septum (Dickinson, Wilkinson, Smith, & et al., 1982) and variants of coronary artery anatomy, with the commonest as origin of anterior descending coronary artery from the right one (Dabizzi et al., 1980; van Son., 1995). *Pulmonary atresia* is present in 7% of patients with Tetralogy of Fallot (ToF) (Chiariello et al., 1975) and in such setting there's an important distinction to be made between the presence or absence of Patent Ductus Arteriosus (PDA). When PDA is present it's most often the only source of pulmonary blood flow and, even can be there a varying degree of pulmonary artery hypoplasia, all or nearly all pulmonary segments are commonly supplied by branches arborizing from left and right pulmonary arteries anyway. Instead, in absence of PDA, varying amount of pulmonary parenchyma is supplied partially or totally by Major Aorto-Pulmonary Collateral Arteries (MAPCAs), determining a condition with distinct clinical presentation, natural history and surgical treatment strategies; an example of the latter is presented in Figure 1.2. However, it's also important to consider that not all cases of pulmonary atresia with VSD necessarily fall within the category of ToF.

ToF and it's variants constitute nearly 10% of all Congenital Heart Diseases (CHDs), representing the most common form between cyanotic CHDs with an incidence of 421 cases per milion live births (Hoffman & Kaplan, 2002). Genetic syndromes are identified in at least 20% of ToF and the most commonly

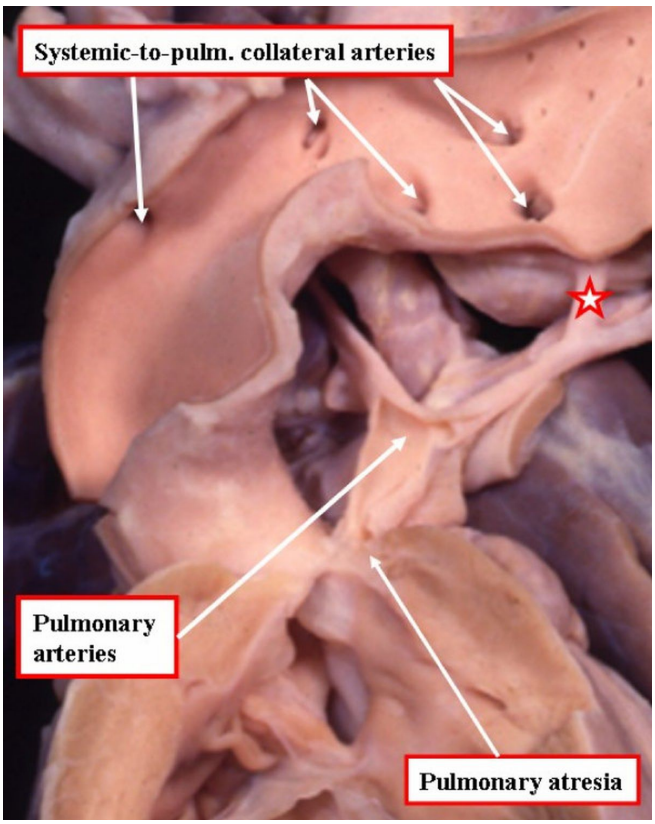


Figure 1.2: **Autopsy specimen of an heart with tetralogy of Fallot with pulmonary atresia.** The pulmonary supply is through multiple systemic-to-pulmonary collateral arteries. The star shows the connection between one of the collateral arteries and the intrapericardial pulmonary arteries. [Reproduced from: *"F. Bailliard and Robert H. Anderson" – Tetralogy of Fallot – Orphanet J Rare Dis. 2009; 4: 2*]

associated are DiGeorge syndrome, which is consequence of one from several deletions on chromosome 22, and trisomy 21 (Michielon, Marino, Formigari, & et al., 2006).

1.2 Embriology[▽]

[▽] "Richard Jonas" – Tetralogy of Fallot with Pulmonary Stenosis
Comprehensive Surgical Management of Congenital Heart Disease
Second Edition, Ed.: CRC Press

1.2.1 Genetic Basis

Various genetic associations with Tetralogy of Fallot have been identified in the last decade, including JAG1, NKX2.5 (Goldmuntz, Geiger, & Benson, 2001), ZFPM2 and VEGF. However the most important association is chromosome 22 microdeletion, a chromosomal defect present in up to 40% of patients with CHDs (Oskarsdóttir, Vujic, & Fasth, 2004), and specifically the 22q11.2 deletion syndrome. This deletion determines defects in neural crest-derived tissues, causing abnormal development of third and fourth brachial pouches, including altered conotruncal development. In addition it can alters normal development of thymus, affecting normal differentiation and tolerance of T-cells, and parathyroid glands, determining an immune dysfunction and hypocalcemia, features of DiGeorge syndrome. Maeda et al. (Maeda, Yamagishi, Matsuoka, & et al., 2000) found that 13% of patients with tetralogy had 22q11.2 deletion, with a significantly higher prevalence in patients with pulmonary atresia and MAPCAs than those with simple tetralogy with pulmonary stenosis. In addition, infants with 22q11 deletion commonly present developmental delay and a increased lifetime risk of 20-30 times for schizophrenia (Bassett, Chow, AbdelMalik, & et al., 2003).

1.2.2 Embryological Development of Tetralogy

To understand the embryology of ToF is crucial the comprehension of pulmonary arteries development. Lung buds arise from the primitive foregut and carry the arteries and veins, that invest the foregut, derived from systemic arterial and venous circulations. Proximal mediastinal arteries, on the other hand, are derived from the sixth dorsal aortic arches that coalescence with more distal

vasculature. The proximal main pulmonary artery is formed by the division of the original conotruncus and, by labeling specific embryo cells with green fluorescent protein, it has been clarified the role of neural crest cells in the development of conotruncal abnormalities, of which tetralogy is part.

Classic Theory of Development of ToF

The conotruncus ("bulbus" or "bulbus cordis") is normally subdivided, through a process of spiral septation, into two relatively equally sized vessels, namely the aorta and the main pulmonary artery (Pexieder, 1995). In case of unequal septation process the main pulmonary artery may become hypoplastic relatively to the aorta. Other points of stenosis may be represented by the transition point between main pulmonary artery and its branches, where the conotruncus is in continuity with the dorsal aorta, and more distally the junction of the sixth dorsal aorta with peripheral pulmonary vasculature, where can develop multiple points of stenosis.

Van Praagh's Theory of the Embriology of ToF

Van Praagh et al. postulated that the ToF represent the consequence of a single defect, namely underdevelopment of subpulmonary conus (Van Praagh, Van Praagh, Nebesar, & et al., 1970). Usually the subpulmonary conus, or infundibulum, is a tube of muscle which normally lifts the pulmonary valve superiorly, anteriorly and leftward, away from the other three valves that are united by a single fibrous skeleton. When the subpulmonary infundibulum is underdeveloped the aortic valve lies more anteriorly, superiorly and rightward relative to the pulmonary valve than usual and besides the infundibulum has a narrower lumen, causing less blood streaming trough the pulmonary valve and main trunk which becomes hypoplastic.

1.3 Presentation and Diagnosis

ToF is a common (Hoffman & Kaplan, 2002) *cyanotic CHDs*, however only a slight number of patients present with deep cyanosis in neonatal period after the closure of PDA and, in the other hand, there is a group of acyanotic ToF patients, with normal oxygen saturation level and even signs of pulmonary overcirculation if the stenosis is mild. More commonly there is a mild desaturation of 80-90% depending on PDA presence and degree of pulmonary stenosis.

Infants with severe cyanosis have severe pulmonary valve stenosis or even atresia, but they can remain undiagnosed until several days to weeks after birth until PDA closure because of cyanosis absence, moment of clinical presentation. If PDA patency cannot be re-established at clinical presentation with prostaglandines, it represents an emergency surgical situation to establish adequate pulmonary blood flow.

The most common natural progression of acyanotic or mildly ToF patients is the gradual baseline reduction of saturation with progressive Right Ventricular Hypertrophy (RVH) and subvalvolar stenosis. Therefore, close-up follow-up of these patients it's crucial for an appropriate timed intervention before the development of severe cyanosis. Despite their usual mild or absent cyanosis these patients can develop *episodes of profound hypercyanosis*, also called *TET spells*, as consequence of dynamic relative changes in pulmonary and systemical resistance which leads to *right to left shunting*, through the VSD, downing saturation well below 50%. The most popular causal hypothesis for these events, though unproven, is an infundibular muscle spasm leading to a dynamic increasing of subvalvular obstruction with resulting right-to-left shunt through VSD.

1.3.1 Clinical Exam

Infant present with *varying degree of cyanosis*, from mild pallor to marked cyanosis, which eventually results in clubbing, that hence can be seen only

in advanced cases.

`Auscultation.` Reveals systolic murmur from RVOT obstruction, which can soften or disappear during TET spells because of reduced flow through the obstruction, while the VSD is not a source, or just a mild one, of murmur for its large size. *II tone splitting* is not appreciable due to a small and abnormal valve paired with low pulmonary pressures, which cause absence of the valve closing sound.

1.3.2 Instrumental Studies

`Chest X-Ray.` Shows classic "boot shaped" heart, from RVH and small pulmonary arterial knob, together with dark lung fields due to relative hypoperfusion. In up to 1/4 of patients is also evident a *right sided aortic arch.*

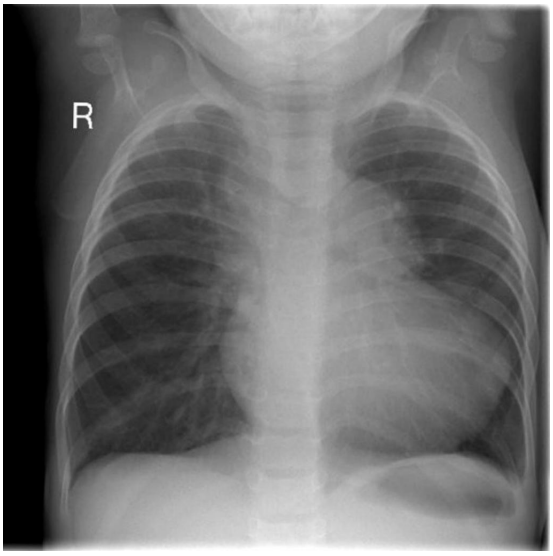


Figure 1.3: Typical radiographic boot-shaped heart in a child with ToF *(Case courtesy of Dr Alexandra Stanislavsky, Radiopaedia.org, rID: 13349)*

`Electrocardiography.` Shows marked *RVH* and *right axis deviation*, but both are neither specific nor diagnostic.

`Echocardiography.` Coupled with Doppler study provides a complete evaluation of ToF anatomy (Dadlani, John, & Cohen., 2008; Gatzoulis, Soukias, Ho, & et al., 1999) and RVOT gradients estimation (see Figs. 1.4 and 1.5). Cardiac

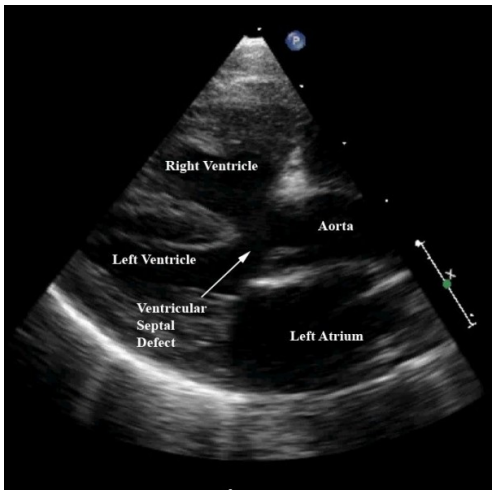


Figure 1.4: Echocardiographic still frame of a modified parasternal long axis view in patient with ToF demonstrates the large ventricular septal defect, aortic override, and right ventricular hypertrophy.
[Reproduced from: *"F. Bailliard and Robert H. Anderson" – Tetralogy of Fallot – Orphanet J Rare Dis. 2009; 4: 2*]

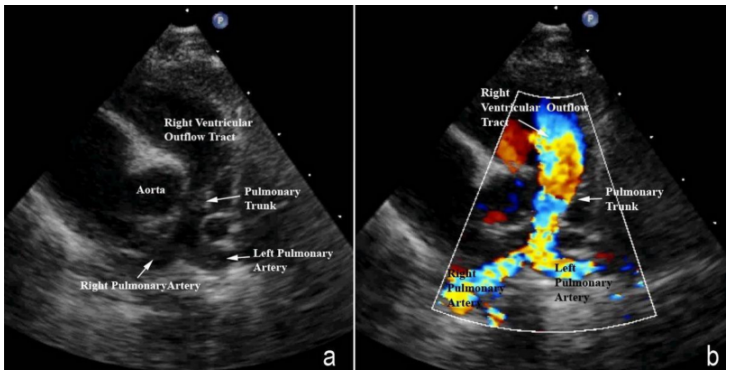


Figure 1.5: (a). Echocardiographic still frame of a slightly modified parasternal short axis evidence significant hypoplasia of the pulmonary trunk and the pulmonary arteries, which result from the anterocephalad deviation of the outlet septum. (b) Doppler has been used, and demonstrates turbulence and acceleration of the flow of blood in the right ventricular outflow tract.
[Reproduced from: *"F. Bailliard and Robert H. Anderson" – Tetralogy of Fallot – Orphanet J Rare Dis. 2009; 4: 2*]

Ultrasound (US) is also reliable in determining the coronary pattern in majority of cases (Need, Powell, del Nido, & et al., 2000) and it's powerfully increasing its prenatal diagnosis capability (Tongsong et al., 2005) even if there's no evidence of benefit in long-term survival with in-utero diagnosis (Lee, Smith, Comstock, & et al., 1995). Three-dimensional echocardiography appear to be an important modality for long-term follow-up for morphological and functional changes in patients with repaired ToF (Kjaergaard, Petersen, Kjaer, & et al., 2006).

`Catheterization.` It is not currently required in majority of infants before reparative surgery, unless an unclear anatomy of pulmonary artery branches is present or to confirm the origin of the anterior descending coronary from the right coronary artery.

`Computed Tomography (CT), Cardiac Magnetic Resonance (CMR) and Magnetic Resonance (MRI).`

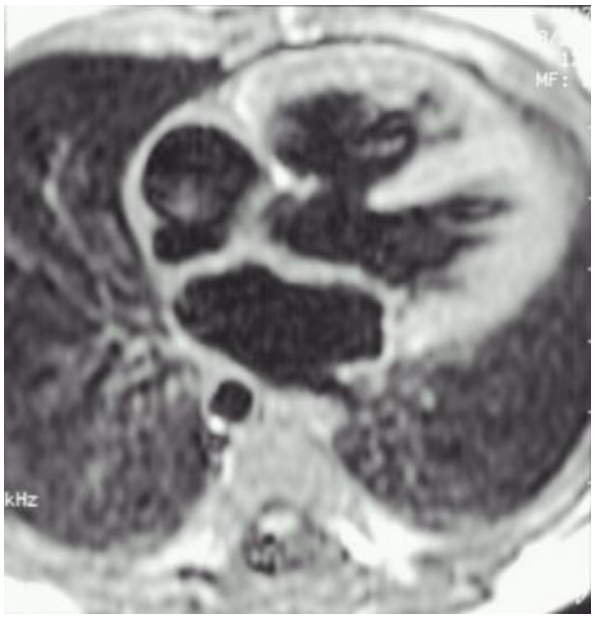


Figure 1.6: (a). Magnetic resonance image of the heart in an infant with tetralogy of Fallot. This image shows a large ventricular septal defect and right ventricular hypertrophy. Descending aorta is on the right. [Reproduced from: *"S. Bruce Greenberg, Bernard D. Coombs, Robert M. Steiner, Eugene C. Lin and Justin D. Pearlman" — Medscape website: http://emedicine.medscape.com/article/350898-overview*]

CT and MRI are useful before the complete repair to evaluate pulmonary artery and aortic arch anatomy and to delineate coronary artery abnormalities. CMR is the most reliable emergent instrument for long-term evaluation of patients with repaired ToF for it's effective quantification ability of Right Ventricle (RV) volume and function and pulmonary regurgitant fraction, even superior to cardio-US (Geva et al., 1998; Roest et al., 2002; van-den Berg et al., 2007). It's measures are becoming the benchmark for reintervention, especially for pulmonary valve insertion or replacement (Therrien et al., 2005; Knauth et al., 2005).

1.4 Medical Management

There is no long-term medical management available for ToF and the only definitive treatment of choice is the surgical repair; however there are several medical adjuncts available.

The most important of medical treatments available is the use of *Prostaglandine E1 (PGE1)* to maintain ductal patency in profoundly cyanotic neonates with ToF (Elliott, Starling, & Neutze, 1975). It's administered as continuous intravenous infusion at rate of $0,01 - 0,1 \mu g/Kg/min$ to maintain an adequate patency of the duct until surgical repair or a surgical systemic to pulmonary shunt are established. However, the use of PGE1 is limited the first week of life, since in infants presenting after this period its administration will less likely open the duct, with success rate being very low after 2 weeks of life. The main adverse effect of PGE1 infusion is apnea, which often requires endotracheal intubation and mechanical ventilation.

Other medical treatments aim to prevent or treat "TET spells". *Beta-blockade* are used by some cardiologists to theoretically prevent the incidence of spasm of infundibular muscle, however there is conflicting evidence regarding the effectiveness of this therapy (Cumming & Carr, 1966; Garson-Jr, Gillette, & McNamara, 1981). The principal side effect of their prolonged use in patients with ToF is an increased need of inotrope use and temporary pacing after sur-

gical repair (Graham, Bandisode, Bradley, & et al., 2008), an evidence which favour an earlier surgical correction for patients with paroxysmal spells. *Acute medical management* for an hypercyanotic patient include oxygen supplement, sedation, volume resuscitation and phenylephrine, an alpha-agonist that determines direct vasoconstriction, causing an increase in systemic resistance, to which follows an increment in pulmonary blood flow as result (Nudel, Berman, & Talner, 1976; Tanaka, Kitahata, Kawahito, & et al., 2003). In patients who require such intervention an early surgical repair or palliation is mandatory.

1.5 Surgical Repair

Surgical timing is still debated because of two issues regarding neonates with ToF. The first addresses the preference in symptomatic neonates between direct early repair of the defect, regardless of size or age, and the choice of palliation before correction in selected patients below a certain age or size. The second relates to acyanotic neonates and young infants and the necessity or not to repair their defect at diagnosis.

Proponents of *early repair* consider rational this approach since shrinks the time exposure of cyanosis, reducing a possible neurological distress development, the entity of RVH and an affliction in pulmonary artery and alveolar development; moreover a palliation procedure means, by definition, the necessity of a future re-intervention for the patient (Jonas, 2009). This choice would be favored by the possibility to perform early operations with low mortality (Derby & Pizarro, 2005; Di Donato, Jonas, Lang, & et al., 1991; Hennein, Mosca, Urcelay, & et al., 1995; Kolcz & Pizarro, 2005; Parry, McElhinney, Kung, & et al., 2000; Pigula, Khalil, Mayer, & et al, 1999; Reddy, Liddicoat, McElhinney, & et al., 1995; Tamesberger, Lechner, Mair, & et al., 2008). However in contrast, an increased morbidity, requirement of inotropes and a prolonged mechanical ventilation after very early repair have also been reported (Kanter, Kogon, Kirshbom, & et al., 2010; van Dongen, Glansdorp, Mildner, & et al., 2003), as well as high rates of early re-interventions in infants who undergo primary repair

under 1 month of age (Hirsch, Mosca, & Bove, 2000).

Advocates of *selective staged management* of neonates and infants with ToF focuses on the negative effects of both transventricular approach for the closure of the VSD and the homografts or transannular patch use in very young patients, in which either are really common. Effectively, the reports evidence a use of homografts or transannular patch in patients under 3 months of age over 50% (van Dongen et al., 2003; Gustafson, Murray, Warden, & et al., 1988), which even ranges from 84-100% in true neonates with less than 1 month (Hennein et al., 1995; Kolcz & Pizarro, 2005; Tamesberger et al., 2008; Hirsch et al., 2000), and a majority of VSD repairs via a transventricular approach. Staged repair permits to avoid the transventricular approach and often preserves pulmonary valve function, and this outweighs, for the supporters of this strategy, the necessity to delay the primary repair. This explains why transatrial-transpulmonary approach with selective shunting in symptomatic neonates is still advocated with excellent results (Fraser-Jr, McKenzie, & Cooley, 2001; Karl, Sano, Pornviliwan, & et al., 1992; Stewart, Backer, Young, & et al., 2005). Transatrial-transupulmonary approach compared with transventricular approach reduces incidence of RV arrhythmias and improve both RV function (Stellin, Milanesi, Rubino, & et al., 1995) and valve-sparing techniques feasibility in over 80% of patients (Stewart et al., 2005). Valve spearing usefulness is shown by the fact that, even significant pulmonary regurgitation caused by transannular patch often evidence a good long-term tolerance (considering symptoms (Bacha, Scheule, Zurakowski, & et al., 2001) and overall mortality (Kirklin, Kirklin, Blackstone, & et al., 1989)), the Pulmonary Insufficiency (PI) eventually increases arrhythmia incidence and risk of Sudden Cardiac Death (SCD) and decreases right ventricular function (Gatzoulis, Balaji, Webber, & et al., 2000; Horneffer, Zahka, Rowe, & et al., 1990; Ilbawi, Idriss, DeLeon, & et al., 1987; Marie, Marcon, Brunotte, & et al., 1992).

1.5.1 Palliative Procedures

`Blalock-Taussig Modified.` The most commonly palliative procedure executed, that has supplanted the classic Blalock-Taussig shunt (de Leval, McKay, Jones, & et al., 1977). It's normally performed trough median sternotomy, even some surgeons still approach via thoracotomy, since it allows the use of cardiopulmonary bypass in case of hemodynamic collapse or severe hypoxia (even the majority are performed without it), allows examination of coronary anatomy and avoids multiple points of incision after complete repair for the patient. The relative comfort in performing re-sternotomy developed nowadays has minimized the rationale of avoiding sternotomy for Modified Blalock-Taussig Shunt (MBTS).

The technique consist in the anastomoses of a 3,5 or 4mm Gore-Tex shunt end to side to innominate artery or subclavian artery (Odim, Portzky, Zurakowski, & et al., 1995) and to the homolateral branch pulmonary artery, typically on the opposing side of the aortic arch, followed by the ligation of the ductus arteriosus (See Fig. 1.7). Duct ligation confirms the adequacy of the shunt and decreases the chance of branch pulmonary artery coarctation that can accompany the natural constriction of the duct.

`Other Procedures.` A transannular patch without VSD repair is performed in small infants with very small pulmonary arteries and it has been reported with success even if reserved for extreme situations (Korbmacher, Heusch, Sunderdiek, & et al., 2005; Seipelt, Vazquez-Jimenez, Sachweh, & et al., 2002). RVOT and pulmonary valve percutaneous balloon plasty and stenting have also been reported; it has shown to be helpful in very small patients and proponents have also evidenced growth of the branch pulmonary arteries (Laudito, Bandisode, Lucas, & et al., 2006; Wu, Wang, Lee, & et al., 2006). However this procedure also demonstrated that effective relief of stenosis determines an irreversible damage to the pulmonary valve (Dohlen, Chaturvedi, Benson, & et al., 2009).

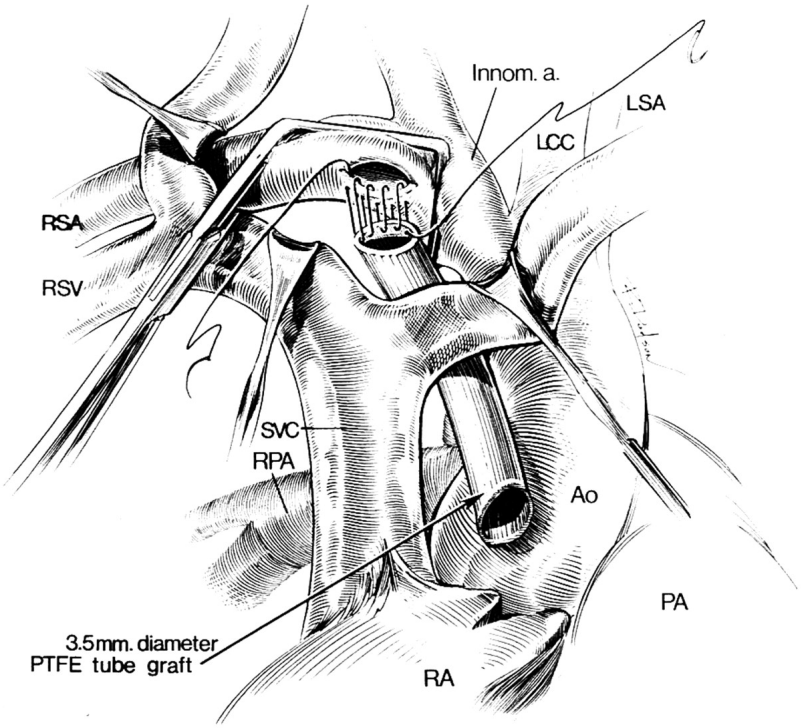


Figure 1.7: Schematic diagram of MBTS via sternotomy approach. RSA indicates right subclavian artery; RSV, right subclavian vein; SVC, superior vena cava; RPA, right pulmonary artery; RA, right atrium; PA, pulmonary artery; Ao, aorta; LCC, left common carotid artery; LSA, left subclavian artery; and Innom.a., innominate artery.
[Reproduced from: *"Johan Odim, Michael Portzky, David Zurakowski, et al." – Sternotomy Approach for the Modified Blalock-Taussig Shunt – Circulation November 1, 1995 vol. 92 no. 9 256-261*]

1.5.2 Complete Repair

Anesthetic induction in patients with ToF is concerning since it causes systemic vascular dilatation with an exacerbation of right-to-left shunting, possibly leading to profound hypoxia and risk of hemodynamic collapse. Crucial basic principles include maintaining adequate volume status with an hemoglobin level of at least 10mg/dl, use of high inspired oxygen level and avoidance of inhalational agents since they have a significant vasodilatory effect. Use of intravenous agents minimize the undesiderated vasodilatation. Transesophageal echocardiography

should be performed, if feasible for patient size, in every patient and should be interpreted by a pediatric cardiologist.

Median sternotomy is performed and the size of the thymus noted before its excision to exclude the association with DiGeorge syndrome. If a prior shunt was performed it's isolated after systemic heparinization and aortic and bicaval cannulaton. Cardiopulmonary Bypass (CPB) is initiated with moderate hypothermia ($28°C$) and if the shunt is present it's ligated proximally and distally and divided to avoid any future tending of the branch pulmonary artery. If the pulmonary artery is narrowed at the shunt site then the shunt is excised from the pulmonary artery and an autopericardium patch is used to perform a patch augmentation. A left ventricular vent is inserted trough the right superior pulmonary vein, the aorta is cross-clamped and an anterograde cold-blood cardioplegia, for short lasting interventions, or custodiol cardioplegia, for long procedures, is delivered trough a cardioplegia cannula inserted into the aortic root. For the cold-blood cardioplegia only an every 15-20 minutes re-administration, or earlier at any sign of cardiac activity, is necessary. A topical saline solution slush is placed together with the cardioplegia into the heart. Cavae are snared, a medial right atriotomy is made (Hirsch & Bove, 2003) and RVOT examined. Any endocardial fibroelastic tissue, which represent areas of turbulent flow, is excised as well as hypertrophyc muscle bundles projecting from septomarginal and septoparietal bands are divided and partially excised, together with any smaller trabecular muscles causing obstruction. Excessive resection must be avoided of either RVOT septal portion, to prevent coronary arteries perforation, and RV free wall, since this can cause coronary fistula from conal branches; moreover, during the resection, the tricuspid subvalvar apparatus must be noted and preserved. The most of RVOT resection can be performed trough right atrium and tricuspid valve but, if necessary, additional resection can be made trough pulmonary valve. In presence of severe obstruction a small infundibular incision, 10-12mm in length and immediately below pulmonary valve annulus, may be required to adequately resolve obstruction, which is closed with a thin-walled

(0,4mm) Gore-Tex patch thereafter (Procedure illustrated in Figs. 1.8 and 1.9)

A longitudinal pulmonary arteriotomy is made and carried up to the two anterior sinuses in presence of a trileaflet valve or into the lateral sinuses of a vertically oriented bicuspid valve. In presence of an horizontally oriented bicuspid valve the incision is carried straight up to the ventricle-pulmonary artery junction. A pulmonary valvotomy is performed to divide the typically partially fused commissures to the level of arterial wall to provide a maximal opening through the preserved annulus, then a probe is inserted to measure the size and if it's larger than -3 Z score the annulus is left intact. Pulmonary arteriotomy is then closed with a pantaloon pericardial patch, if the annulus has not been incised, to maximize the size of pulmonary root and completely relieve any supravalvar obstruction (Stewart et al., 2005) (Procedure shown in Figure 1.10). Instead, when pulmonary annulus incision is performed, a simple pericardial patch is used. Inspection of pulmonary branches orifices should be done, being often stenotic in patients with ToF, and can be corrected with an extension of pericardial patch, or with a separate one, into the branch.

The VSD is closed with a continuous horizontal mattress suture, using a 5-0 Ethibond, to place a glutaraldehyde fixed autologous pericardium around the circumference of the defect. If autologous pericardium is not available then bovine or porcine pericardium is used. Superiorly the suture must be placed nearly the aortic annulus to avoid residual defects trough the trabeculations. Inferiorly, between the muscle of Lancisi and tricuspid annulus, avoiding deep suture bites is critical to avoid damage to Atrio-Ventricular (AV) node and bundle of His. The patch is cut to slightly oversize the defect to avoid potential subaortic narrowing which could results from anterior malalignment of VSD. The Tricuspid valve is tested and the Patent Forame Ovale (PFO), which is nearly always present, is closed primarily with a 5-0 Prolene suture, except in neonatal period during which is left open. The right atrial incision is then closed with two layers of running Prolene suture, the heart is carefully de-aired and the cross-clamp removed.

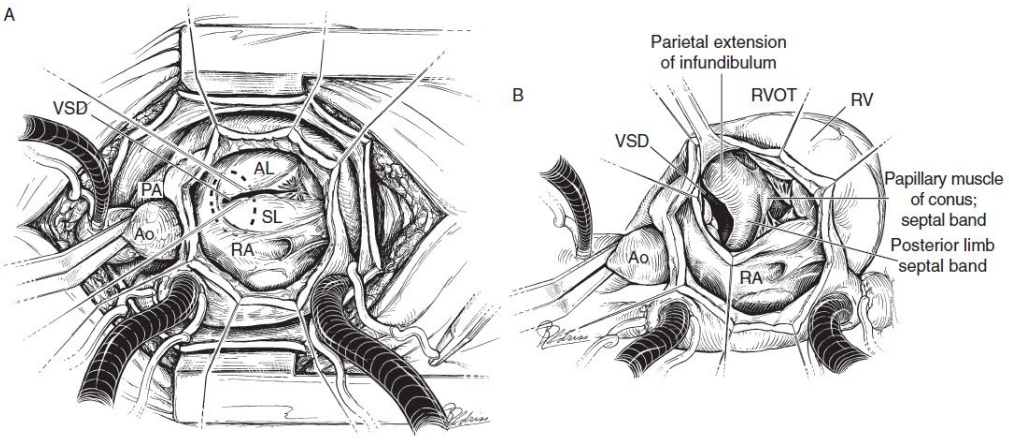


Figure 1.8: The surgical anatomy as viewed through a right atriotomy. The free edge of the atrial wall is retracted with stay sutures. The location of the VSD is denoted by the dashed line. (A) Stay sutures are placed in the septal and anterior leaflets of the tricuspid valve for retraction. (B) The tricuspid valve leaflets have been retracted and a single valve retractor is in place to aid exposure. The inferior margin of the VSD can be seen superior to posterior limb of the septal band.

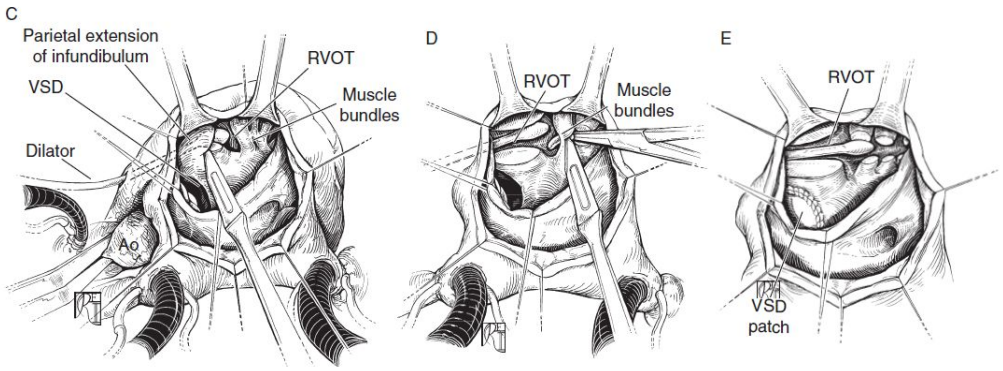


Figure 1.9: (C) A dilator placed through the pulmonary annulus delineates the course of the right ventricular outflow tract. The parietal extension of the infundibulum is visible at the tip of the dilator. The parietal extension can be resected at its origin from the infundibular septum, dissected up toward the free wall, and amputated at the free wall. (D) Division of the obstructing muscle bundles along the anterior limb of the septal band. (E) View through the right atriotomy and tricuspid valve following patch closure of the VSD. (AL, atrial leaflet; Ao, aorta; PA, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; SL, septal leaflet)

[Either reproduced from: *"C. Mavroudis" – Tetralogy of Fallot – in Pediatric Cardiac Surgery*]

After separation from cardiopulmonary bypass direct measurement of right and left ventricle pressure is made with a 21-gauge spinal needle attached to a pressure transducing line. If the RV/Left Ventricle (LV) pressure ratio is grater than 0,7 (Hirsch et al., 2000; Stewart et al., 2005) the transesophageal echocardiography is assessed to evidence and level any residual obstruction. If it's predominantly at the annulus the CPB is recommenced and a transannular patch is performed, while if it's exclusively subvalvar only an infundibular patch is created immediately below the annulus extending 10-12mm. Temporary atrial and ventricular pacing wires are always placed, regardless of the rhythm, because of the high incidence of Juctional Ectopic Tachycardia (JET) following the repair of the ToF.

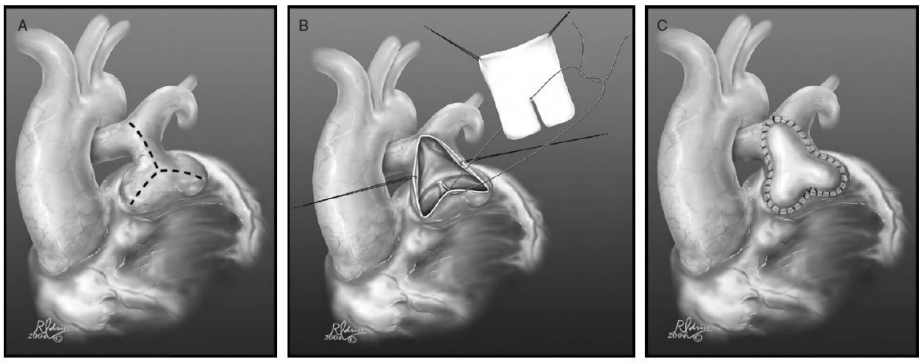


Figure 1.10: (A) Pulmonary arteriotomy. (B) Autologous pantaloon pericardial patch. (C) Completed pulmonary artery pantaloon patch. [Reproduced from (Stewart et al., 2005)]

1.6 Surgical Results

1.6.1 Mortality

The morality rate for complete repair of ToF has sharply decreased from an initial 40% (Lillehei, Cohen, Warden, & et al., 1955), to a 20% revealed between 1955-1960 at Mayo clinic (Murphy, Gersh, Mair, & et al., 1993) and reaching a 4,9% from 1960 to 1982 at Stanford (Zhao, Miller, Reitz, & et al., 1985).

However in that era the age of repair was older, with a mean of 12,2 years considering a series of over 650 patients from 1958 to 1977 (Nollert, Dabritz, Schmoeckel, & et al., 2003), and the advent of the neonatal surgery determined a recrudescence in mortality levels (Nollert et al., 2003; Ebert & Turley, 1984; Turley, Mavroudis, & Ebert, 1982; Barratt-Boyes & Neutze, 1973; Castaneda, Freed, Williams, & et al., 1977). Nevertheless, improvements in the last three decades in surgical technique, anesthetic management and perioperative care let a dramatic reduction of mortality even for infant and neonatal ToF repair, reaching nowadays even levels of 0,5% (Karl et al., 1992) and with a global of 0-3% (Derby & Pizarro, 2005; Kolcz & Pizarro, 2005; Parry et al., 2000; Reddy et al., 1995; Tamesberger et al., 2008; Kanter et al., 2010; van Dongen et al., 2003).

Long-term survival rate for patients with ToF is excellent, even for patients operated in the earliest era, with a 30 years actuarial survival of 86-89% (Murphy et al., 1993; Nollert, Fischlein, Bouterwek, & et al., 1997) that must be compared to an expected rate of 96% of the control population matched for age and sex.

1.6.2 Morbidity

The most significant complications following ToF repair are arrhythmias, early reoperation or catheter reintervention, residual VSD and heart block. *Heart block* requiring pacemaker has an incidence of 0-2% and usually occurs late after intervention (Friedli, 1999), and an early postoperative transient heart block is a risk factor for the development of late heart block (Hokanson & Moller, 2001). Others complications include *phrenic nerve injury, chylothorax, delayed sternal closure.*

Early Reoperation and Reinterventions

The RV can tolerate the volume load of PI for a number of years, therefore the reoperation for this reason is a rare early event, while is a significant one late after repair. Instead, the most common reason for an early reoperation after ToF

repair is residual RVOT obstruction, which can be located at the infundibular, valvular or branch pulmonary arteries level, the latter often amenable of catheter-based balloon plasty and/or stent placement. The incidence of reoperation in electively operated patients varies greatly among different patient populations, spacing globally from 3-8% (Fraser-Jr et al., 2001; Tamesberger et al., 2008) but reaching level as high as 30% in primary repair of symptomatic neonates (Hirsch et al., 2000). When primary repair is compared with staged repair no statistically significant difference has been revealed regarding freedom from reoperation (Knott Craig, Elkins, Lane, & et al., 1998).

The amount of residual obstruction after initial repair, evidenced by RV/LV pressure ratio, is directly related to incidence of reoperation, a study of the University of Alabama demonstrated that a ratio grater than 0,85 is a associated with a 2,5 times increased risk of death and 7,5 risk of reintervention (Katz, Blackstone, Kirklin, & et al., 1982).

Other indications for early reoperations include *residual VSD, residual ASD, RVOT aneurysm, severe tricuspid regurgitation, heart block, phrenic nerve injury and chylothorax.*

Arrhythmias and Sudden Death

Arrhythmias and conduction disturbances are important both for their prevalence and consequences, especially considering that SCD is the most common cause of mortality late after ToF repair, most probably related to ventricular arrhythmias (Gatzoulis et al., 2000).

In the early post-operative period the *right bundle branch block* is the most common conduction disturb due to suture damage or RVOT incision and it involves over 90% of patients when ventriculotomy is performed (Friedli, 1996); while the *complete heart block* is relatively uncommon with a reported incidence of 1-3% (Kolcz & Pizarro, 2005; Pigula et al., 1999; Tamesberger et al., 2008; Kanter et al., 2010). Instead, the most common after repair early arrhythmia is JET, which incidence varies greatly based on age at surgery and surgical ap-

proach, but it's grater when transventricular repair is performed (Pigula et al., 1999) rather than transatrial/transpulmonary approach, spacing for the latter from 12% (Stewart et al., 2005) to 6% (Fraser-Jr et al., 2001). JET can result in major hemodynamic instability in the immediate postoperative period.

Late arrhythmias after ToF repair include both atrial and ventricular tachycardias, with an evidenced global incidence of over 43% in a retrospective study from The Alliance for Adult Research in Congenital Cardiology (20% atrial and 15% ventricular arrhythmias) (Khairy, Aboulhosn, Gurvitz, & et al., 2010), even this might be an overestimation in a selected population. The paroxysmal Sopra-Ventricular Tachycardia (SVT) is the most common late type arrhythmia, as a re-entry tachycardia with re-entrant circuits that can develop even in atrial incision scars, with development risks as older age at surgery, tricuspid regurgitation, right atrial enlargement and poor RV function (Khairy et al., 2010; Harrison, Siu, Hussain, & et al., 2001; Roos-Hesselink, Perlroth, McGhie, & et al., 1995; Le-Gloan, Guerin, Mercier, & et al., 2010; Wessel, Bastanier, Paul, & et al., 1980). Ventricular arrhythmias instead include as risk factors older age at repair, ventriculotomy, severe pulmonary regurgitation, poor right or left ventricle function and elongated QRS duration (Gatzoulis et al., 2000; Harrison et al., 2001; Dietl, Cazzaniga, Dubner, & et al., 1994; Khairy, Landzberg, Gatzoulis, & et al., 2004).

1.6.3 Long-term Complications Following Repair of Tetralogy of Fallot

The major late complications represent a consequence of a disarrangement in right ventricle physiology, specifically caused by *volume overload*, as a consequence of pulmonary insufficiency, tricuspid regurgitation and any possible residual shunt, together with *pressure overload* resulting from residual pulmonary stenosis. The sequelae to this event might include RV disfunction, ventricular arrhythmias including SCD, late LV disfunction and aortic aneurysmal dilatation and the long-standing PI is the primary etiology for their devel-

opment. The cause of PI is directly related to the use of the *transannular patch* and, even if some authors report a good long-term functional outcomes after repair of ToF with the transannular patch (Bacha et al., 2001; Kirklin et al., 1989), others have reported a deleterious effect of PI on the RV when more sensitive measures are made (Roest et al., 2002; Horneffer et al., 1990), with severe RV dysfunction evident at CMR even in asymptomatic patients (Roest et al., 2002; Singh, Greenberg, Yap, & et al., 1998). Moreover, exercise testing shown impaired functional status in ToF patients with long term PI (Horneffer et al., 1990; Carvalho, Shinebourne, Busst, & et al., 1992), which is relieved, together with RV function, after pulmonary valve late insertion (Discigil, Dearani, Puga, & et al., 2001; Eyskens, Reybrouck, Bogaert, & et al., 2000; Warner, O'Brien, Rhodes, & et al., 2003).

Pulmonary Valve Replacement

Pulmonary Valve Replacement (PVR) in patients with severe PI late after ToF repair, has shown functional improvement in several reports, however correct timing and effect of PVR still remain debated. In fact, while one study showed a decrease from 23% to 9% in Ventricular Tachycardia (VT) after PVR (Therrien, Siu, Harris, & et al., 2001), another demonstrated no difference in VT or SCD incidence (Harrild, Berul, Cecchin, & et al., 2009); in addition the effect and lasting of it on QRS duration is variable (van Huysduynen, van Straten, Swenne, & et al, 2005; Oosterhof, Vliegen, Meijboom, & et al, 2007). Regarding RV the PVR demonstrated an improvement both in function and size of RV (van Huysduynen et al., 2005; van Straten, Vliegen, Lamb, & et al., 2005), however the gain was limited if the ventricle reached a critical size.

Considering all this variable outcomes there are no universally accepted indication for PVR, however most authors consider it an important late intervention in patients with repaired ToF, unless executed too late in which the benefits become limited. Geva and colleagues consider an indication the presence of any two between: Right Ventricle End-Diastolic Volume index (RVEDVi) $> 160ml/m^2$,

Right Ventricle End-Sistolic Volume index (RVESVi) $> 70ml/m^2$, Left Ventricle End-Diastolic Volume index (LVEDVi) $> 65ml/m^2$, RV ejection fraction $< 45\%$, RVOT aneurysm and clinical symptoms or signs (Geva, 2006).

The main technical modalities of PVR include: *homograft replacement, valved conduit replacement and orthotopic bioprosthetic valve insertion with creation of RVOT hood with Gore-Tex or heterograft pericardium* (Champsaur, Robin, Curtil, & et al., 1998; Chan, Fyfe, McKay, & et al., 1994; Homann, Haehnel, Mendler, & et al., 2000).

Neurological Outcomes

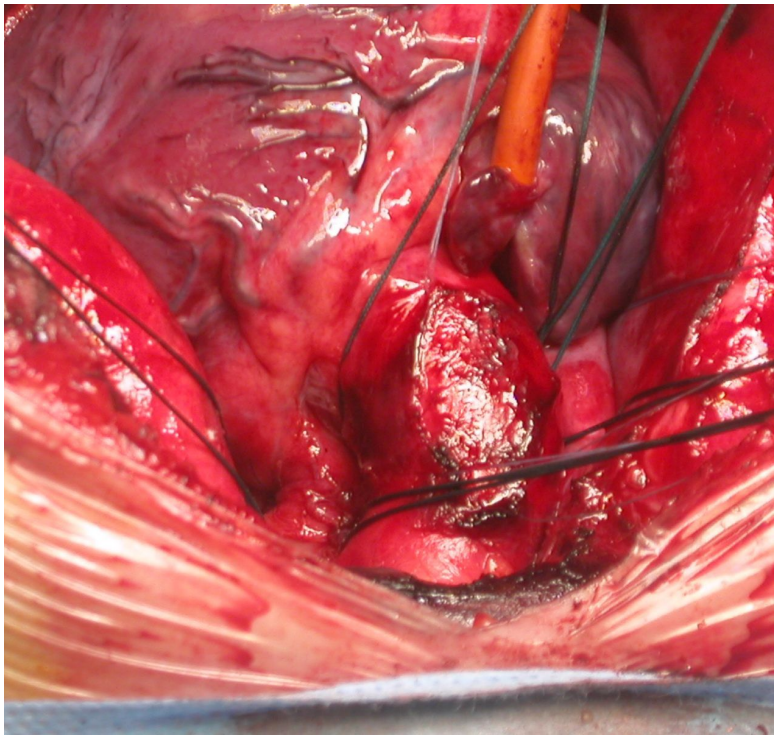
Children with repaired ToF evidenced an inferior full-scale IQ than the general age-matched population (Miatton, De-Wolf, Francois, & et al., 2007), however, when they were stratified according to the presence of genetic abnormalities, those without any defect had scores within normal ranges per age (Zeltser, Jarvik, Bernbaum, & et al., 2008).

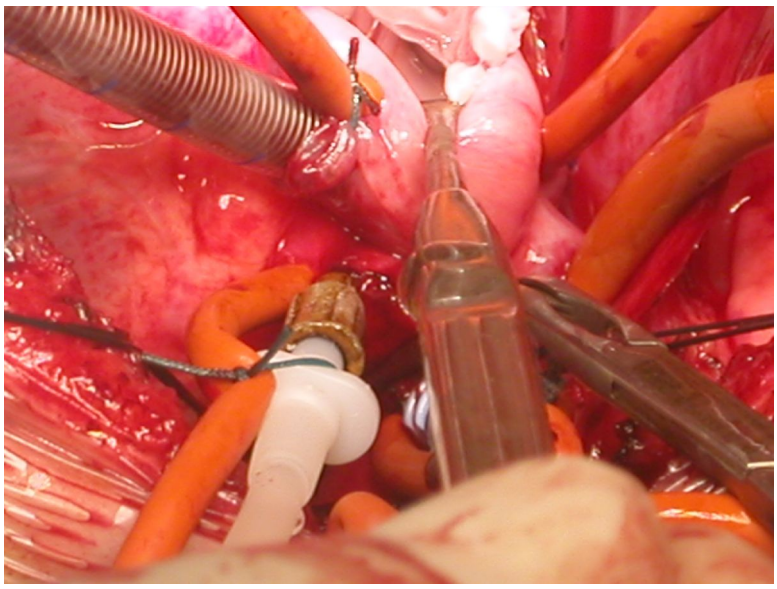
It has also been evidenced an higher incidence of stroke in adult patients with repaired ToF compared with general population, even if no clear etiology has been demonstrated (Chow, Amos, & Celermajer, 2005).

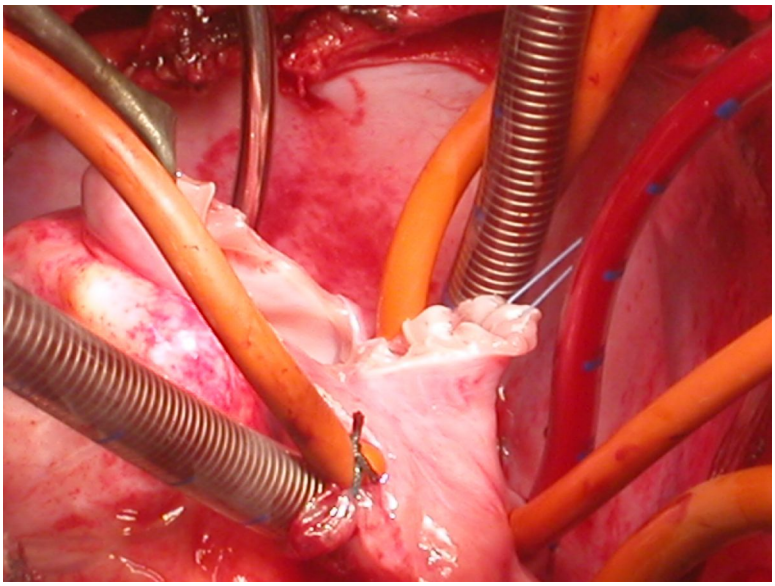
Aortic complications

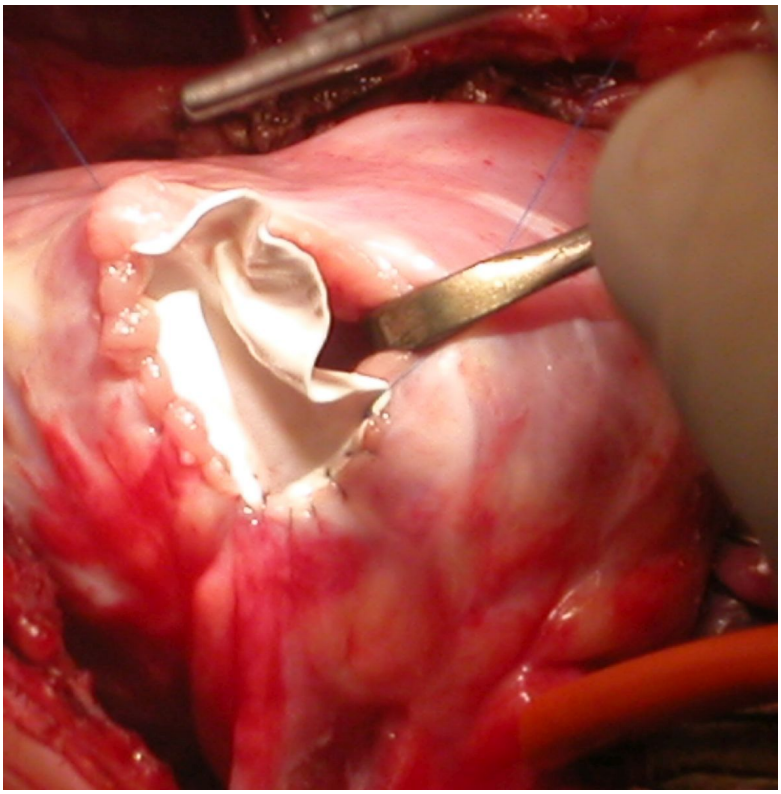
Aortic valve and root complications late after ToF repair have been well documented; specifically Zahka and collegues noted a severe aortic regurgitation incidence of 21% at 18 years from primary repair (Zahka, Horneffer, Rowe, & et al., 1988). It has also been evidenced that it becomes in the childhood and that it's associated with high level of elastic fiber fragmentation in ToF patients aorta (Chong, Wong, Chiu, & et al., 2006). This and other aortic parietal lesions present in ToF patients are responsible of aortic aneurism (Dimitrakakis, Von-Oppell, Bosanquet, & et al., 2009) and dissection (Kim, Seo, Kim, & et al., 2005) development late after ToF repair, but their interventional criteria are similar to non-ToF patients (Crestanello, Cook, Daniels, & et al., 2010).

Tetralogy of Fallot Surgical Correction Intraoperative Pictures









Chapter 2

Ventricular to pulmonary artery conduits[∞]

[∞] "John Brown, Osama Eltayeb, Mark Ruzmetov, Mark Rodefeld, and Mark W. Turrentine" Ventricular to Pulmonary Artery Conduits – Pediatric Cardiac Surgery Fourth Edition, Ed.: Wiley-Blackwell

In infants with valve pathology *surgical reconstruction* is the primary goal in all interventions because anatomy and physiology restoration using native tissues permits growth and a potentially better long term outcome. However when repair fails or is not feasible then *valve replacement* becomes the only available option (Husain & Brown., 2007). This procedure in neonates, infants and children is challenging because of the strict interrelation of valve pathology, patient size and growth requirement.

Pulmonary valve is the most common valve replaced in congenital population and *RVOT reconstruction* is performed in patients with CHD who present *discontinuity between RV and the branch pulmonary arteries* or in whom significant *pulmonary stenosis or insufficiency is present.* In 1964 Rastelli and colleagues inserted the first Right Ventricle-to-Pulmonary Artery (RV-PA) conduit, a *pericardial non valved tube*, in a child with pulmonary atresia (Rastelli, Ongley, Davis, & Kirklin., 1965), while in 1966 Ross and Somerville introduced the *aortic valved allograft* for RVOT reconstruction (Ross & Somerville., 1966).

Extracardiac conduits now permit routine repair of CHD in which *pulmonary atresia* or *RVOT hypoplasia* is involved. These lesions are part of complex CHDs

including *Tetralogy of Fallot with or without pulmonary atresia* (the case we studied), *Truncus Arteriosus*, *Pulmonary Atresia* or *Stenosis* with or without *VSD*, *Transposition of Great Arteries*, certain subtypes of *Double Outlet Right Ventricle* and *Pulmonary Autograft Replacement in the Ross operation*. Many of these condition are corrected in neonates, the most challenging context for any prothesis selected for RVOT reconstruction.

The *porcine valve Dacron conduit* was extensively used between 1970s and early 1980s, but after, for a while, it had been abandoned due to late obstructive complications related to the development of a neointimal peel within the tube (Jonas, Freed, Mayer, & et al., 1985). Nowadays however it's use is increasing again and new trials and retrospective evaluation are performed. *Aortic and pulmonary cryopreserved allografts* became the main choice for RVOT reconstruction from mid 1980s to late 1990s, this favoured by the development of cryopreservation techniques which improved considerably either durability and availability of allograft. At present a wide range of valved conduits have been introduced and the most notably are: *aortic xenografts in Dacron tubes*, *stented bovine pericardial or porcine xenografts in pericardial tubes*, *glutaraldehyde fixed aortic and pulmonary roots*, *aortic and pulmonary allografts* and *bovine jugular vein conduits* (Forbess, Shah, Louis, & et al., 2001; Dearani, Danielson, Puga, & et al., 2003; Sinzobahamvya, Wetter, Blaschczok, & et al., 2001; Tweddell, Pelech, Frommelt, & et al., 2000; Chan et al., 1994; Bando, Danielson, Schaff, & et al., 1995).

2.1 Monocusp Right Ventricular Outflow Tract Reconstruction

Patients with ToF and significant pulmonary valve annulus or leaflet hypoplasia historically have been treated in two distinct possible ways: *transannular patch* or *valved conduit insertion*. Transannular patch relieves immediately RV hypertension and enhances RV growth proportionally with patient growth, moreover reoperation for RVOT stenosis is uncommon. However it determines a sudden

hemodynamic conversion from an obstructed and pressure overloaded RV to a volume overloaded RV, with the chronic volume overload which can lead to a late biventricular dysfunction and Tricuspid Valve (TV) insufficiency, possibly necessitating a pulmonary valve insertion (Feier, Collart, Ghez, & et al., 2005; Wells, Arroyo-Jr, Bremner, & et al., 2002). Valved conduits have the advantage of an immediate pulmonary valve competency and are particularly useful for patients who present with a peripheral pulmonary stenosis or with an elevated Pulmonary Vascular Resistance (PVres) (PVres $>$ 4 Wood units). Opposingly the main disadvantage of current conduits it's the structural deterioration caused by calcification, shrinkage and lack of growth which determine early or late valve disfunction. However pulmonary allograft conduits remain popular at present despite a freedom from reoperation of 50% at 5 years in patients undergoing a non-Ross RVOT conduit insertion (Bando et al., 1995; Wells et al., 2002).

An attractive alternative strategy is the concept of *RVOT reconstruction with a monocusp patch*, which can have specific advantages in selected populations of infants. A monocusp valve can be placed in any sized patient, being the patch tailor-made to fit the RVOT after its enlargement with a transannular outflow patch, is less expensive and usually last longer than a valved conduit in an infant. The monocusp RVOT patch can be made with *autologus* or *bovine pericardium* (Raanani, Yau, David, & et al., 2000; Discigil et al., 2001), *allograft pulmonary valve cusp* (Gundry., 1999) or a *Polytetrafluoroethylene (PTFE) membrane* traditionally employed as pericardial substitute (Ando, Imai, Takanashi, & et al, 1997; Bogers, Roofthooft, Pisters, & et al., 1994; Yamagishi & Kurosawa, 1993; Oku, Matsumoto, Kitayama, & et al., 1993; Turrentine, McCarthy, Vijay, & et al., 2002b). Each material has proven a good immediate postoperative valve competency and reduced early PI (Bogers et al., 1994; Oku et al., 1993; Turrentine et al., 2002b; Gundry, Razzouk, Boskind, & et al., 1994).

In 1993 Yamagishi and Kurosawa and Oku and colleagues independently introduced a readily 0.1mm PTFE pericardial membrane for monocusp construction

and found it superior when compared to biologic leaflets materials. Clinical application of this material in patients with ToF, in whom transannular patching was necessary, permitted an improved RV perioperative function as demonstrated by a lower postoperative central venous pressure, less need of postoperative inotropic agents, less chest tube drainage and a decrease in hospital and Intensive Care Unit (ICU) stay (Turrentine, McCarthy, Vijay, & et al., 2002a). This material it's now the authors (Brown, Eltayeb, Ruzmetov, Rodefeld, & Turrentine., 2013) choice for monocusp construction in RVOT disorders, either obstructive and regurgitant, and especially in infants undergoing primary ToF repair and in whom transannular patching is necessary.

Construction of a pericardial or PTFE monocusp is simple, relatively inexpensive and reproducible, while pulmonary allografts are considerably more expensive and possibly difficult to fit adequately into the RVOT. The main potential disadvantage of monocusp patches is a possibly quicker recurrence of PI if the monocusp leaflet stick in open position, as has been reported with some biologic monocusps (Bogers et al., 1994; Turrentine et al., 2002b; Gundry et al., 1994), while recurrent stenosis at the monocusp valve level is rarely seen with any type of material. The major PTFE-specific advantage is the absence of in-growth of tissue and therefore a much longer lasting valve mobility and function.

The *monocusp insertion* is a relatively standardized technique. It consists in determining the length and width of monocusp membrane, which are usually kept mildly redundant to guarantee coaptation to conal septum and/or residual pulmonary leaflets tissue, followed by its sewn into the RVOT, together with the sew of a second patch of 0,4mm PTFE across the entire RVOT into the pulmonary artery with a second suture line. Specifically, in patients with an intact pulmonary annulus its dimensions, following valvotomy, are measured with a Hegar dilator and if the annular Z value is ≥ -2 then transannular patching is not perfmormed. Instead, with a moderate hypoplasia (Z score <-2) or with a postvalvotomy RVOT gradient >30mmHg and/or RV pressure >80% of sys-

temic pressure the transuannular patch repair with a monocusp valve insertion is performed (Entire procedure is shown in Figs. 2.1 to 2.6).

PTFE monocusp with separate RVOT patch has been demonstrated useful in patients with ToF or with pulmonary atresia and VSD who require transannular patch and in patients requiring a second RVOT procedure after a failed initial conduit reconstruction. Referring to authors experience they have described a well-functioning monocusp valve for a mean of 3–4 years in most patients, reaching up to 10–12 years in some of them. The majority of patients developed a pulmonary regurgitation as RVOT grew, however they didn't observed recurrent outflow obstruction at the leaflet level. Another important indication for PTFE monocusp reconstruction is the primary allograft conduit failure since the positioning of a second conduit has been associated with an accelerated structural failure (Wells et al., 2002). The only anticoagulant used after PTFE monocusp positioning is aspirin with dose of 10mg/kg a day or 80mg/day as limit.

Several *bicuspid PTFE* reconstructions and a *folding monocusp PTFE leaflet* have been recently introduced (Turrentine et al., 2002a; Brown, Ruzmetov, Vijay, & et al., 2007) and early results seem promising, however longer follow-up will be necessary to evaluate their durability.

Quintessenza and colleagues described a bicuspid RVOT outflow reconstruction (Quintessenza, Jacobs, Chai, & et al., 2010) and their early results at 3 years, with a 0.1 PTFE, are considerably better than those obtained with 0.6mm PTFE observed for 8 years. Nunn and colleagues described a folding monocusp with 0.1mm PTFE and evidenced a lesser degree of RVOT regurgitation traded with an higher gradient at mid-term follow-up, respectively to the simple horizontal monocusp (Nunn, Bennetts, & Onikul., 2008). Morell and colleagues described a PTFE tube with a bicuspid PTFE valve constructed into the conduit with satisfactory results even after a short (less than 1 year) follow up.

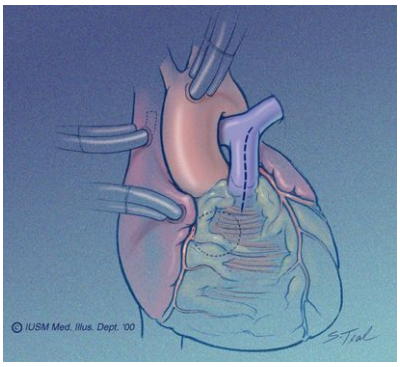


Figure 2.1: Pulmonary Artery Incision. If patient presents a moderate/severe annulus hypoplasia (< -2 Z value) or a persistent high gradient after valve sparing decompression a monocusp reconstruction is performed.

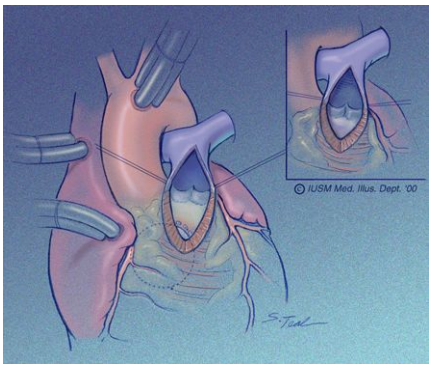


Figure 2.2: Ventriculotomy. The incision is carried out as long as necessary to alleviate the infundibular narrowing, with a mean length of 1–2cm.

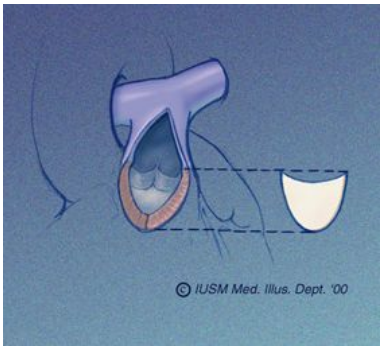


Figure 2.3: Monocusp creation. A cusp is fashioned from a PTFE membrane or autologous pericardium and placed in the ventricular portion of the opening to allow it to flush along ventricular walls, thereafter the cusp is cut to the precise patient outflow dimensions. The monocusp must be longer for a patient with a longer ventriculotomy.

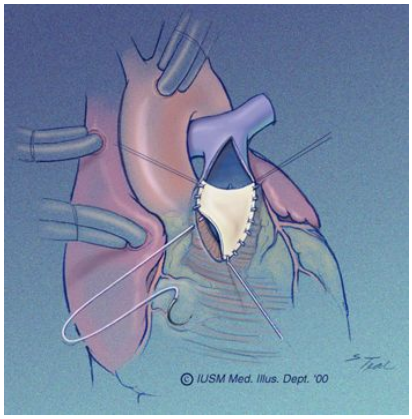


Figure 2.4: Monocusp insertion. The monocusp is sutured to the ventriculotomy opening with running 6-0 PTFE suture. The suturing begins at the proposed hinge point and extends onto the epicardial surface of the ventricle with bites that include at least one-half the depth of the myocardium.Care is taken to ensure that the superior edge of the monocusp matches that of the retained posterior leaflets

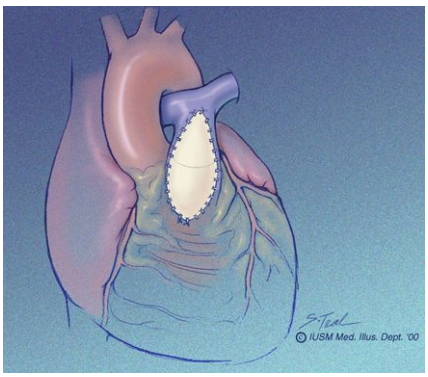


Figure 2.5: Outflow Tract Patch. The patch forms a roof over the monocusp. This patch is sutured to the main pulmonary artery and to the ventriculotomy edge and in effect reinforces the suture line of the monocusp itself to the ventriculotomy. The dotted line in the mid-portion of this illustration shows the location of the monocusp within the PTFE outflow tract patch

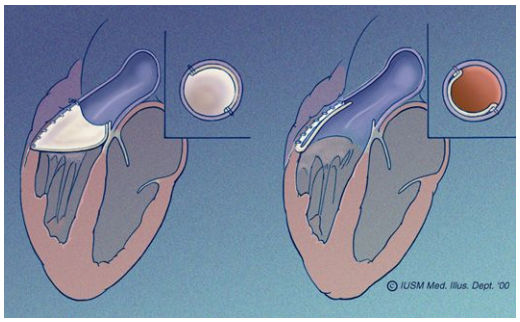


Figure 2.6: Monocusp Function. The functional characteristics of the monocusp are demonstrated here. The illustration on the left shows the monocusp in diastole. Blood from the pulmonary artery has filled the monocusp and presses it against the septum and remaining posterior pulmonary valve leaflet. This is the coaptation site of the monocusp. In the illustration to the right, the monocusp is in the open position; this would be during systole. The monocusp is flush with the RVOT anterior RV wall and PTFE outflow tract patch. The function of the monocusp can be evaluated intraoperatively with transesophageal echocardiography.

Figures reproduced from CTSNet Website at url:

http://www.ctsnet.org/sections/clinicalresources/congenital/expert_tech-1

2.2 Allograft Conduits

Cryopreserved pulmonary allografts were the "gold standard" in the United Stases from mid-1980s to up to late 1990s (Forbess et al., 2001; Dearani et al., 2003; Bando et al., 1995) favored over aortic allografts (see Fig. 2.7), being the

latter prone to calcification and disfunction (Perron, Moran, Gauvreau, & et al., 1999). In fact, high elastine content of aortic allograft increase their calcification and adherence propensity, hence making their removal or revision challenging.

Allograft Conduits (ACs) are frequently prone to early significant valve regurgitation or to late conduit stenosis consequent to its shrinkage (Wells et al., 2002), however their use in Ross operation represent an exception to this behaviour since their performance and longevity are greatly increased. This latter case is probably related to an usual patients older age and the allograft insertion in orthotopic position, which probably reduces the turbulence normally observed in extracardiac conduits.

Durability's a critical factor in determining prothesis' choice for pulmonary valve replacement. Forbes et al. (Forbess et al., 2001) evaluated pulmonary AC implanted at the same single institution over 14 consecutive years in three separate age groups. They demonstrated in *univariate analysis* that conduit smaller size ($<$ 14mm), younger aged patients ($<$ 1 year) and truncus arteriosus were all risk factors for failure, while in *multivariate analysis* allograft size was the only predictor. AC Implants positioned through a Ross operation had the best outcome with a 5 year survival of 94% (Forbess et al., 2001), while non-Ross AC implants in patients over 10 years of age had a 5 year survival of 76% (Forbess et al., 2001).

In other authors studies univariate analysis identified younger age, smaller AC, diagnosis of truncus arteriosus and aortic AC subtype as risk factors for disfunction and failure, while *multivariate analysis* identified smaller AC size and truncus arteriosus diagnosis as risk factors for dysfunction and failure (Brown, Ruzmetov, Rodefeld, & et al., 2005; Sinzobahamvya et al., 2001; Tweddell et al., 2000; Bando et al., 1995; Brown et al., 2005; Hawkins, Bailey, Dillon, & et al., 1992; Yankah, Alexi-Meskhishvili, Weng, & et al., 1995; Niwaya, Knott-Craig, Lane, & et al., 1999; Bielefeld, Bishop, Campbell, & et al., 2001; Askovich, Hawkins, Sower, & et al., 2007; Boethig, Goerler, Westhoff-Bleck, & et al., 2007; Gerestein, Takkenberg, Oei, & et al., 2001).

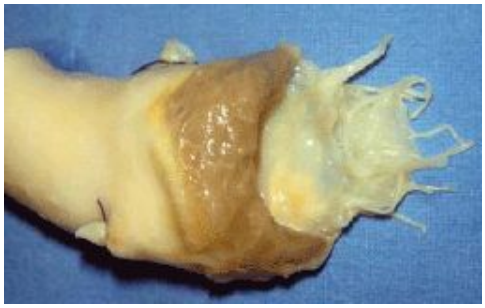


Figure 2.7: Aortic Allograft

[Reproduced from: *"Leonardo A. Mulinari; Fábio B. Navarro; Gustavo K. Pimente et al." – The use and midium-term evaluation of decellularized allograft cusp in the surgical treatment of the tetralogy of Fallot – Rev Bras Cir Cardiovasc vol.23 no.2*]

2.3 Bioprothesic Porcine Valved Dacron Conduits[Π]

[Π] "Richard Jonas" – Choosing the Right Biomaterial
Comprehensive Surgical Management of Congenital Heart Disease
Second Edition, Ed.: CRC Press

Very low density woven Dacron conduits with a glutaraldehyde-treated pig valve within were introduced in the 1970s (Bowman, Hancock, & Malm., 1974; Carpentier, Lemaigre, Robert, & et al., 1969). Their immense logistic advantages, firstly the possibility of stocking in a complete range of sizes, proved attractive and therefore in the ensuing decade thousands of Hancock® and Carpentier-Edwards® conduits were implanted. However, unsatisfactory outcome reports soon appeared (Alfieri, Blackstone, Kirklin, & et al., 1978; Bailey, Kirklin, Bargeron, & et al., 1976) since, as could had been predicted from Wesolowski 1963 studies, a pseudointima frequently accumulated rapidly and, moreover, the glutaraldehyde tanning of porcine valve resulted in rapid calcification in children (Geha, Laks, Stansel, & et al., 1979; Williams, Danielson, McGoon, & et al., 1982). Combination of this two events determined a less than 50% freedom from failure at 10 years and other than that these early bioprothesic conduits were too rigid and large to be successfully applied in neonates and small infants, with

major risk of stent coronary artery compression. However, it should be noted that, after successful implantation, their mode of failure was only very rarely catastrophic and simple monitoring of the systolic murmur and RVH at ECG allowed elective replacement of these conduits, moreover balloon dilatation of stenotic valve usually let to lengthen implantation duration. By the mid-1980s superior results of Ross and others with allografts (Shabbo, Wain, & Ross., 1980; Kay & Ross., 1985) let these once again to become the conducts of first choice, even nowadays have been a resurgence of interest in porcine valve Dacron conduit, particulary as replacement conduit in the adult-sized teenager or adult.

Figure 2.8: Hancock®

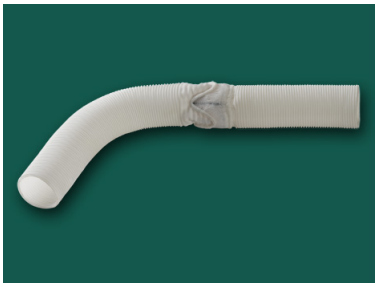


Figure 2.9: Carpentier-Edwards®

2.4 Bovine Jugular Venus Valved Conduit

Limited availability and durability of ACs, especially for lower sizes, in patients with CHD and who don't undergo Ross Aortic Valve Replacement procedure (Ross-AVR) operation have pushed forward the research of new and alternative prothesis. In 1999 the Contegra® Bovine Jugular Vein Conduit (BJVC) was introduced as an alternative to allografts in RVOT reconstruction and it represents a low-pressure, glutaraldehyde fixed section of bovine jugular vein (12–15cm in lenght and 12–22mm in diameter) with three-cusp naturally occurring valves located centrally, each provided with natural sinuses. The conduit wall is compliant with excellent saturability.

Early animal studies (Ichikawa, Noishiki, Kosuge, & et al., 1997; Scavo-Jr,

Turrentine, Aufiero, & et al., 1999) reported excellent results, with good leaflet preservation and freedom from structural degeneration and valve regurgitation at 3 years, moreover Herijers and colleagues reported resistance to calcification of Contegra BJVC implanted in sheep, even for just 5 months (Herijgers, Ozaki, Verbeken, & et al., 2002).

These animal studies have been confirmed by early human clinical trials with up to 27 months of follow-up reported by Breymann and colleagues, whom evidenced Contegra BJVC as a promising allografts alternative, and by a report from Bove and colleagues (Bove, Demanet, Wauthy, & et al., 2002) that compared a modified bicuspid pulmonary allograft with Contegra BJVC and supported these findings. Specifically the Contegra BJVC, respectively to AC, demonstrates several advantages: better hemodynamic, greater shelf availability, natural continuity between valve and conduit and no requirement for proximal extension.

Contegra® BJVC insertion includes: 1) 5 minutes conduit rinsing with continuous manual agitation in four 500-cc baths into regular Saline or Ringer's lactate; 2) conduit positioning into main and left PA to avoid sternal compression; 3) conduit outflow end is cutted so as placing valve conduit as far distally as possible, near the PA bifurcation, to avoid valve distortion with sternal compression (Sinzobahamvya et al., 2001); 4) Conduit inflow end is spatulated and sewn with continuous monofilament suture to the right ventriculotomy without additional prosthetic material. Contegra® has been approved for Humanitarian Device Exemption (HDE) in United States in November 2000 and more than 17000 have been implanted and meanwhile European investigators have published their results as well (Brown et al., 2005; Dave, Kadner, Bauersfeld, & et al., 2003; Breymann, Thies, Boethig, & et al., 2002; Bove et al., 2002; Brown, Ruzmetov, Rodefeld, & et al., 2006; Corno, Hurni, Griffin, & et al., 2002; Carrel, Berdat, Pavlovic, & et al., 2002; Chatzis, Giannopoulos, Bobos, & et al., 2003; Rastan, Walther, Daehnert, & et al., 2006; Morales, Braud, Gunter, & et al., 2006; Sekarski, van Meir, Rijlaarsdam, & et al., 2007).

In authors series, during 11 years of follow up, no Contegra BJVC shrinkage has been evidenced using echocardiography, and explantation rate, the most stringent measure of performance, has been significantly better at 5 and 10 years compared with allografts (Fiore, Rodefeld, Turrentine, & et al., 2010), being their experience comparable with a recent work of Boething and colleagues, who demonstrated a freedom from explantation of 90% at 5 years (Boethig, Thies, Hecker, & et al., 2005).

Seen these evidences, although longer-term follow-up will better determine actual conduit durability, this conduit represents the authors' prothesis of choice in neonates, infants and young children for RVOT reconstruction, with the exception in Ross-AVR patients over 5 years of age, where allograft are preferred (Brown et al., 2006).

On the basis of these facts Contegra BJVC can be considered a promising alternative for RVOT reconstruction compared with AC pulmonary conduits for several reasons: early better hemodynamic and long term functional performance, more readily availability in smaller sizes, valve localization within the conduit which permits proximal infudibular anastomosis without adding prothetic material and the cost of bovine jugular valve that is nearly one half of many ACs.

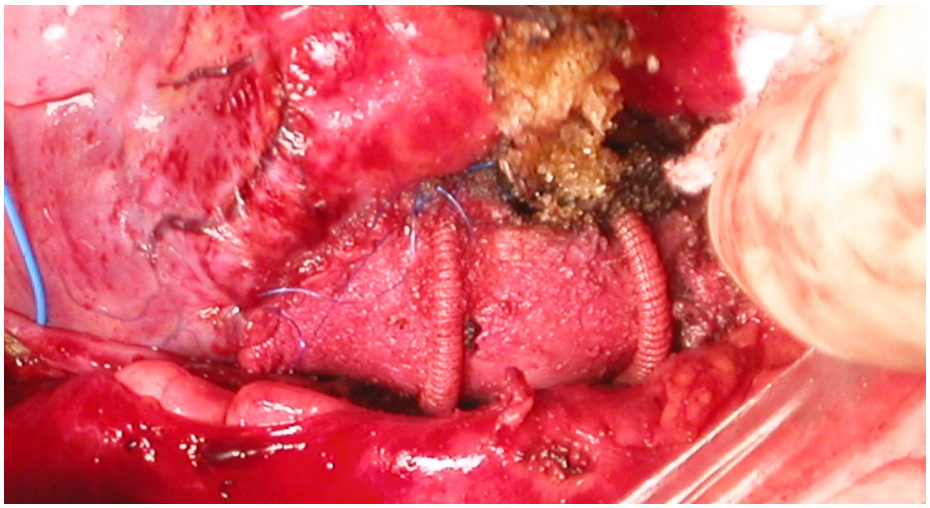


Figure 2.10: Intraoperative picture of an implanted Contegra®

2.5 Percutaneous Pulmonary Valves

In January 2010 the Melody® (Medtronic^{TM}), stented bovine jugular venous valved RV-PA conduits to be placed percutaneously via venous access, were released in the United States and its initial results are promising, even with short follow-up.

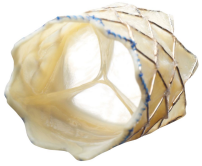


Figure 2.11: Melody® Valve

2.6 Nonvalved Right Ventricular to Pulmonary Artery Conduits

Non valved RV-PA conduits are still used in some centers with early satisfactory results, however many patients develop late RV dilatation within 10 years. Derani and colleagues reported on 126 nonvalved RV-PA conduits and concluded that freedom from failure was the same as with valved conduit (Dearani et al., 2003), hence they don't use them no more, nor the authors do as well.

2.7 Stented and Stentless Xenograft Valves in the Right Ventricular to Pulmonary Artery Position

The optimal prothesis to implant in young adults (over 18 years) and adults is still debated, considering that Contegra BJVC is not a feasible option (US restriction due to HDE category).

Basing on Brown et al.works, authors consider porcine aortic bioprothesis as an ideal choice for older teenagers (over 18 years) and young adults with

congenital abnormalities of the RVOT, especially if they require reintervention (Brown, Ruzmetov, Yurdakok, & et al., in press), with the recommendation to use a stentless valve if a size $\geq$ 25mm stented valve cannot be implanted. Their implantation technique for *stented valves* is to locate them in situ in the RVOT as distally as possible and to roof them over with a small gusset of bovine pericardium if necessary, while for *stentless porcine valves* is to resect a short section of conduit or native Pulmonary Artery (PA) and place the valve in situ with end-to-end proximal and distal suture lines to eliminate turbulence as much as possible.

2.8 Mechanical Valves in Pulmonary Position

Mechanical valves have been used for pulmonary valve replacement only in a few centers (Horer, Vogt, Stierle, & et al., 2009; Haas, Schreiber, Horer, & et al., 2005) with most of them recommending relatively large doses of Warfarin (INR 3.5-4.5); nevertheless several cases of thromboses have been reported. Authors have used just three mechanical valves in their series of 800 pulmonary valve replacements, considering this option only for patients who already carry a mechanical valve and therefore use Warfarin.

2.9 Bioengineered Valved Conduits for Right Ventricular Outflow Tract Reconstruction

Bioengineered valved conduits hold promise for RV-PA reconstruction; they are constructed with biologic or biodegradable scaffold which are being populated by host cells after the implantation even causing, in some cases, the scaffold to disappear.

Gottlieb and colleagues demonstrated autologous, engineered tissue, valved conduits that function well at implantation, and monitored dimensions and functions in real-time (Gottlieb, Kunal, Emani, & et al., 2010). They evidenced an in-vivo structural and functional remodelling without stenosis but worsening of PI after 6 weeks, insights that might be useful for future iterations of engi-

neered heart valves (Gottlieb et al., 2010).

Critical to current approaches to tissue-engineered heart valves is scaffold design, which must provide immediate function together with stress transfer to the new extracellular matrix.

2.10 When to Operate for Right Ventricular Outflow Tract Dysfunction

RVOT disfunction, either in children and adults, is defined as moderate outflow obstruction ($>$ 40mmHg) and/or greater than moderate (2+) PI. Patients with less than moderate dysfunction may remain asymptomatic or mildly symptomatic for many years, but detecting dysfunction before symptoms occur is increasingly becoming evident since RV recovery may be incomplete if reconstruction is performed late. Specifically, preintervention RV volumes are crucial, since independently associated with RV remodelling, and normalization can be achieved when pre-operative RV End-Diastolic Volume (EDV) is $< 160ml/m^2$ or End-Sistolic Volume (ESV) is $< 82ml/m^2$ (Oosterhof, van Straten, Vliegen, & et al., 2007).

The indication for intervention on dysfunctional RVOT are controversial, but patients with significant RV failure symptoms and objective evidence of RVOT dysfunction should undergo reintervention. Symptoms include *palpitations, decreased exercise tollerance and fatigue*, while signs include *ascites, peripheral edema, atrial and ventricular arrhythmias, decreased RV ejection fraction, tricuspid valve insufficiency, RV EDV progressive increase* and eventually *LV dysfunction*.

Echocardiography accurately defines pulmonary stenosis entity but it's less accurate in quantify pulmonary regurgitation and/or RV dilatation degree, which are instead markedly more accurately defined by CMR.

Indications for intervention on a dysfunctional RVOT are evolving but now include patients with moderate to severe PI and/or stenosis ad any of the following problems (Quintessenza et al., 2010; Frigiola, Tsang, Nordmeyer, & et

al., 2008; Gerestein et al., 2001):

1. **Exertional symptoms of New York Heart Association class II or greater;**
2. **Decreased performance capacity on exercise testing;**
3. **Significant RV dilatation ($> 150ml/m^2$ by CMR);**
4. **A RV/LV volume ratio > 1.5 in symptomatic patients and ≥ 2 in asymptomatic patients;**
5. **Pulmonary regurgitation fraction $> 35\%$ on CMR or 3+ on echocardiography**
6. **RVOT gradient above 65mmHg**
7. **Significant RV dysfunction;**
8. **Atrial or ventricular arrhythmias;**
9. **QRS duration $> 180ms$.**

Chapter 3

"Fondazione Monasterio" experience with Hancock® conduits in Tetralogy of Fallot late repair

The Introduction in this work describes embryological, anatomical and clinical features of Tetralogy of Fallot together with a brief discussion on its surgical correction and a generical description of all the available solutions for the RVOT reconstruction. In our study we focus exclusively with performances and outcomes of the RVOT reconstruction with Hancock® conduits in patients with Tetralogy of Fallot previously operated for complete surgical repair. Data and results of the study have been obtained by the retrospective evaluation of these group of patients to define short-term and long-term outcomes of conduit implantation.

3.1 Patients and Methods

3.1.1 Patients Characteristics

Between February 2003 and May 2015, 32 patients with an early repaired Tetralogy of Fallot, 23 males and 9 females, underwent RVOT reconstruction with Hancock conduit at Fondazione Toscana "G. Monasterio" Pediatric Cardiac

Surgery department, Massa, Italy. They underwent to 32 first implantations and 2 conduit replacement due to its failure. Patients *mean age* was $17,6 \pm 11,32$ years with a minimum of 13 months and a most of 41 years and 8 months; specifically 12 (35,3%) were less than 12 years of age, 6 were between 12 and 16 years (17,64%) and 16 were over 16 years of age (47,05%). Their physical features included a mean *Body Surface Area (BSA)* of $1,4 \pm 0,54m^2$ (0,34 m^2 minimum and 2,12 m^2 most), mean *height* of $148,1 \pm 33,6$ cm (61 cm minimum and 195 cm most) and a mean *weight* of $49,5 \pm 26,35$ Kg (6,9 Kg minimum and 96 Kg maximum).

As defined by this study at the moment of intervention all the patients had already had a previous RVOT reconstruction procedure as step in ToF correction, all specified in Table 3.1. It's significant that Hancock® implantation was not performed in first instance in the management of RVOT reconstruction, in patients with ToF. In fact the 32 patients with ToF successively treated with Hancock® implantation mostly (75%) had a RVOT reconstruction with a patient-tailored autopericardium transannular patch, while in a minority the RVOT reconstruction was by homograft, xenograft and mechanical valve conduit.

The reason for which we don't normally implant an Hancock® conduit as first line solution in patients with ToF is mainly related to the *patient early age at first intervention* and the *conduit behaviour*.

Regarding the former, the usual very early age at first intervention is often imposed by the necessity of an immediate correction of tetralogy of Fallot, in which the use of transannular patch represents the optimal technical solution for very restricted pulmonary annulus. Moreover, nowadays the RV disfunction late after ToF correction, despite frequent, is unpredictable because of the possibility of a *restrictive physiology*. The restrictive physiology is normally present when a late-diastolic pulmonary blood flow is evident on echocardiography (even possibly boundary conditions can contribute to it), due to a right atrial pressure that overrides the main pulmonary pressure. On short term it represents an

Previous RVOT Reconstructions	Number
Total Reconstructions	32
with transannular patch	28
with homograft	2
with xenograft	1
with mechanical valve conduit	1

Table 3.1: Prior first-line RVOT Reconstruction Procedures

adverse hemodynamic event since causes, in the absence of significant residual VSD or obstructive lesions, a low cardiac output, fluid retention, ascites, pleural effusions and an increased central venous pressure. Nonetheless, its presence is advisable since the anterograde diastolic flow contributes to augment total pulmonary anterograde flow and limits diastolic regurgitation, further improving total forward cardiac output. On long term the restrictive RV physiology is even more of crucial importance, explaining the reasons for which the affected patients have a better long-term outcome after surgical repair. A stiff poorly compliant right ventricle fail to have the otherwise normal adverse remodelling, resulting in a smaller heart and RV, hence determining a shorter QRS value with a lower incidence of arrhythmias. Moreover they present a better exercise tolerance, presumably because of the limiting effects of restrictive physiology on PI (Redington, Arsdell, & Anderson, 2009).

Considering the conduit behaviour it is not advisable to implant it during an early complete correction because of its tendency to degenerate (calcification), which limits the duration of its function. Furthermore an inevitable mismatch will occur due to the growth of the child without a consequent growth of the conduit. Degeneration is especially evident among younger infants in which the *calcium metabolism is sharply increased*, due to the growth requirements, further accelerating conduit calcification. In addition, the sooner a conduit is implanted, the earlier will be reached the mismatch between conduit diameter and patient expected pulmonary diameter (and hence the necessity of an earlier replacement). Therefore it's rational to delay its implantation to delay a future

reintervention.

3.1.2 Surgical Considerations

Surgical Indication

Hancock® conduit placement in patients with an early repaired ToF is the consequence of their primary repair failure, which can affect up to 25% of operated patients. This event can manifest with several different patterns:

- Symptoms of right heart failure or altered cardiac exercise stress test
- RV or evidence of RV dysfunction, especially if PI is present
- Clinically significant arrhythmias (atrial or ventricular)
- Progressive aneurysmal dilatation of an RVOT patch
- Onset or progression of Tricuspid Regurgitation (TR)
- Residual VSD with shunt $> 1,5 : 1$
- Residual patent aorto-pulmonary shunts leading to LV volume overload
- Residual RVOT stenosis

Table 3.2 specifically consider the *failure causes of the previously performed RVOT reconstructions* among the 32 patients who required reintervention.

In addition, we have recently introduced as a reference for surgical indication to Hancock® re-implantation, currently studied and applied only the patients with ToF, the *Right Ventricle end-diastolic Volume index* measured with *CMR*. When referring to this parameter, we consider by definition the cut-off for a correct surgical timing an RVEDVi value over $140 - 170ml/m^2$; however it had not been always strictly applied, occasionally waiting for values even over $170 - 200ml/m^2$ (Oosterhof, van Straten, et al., 2007; van Huysduynen et al., 2005), since we and others consider fot this purpose also patients' echocardiographical conduit parameters and clinical features for making the decision.

Hancock® Conduit Selection

The selected valved conduit must satisfy *anatomical and physiological patient needs*, usually favouring, especially in younger infants, a lager graft which produces a lower gradient with an higher cardiac flow, delaying the reoperation time for conduit replacement. The 34 adopted conduits had $22 \pm 3,61$ mm as mean *diameter*, with a minimum of 14 mm and a most of 25 mm; Table 3.3 accurately shows diameters distribution per age. The best suitable conduit per patient was chosen considering the *expected pulmonary valve annulus physiological diameter*, which was retrospectively determinable in all cases. It had a mean value of $20,5 \pm 4,49$ mm with a minimum of 11,8 mm and a most of 26,32 mm. This value was than related to available conduit diameters in order to define the conduit diameter-pulmunary valve annulus diameter ratio (mean value $1,1 \pm 0,12$, 0,9 minimum and 1,4 most), the actual parameter used to decide the diameter's conduit eventually employed.

The Figure 3.1 evidences the distribution per age of chosen conduits referring to their ratio. The graph clearly demonstrates our tendency in *oversizing*

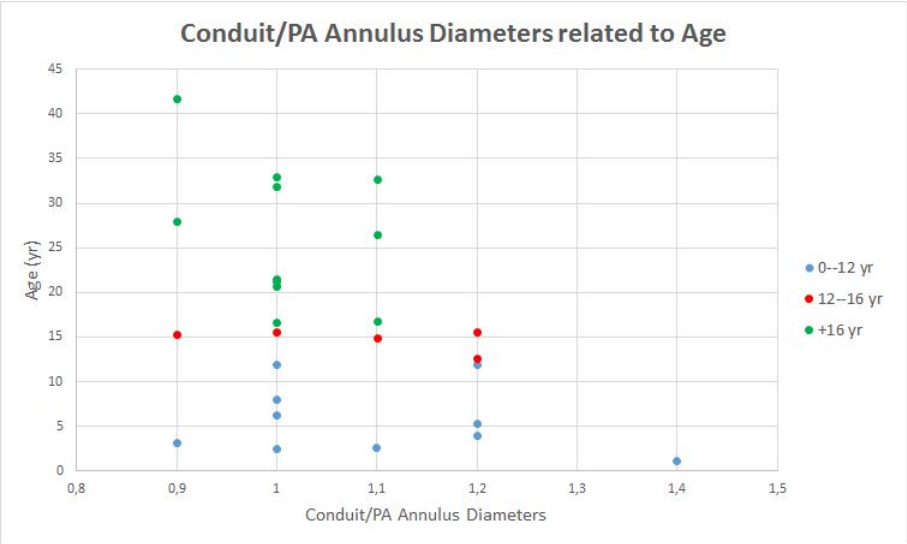


Figure 3.1: PA–Conduit diameter ratios related to patients age

conduit size relatively to the expected PA annulus in *younger patients*, particularly under 10 years of age, with the aim to reduce either the impact of *patient growth* and the *RV-PA gradient* after implantation, therefore delaying conduit failure and moment of mandatory surgical replacement.

Surgical Data and Technique

Conventional continuous bicaval cardiopulmonary bypass was used in 16 procedures, in which median sternotomy or re-sternotomy was considered reasonably safe. Instead, in 4 patients we *isolated femoral vessels* as safety measure, even cannulation was not eventually needed, while in 14 were *cannulated*, being sternotomy considered at risk in damaging major vessels with the risk of intractable bleeding. Globally the mean *CPB duration* was $165 \pm 69,02$ minutes, with a minimum of 78 and a most of 419 minutes, while *myocardial protection*, was obtained in 16 cases. Specifically the protection was obtained with anterograde blood cardioplegia in 14 cases and with custodiol anterograde cardioplegia in 2, whilst no cardioplegia was used in remaining 12 cases being the procedure performed on beating heart. *Aortic crossclamp* had a mean duration of $98,5 \pm 35,00$ min (minimum 51 and most of 193 minutes), while *hypotermia* was the rule, spacing from a minimum value of 15 to a maximum of 32 C° and with a mean of $28 \pm 4,46$ C°. Specifically when we performed the surgical procedure on beating heart the temperature was 32 C°, while when we performed the procedure with aortic crossclamp was 28 C° or lower.

The intraoperative conduit placement (see Fig. 3.2) begins with the identification of the inflow and outflow aspects of the conduit and a green suture, sewn on distal extremity indicating the flow direction, makes this procedure easier. After that, the conduit must be cut to the desiderated length, in accordance to the patient specific anatomical features and preferred anastomosis angle, while the extremities must be tailored for the anastomoses. Belli and colleagues (Belli, Salihoğlu, Leobon, & et al., 2010) in most cases removed the metallic ring to

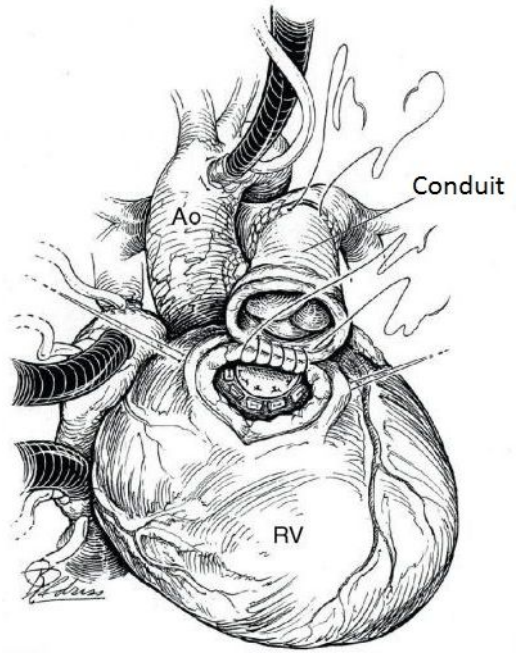


Figure 3.2: Surgical Hancock® implantation technique

[Reproduced from *"Paolo de Siena; Mohamed Ghorbel; Qiang Chen; Deana Yim; Massimo Caputo" – Common Arterial Trunk – Expert Rev Cardiovasc Ther. 2011;9(12):1527-1538*]

avoid potential compression of cardiac structures and cut conduit closely to the top of commissures to place the valve as far distally as possible, the latter also did by Champsaur et al.(Champsaur et al., 1998), while Rüffer et al. (Rüffer, Wittmann, Potapov, & et al., 2012) left the metallic ring in place in all patients. In our technique the decision is always to leave in place the metallic ring and to implant the conduit with the valve as far as possible at the pulmonary bifurcation. Before the implantation the conduit's valve must be accurately cleaned with saline solution, to remove glutaraldehyde from conduit's surface. The graft is implanted using separate pledgets stitches on the ventricular aspect and with a continuous running 4/0 prolene suture on the pulmonary distal anastomosis. Normally all the dilated pericardial patch, previously used during the early total correction, is removed and the border of ventriculotomy are inspected to remove thin dilated muscular tissue.

In between the 34 surgical interventions for RVOT reconstruction 22 *associated procedures* were made, occasionally more than one per intervention. The most frequently performed procedure was the *pulmonary branches reconstruction*, encompassing with this all forms of pulmonary branches reconstruction (right, left or both) and/or bifurcation plasty, variably accomplished using autopericardium, bovine/porcine pericardium or prothetic patches (Dacron or PTFE); all others procedures are listed in Table 3.4.

Before cardiac electrodes placement and sternal closure we usually perform a *transepicardial echocardiography* together with an invasive measurement of *RV pressure* to immediately evaluate the post-implantation conduit function and the related cardiac performance.

Postoperative Evaluation

All the patients, during the post-operative hospital stay after the intervention, underwent *seriated echocardiographic evaluations* to measure the actual immediate surgical results. RVOT peak gradient, RV mean pressure and PA regurgitation were measured to determine conduit function, together with the searching for VSD persistence and possible residual shunt. Moreover, as completion, when feasible, mitral, tricuspid and aortic valves functioning were studied.

As integration a *control CMR*, when possible, was performed. This specific evaluation, as previously already stated, had been reserved for patients with ToF and surgically corrected RVOT defect. The aim of this study was to determine the RVEDVi after the surgical procedure to compare its value to the pre-operative measure, as parameter for RV outflow surgical correction effectiveness.

3.1.3 Follow-up

In 27 cases, excluded patients referred back to the cardiologists of the country of origin, patients underwent follow-up after intervention, whose schedule consisted in *1st, 3rd, 6th and 12th months* echocardiographic evaluation dur-

ing first year after surgical intervention, followed by yearly recurring controls. These controls were made directly at our center or by the referring pediatric cardiologist. These 27 cases were followed for a mean period of $31,6 \pm 34,42$ months, with a peak of 8 years.

Echocardiographic follow-up aimed to determine *conduit fuctioning* by evaluating possible presence of either conduit *stenosis* or *insufficiency*. The former was studied by measuring both the *speed flow through the conduit* and the *RVOT peak gradient*, while the latter by determining *regurgitation jet*, with colour flow doppler, and the possible presence of *pulmonary ventricle dilatation* with its entity.

Stenosis was graded as follows (Baumgartner, Hung, Bermejo, & et al., 2009):

1. Mild: peak velocity < 3 m/s and peak gradient < 36 mmHg
2. Moderate: peak velocity $3 - 4$ m/s and peak gradient $36 - 64$ mmHg
3. Severe: peak velocity > 4 m/s and peak gradient > 64 mmHg

Insufficiency was graded as follows (Baumgartner et al., 2009):

1. Trivial
2. Mild
3. Moderate
4. Severe

In addition to conduit study, on echocardiographic follow-up *RV contractility* and *AV and aortic valves functioning* were also evaluated.

Failure of Previous RV-PA Reconstruction	*<12 yrs (n.12)*	*12–16 yrs (n.6)*	*+16 yrs (n.16)*	*Total (n.34)*
Stenosis	3 (25%)	1 (16,6%)	4 (25%)	8 (23,52%)
Insufficiency	7 (58,3%)	5 (83,3%)	12 (75%)	24 (70,58%)
Combined	2 (16,6%)			2 (5,88%)

Table 3.2: Causes of previous RVOT reconstruction failure

Conduit Diameter	*<12 yrs (n.12)*	*12–16 yrs (n.6)*	*+16 yrs (n.16)*	*Total (n.34)*
14 mm	2 (16,66%)			2 (5,88%)
16 mm	3 (25%)			3 (8,82%)
18 mm	3 (25%)			3 (8,82%)
20 mm	1 (8,33%)			1 (2,94%)
22 mm	2 (16,66%)	3 (50%)	4 (25%)	9 (26,47%)
25 mm	1 (8,33%)	3 (50%)	12 (75%)	16 (47,05%)

Table 3.3: Conduit diameters per age distribution

Associated Procedure	**Total**
Pulmonary branches reconstruction	10
Tricuspid plasty	8
Residual IVD closure	1
Maze procedure	1
Aortic valve plasty	1
Monocusp RVOT reconstruction previous attempt	1

Table 3.4: Surgical associated procedures

3.2 Results

3.2.1 Early results and patient survival

Patients *mean hospital stay* was $17,2 \pm 6,86$ days while mean *postoperative period duration* was $13,8 \pm 6,46$ days with a minumum of 2 and a most of 40 days for the latter.

Two patients died in hospital after surgical intervention (a 30 days mortality of 6,25% after 34 surgical procedures), one for *low cardiac output syndrome* and one for *intraoperative adverse event* (massive air embolism due to extracorporeal circulation accident). In *three patients* a re-intervention was imposed by an adverse event and the causes were *cardiac tamponade* for 2 patients and *aortic valve insufficiency* in 1 patient. No *conduit-related complications* were observed during patients hospital stay.

Hancock® conduit performance on early post-operative evaluation

`RVOT peak gradient and RV pressure.` Patients presented before intervention, regardless of surgical indication for implantation, with a mean *RVOT peak gradient*, determined with pre-operative transthoracic echocardiography, of $60,4 \pm 30,06$ mmHg (with minimum 18 and maximum 111 mmHg). The same parameter, evaluated with seriated transthoracic echocardiography during post-operative period before discharge, had a mean value of $29,1 \pm 11,48$ mmHg with a most of 60 mmHg. In Table 3.5 this is illustrated, with age specification.

RV pressure was determinated with echocardiography pre-operationally, considering both first conduit implantation and replacement, with a mean value of $53,3 \pm 27,73$ mmHg, and post-operationally with mean value of $41,6 \pm 12,71$ mmHg. Detailed per age values are available in Table 3.5.

`RV end-diastolic volume index.` The RVEDVi was calculated both before and after the surgical correction, when feasible, through *cardiac RMI*. *Pre-operational RVEDVi* was available for 18 patients with a mean of $218,3 \pm$

$57,94ml/m^2$, a most of $380ml/m^2$ and a minimum of $109ml/m^2$, while *post-operational RVEDVi* was available for 9 patients with $126,1 \pm 14,49ml/m^2$, as mean, $143ml/m^2$ as most and $103ml/m^2$ as minimum. Detailed per age values are available in Table 3.5.

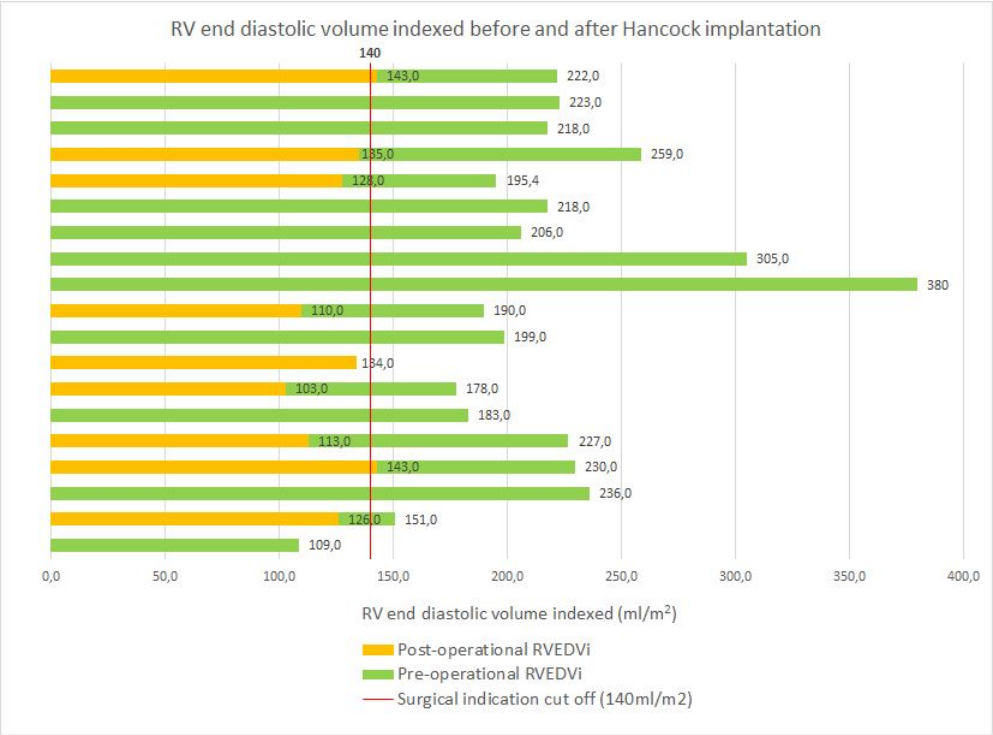


Figure 3.3: Effect of Hancock® conduit on RVEDVi

The Figure 3.3 shows all the available values both pre- and post-surgical intervention. From it we can infer the *mean value of RVEDVi values differences* for the 8 patients for whom the pre- and post-operational values where available, which was $81,42 \pm 30,08ml/m^2$, and also the surgical cut-off value is highlighted.

`Pulmonary artery insufficiency.` Pulmonary regurgitation jet severity was evaluated pre- and post-operatively through echocardiographic color-doppler study based on above criteria (see page 51). Regardless from surgical

indication we evidenced the values specified on page 55 (per age detailed results are in Table 3.6).

Pre-operational jet regurgitation severity:

- **0 (absent):** 0 patients
- **1 (trivial):** 11 patients
- **2 (mild):** 2 patients
- **3 (moderate):** 6 patients
- **4 (severe):** 15 patients
- **Total:** 34 measures

Post-operational jet regurgitation severity:

- **0 (absent):** 6 patients
- **1 (trivial):** 28 patients
- **2 (mild):** 0 patient
- **3 (moderate):** 0 patient
- **4 (severe):** 0 patients
- **Total:** 34 measures

RV parameter	**< 12 yrs**	**12–16 yrs**	**+16 yrs**
Mean RVOTpg		*Preoperative*	
(mmHg)	$74,5 \pm 28,93$	70	$42,85 \pm 28,95$
		Postoperative	
	$30,1 \pm 14,08$	$30,33 \pm 6,62$	$27,76 \pm 11,70$
Mean RV pressure		*Preoperative*	
(mmHg)	$69,14 \pm 27,17$	$32,5 \pm 6,45$	$51 \pm 28,3$
		Postoperative	
	$45,44 \pm 15,66$	$40 \pm 8,66$	$39,16 \pm 11,24$
Mean RV end-diastolic		*Preoperative*	
volume index (ml/m^2)	$130 \pm 29,69$	$210,8 \pm 27,09$	$237,76 \pm 57,47$
		Postoperative	
	126	$119,66 \pm 20,81$	$130 \pm 12,38$

Table 3.5: RV pressures and volumes values per age distribution

PA regurgitation	**< 12 yrs**	**12–16 yrs**	**+16 yrs**
		Pre-operative	
None	0	0	0
Trivial	8	3	3
Mild	1	0	1
Moderate	1	1	4
Severe	3	4	8
		Post-operative	
None	1	1	5
Trivial	12	7	13
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

Table 3.6: PA insufficiency values per age distribution

3.2.2 Late results

Follow-up duration and status

The follow-up mean duration was $31,6 \pm 34,42$ months with a minimum of 2,39 and a most of 100,92 months, this considering exclusively the 27 patients who were not lost during the observation period. Per age detailed FU means spans are listed in Table 3.7.

In 5 patients we observed the *Hancock® conduit failure* during follow-up, which in 4 imposed a percutaneous procedure to try to delay conduit replacement and in 1 a re-implantation surgical procedure for a new device. However, between the 4 percutaneous procedure 2 had failed and needed thereafter surgical replacement. The mean *freedom from conduit failure* for this group of patients was $70,56 \pm 15,02$ months, with a minimum of 55,15 and a maximum 91,64 months, while their *mean age* at conduit failure was $6,86 \pm 1,78$ years, clearly ascribing the event only to conduits implanted in younger patients. Criteria used to define conduit failure were one, or a combination, from: *severe RV-PA peak gradient*, *severe PI* (see page 51), conduit-patient mismatch or symptoms (see page 41). We clearly evidenced in our series that *stenosis* and *mismatch* represented the causes for the 5 whom underwent Hancock® failure.

`Percutaneous interventions for conduit failure.` Between the 5 patients whose conduits failed, in 4, with stenosis as cause, we decided to try to delay the re-intervention by submitting them to a percutaneous intervention. The chosen procedure in 2 cases was the *ballooning conduit dilatation*, performed 78 months after the primary conduit placement in one patient and after 58 months in the other. Instead, in the remaining 2 patients were implanted a *Medtronic Melody® valve*, in one of them 72 months after conduit implantation, while in the other after 56 months. In the former group one is still bearing the original conduit after 45 months from the procedure, while the other had conduit failure after 17 months. In the second group one had the valve failure and

needed reintervention after 38 months from original valve implantation, while the other is still bearing the functional percutaneously implanted valve after 71 months from implantation.

Hancock® conduit performance on last follow-up evaluation

The conduit-related RV parameters means obtained during follow-up, which didn't included RVEDVi that was not evaluated, are listed in Tab. 3.7, while PA insufficiency entity, with per age distribution, on Tab. 3.8.

Parameter	**Global**	**< 12 yrs**	**12–16 yrs**	**+16 yrs**
Mean RVOTpg (mmHg)	$45,3 \pm 26,02$	$66,87 \pm 28,65$	$31,25 \pm 4,78$	$32,33 \pm 14,59$
Mean RV pressure (mmHg)	$53,6 \pm 18,8$	$63,5 \pm 21,3$	$55 \pm 14,14$	$44,44 \pm 13,56$
Mean FU span (months)	$31,6 \pm 34,42$	$52,77 \pm 37,56$	$19,23 \pm 17,59$	$21,77 \pm 31,89$

Table 3.7: Pressures and follow-up spanning mean values

PA regurgitation	**< 12 yrs**	**12–16 yrs**	**+16 yrs**	**Total**
None	0	0	1	1
Trivial	6	4	10	20
Mild	3	0	0	3
Moderate	0	0	0	0
Severe	0	0	0	0

Table 3.8: PA insufficiency values per age distribution

3.3 Discussion

The Hancock® is the oldest xenograft biologically valved conduit still available (Bowmann-Jr, Hancock, & Malm, 1973; Champsaur et al., 1998). It's initial spreading was related to the easy availability, due to the wide range of sizes available, including the smallest which are hard to obtain for an allograft, and the avoidance of the cryopreservation. However its role, and the enthusiasm related, had been gradually reduced after the supposed usual inferior mean duration of this kind of conduit, compared to allograft, and the adoption of newer xenografts, like the Medtronic Contrega® (Jonas., 2014). The main reasons behind conduit disfunctions are well described in literature and firstly regard valve degeneration or calcification either causing the development of valvular stenosis (Belli et al., 2010; Agarwal, Edwards, Feldt, & et al., 1981; Jonas, Freed, Mayer-Jr, & Castaneda, 1985; McGoon, Danielson, Puga, & et al., 1982). Considering current literature results the mean conduit durability in patients with ToF and possibly pulmonary atresia is among the best (including not only xenograft) between all types of CHDs (Dearani et al., 2003); specifically Champsaur et al observed an actuarial freedom from re-operation of 93% at 5 years and 80% at 10 years (Champsaur et al., 1998).

Nowadays the Hancock® application is gradually increasing again and, at our institution, it has been positioned for CHD in over 100 patients in the last 15 years. Specifically in patients with already palliated ToF, we usually consider it a saving solution when a first RV-to-PA reconstruction, either from transannular patch or allograft, has failed. In our series of 32 patients the results are encouraging at present, considering the failure in only 5 patients after more than 5 years of follow-up. Moreover in four of these patients a percutaneous procedure (2 ballooning and 2 Melody® implantation) were made and in 2 of them this successfully avoid at present the reintervention. In addition we have clearly evidenced several cornerstone elements regarding the Hancock® conduit management criteria together with failure and duration patterns:

- Delaying as much as possible the conduit implantation, granting an older patient age at intervention, reduces the mismatch impact issue that inevitably develops because of patient's growth, allowing to move forward the mandatory conduit replacement.

- When an Hancock® is necessarily implanted in a younger patient, if it's feasible to force a significant conduit oversize, relatively to the expected per age pulmonary valve annulus, it will be the best long term solution in terms of conduit duration. In fact, this strategy determines either initial lower trans-conduit turbulence, with minor impact on conduit degeneration, and delays the moment in which the mismatch between conduit flow and patient's physiological stream, because of patient growth, becomes clear. An heavily oversized conduit often let a long enough graft duration (even over 10 years).

- Hancock®, if still permits an adequate stream for patient needs, offer the feasibility for a percutaneous procedure as save measure for conduit patency to avoid a newly surgical procedure. This possibility to re-establish its flow , through ballooning dilatation or stented Melody® valve implantation inside the conduit, is an actual and peculiar Hancock® propriety, which can efficiently reduce re-intervention incidence and has favoured its newly current usage spreading.

- The stenosis is clearly the main cause of conduit failure being the insufficiency exceedingly rare due to conduit valve long term efficiency. This favourably contribute to conduit duration since stenosis development is gradual and causes conduit failure only on the long term.

In conclusion, the best conduit type to employ in restoring the continuity between right ventricle and pulmonary artery is still debated, however we consider the Hancock® as a valid solution, since, despite the usual necessity to stent or replace it after a defined period of time, it grants a good duration together with a good quality of life for patients.

References

Abbott, M., & Dawson, W. (1924). The clinical classification of congenital cardiac disease. *Int Clin*, *4*, 156-188.

Agarwal, K., Edwards, W., Feldt, R., & et al. (1981). Clinicopathological correlates of obstructed right-sided porcinevalved extracardiac conduits. *J Thorac Cardiovasc Surg*, *81*, 591–601.

Alfieri, O., Blackstone, E., Kirklin, J., & et al. (1978). Surgical treatment of tetralogy of fallot with pulmonary atresia. *J Thorac Cardiovasc Surg*, *76*, 321–335.

Altrichter, P., Olson, L., Edwards, W., & et al. (1989). Surgical pathology of the pulmonary valve: a study of 116 cases spanning 15 years. *Mayo Clin Proc*, *64*, 1352-1360.

Anderson, R., & Weinberg, P. (2005). The clinical anatomy of tetralogy of fallot. *Cardiol Young*, *15*, 38-47.

Ando, M., Imai, Y., Takanashi, Y., & et al. (1997). Fate of trileaflet equine pericardial extracardiac conduit used for the correction of anomalies having pulmonic ventricle-pulmonary arterial discontinuity. *Ann Thorac Surg*, *64*, 154–158.

Askovich, B., Hawkins, J., Sower, C., & et al. (2007). Right ventricle-to-pulmonary artery conduit longevity: is it related to allograft size? *Ann Thorac Surg*, *84*, 907–911; discussion 911-912.

Bacha, E., Scheule, A., Zurakowski, D., & et al. (2001). Longterm results after early primary repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*, *122*, 154–161.

Bailey, W., Kirklin, J., Bargeron, L., & et al. (1976). Late results with synthetic valved external conduits from venous ventricle to pulmonary arteries. *Circulation*, *56*, II73–II79.

Bando, K., Danielson, G., Schaff, H., & et al. (1995). Outcome of pulmonary and aortic homografts for right ventricular outflow tract reconstruction. *J Thorac Cardiovasc Surg*, *109*, 509–517; discussion 517-518.

Barratt-Boyes, B., & Neutze, J. (1973). Primary repair of tetralogy of fallot in infancy using profound hypothermia with circulatory arrest and limited cardiopulmonary bypass: a comparison with conventional two stage management. *Ann Surg*, *178*, 406–411.

Bassett, A., Chow, E., AbdelMalik, P., & et al. (2003). The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry*, *160*, 1580–1586.

Baumgartner, H., Hung, J., Bermejo, J., & et al. (2009). Echocardiographic assessment of valve stenosis: Eae/ase recommendations for clinical practice.

Eur J Echocardiogr, *10*, 1–25.

Becker, A., Connor, M., & Anderson, R. (1975). Tetralogy of fallot: a morphometric and geometric study. *Am J Cardiol*, *35*, 400-412.

Beland, M., Franklin, R., Jacobs, J., & *et al.* (2004). Update from the international working group for mapping and coding of nomenclatures for paediatric and congenital heart disease. *Cardiol Young*, *70*, 225–229.

Belli, E., Salihoğlu, E., Leobon, B., & et al. (2010). The performance of hancock porcine-valved dacron conduit for right ventricular outflow tract reconstruction. *Ann Thorac Surg*, *89*, 152–158.

Bielefeld, M., Bishop, D., Campbell, D., & et al. (2001). Reoperative homograft right ventricular outflow tract reconstruction. *Ann Thorac Surg*, *71*, 482–487; discussion 487–488.

Boethig, D., Goerler, H., Westhoff-Bleck, M., & et al. (2007). Evaluation of 188 consecutive homografts implanted in pulmonary position after 20 years. *Eur J Cardiothorac Surg*, *32*, 133–142.

Boethig, D., Thies, W., Hecker, H., & et al. (2005). Mid term course after pediatric right ventricular outflow tract reconstruction: a comparison of homografts, porcine xenografts and contegras. *Eur J Cardiothorac Surg*, *27*, 58–66.

Bogers, A., Roofthooft, M., Pisters, H., & et al. (1994). Long-term results of the gamma-irradiation-preserved homograft monocusp for transannular reconstruction of the right-ventricular outflow tract in tetralogy of fallot. *Thorac Cardiovasc Surg*, *42*, 337–339.

Bove, T., Demanet, H., Wauthy, P., & et al. (2002). Early results of valved bovine jugular vein conduit versus bicuspid homograft for right ventricular outflow tract reconstruction. *Ann Thorac Surg*, *74*, 536–541; discussion 541.

Bowman, F., Hancock, W., & Malm., J. (1974). A valve containing dacron prosthesis. *Arch Surg*, *107*, 724–728.

Bowmann-Jr, F., Hancock, W., & Malm, J. (1973). A valve-containing dacron prosthesis: its use in restoring pulmonary artery right ventricular continuity. *Arch Surg*, *107*, 724–728.

Breymann, T., Thies, W., Boethig, D., & et al. (2002). Bovine valved venous xenografts for rvot reconstruction: results after 71 implantations. *Eur J Cardiothorac Surg*, *21*, 703-710; discussion 710.

Brown, J., Eltayeb, O., Ruzmetov, M., Rodefeld, M., & Turrentine., M. (2013). Ventricular to pulmonary artery conduits. In *Pediatric cardiac surgery* (4th ed.). Wiley-Blackwell.

Brown, J., Ruzmetov, M., Rodefeld, M., & et al. (2005). Right ventricular outflow tract reconstruction with an allograft conduit in non-ross patients: risk factors for allograft dysfunction and failure. *Ann Thorac Surg*, *80*, 655–663; discussion 663-664.

Brown, J., Ruzmetov, M., Rodefeld, M., & et al. (2006). Valved bovine jugular vein conduits for right ventricular outflow tract reconstruction in children: an attractive alternative to pulmonary homograft. *Ann Thorac Surg*, *82*, 909–916.

Brown, J., Ruzmetov, M., Vijay, P., & et al. (2007). Right ventricular outflow tract reconstruction with a polytetrafluoroethylene monocusp valve: a twelve-year experience. *J Thorac Cardiovasc Surg*, *133*, 1336–1343.

Brown, J., Ruzmetov, M., Yurdakok, O., & et al. (in press). (in press) intermediate follow-up of porcine xenografts for right ventricular outflow tract reconstruction in children and adults. *Ann Thorac Surg*.

Carpentier, A., Lemaigre, G., Robert, L., & et al. (1969). Biological factors affecting long-term results of valvular heterografts. *J Thorac Cardiovasc Surg*, *58*, 467–483.

Carrel, T., Berdat, P., Pavlovic, M., & et al. (2002). The bovine jugular vein: a totally integrated valved conduit to repair the right ventricular outflow. *J Heart Valve Dis*, *11*, 552–556.

Carvalho, J., Shinebourne, E., Busst, C., & et al. (1992). Exercise capacity after complete repair of tetralogy of fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J*, *67*, 470–473.

Castaneda, A., Freed, M., Williams, R., & et al. (1977). Repair of tetralogy of fallot in infancy. early and late results. *J Thorac Cardiovasc Surg*, *74*, 372–381.

Champsaur, G., Robin, J., Curtil, A., & et al. (1998). Long-term clinical and hemodynamic evaluation of porcine valved conduits implanted from the right ventricle to the pulmonary artery. *J Thorac Cardiovasc Surg*, *116*, 793–804.

Chan, K., Fyfe, D., McKay, C., & et al. (1994). Right ventricular outflow reconstruction with cryopreserved homografts in pediatric patients: intermediate-term follow-up with serial echocardiographic assessment. *J Am Coll Cardiol*, *24*, 483–489.

Chatzis, A., Giannopoulos, N., Bobos, D., & et al. (2003). New xenograft valved conduit (contegra) for right ventricular outflow tract reconstruction. *Heart Surg Forum*, *6*, 396–398.

Chiariello, L., Meyer, J., Wukasch, D., & et al. (1975). Intracardiac repair of tetralogy of fallot. five-year review of 403 patients. *Thorac Cardiovasc Surg*, *70*, 529-535.

Chong, W., Wong, W., Chiu, C., & et al. (2006). Aortic root dilation and aortic elastic properties in children after repair of tetralogy of fallot. *Am J Cardiol*, *97*, 905–909.

Chow, C., Amos, D., & Celermajer, D. (2005). Cerebrovascular events in young adults after surgical repair of tetralogy of fallot. *Cardiol Young*, *15*, 130–132.

Corno, A., Hurni, M., Griffin, H., & et al. (2002). Bovine jugular vein as right ventricle-to-pulmonary artery valved conduit. *J Heart Valve Dis*, *11*, 242–247; discussion 248.

Crestanello, J., Cook, S., Daniels, C., & et al. (2010). Medial necrosis in aortic root aneurysm after repair of tetralogy of fallot. *J Card Surg*, *25*, 230–232.

Cumming, G., & Carr, W. (1966). Relief of dyspnoeic attacks in fallots tetralogy with propanolol. *Lancet*, *1*, 519–522.

Dabizzi, R., Caprioli, G., Aiazzi, L., & et al. (1980). Distribution and anomalies of coronary arteries in tetralogy of fallot. *Circulation*, *61*, 95-102.

Dadlani, G., John, J., & Cohen., M. (2008). Echocardiography in tetralogy of fallot. *Cardiol Young 18*, *Suppl 3*, 22-28.

Dave, H., Kadner, A., Bauersfeld, U., & et al. (2003). Early results of using the bovine jugular vein for right ventricular outflow reconstruction during the ross procedure. *Heart Surg Forum*, *6*, 390–392.

Dearani, J., Danielson, G., Puga, F., & et al. (2003). Late followup of 1095 patients undergoing operation for complex congenital heart disease utilizing pulmonary ventricle to pulmonary artery conduits. *Ann Thorac Surg*, *75*, 399–410; discussion 411.

de Leval, M., McKay, R., Jones, M., & et al. (1977). Modified blalocktaussig shunt. use of subclavian artery orifice as flow regulator in prosthetic systemic-pulmonary artery shunts. *J Thorac Cardiovasc Surg*, *81*, 112–119.

Derby, C., & Pizarro, C. (2005). Routine primary repair of tetralogy of fallot in the neonate. *Expert Rev Cardiovasc Ther*, *3*, 857–863.

Dickinson, D., Wilkinson, J., Smith, A., & et al. (1982). Variations in the morphology of the ventricular septal defect and disposition of the atrioventricular conduction tissues in tetralogy of fallot. *Thorac Cardiovasc Surg*, *30*, 243-249.

Di Donato, R., Jonas, R., Lang, P., & et al. (1991). Neonatal repair of tetralogy of fallot with and without pulmonary atresia. *J Thorac Cardiovasc Surg*, *101*, 126–127.

Dietl, C., Cazzaniga, M., Dubner, S., & et al. (1994). Life-threatening arrhythmias and rv dysfunction after surgical repair of tetralogy of fallot. comparison between transventricular and transatrial approaches. *Circulation*, *90*, II7–II12.

Dimitrakakis, G., Von-Oppell, U., Bosanquet, D., & et al. (2009). Aortic aneurysm formation five decades after tetralogy of fallot repair. *Ann Thorac Surg*, *88*, 1000–1001.

Discigil, B., Dearani, J., Puga, F., & et al. (2001). Late pulmonary valve replacement after repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*, *121*, 344–351.

Dohlen, G., Chaturvedi, R., Benson, L., & et al. (2009). Stenting of the right ventricular outflow tract in the symptomatic infant with tetralogy of fallot. *Heart*, *95*, 142–147.

Ebert, P., & Turley, K. (1984). Surgery for cyanotic heart disease in the first year of life. *J Am Coll Cardiol*, *1*, 274–279.

Elliott, R., Starling, M., & Neutze, J. (1975). Medical manipulation of the ductus arteriosus. *Lancet*, *1*, 140–142.

Eyskens, B., Reybrouck, T., Bogaert, J., & et al. (2000). Homograft insertion for pulmonary regurgitation after repair of tetralogy of fallot improves cardiorespiratory exercise performance. *Am J Cardiol*, *85*, 221–225.

Fallot, E. (1888). Contribution a lanatomie pathologique de la maladie bleue. *Marseille Med.*, *25*, 77-93, 138-158, 207-223, 270-286, 341-354, 403-420.

Feier, H., Collart, F., Ghez, O., & et al. (2005). Risk factors, dynamics, and cutoff values for homograft stenosis after the ross procedure. *Ann Thorac Surg*, *79*, 1669-1675; discussion 1675.

Fiore, A., Rodefeld, M., Turrentine, M., & et al. (2010). Pulmonary valve replacement: A comparison of three biological valves. *Ann Thorac Surg*, *85*, 1712–1718.

Forbess, J., Shah, A., Louis, J. S., & et al. (2001). Cryopreserved homografts in the pulmonary position: determinants of durability. *Ann Thorac Surg*, *71*, 54–59; discussion 59–60.

Fraser-Jr, C., McKenzie, E., & Cooley, D. (2001). Tetralogy of fallot: surgical management individualized to the patient. *Ann Thorac Surg*, *71*,

15561561; discussion 15611563.
Friedli, B. (1996). Arrhythmia after surgery for congenital cardiopathies. what studies? what treatment? *Arch Mal Coeur Vaiss*, *89*, 351–357.
Friedli, B. (1999). Electrophysiological follow-up of tetralogy of fallot. *Pediatr Cardiol*, *20*, 326–330.
Frigiola, A., Tsang, V., Nordmeyer, J., & et al. (2008). Current approaches to pulmonary regurgitation. *Eur J Cardiothorac Surg*, *34*, 576–580; discussion 581–582.
Garson-Jr, A., Gillette, P., & McNamara, D. (1981). Propranolol: the preferred palliation for tetralogy of fallot. *Am J Cardiol*, *47*, 1098–1104.
Gatzoulis, M., Balaji, S., Webber, S., & et al. (2000). Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of fallot: a multicentre study. *Lancet*, *356*, 975–981.
Gatzoulis, M., Soukias, N., Ho, S., & et al. (1999). Echocardiographic and morphological correlations in tetralogy of fallot. *Eur Heart J*, *20*, 221-231.
Geha, A., Laks, H., Stansel, H., & et al. (1979). Late failure of porcine valve heterografts in children. *J Thorac Cardiovasc Surg*, *78*, 351–364.
Gerestein, C., Takkenberg, J., Oei, F., & et al. (2001). Right ventricular outflow tract reconstruction with an allograft conduit. *Ann Thorac Surg*, *71*, 911-917; discussion 917-918.
Geva, T. (2006). Indications and timing of pulmonary valve replacement after tetralogy of fallot repairs. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*, *9*, 11–22.
Geva, T., Powell, A., Crawford, E., & et al. (1998). Evaluation of regional differences in right ventricular systolic function by acoustic quantification echocardiography and cine magnetic resonance imaging. *Circulation*, *98*, 339-345.
Goldmuntz, E., Geiger, E., & Benson, D. (2001). NKX2.5 mutations in patients with TOF. *Circulation*, *104*, 2565–2568.
Gottlieb, D., Kunal, T., Emani, S., & et al. (2010). In vivo monitoring of function of autologous engineered pulmonary valve. *J Thorac Cardiovasc Surg*, *139*, 723–731.
Graham, E., Bandisode, V., Bradley, S., & et al. (2008). Effect of preoperative use of propranolol on postoperative outcome in patients with tetralogy of fallot. *Am J Cardiol*, *101*, 693–695.
Gundry., S. (1999). Pericardial and synthetic monocusp valves: Indication and results. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*, *2*, 77–82.
Gundry, S., Razzouk, A., Boskind, J., & et al. (1994). Fate of the pericardial monocusp pulmonary valve for right ventricular outflow tract reconstruction. early function, late failure without obstruction. *J Thorac Cardiovasc Surg*, *107*, 908–912; discussion 912–913.
Gustafson, R., Murray, G., Warden, H., & et al. (1988). Early primary repair of tetralogy of fallot. *Ann Thorac Surg*, *45*, 235–241.
Haas, F., Schreiber, C., Horer, J., & et al. (2005). Is there a role for mechanical valved conduits in the pulmonary position? *Ann Thorac Surg*, *79*, 1662–1667; discussion 1667–1668.
Harrild, D., Berul, C., Cecchin, F., & et al. (2009). Pulmonary valve replacement in tetralogy of fallot: impact on survival and ventricular tachycardia.

Circulation, *119*, 445–451.

Harrison, D., Siu, S., Hussain, F., & et al. (2001). Sustained atrial arrhythmias in adults late after repair of tetralogy of fallot. *Am J Cardiol*, *87*, 584–588.

Hawkins, J., Bailey, W., Dillon, T., & et al. (1992). Midterm results with cryopreserved allograft valved conduits from the right ventricle to the pulmonary arteries. *J Thorac Cardiovasc Surg*, *104*, 910–916.

Hennein, H., Mosca, R., Urcelay, G., & et al. (1995). Intermediate results after complete repair of tetralogy of fallot in neonates. *J Thorac Cardiovasc Surg*, *109*, 332–344; discussion 342–343.

Herijgers, P., Ozaki, S., Verbeken, E., & et al. (2002). Valved jugular vein segments for right ventricular outflow tract reconstruction in young sheep. *J Thorac Cardiovasc Surg*, *124*, 798–805.

Hirsch, J., & Bove, E. (2003). Tetralogy of fallot. In *Pediatric cardiac surgery* (3rd ed.). Mosby, Inc.

Hirsch, J., Mosca, R., & Bove, E. (2000). Complete repair of tetralogy of fallot in the neonate: results in the modern era. *Ann Surg*, *232*, 508–514.

Hoffman, J., & Kaplan, S. (2002). The incidence of congenital heart disease. *J Am Coll Cardiol*, *39*, 1890-1900.

Hokanson, J., & Moller, J. (2001). Significance of early transient complete heart block as a predictor of sudden death late after operative correction of tetralogy of fallot. *Am J Cardiol*, *87*, 1271–1277.

Homann, M., Haehnel, J. C., Mendler, N., & et al. (2000). Reconstruction of the RVOT with valved biological conduits: 25 years experience with allografts and xenografts. *European Journal of Cardio-thoracic Surgery*, *17*, 624–630.

Horer, J., Vogt, M., Stierle, U., & et al. (2009). A comparative study of mechanical and homograft prostheses in the pulmonary position. *Ann Thorac Surg*, *88*, 1534–1539.

Horneffer, P., Zahka, K., Rowe, S., & et al. (1990). Long-term results of total repair of tetralogy of fallot in childhood. *Ann Thorac Surg*, *50*, 179183; discussion 183185.

Howell, C., Ho, S., Anderson, R., & et al. (1990). Variations within the fibrous skeleton and ventricular outflow tracts in tetralogy of fallot. *Ann Thorac Surg*, *50*, 450-457.

Husain, S., & Brown., J. (2007). When reconstruction fails or is not feasible: valve replacement options in the pediatric population. *Semin Thorac Cardiovasc Surg Pediatr Card*, Surg Annu 117-124.

Ichikawa, Y., Noishiki, Y., Kosuge, T., & et al. (1997). Use of a bovine jugular vein graft with natural valve for right ventricular outflow tract reconstruction: a one-year animal study. *J Thorac Cardiovasc Surg*, *114*, 224-233.

Ilbawi, M., Idriss, F., DeLeon, S., & et al. (1987). Factors that exaggerate the deleterious effects of pulmonary insufficiency on the right ventricle after tetralogy repair. surgical implications. *J Thorac Cardiovasc Surg*, *93*, 36–44.

Jonas, R. (2009). Early primary repair of tetralogy of fallot. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*, *12*, 39–47.

Jonas., R. (2014). Choosing the right biomaterial. In *Comprehensive surgical management of congenital heart disease.* (2nd ed.). CRC Press.

Jonas, R., Freed, M., Mayer, J., & et al. (1985). Long-term follow-up of patients with synthetic right heart conduits. *Circulation*, *72*, II77–II83.

Jonas, R., Freed, M., Mayer-Jr, J., & Castaneda, A. (1985). Long-term follow-up of patients with synthetic right heart conduits. *Circulation*, *72*, II77–II83.

Kanter, K., Kogon, B., Kirshbom, P., & et al. (2010). Symptomatic neonatal tetralogy of fallot: repair or shunt? *Ann Thorac Surg*, *89*, 859–863.

Karl, T., Sano, S., Pornviliwan, S., & et al. (1992). Tetralogy of fallot: favorable outcome of nonneonatal transatrial, transpulmonary repair. *Ann Thorac Surg*, *54*, 903–907.

Katz, N., Blackstone, E., Kirklin, J., & et al. (1982). Late survival and symptoms after repair of tetralogy of fallot. *Circulation*, *65*, 403–410.

Kay, P., & Ross., D. (1985). Fifteen years experience with the aortic homograft: the conduit of choice for right ventricular outflow tract reconstruction. *Ann Thorac Surg*, *40*, 360–364.

Khairy, P., Aboulhosn, J., Gurvitz, M., & et al. (2010). Arrhythmia burden in adults with surgically repaired tetralogy of fallot. a multi-institutional study. *Circulation*, *122*, 868–875.

Khairy, P., Landzberg, M., Gatzoulis, M., & et al. (2004). Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. *Circuation*, *109*, 1994–2000.

Kim, W., Seo, J., Kim, S., & et al. (2005). Aortic dissection late after repair of tetralogy of fallot. *Int J Cardiol*, *101*, 515–516.

Kirklin, J., Kirklin, J., Blackstone, E., & et al. (1989). Effect of transannular patching on outcome after repair of tetralogy of fallot. *Ann Thorac Surg*, *48*, 783–791.

Kjaergaard, J., Petersen, C., Kjaer, A., & et al. (2006). Evaluation of right ventricular volume and function by 2d and 3d echocardiography compared to mri. *Eur J Echocardiogr*, *7*, 430-438.

Knauth, A., Gauvreau, K., & Landzberg., M. (2005). Right ventricular size and function and age at repair predict major adverse outcomes late after tetralogy of fallot repair (abstr). *Circulation*, *112*, II681.

Knott Craig, C., Elkins, R., Lane, M., & et al. (1998). A 26-year experience with surgical management of tetralogy of fallot: risk analysis for mortality or late reintervention. *Ann Thorac Surg*, *66*, 506–511.

Kolcz, J., & Pizarro, C. (2005). Neonatal repair of tetralogy of fallot results in improved pulmonary artery development without increased need for reintervention. *Eur J Cardiothorac Surg*, *28*, 394–399.

Korbmacher, B., Heusch, A., Sunderdiek, U., & et al. (2005). Evidence for palliative enlargement of the right ventricular outflow tract in severe tetralogy of fallot. *Eur J Cardiothorac Surg*, *27*, 945–958.

Laudito, A., Bandisode, W., Lucas, J., & et al. (2006). Right ventricular outflow tract stent as a bridge to surgery in a premature infant with tetralogy of fallot. *Ann Thorac Surg 81*, *81*, 744–746.

Lee, W., Smith, R., Comstock, C., & et al. (1995). Tetralogy of fallot: prenatal diagnosis and postnatal survival. *Obstet Gynecol*, *86*, 583-588.

Le-Gloan, L., Guerin, P., Mercier, L., & et al. (2010). Clinical assessment of arrhythmias in tetralogy of fallot. *Expert Rev Cardiovasc Ther*, *8*, 189–197.

Lillehei, C., Cohen, M., Warden, H., & et al. (1955). Direct vision intracardiac surgical correction of the tetralogy of fallot, pentalogy of fallot, and pulmonary atresia defects; report of first ten cases. *Ann Surg*, *142*, 418-442.

Maeda, J., Yamagishi, H., Matsuoka, R., & et al. (2000). Frequent association of 22q11.2 deletion with tof. *Am J Med Genet*, *92*, 269–272.

Marie, P., Marcon, F., Brunotte, F., & et al. (1992). Right ventricular overload and induced sustained ventricular tachycardia in operatively repaired tetralogy of fallot. *Am J Cardiol*, *69*, 785–799.

McGoon, D., Danielson, G., Puga, F., & et al. (1982). Late results after extracardiac conduit repair for congenital cardiac defects. *Am J Cardiol*, *49*, 1741–1749.

Miatton, M., De-Wolf, D., Francois, K., & et al. (2007). Intellectual, neuropsychological, and behavioral functioning in children with tetralogy of fallot. *J Thorac Cardiovasc Surg*, *133*, 449–455.

Michielon, G., Marino, B., Formigari, R., & et al. (2006). Genetic syndromes and outcome after surgical correction of tetralogy of fallot. *Ann Thorac Surg*, *81*, 968-975.

Morales, D., Braud, B., Gunter, K., & et al. (2006). Encouraging results for the contegra conduit in the problematic right ventricle-to-pulmonary artery connection. *J Thorac Cardiovasc Surg*, *132*, 665–671.

Murphy, J., Gersh, B., Mair, D., & et al. (1993). Long-term outcome in patients undergoing surgical repair of tetralogy of fallot. *N Engl J Med*, *329*, 593–599.

Need, L., Powell, A., del Nido, P., & et al. (2000). Coronary echocardiography in tetralogy of fallot: diagnostic accuracy, resource utilization and surgical implications over 13 years. *J Am Coll Cardiol*, *36*, 1371-1377.

Niwaya, K., Knott-Craig, C., Lane, M., & et al. (1999). Cryopreserved homograft valves in the pulmonary position: risk analysis for intermediate-term failure. *J Thorac Cardiovasc Surg*, *117*, 141-146; discussion 146-147.

Nollert, G., Dabritz, S., Schmoeckel, M., & et al. (2003). Risk factors for sudden death after repair of tetralogy of fallot. *Ann Thorac Surg*, *76*, 1901–1905.

Nollert, G., Fischlein, T., Bouterwek, S., & 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. *J Am Coll Cardiol*, *30*, 1374–1383.

Nudel, D., Berman, M., & Talner, N. (1976). Effects of acutely increasing systemic vascular resistance on oxygen tension in tetralogy of fallot. *Pediatrics*, *58*, 248–251.

Nunn, G., Bennetts, J., & Onikul., E. (2008). Durability of handsewn valves in the right ventricular outlet. *J Thorac Cardiovasc Surg*, *136*, 290–296.

Odim, J., Portzky, M., Zurakowski, D., & et al. (1995). Sternotomy approach for the modified blalock-taussig shunt. *Circulation*, *92*, 256–261.

Oku, H., Matsumoto, T., Kitayama, H., & et al. (1993). Semilunar valve replacement with a cylindrical valve. *J Card Surg*, *8*, 666–670.

Oosterhof, T., van Straten, A., Vliegen, H., & et al. (2007). Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of fallot using cardiovascular magnetic resonance. *Circulation*, *116*, 545–551.

Oosterhof, T., Vliegen, H., Meijboom, F., & et al. (2007). Longterm effect of pulmonary valve replacement on qrs duration in patients with corrected tetralogy of fallot. *Heart*, *93*, 506–509.

Oskarsdóttir, S., Vujic, M., & Fasth, A. (2004). Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in western sweden.

Arch Dis Child, *89*, 148–151.

Parry, A., McElhinney, D., Kung, G., & et al. (2000). Elective primary repair of acyanotic tetralogy of fallot in early infancy: overall outcome and impact on the pulmonary valve. *J Am Coll Cardiol*, *36*, 2279–2283.

Perron, J., Moran, A., Gauvreau, K., & et al. (1999). Valved homograft conduit repair of the right heart in early infancy. *Ann Thorac Surg*, *68*, 542–548.

Pexieder, T. (1995). Conotruncus and its septation at the advent of the molecular biology era. In *Developmental mechanisms of heart disease* (pp. 227–248). Futura Publishing.

Pigula, F., Khalil, P., Mayer, J., & et al. (1999). Repair of tetralogy of fallot in neonates and young infants. *Circulation*, *100(19 Suppl)*, II157–II161.

Quintessenza, J., Jacobs, J., Chai, P., & et al. (2010). Polytetrafluoroethylene bicuspid pulmonary valve implantation: experience with 126 patients. *World J Ped Congenital Heart Surg*, *1*, 20–27.

Raanani, E., Yau, T., David, T., & et al. (2000). Risk factors for late pulmonary homograft stenosis after the ross procedure. *Ann Thorac Surg*, *70*, 1953–1957.

Rastan, A., Walther, T., Daehnert, I., & et al. (2006). Bovine jugular vein conduit for right ventricular outflow tract reconstruction: evaluation of risk factors for mid-term outcome. *Ann Thorac Surg*, *82*, 1308–1315.

Rastelli, G., Ongley, P., Davis, G., & Kirklin., J. (1965). Surgical repair for pulmonary valve atresia with coronarypulmonary artery fistula: report of case. *Mayo Clin Proc*, *40*, 521–527.

Reddy, V., Liddicoat, J., McElhinney, D., & et al. (1995). Routine primary repair of tetralogy of fallot in neonates and infants less than three months of age. *Ann Thorac Surg*, *60 (6 Suppl)*, S592–S596.

Redington, A., Arsdell, G. V., & Anderson, R. (2009). Restrictive right ventricular physiology: Early and late effects. In *Congenital diseases in the right heart* (First ed.). Springer.

Roest, A., Helbing, W., Kunz, P., & et al. (2002). Exercise mr imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. *Radiology*, *223*, 204-211.

Roos-Hesselink, J., Perlroth, M., McGhie, J., & et al. (1995). Atrial arrhythmias in adults after repair of tetralogy of fallot. correlations with clinical, exercise, and echocardiographic findings. *Circulation*, *91*, 2214–2219.

Ross, D., & Somerville., J. (1966). Correction of pulmonary atresia with a homograft aortic valve. *Lancet*, *2*, 1446–1447.

Rüffer, A., Wittmann, J., Potapov, S., & et al. (2012). Mid-term experience with the hancock porcine-valved dacron conduit for right ventricular outflow tract reconstruction. *European Journal of Cardio-Thoracic Surgery*, *42*, 988–995.

Scavo-Jr, V., Turrentine, M., Aufiero, T., & et al. (1999). Valved bovine jugular venous conduits for right ventricular to pulmonary artery reconstruction. *ASAIO J*, *45*, 482–487.

Seipelt, R., Vazquez-Jimenez, J., Sachweh, J., & et al. (2002). Antegrade palliation for diminutive pulmonary arteries in tetralogy of fallot. *Eur J Cardiothorac Surg*, *21*, 721–724; discussion 724.

Sekarski, N., van Meir, H., Rijlaarsdam, M., & et al. (2007). Right ventricular outflow tract reconstruction with the bovine jugular vein graft: 5 years experience with 133 patients. *Ann Thorac Surg*, *84*, 599–605.

Shabbo, F., Wain, W., & Ross., D. (1980). Right ventricular outflow reconstruction with aortic homograft conduit: analysis of the long term results. *Thorac Cardiovasc Surg*, *28*, 21–25.

Singh, G., Greenberg, S., Yap, Y., & et al. (1998). Right ventricular function and exercise performance late after primary repair of tetralogy of fallot with the transannular patch in infancy. *Am J Cardiol*, *81*, 1378–1392.

Sinzobahamvya, N., Wetter, J., Blaschczok, H., & et al. (2001). The fate of small-diameter homografts in the pulmonary position. *Ann Thorac Surg*, *72*, 2070–2076.

Stellin, G., Milanesi, O., Rubino, M., & et al. (1995). Repair of tetralogy of fallot in the first six months of life: transatrial versus transventricular approach. *Ann Thorac Surg*, *60 (6 Suppl)*, S588-S591.

Steno, N. (1671). Anatomicus regij hafniensis, embryo monstro affinis parisiis dissectus. *Acta Medica et Philosophia Hafniencia*, 200-203.

Stewart, R., Backer, C., Young, L., & et al. (2005). Tetralogy of fallot: results of a pulmonary valve-sparing strategy. *Ann Thorac Surg*, *80*, 1431-1438; discussion 1438-1439.

Tamesberger, M., Lechner, E., Mair, R., & et al. (2008). Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. *Ann Thorac Surg*, *86*, 1928–1935.

Tanaka, K., Kitahata, H., Kawahito, S., & et al. (2003). Phenylephrine increases pulmonary blood flow in children with tetralogy of fallot. *Can J Anaesth*, *50*, 926–929.

Therrien, J., Provost, Y., Merchant, N., & et al. (2005). Optimal timing for pulmonary valve replacement in adults after tetralogy of fallot repair. *Am J Cardiol*, *95*, 779-782.

Therrien, J., Siu, S., Harris, L., & et al. (2001). Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of fallot. *Circulation*, *103*, 2489–2494.

Tongsong, T., Sittiwangkul, R., Chanprapaph, P., & et al. (2005). Prenatal sonographic diagnosis of tetralogy of fallot. *J Clin Ultrasound*, *33*, 427-431.

Turley, K., Mavroudis, C., & Ebert, P. (1982). Repair of congenital cardiac lesions during the first week of life. *Circulation*, *66*, I214–I219.

Turrentine, M., McCarthy, R., Vijay, P., & et al. (2002a). Polytetrafluoroethylene monocusp valve technique for right ventricular outflow tract reconstruction. *Ann Thorac Surg*, *74*, 2202–2205.

Turrentine, M., McCarthy, R., Vijay, P., & et al. (2002b). Ptfe monocusp valve reconstruction of the right ventricular outflow tract. *Ann Thorac Surg*, *73*, 871–879; discussion 879–880.

Tweddell, J., Pelech, A., Frommelt, P., & et al. (2000). Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. *Circulation*, *102(Suppl 3)*, III130-III135.

van-den Berg, J., Wielopolski, P., Meijboom, F., & et al. (2007). Diastolic function in repaired tetralogy of fallot at rest and during stress: assessment with mr imaging. *Radiology*, *243*, 212-219.

van Dongen, E., Glansdorp, A., Mildner, R., & et al. (2003). The influence of perioperative factors on outcomes in children aged less than 18 months after repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*, *126*, 703–710.

van Huysduynen, B., van Straten, A., Swenne, C., & et al. (2005). Reduction of qrs duration after pulmonary valve replacement in adult fallot patients is related to reduction of right ventricular volume. *Eur Heart J*, *26*, 928–932.

Van Praagh, R., Van Praagh, S., Nebesar, R., & et al. (1970). TOF: underdevelopment of the pulmonary infundibulum and its sequelae. *Am J Cardiol*, *26*, 25–33.

van Son., J. (1995). Repair of tetralogy of fallot with anomalous origin of left anterior descending coronary artery. *Thorac Cardiovasc Surg*, *110*, 561-562.

van Straten, A., Vliegen, H., Lamb, H., & et al. (2005). Time course of diastolic and systolic function improvement after pulmonary valve replacement in adult patients with tetralogy of fallot. *J Am Coll Cardiol*, *46*, 1559–1564.

Warner, K., O'Brien, P., Rhodes, J., & et al. (2003). Expanding the indications for pulmonary valve replacement after repair of tetralogy of fallot. *Ann Thorac Surg*, *76*, 1066–1071; discussion 10711072.

Wells, W., Arroyo-Jr, H., Bremner, R., & et al. (2002). Homograft conduit failure in infants is not due to somatic outgrowth. *J Thorac Cardiovasc Surg*, *124*, 88–96.

Wessel, H., Bastanier, C., Paul, M., & et al. (1980). Prognostic significance of arrhythmia in tetralogy of fallot after intracardiac repair. *Am J Cardiol*, *46*, 843–848.

Williams, D., Danielson, G., McGoon, D., & et al. (1982). Porcine heterograft valve replacement in children. *J Thorac Cardiovasc Surg*, *84*, 446–450.

Wu, E., Wang, J., Lee, W., & et al. (2006). Balloon valvuloplasty as an initial palliation in the treatment of newborns and young infants with severely symptomatic tetralogy of fallot. *Cardiology*, *105*, 52–56.

Yamagishi, M., & Kurosawa, H. (1993). Outflow reconstruction of tetralogy of fallot using a gore-tex valve. *Ann Thorac Surg*, *56*, 1414–1416; discussion 1416-1417.

Yankah, A., Alexi-Meskhishvili, V., Weng, Y., & et al. (1995). Accelerated degeneration of allografts in the first two years of life. *Ann Thorac Surg*, *60(2 Suppl)*, S71–S76; discussion S76–S77.

Zahka, K., Horneffer, P., Rowe, S., & et al. (1988). Longterm valvular function after total repair of tetralogy of fallot. relation to ventricular arrhythmias. *Circulation*, *78*, III14–III19.

Zeltser, I., Jarvik, G., Bernbaum, J., & et al. (2008). Genetic factors are important determinants of neurodevelopmental outcome after repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*, *135*, 91–97.

Zhao, H., Miller, D., Reitz, B., & et al. (1985). Surgical repair of tetralogy of fallot. long-term follow-up with particular emphasis on late death and reoperation. *J Thorac Cardiovasc Surg*, *89*, 203–220.