CLINICAL AND EXPERIMENTAL STUDY OF THE RIGHT VENTRICLE IN RELATION TO ITS OUTFLOW TRACT

A CONTRIBUTION TO THE SURGICAL MANAGEMENT OF TETRALOGY OF FALLOT

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Abbreviation list

CMRI = cardiac magnetic resonance imaging

EDV = end-diastolic volume

EDPVR = end-diastolic pressure-volume relationship

ESV = end-systolic volume

ESPVR = end-systolic pressure-volume relationship

LV = left ventricle

MAP = monophasic action potential

NYHA = New York Heart Association

PA = pulmonary artery

PAB = pulmonary artery banding

PI = pulmonary insufficiency

PR = pulmonary regurgitation

PRF = pulmonary regurgitant fraction

PRSW = preload recruitable stroke work

PV = pulmonary valve

PVR = pulmonary valve replacement

RBBB = right bundle branch block

RV = right ventricle

RVEF = right ventricular ejection fraction

RVH = right ventricular hypertrophy

RVOT = right ventricular outflow tract

RVOTO = right ventricular outflow tract obstruction

TAP = transannular patch

TAPSE = tricuspid annular plane systolic excursion

TOF = tetralogy of Fallot

VSD = ventricular septal defect

VT = ventricular tachycardia

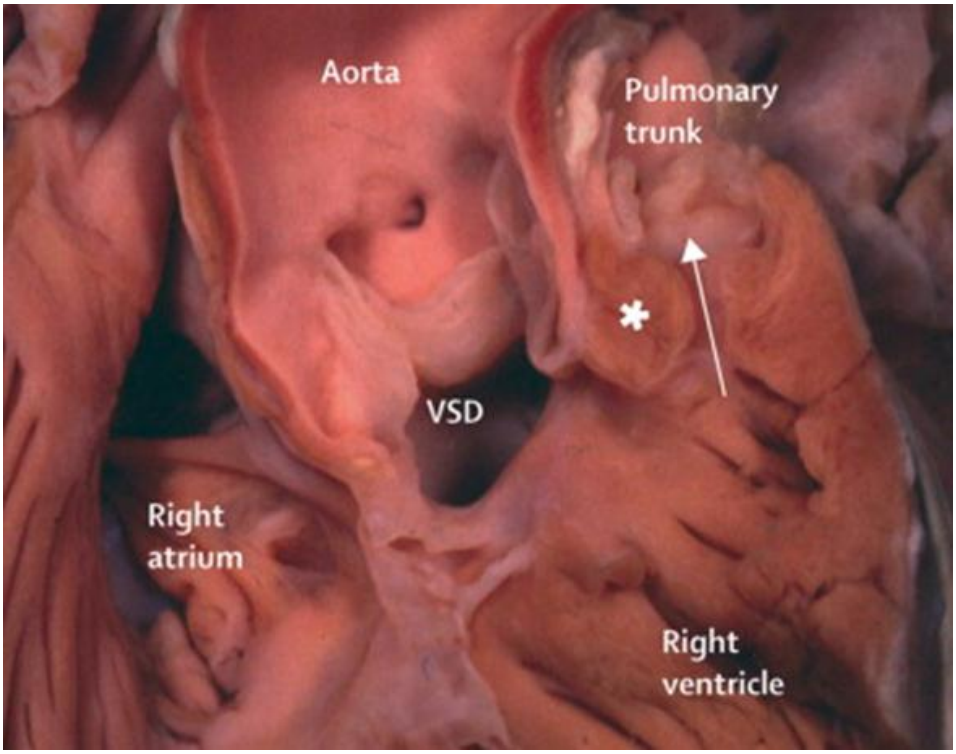
Chapter I : General introduction

A. Tetralogy of Fallot : From 'curable' disease to surgical paradigm

1. Historical background

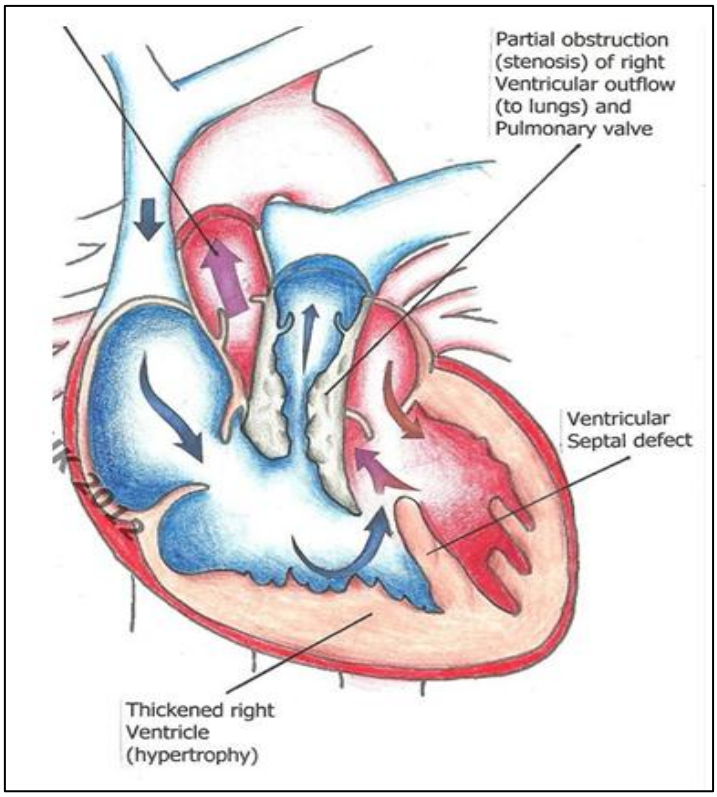
In 1888, the French physician Etienne-Louis Fallot reported on a congenital heart disease consisting of four cardiac abnormalities, i.e. a ventricular septal defect, an aorta overriding both right and left ventricle, narrowing of the right ventricular outflow tract with infundibular and/or pulmonary valve stenosis, and right ventricular hypertrophy. Based on these four elements, the malformation was named 'tetralogy of Fallot'. Later anatomo-pathological analysis cleared out that the basic feature was the presence of the VSD with anterior deviation of the outlet septum, leading to infundibular subpulmonary stenosis and positioning the aorta partially over both ventricles.

Figure. Anatomical heart specimen showing the relationship between the VSD, the aorta and morphology of the RVOTO



Tetralogy of Fallot (TOF) occurs in approximately 1 in 3600 live births, accounting for 3.5 % of all congenital heart defects, and is known as the most common cyanotic heart disease. [1]

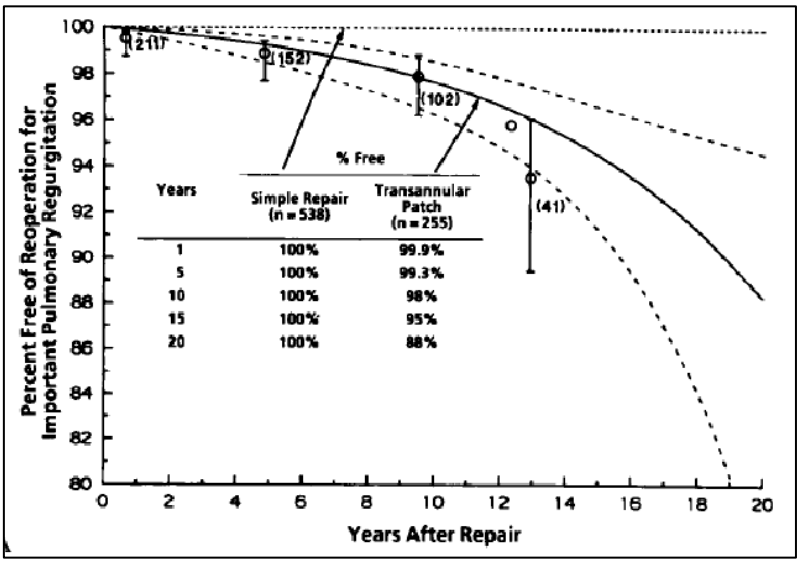
Figure. Physiology of the right-to-left shunt across the VSD, depending on the severity of RVOTO, resulting in systemic hypoxemia



The surgical treatment started in 1945, when Alfred Blalock and Hellen Taussig initiated a method to improve the severe hypoxemia by placing a shunt between the systemic circulation and the pulmonary artery, in order to increase the pulmonary flow [2]. The first complete correction of TOF was performed by Walter Lillehei in 1955, in an 11-year old boy, with the use of cross-circulation. Six out of the first 10 patients survived the operation, making this disease amenable for definitive treatment [3]. Due to rapid improvement of cardiopulmonary bypass technology and myocardial protection, many TOF patients were offered surgical therapy, obviating them from a near-certain death from cyanosis. Early experience with complete repair usually involved children at the median age of 5 to 8 years, treated first with a shunt in 20-30 %. The operative technique yielded a generous right ventriculotomy, large enough to allow closure of the VSD, and wide relief of the RVOT obstruction. Although this approach remained fundamentally unchanged for the ensuing 20 to 30 years, operative mortality progressively declined due to increased experience with the cardiac surgical management in general. The perspective on a survival rate of more than 80 % after 30- to 36 years, strengthened the idea that repair of TOF

was ‘curative’, even though a small number of patients succumbed lately from sudden death [4, 5]. However, Kirklin et al. were the first to point on the deleterious effect of chronic pulmonary insufficiency (PI) on RV function, advanced by the use of extensive transannular patches (TAP). Within 20 years of follow-up, 7 % of the patients needed reoperation by pulmonary valve implantation for RV failure, whereas this number increased to even 20 % in presence of co-existent distal pulmonary artery stenosis [6].

Figure. Freedom from reoperation-plot for simple repair versus transannular patch repair of TOF : Use of TAP repair increases the late risk for reoperation due to PI (Kirklin et al. Ann Thorac Surg 1989)



2. Pulmonary regurgitation: A not so benign lesion

2.1 Pathophysiology of pulmonary incompetence

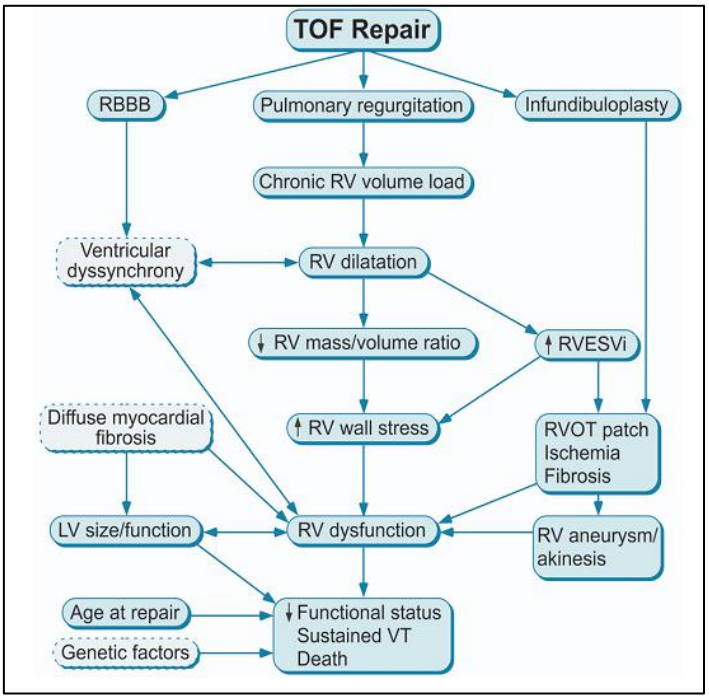
Loss of anatomical integrity of the pulmonary valve leaflets and/or annulus results in pulmonary insufficiency. Its effect on the RV depends on the degree and the time duration of the regurgitation, as well as on the intrinsic properties of the RV and of the distal pulmonary arteries.

One of the main reasons for PI to be well tolerated for several years, is related to the low resistant pulmonary microvascular bed. Moreover, the pulmonary capillary system has a valve-like effect in presence of severe PI, as the blood compelled through the alveolar capillaries in systole is unlikely to flow back in diastole, by absence of a significant reversal of gradient.

Based on the Torricelli principle [7], the severity of PI is proportional to the regurgitation orifice area (= RAO), the diastolic pressure gradient between RV and PA (= $P_1 - P_2$), the diastolic time (= DT) and the compliance of the pulmonary arterial circuit (= C), according to the formula:

$$\text{PR-volume} = \text{RAO. C. DT. } (P_2 - P_1)^{0.5}$$

The chronic volume-overload entails some functional changes to the RV function, which are additionally furthered by procedure- and patient-related factors, finally resulting in progressive RV dysfunction with clinical impairment, as depicted in this diagram.



2.1.1 Role of the pulmonary artery characteristics

Alterations at macro- or microscopic level of the pulmonary arteries may affect the amount of PI. Albeit pulmonary vascular disease with pulmonary hypertension in TOF is uncommon, branch pulmonary artery stenosis is frequently observed. Distal pulmonary artery stenosis enhances right ventricular afterload and increases PI. It has been shown in a neonatal animal model that relief of a left pulmonary branch stenosis by stenting resulted in significant regression of the pulmonary regurgitant fraction from 39% to 27%, with secondary improvement of RV performance [8]. In particular, the contribution of the left pulmonary artery to the regurgitant fraction appears to be important but physiologically unclear [9]. In a MRI study of TOF patients with significant PI, the left pulmonary artery

participated in 54% of the regurgitant fraction, while it received only 44% of the forward flow. They speculated that the smaller left lung is responsible for a higher vascular impedance, which is furthered by the cardiomegaly in TOF.

Another pulmonary artery component with impact on the degree of PI, is the pulmonary artery compliance. Pulmonary artery compliance is quantified by the volume change of that elastic wall-compartment per unit of pressure change during the cardiac cycle. Based on a mathematical model extracted from CMRI-images from various RVOT configurations, Kilner et al. has demonstrated that the high compliance of the proximal pulmonary artery increases the amount of PI, in absence of a competent pulmonary valve. Conversely, a greater proportion of blood volume ejected from the RV, is propagated through the pulmonary arterial system when the compliance of the pulmonary arteries is reduced. This phenomenon underscores the negative effect of large akinetic RVOT patches, but with preserved elastic properties, on the pulmonary regurgitant fraction [10]. Such capacitance effect is even more pronounced in presence of a real aneurysmal dilatation of the RVOT after TAP. The deleterious effect of RVOT aneurysm on the degree of PI and the RV function has been clearly shown by CMRI-investigation of the RV in adult patients late after TOF repair [11].

2.2.2 Role of the right ventricular properties

Pulmonary insufficiency results in diastolic volume-overload of the RV, with first increase of the end-diastolic volume, and with time, gradual increase of end-systolic volume and impairment of the systolic pump function. The extent of RV dilation is commonly related to the severity of PI as well as to the duration of volume-overload exposure. This process is often slow and insidious, and evokes clinical symptoms in 6% at 20 years and in 20% at 40 years for isolated congenital pulmonary insufficiency [12]. Hence, this course is certainly accelerated after TAP repair of TOF.

Pulmonary regurgitation is driven by the diastolic pressure difference between the pulmonary artery and the RV. This pressure difference is determined by the compliance of the RV, as a poorly compliant RV will raise the intraventricular diastolic pressure and systemic venous pressure proportionally, thereby decreasing the gradient for PI. In consequence, the intrinsic diastolic properties of the RV undeniably affect the adaptive response of the RV to chronic volume-overload. The group of London has identified the phenomenon of restrictive RV physiology by echocardiography, through demonstrating the presence of an atrial wave in the pulmonary artery flow wave pattern at late diastole, throughout the respiratory cycle, which corresponds to the transmission of the contraction kick of the right atrium at elevated pressure [13]. Physiologically the RV acts then as a stiff and passive conduit during diastole, limiting thereby the amount and the duration of diastolic regurgitation. According to the same physiological mechanism active in the non-compliant hypertrophied RV, increased resistance proximal to the origin of PI reduces the regurgitant fraction by resisting the diastolic

backflow, but often at the cost of some remnant obstruction [10]. Limitation of PI has been illustrated similarly in an animal model wherein the RV has been subjected to the chronic effect of combined PI and pulmonary stenosis [14].

3. Clinical manifestations of chronic pulmonary incompetence

Although many patients with PI after TOF repair may remain asymptomatic for several years to decades, there is growing awareness of increased morbidity as well as mortality related to progressive RV dysfunction by chronic volume-overload. Actually the relationship between RV dysfunction and the clinical status could be inconstant. The majority of adult TOF patients, having undergone repair during childhood, reports subjectively on a good level of functional health status and quality of life, allowing a normal social participation, despite significant constraints of physical activity [15].
However, when clinical symptoms appear, common manifestations are exercise intolerance, congestive heart failure, atrial and ventricular arrhythmia and sudden cardiac death.

3.1 Exercise intolerance

Wessel et al. examined the factors leading to diminished exercise capacity in a large group of TOF patients, at least one year after repair. They found a close correlation with cardiomegaly, residual RV hypertension, pulmonary regurgitation, residual VSD and documented arrhythmia [16]. Carvalho et al. found that patients with a predicted peak oxygen consumption of less than 85 % had more PI, pointing on a direct relationship between exercise performance and the degree of PI [17]. Several reports have further investigated the relation between variables of RV function and clinical status after repair of TOF, based on new insights into the mechanisms of RV dysfunction through the use of CMRI.
Geva et al. demonstrated the negative impact of moderate to severe LV and/or RV dysfunction on the NYHA functional status of long-term survivors of TOF, suggesting the unfavorable role of RV distension on inter-ventricular interaction.[18] The same group later specified that, before concomitant impairment of LV function occurred, the systolic function of the RV, expressed by RV ejection fraction, correlated best with the exercise capacity [19]. Exercise capacity also appeared to deteriorate over time, but this longitudinal change was subjected to individual variability and was primarily related to the incapacity to maintain forward stroke volume at peak exercise [20].
Increasing focus on the effects of regional RV dysfunction demonstrated that a greater extent of RVOT dysfunction is probably one of the main contributors to exercise intolerance after TOF repair [21].
In addition, extensive myocardial fibrosis of the RV on late gadolinium enhancement suggested decreased RV function and was associated with adverse clinical markers as poor exercise performance, arrhythmia and increased neuro-hormonal activation [22].

Considering specifically the functional properties of the RV, the presence of a restrictive RV physiology has been associated with improved exercise performance by limiting the RV dilation [23]. However, in TOF patients with severely dilated RV, a restrictive RV physiology on the long-term has been related to impaired exercise capacity [24, 25]. This controversial issue has been clarified later by identifying different subtypes of restrictive RV function, entailing on one hand smaller right ventricles with so-called 'primary restriction' and better exercise function, and on the other hand, massively dilated and dysfunctional right ventricles with unfavorable functional capacity [26, 27].
Finally, an abnormal heart rate response during exercise is commonly noticed in many adult patients with congenital heart disease. More than half of the adult TOF patients showed evident chronotropic incompetence, correlating strongly with decreased peak oxygen consumption. Based on the dismal impact of these findings on prognosis, it has been advocated to include exercise testing routinely into the late follow-up evaluation of repaired TOF patients [28].

3.2 Arrhythmia and sudden death

The incidence of sudden death during the late follow-up after repair of TOF has been estimated to vary from 2 to 6 % [4, 29]. The main cause of arrhythmic death is largely attributed to the occurrence of ventricular tachycardia and ventricular fibrillation [29-31]. In rare instances, a complete heart block accounts for mortality in these patients [32, 33]. Although ventricular ectopy yielded most emphasis for its impact on mortality, atrial arrhythmia are a major cause of morbidity in one third of the repaired TOF patients [34].
Malignant ventricular arrhythmia in TOF is primarily based on re-entrant circuits originating from the RVOT, that includes the scarred areas from closure of the VSD, from the ventricular incision and RVOT aneurysm formation [35, 36]. Electrophysiological mapping has supported this reentry phenomenon by showing fractionated potentials as well as inducible ventricular arrhythmia by premature excitation [37, 38]. Another important substrate of arrhythmia is related to the mechano-electrical interaction between the RV dilation by chronic volume-overload and secondary alterations of intrinsic conduction properties [39]. Histopathological analysis of the RV myocardium has demonstrated degenerative cellular changes and increased interstitial fibrosis, as co-existent features of both increased RV dysfunction and arrhythmia. These changes were more pronounced if patients were older at the time of repair, suggesting here the negative role of long-standing cyanosis and pressure-overload on RV tissue characteristics [40].
Risk assessment of malignant ventricular arrhythmia in TOF has merely been based on retrospective studies of relatively small patient cohorts. The timing and type of corrective surgery has an important influence on the arrhythmogenic potential. Older age at repair was a significant risk factor in studies reporting on a population of TOF patients treated in former eras, as well as the use of extensive RVOT

patches and large ventriculotomies [32, 40, 41]. In a comparison between the transventricular versus transatrial approach, Dietl et al. has shown a risk reduction of arrhythmia by the more recent technique, without concomitant increase of atrial arrhythmia [42].

Pioneering work on the prediction of sudden death in TOF patients has been done by Gatzoulis and co-workers, emphasizing the relation between surface ECG changes and the risk of malignant arrhythmia as the so-called mechano-electrical feedback within the RV. Based on the duration of the QRS complex as a marker of arrhythmia propensity, they found a QRS duration ≥ 180 msec to be a sensitive predictor of sustained VT and sudden death in TOF patients with more than 20 years of follow-up since complete repair [43]. In a multicenter study, the same author not only confirmed the value of QRS duration as such, but also identified the rapid progression of the QRS duration as an additional risk factor [44]. The utility of monitoring this simple parameter has been validated later, by showing stabilization and even reduction of QRS duration after effective pulmonary valve implantation, reversing the mechanical as well as the electrical remodeling of the RV [45]. Accordingly, an increased QT dispersion > 60 msec has been withhold as predictive marker of arrhythmia, unrelated to the presence of right bundle branch pattern, and independent of the size of the RV [46].

Late RV dysfunction in TOF is associated with perturbation of autonomic cardiac regulation. Blunting of cardiovascular response at exercise with decreased heart rate variability correlates with RV dilation and with QRS duration [47, 48]. However, its predictive effect for arrhythmia remains unproven.

Further evolution into the understanding of the different mechanisms of tachy-arrhythmia focused also on the adverse influence of LV dysfunction in TOF [49]. Besides the functional effect of the dilated RV on the LV through ventricular interdependency, impairment of the LV function has been attributed to LV asynchrony in the setting of the usual RBBB in TOF patients [50]. However, its value in the risk stratification of ventricular arrhythmia remains unclear.

While ventricular ectopy on ambulatory ECG monitoring is frequently observed in adult TOF patients, the question raised whether this potential precursor of inducible ventricular tachycardia has to be investigated more properly by electrophysiological testing. Several studies on the role of prophylactic screening of asymptomatic TOF patients have produced conflicting results. In a multicenter cohort of 252 TOF patients, sustained VT and polymorphic VT were induced in respectively 30% and 4% in a programmed ventricular stimulation protocol. The authors concluded that such program has a diagnostic and prognostic value in the risk assessment. Especially the induction of sustained polymorphic VT should not be disregarded as a non-specific finding[51]. Otherwise, the yield of electrophysiological testing in asymptomatic TOF patients is low, revealing a positive study in only 10%[52].

Regarding the therapeutical implications, the risk of ventricular arrhythmia and sudden death is usually reversed by timely pulmonary valve implantation with or without concomitant cryoablation, which parallels the secondary RV size remodeling [53]. The favorable effect of this surgery on the

regression of QRS duration and improvement of the repolarization properties has already been mentioned [45, 54]. The use of implantable cardioverter-defibrillator devices in the secondary prevention of sudden death is of proven benefit, although increasing experience with guided electrical mapping enhances the chance to successfully identify the unstable circuit at the critical right ventricular isthmus for effective catheter ablation therapy [55, 56]. The role of resynchronization therapy in TOF seems promising in improving biventricular function, but needs further investigation [57, 58].

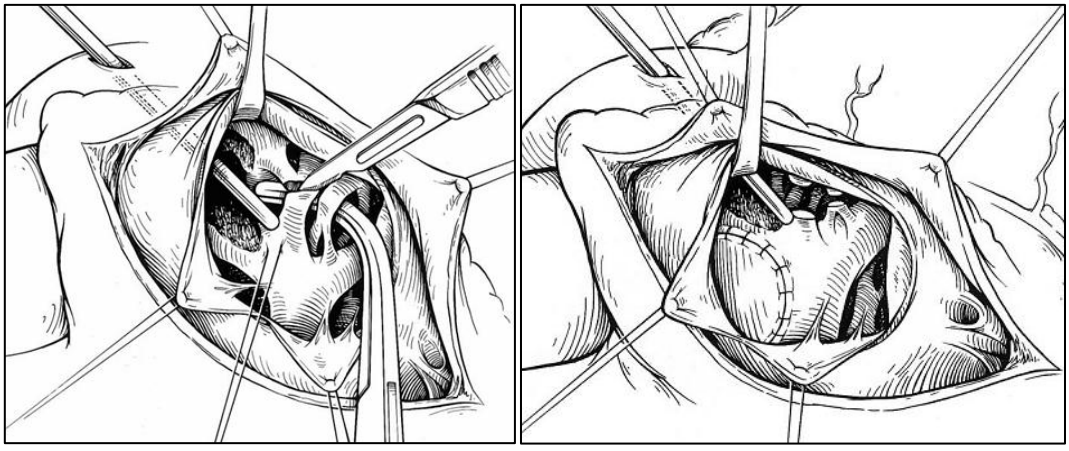
4. Contemporary surgery of tetralogy of Fallot: the search for the ideal repair

4.1 Technical evolution of the RVOT reconstruction

Early surgery of TOF focused mainly on complete relief of the RVOTO, but usually at the cost of free and severe PI. Based on the growing knowledge of its deleterious long-term sequelae, changes in the surgical approach were justified.

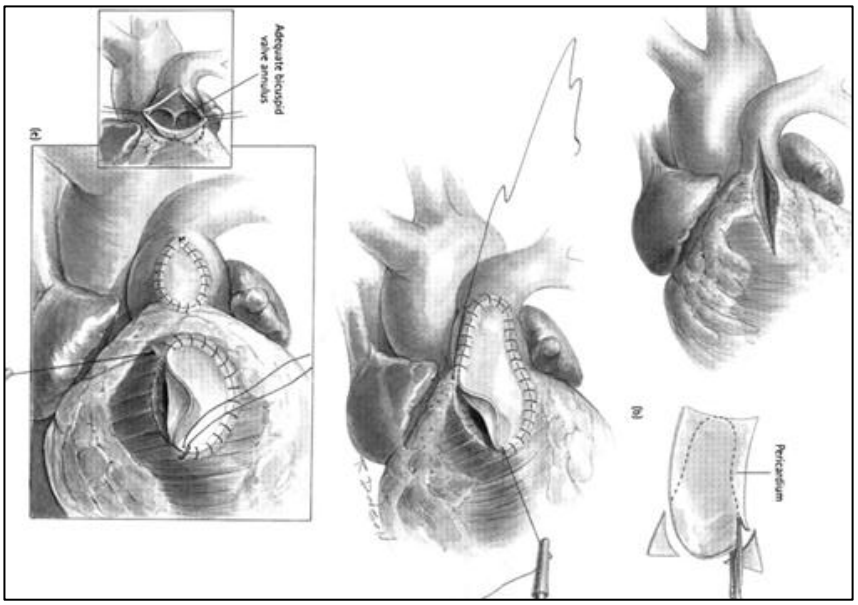
In 1976, Edmunds et al. reported on the closure of the VSD in TOF via the transatrial route [59]. The transition towards a transatrial-transpulmonary repair of TOF was further popularized by the surgeons of Melbourne [60]. Their technique consisted of a transatrial approach for closure of the VSD and resection of the obstructive muscle bundles in the infundibulum. Additional relief of the RVOT was achieved through the pulmonary artery, using a TAP incision not extending beyond the anatomical basis of the infundibular part of the RV. Early survival was excellent, with an operative mortality of 0.5% in 366 patients. Freedom from reoperation at 5 years was 95%.

Figure. Transatrial approach for closure of VSD and resection of hypertrophic infundibular muscle bundles in the RVOT (from Hirsch et al., Ann Surg 2000, 232(4):508-514)



As TOF patients show a widely variable morphological spectrum, most attention was directed at the particular group of TOF patients with small PV annulus, initiating the quest 'how small is too small' for the adequate pulmonary valve size. Based on the use of z-values for PV annulus size, the believers of a pulmonary-valve preserving strategy adapted this surgical strategy successfully in more than 80% of the TOF patients with a PV z-score > - 4, often concomitantly with an additional infundibular incision. The success rate was guaranteed particularly in presence of a trileaflet PV, in contrast to those with a bicuspid PV [61]. Similar results were reported by Rao et al, claiming that preservation of the PV annulus was facilitated by operating on younger aged patients [62]. Other surgical groups focused preferably on the preservation of the RV, by an infundibulum-sparing approach [63, 64]. Here the infundibular incision was kept minimal, even when the PV size needed a transannular extent. In comparison with the prior technique, separate patch enlarging of the infundibulum was obsolete.
A drawback of the RVOT-sparing strategy is the increased rate of reoperation for residual obstruction. Peri-operative revision was required in up to 16%, while reoperation after transventricular repair was necessary in less than 10% [61, 65]. Intra-operative assessment of the RVOT relief became crucial, in order to differentiate between a fixed, anatomical obstruction versus a dynamic residual gradient. Besides relying on the post-repair measurement of the RV/LV pressure ratio, the addition of transoesophageal echocardiography appeared to be essential [64, 65].
Long-term results of this novel approach are limited. Nevertheless, 10-year follow-up of such transatrial-transpulmonary repair of TOF showed smaller RV size and better RV function, shorter QRS duration and less ventricular ectopy in comparison with conventional repair techniques [66].

Figure. Transpulmonary access for relief of pulmonary valve obstruction with additional infundibular patch or transannular patch (from Jonas R, Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2009; 12: 39-47)



Lastly, the application of a hybrid approach has recently gained interest in the pursuit of a valve-sparing repair, through intra-operative balloon dilatation of the hypoplastic PV annulus [67, 68]. Preservation of the PV was possible in 37% of patients with a PV annulus z-score of -2 to -4, without compromising the growth rate of the valve. The early results seemed promising, except for a higher rate of early reintervention.

4.2 What about the age versus strategy for repair ?

In addition to the change in surgical technique for RVOTO relief, there has been an increasing trend to perform primary repair at an earlier age. It has been shown that lowering the age of repair to less than 1 year of age has been performed without major impact on the surgical outcome. Based on the use of physiological end-points as ventilation time, length of stay and lactate clearance, the group of Toronto has revealed that the optimal age for TOF repair might be between 3 and 11 months of age [69]. In contrast, routine primary correction of TOF in neonates or infants less than 3 months of age has been advanced by Hanley and colleagues [70]. The claimed advantage relates to the avoidance of cyanosis and its negative effect on organ maturation, the decrease of RV hypertrophy and the beneficial effect on myocardial function and pulmonary angiogenesis and alveologenesis in a situation of decreased lung perfusion as in TOF. At the same time, the use of a palliative shunt with its associated risks is abolished. However, repair yielded the use of a TAP in 60%. A comparable policy was adopted by other groups, resulting in a higher frequency of TAP repair, reaching even 100% in some series [71-73]. The common conclusion from the results of this strategy, aiming early primary correction of TOF in infants before the age of 3 months, is that operative mortality remains low, but at the cost of increased morbidity resulting in prolonged ventilation time and hospital stay. Within the available follow-up of maximum 5 years, the need for secondary reoperation and reintervention is substantial, with 24 reoperations in 22 of the 61 patients in the series of Hirsh et al.[73], and 20% of additional procedures for residual stenosis and severe intolerable PI in others [71].

Albeit the transatrial-transpulmonary approach is favored as the first choice in the surgical therapy of TOF, there is less consensus in the surgical community regarding the strategy on a direct one-stage complete correction versus a two-stage approach including first a palliative shunt, in symptomatic young TOF infants. In contrast with the aforementioned results, the polemic on the choice between immediate repair versus shunt has recently been addressed by Kanter et al. on a series of 37 symptomatic neonates with TOF. The results showed no difference in mortality, but a shorter intensive care and hospital stay in the shunted group compared to the repaired group. Moreover, a TAP repair was necessary in all patients undergoing primary repair [74]. Based on a 40 years' experience in 2175 TOF patients, Fraser and coworkers from Houston derived a surgical management protocol for each

patient individualized to its age and to its RVOT morphology. In a series of 144 patients, this concept offered excellent results with no operative mortality, a late death rate of 2.1% and a reoperation rate of 3% within a follow-up of 5 years. They concluded that there is still a place for judicious shunting in symptomatic young infants, while elective complete repair at the age of 6 to 12 months affords a rational strategy that optimizes the outcome and minimizes the surgical risk [75]

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B. The right ventricle in tetralogy of Fallot : understanding the target

Increased understanding of the mechanisms involved in the progressive RV remodeling and RV dysfunction has directed the focus on serial investigation of the RV during the follow-up of TOF patients after surgical repair. Beside to the easily performed bed-side echocardiography, CMRI has evolved to the golden standard for clear determination of the cardiac status in TOF. Over the past decade, many efforts have been made, both in the field of echocardiography and CMRI, to search for early predictors of RV dysfunction, before reaching an irreversible status. In addition, the impact of the culprit lesions has gradually been refined.

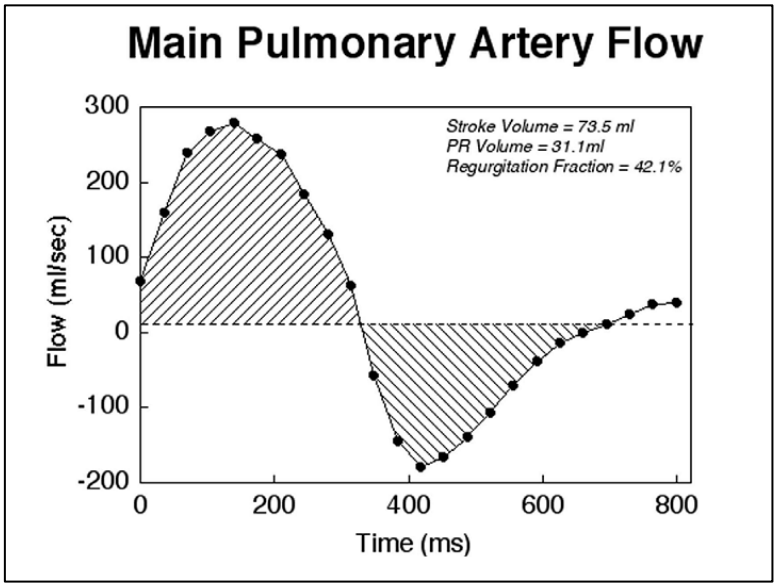
1.1 Follow-up of the pulmonary regurgitation and RV remodeling process

Based on the crucial role of PI on prognosis of repaired TOF, proper quantification of the severity of PI has emerged beyond the commonly used semi-quantitative grading of PI by echocardiography. Assessing PI by CMRI is currently done by calculation of the pulmonary regurgitant fraction (PRF) as the ratio of backward to forward pulmonary artery flow. Because this parameter might underestimate the physiological magnitude of PI, the use of regurgitant volume has been proposed as a more accurate reflection of RV volume-overload [76]. Quantification of PI by echocardiography has been attempted by calculation of the duration of the PI over the total diastolic time by continuous-wave Doppler analysis of the pulmonary artery, but this method appeared to be poorly contributive to the common assessment of PI [77, 78].

Closely related to the degree of PI, progressive increase of diastolic volumes and stroke volumes can be followed by CMRI, until decrease of RVEF occurs by loss of systolic compensation [79]. Presently, identification of significant RV dysfunction has been solely based on the determination of global RV volume at end-diastole and end-systole. Chronic follow-up of TOF after repair is therefore focused on the longitudinal evaluation of the RV dilation process. The impact of regional RV deformation after repair has been forwarded firstly for the adverse effect of a RVOT aneurysm or a large akinetic

ventricular patch, in a qualitative way [11, 80]. In the majority of TOF patients, the global RV volume and systolic RV function are significantly affected by the post-surgical RVOT anatomy [81-83]. Based on the use of late gadolinium enhancement, CMRI allows to quantify the magnitude of RVOT dysfunction, by determining the spatial extent and displacement of dyskinesia. [21, 54]. In contrast, echocardiography is limited in the accurate assessment of global RV volumes. Moreover, specific investigation of the RVOT component by this technique is hazardous by difficult and inconsistent windowing of that area.

Figure. Flow pattern of the main pulmonary artery showing forward flow at systole and backward flow at diastole, allowing measurement of regurgitation volume and duration



1.2 Follow-up of the systolic and diastolic RV function

Determination of proper systolic RV function by echocardiography is mainly based on the measurement of longitudinal contraction changes at the level of the RV basis. The longitudinal function of the RV free wall by TAPSE is mostly decreased in TOF, but this parameter rarely allows to differentiate between a preserved or impaired systolic RV function within this population [84]. Contrary to the prognostic value of TAPSE as marker of RV dysfunction in left-sided heart disease and primary pulmonary hypertension, its validity in the serial follow-up of TOF is less clear [85]. Using color Doppler myocardial imaging techniques, longitudinal strain and strain rate are already decreased in asymptomatic children with TOF, in correlation with the degree of PI [86]. Recently, this specific echocardiographic feature has been demonstrated to be an important determinant of exercise performance in TOF patients, superior to global RVEF by CMRI [87]. However, longitudinal tissue

velocity at the base of the RV free wall incompletely reflects the global systolic RV function, excluding the variable impact of RVOT dysfunction on systolic performance [88].
Validated as a less load-sensitive marker of contractile function, the isovolumic contraction acceleration of the RV myocardium has been correlated with the severity of PI [89]. Albeit proposed as an early and sensitive index of subclinical RV dysfunction, it has not yet been included into the decision-tree to justify pulmonary valve implantation for severe PI.

Diastolic dysfunction has been identified early in the history of TOF. Decreased RV compliance through restrictive RV physiology is confirmed by echocardiography, as the presence of antegrade diastolic flow in the pulmonary artery throughout the respiratory cycle. Investigation of its underlying substrate has revealed that the early presence of restrictive RV physiology occurred more frequently in patients older at the time of operation, often presenting with more RV hypertrophy and cyanosis, and treated with a TAP [90]. Clinically, TOF patients with restrictive RV physiology had a slower postoperative recovery through a temporary state of low cardiac output and increased fluid retention [13]. Accordingly, younger age at repair yielded a decreased incidence of restrictive physiology, regardless of the use of TAP [91]. A restrictive physiology seemed to have a beneficial long-term effect on the RV remodeling, with a less dilated RV and a better exercise tolerance in adulthood [23]. Intrigued by the paradoxical effect, further study observed that presence of restrictive physiology in the postoperative phase was a significant predictor of late restriction [92].
However, it has been noticed that not all patients with a restrictive physiology at late follow-up have a small RV. A restrictive RV physiology has also been described in the severely dilated RV with impaired systolic and diastolic RV function, in correlation with poor exercise performance. CRMI investigation in this more contemporary cohort of TOF patients indicated that poor RV compliance in this condition was a precursor of subclinical RV failure with marked ventricular dilation and systolic dysfunction [93].
The difference between echocardiography and CMRI in assessing the pulmonary artery flow pattern is that the end-diastolic forward flow might be more easily interfered by the respiratory cycle during CMRI. The additional value of CMRI relates to information on the myocardial structure, revealing more fibrosis in the RV and RVOT of the dilated RV [93, 94]. This contradictory finding has later been elaborated by Lee et al., highlighting the difference between ‘primary’ restriction in relation to hypertrophy and fibrosis, and ‘secondary’ restriction in relation to RV dilation [27]. The first group commonly had a smaller RV and preserved exercise capacity, the latter had a larger and dysfunctional RV and decreased exercise tolerance. There is however growing agreement that the notice of late restrictive RV physiology in contemporary operated TOF patients often coincides with an over-distended RV, beyond its compensatory state [25, 95, 96]. Here, a relationship between the early postoperative and the late appearing decreased RV compliance has not yet been confirmed.

Study of diastolic RV function based on transtricuspid flow assessment of early RV filling, indicated decreased E/A-ratio and reduction of E-wave deceleration in correlation with RV enlargement [97]. Others groups have similarly found larger RV volumes in TOF patients and end-diastolic forward flow at CMR, but failed to show any relationship between passive RV compliance and indices of early relaxation through echocardiographic assessment of transtricuspid flow signals and diastolic strain rate measurement [95, 96]. Although the identification of advanced diastolic dysfunction of the RV, concomitant to RV dilation, has been proposed as a criterion for pulmonary valve replacement (PVR) [98], its actual value in the longitudinal follow-up of TOF remains a topic for further research.

C. Pulmonary valve replacement in Tetralogy of Fallot : the definite solution ?

Surgical implantation of a competent pulmonary valve has been proposed as an effective therapy to tackle the adverse effects of chronic PI-related volume-overload on RV performance and clinical status. For many years, TOF patients with severe PI have been referred for PVR based on overt symptoms, attributed to RV dysfunction and PI. Since it has been shown that objective RV function impairment might be out of proportion to the subjective clinical tolerance, the focus has been directed to select proper criteria on indications and timing of PVR in asymptomatic TOF patients during long-term follow-up.

1. Timing of pulmonary valve replacement

The benefit of PVR in TOF has first been demonstrated by Bove et al. showing that RV dysfunction due to PI is reversible, entailing a reduction of RV size and improvement of RVEF, in association with subjective improvement of exercise tolerance [99]. Despite successful PVR, a few studies reported on the absence of RV function recovery in some patients with severely dilated RV and longstanding PI, emphasizing the key role of timing PVR [100, 101]. Subsequently, efforts have been elaborated on the quantification of the extent of RV dilation in relation to massive PI, to identify the best cut-off value of RV size that should lead to the optimal chance of restoring RV volume and normalization of RV function. Therrien et al. noticed that patients with a preoperative end-diastolic volume > 170 ml/m² evolved worse than those with a smaller RV [101]. Buechel et al. found an upper threshold of 200 ml/m² of diastolic volume responsible for incomplete recovery of RV function, while normalization was certified when the lower limit was taken at 150 ml/m² [102]. Most series were however not able to demonstrate significant improvement of RVEF, unless correction of the effective stroke volume for

the amount of regurgitant volume was considered. In contrast to the usual reduction of both end-diastolic and end-systolic RV volumes after PVR, part of the inconsistency concerning RV function improvement has been attributed to lack of integrating the effect of surgical reduction of the akinetic RVOT, and on the preferential use of end-diastolic volumes for cut-off. Based on the modest correlation between EDV and EF, the additional importance of an end-systolic RV volume of 80 ml/m² has been suggested for PVR [103-105].

Another issue regarding timing of PVR is related to the issue of ventricular arrhythmia. A QRS duration > 180 msec has been shown to be a significant risk factor of malignant arrhythmia in TOF patients with severely dilated RV [43]. It has been observed that PVR favorably affects the electrical component by decreasing the QRS duration and improving the depolarization characteristics, concomitant to reduction of RV size [45, 54]. Since the risk of arrhythmia after PVR remains substantial in 25% of the patients with a QRS > 180 msec, PVR is recommended before that specific threshold is achieved [106].

There is common agreement that PVR should be proposed to the TOF patient with evident symptoms due to its cardiac disease, showing significant PI and RV dilation. In the asymptomatic TOF patient with significant PI (PRF > 25%), the co-existence of at least 2 of the following criteria should be considered for PVR [107] :

- RVEDV index > 150 ml/m²
- RVESV index > 80 m:/m²
- RVEF < 45 %
- LVEF < 55 %
- QRS > 160 msec
- Sustained tachyarrhythmia related to RV volume load
- Associated hemodynamically significant abnormalities :
    - Residual RVOT obstruction with RV systolic pressure > 2/3 of systemic pressure
    - Severe branch pulmonary stenosis poorly amenable for prior transcatheter therapy
    - Residual VSD resulting in pulmonary-to-systemic flow ratio > 1.5
    - Significant aortic regurgitation with/without aortic dilatation (> 5 cm)

Exercise performance criteria have not yet been validated to be incorporated into the decision for PVR. According to the prognostic value of the anaerobic threshold based on determination of the V_E/V_{CO2} slope on long-term survival in non-cyanotic congenital heart disease, this variable has been advanced for eventual inclusion by Frigiola et al. who observed complete normalization of the VE/VCO2 ratio when PVR was performed before the age of 17.5 years, in TOF patients that were repaired at the mean age of 3.3 years, with 77% use of a TAP [108].

2. Effects of pulmonary valve replacement

Numerous publications have reported on the positive effect of PVR on the clinical status, commonly in relation to elimination of PI and reverse RV remodeling. Most patients have less cardiac symptoms and show improvement of the NYHA functional class. In addition, improved exercise capacity has been shown quantitatively based on the use of respiratory anaerobic threshold, unrelated to the change of contractile RV performance [109, 110].

Beside shortening of QRS duration, the data on the effect of PVR on arrhythmia propensity are inconsistent. In contrast to Therrien et al, who observed a significant decrease of ventricular tachycardia from 23% to 9% after PVR [53], such favorable results were not confirmed by others [110, 111], suggesting a role for adjuvant intra-operative ablation therapy of the re-entrant isthmus circuits.

The effect of PVR on RV size remodeling has already been described. Based on the use of CMRI, rapid restoration of systolic function is achieved, in contrast to the delayed improvement of diastolic function [112]. According to the LV changes after aortic valve replacement for chronic aortic insufficiency, one may speculate here on the effect of a disproportionate regression of RV mass to RV size. Nonetheless, recovery of diastolic RV function was identical for patients with proven restrictive RV physiology as for patients without end-diastolic forward flow in the main pulmonary artery. Similar changes in systolic and diastolic RV performance have been noticed after PVR by a percutaneous implantable pulmonary valve [113].

3. Techniques and outcome of pulmonary valve replacement

The operative mortality of surgical PVR is commonly low (1%), but there is an ongoing risk of late death after PVR. While Therrien et al. reported respectively 92% and 86% survival at 5 and 10 years [53], the 10-year survival in the series of Discigil et al. and Harrild et al. dropped to respectively 76% and 41% [111, 114].

Commonly, homografts have been used to valvulate the RVOT after TOF repair. These have the advantage of avoiding the need for anticoagulation treatment, but are susceptible for degenerative changes, limiting their life-expectancy. A long-term study of Caldarone et al. showed a freedom from reoperation for homograft failure of 81% at 5 years, 58% at 10 years and 41% at 15 years [115]. In many series, younger age at implantation has been associated with an increased rate of conduit failure.

The use of a bovine valved jugular vein conduit has been suggested as an attractive alternative, providing excellent hemodynamics, but these are equally prone to structural failure [116, 117]. Other alternatives such as xenografts and mechanical prostheses have been used for PVR in adult TOF patients with acceptable results, despite their well-known shortcomings [118-120].

Based on the adverse effect of RVOT dysfunction through a largely akinetic or aneurysmal patch, surgical remodeling of the RVOT at the time of PVR has been proposed in order to enhance the RV mechanics, concomitant to correction of PI [21]. However, in a randomized trial, the additional value of such procedure appeared to be limited in comparison with isolated PVR. The sole predictors of early normalization of RV size and function at 6 months were a preoperative end-systolic RV volume < 90 ml/m² and a QRS duration < 140 msec [103].

During the past decade, the percutaneous implantation of a stent-mounted bovine jugular vein valved conduit has been introduced for valvulation of the RVOT in congenital heart diseases [121]. This technique has been proven to be equally effective as surgical PVR, for relief of RVOT obstruction and/or elimination of PI, in case of failure of a pre-existing RV-PA conduit [122]. At this time, its role in restoring a competent pulmonary valve in TOF is hindered by the huge variability of RVOT malformation after surgery. But technological adaptations of the stent profile based on sophisticated CMRI calculations, have entered the experimental phase [123]

Based on these findings, the decision for PVR in patients with repaired TOF and significant PI has to balance the risk-benefit ratio between protecting the right ventricle at one hand and choosing a pulmonary valve substitute with limited durability on the other hand. Initiating PVR too early will inevitably compromise the patient by an increased risk for reintervention, whereas deciding PVR too late might be detrimental for RV function recovery. Even with the advent of a less invasive PVR by transcatheter techniques, further refining of the criteria that establish the optimal timing of PVR is mandatory.

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Chapter II : Objectives of the thesis

During repair of TOF, the surgeon mainly has to deal with the morphology of the RVOT. Particularly concerning the TOF spectrum with hypoplasia of the RVOT components, the surgical therapy is challenged in coupling the immediate operative result with an optimal long-term outcome in terms of survival, quality of life and risk of late reoperation. Up to now, the surgical management of TOF is weighing the choice of surgical technique to reconstruct the RVOT and the timing of complete primary repair, taking specific interfering anatomical and physiological issues into consideration. Despite more than 60 years experience with the surgical treatment of TOF, there is still debate on that subject within the surgical community.
The physiological adaptation of the RV to volume- and/or pressure-overload in the setting of TOF has extensively been studied. However, the continuous changes in surgical management has put the understanding of the RV mechanical and electrical properties into an indistinct perspective.
The aim of this work is to elucidate some of the controversial aspects regarding the contemporary surgical management of TOF, through investigating the mechanical alterations of the RV in relation to RVOT dysfunction, and through delineating a proper vision on the RV performance in order to improve the clinical outcome of the individual patient with TOF.

To investigate purely the physiological effect of a surgical intervention on cardiac performance, animal models are a well established method of experimental design. Some of the intriguing clinical questions relevant to the actual treatment of TOF, have been characterized in an animal model of growing, immature swine, concordant to the growing child after TOF repair. As part of the contribution of this thesis is related to the study of the RV by mimicking the culprit pathophysiological features of repaired TOF in an animal model, the used experimental methodology is presented in **chapter III**. Assessment of RV function in the acute and chronic setting is based on the analysis of pressure-volume loops by the conductance catheter technique. The relationship with the commonly used clinical tools as echocardiography and magnetic resonance imaging is additionally discussed.

Regarding the late attrition of TOF, most attention has been focused on pulmonary valve insufficiency, usually in the context of a large transannular RVOT patch. The role of the infundibulum has only occasionally been touched. In view of the unknown long-term result of the RVOT-sparing strategy, the interactive effect of both RVOT components, i.e. pulmonary valve and infundibulum, on RV performance deserves renewed interest. In **chapter IV**, the differential contribution of infundibular dysfunction versus pulmonary valve insufficiency is studied for its acute and chronic effects on RV performance, in a juvenile porcine model. Assessment of RV performance was based on the conductance technique and validated by CMRI.

The management of TOF concerning age and strategy of repair has to be taken in consideration with the RVOT morphology and the eventual physiological consequence after surgical repair. Relying on the relationship between the duration of pressure-overload and age at repair, the physiological effect of RV hypertrophy on RV performance merits closer analysis. In **chapter V**, we describe the role of RV hypertrophy on the acute and chronic effects of PI-related volume-overload of the RV, by performing a TAP reconstruction of the RVOT in a growing swine model. RV function was analyzed with the conductance technology, and correlated with basic echocardiographic observations.

In **chapter VI**, the clinical outcome of the contemporary surgical management of TOF in our department has been investigated through a retrospective analysis. The effect on RV remodeling has been evaluated based on the differential contribution of surgically-induced dysfunction of the main components of the RVOT, transmitting the link between the clinical setting and the research theorem of the experimental study reported in chapter IV.

In **chapter VII**, the focus has been moved to the long-term alterations of the RV after TOF repair, by examining the functional impact of the main anatomical components of the RV on global RV function and exercise performance. A suggestion for eventual refining the assessment of the RV during follow-up of TOF patients is made to help the decision-making for pulmonary valve replacement.

In **chapter VIII**, the findings of the experimental and clinical studies are integrated in order to offer a new perspective on the surgical management of TOF. Deeper insights into the mechanisms of RV adaptation in relation to dysfunction of the main components of its outflow tract, as commonly is observed after repair of TOF, are discussed for their clinical relevance.

Chapter III : Experimental methodology and design

Extrapolation of the acquired knowledge on LV function to the RV has been limited by the various anatomical and physiological differences between both ventricles. The main differences are:

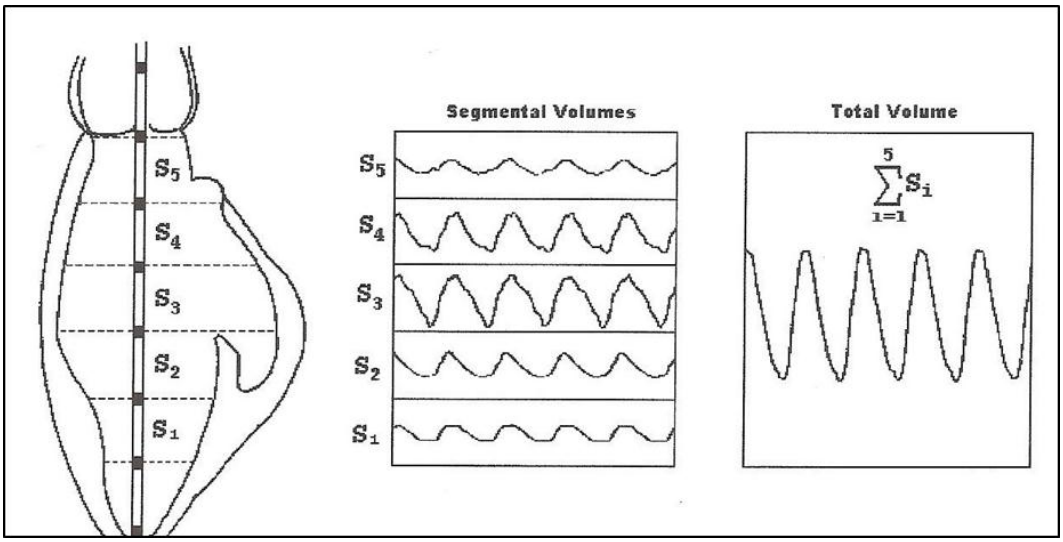
1) *Morphological geometry :* the RV has a complex, banana-like shape composed of three components, i.e. the inlet, the trabecular apical part and the outlet or infundibulum.
2) *Myocardial architecture:* the RV myocardium consists of two muscle layers with a longitudinal organization for the inner layer and a circumferential arrangement for the outer. This myofiber structure explains the particular contraction pattern, producing an effect of peristalsis, with greater longitudinal than radial shortening.
3) *Location into the circulatory system:* the RV is coupled with the pulmonary vascular bed characterized by it low impedance and high capacitance. Consequently, the right-sided pressures are normally much lower than in the LV. As the RV systolic pressure exceeds rapidly the low pulmonary artery diastolic pressure, the isovolumic contraction time of the RV is shortened. This entails that the end-systolic flow may continue in presence of a negative ventriculo-arterial pressure gradient, referred to as the 'hangout interval' [1].
4) *Heart-lung interference:* the RV functions mainly as a volume-pump, making the hemodynamic response susceptible to pre-load alterations during the respiratory cycle in relation to changes of intrathoracic pressure. Even modest changes in pulmonary airway resistance can affect the RV performance significantly.
5) *Effect of the LV by the ventricular interdependency:* the influence of the LV function on RV function has been documented by Damiano et al., showing that 30% of the contractile energy of the RV is generated by the LV [2]. This physiological effect is mediated by the parallel interaction through the interventricular septum, and is dependent on the preserved RV geometry. Once the RV size is distorted by right-sided pressure- or volume-overload, the contribution of the LV is attenuated by adverse interaction.

1.1. Introduction to the conductance technology

Assessment of ventricular function is ideally based on the simultaneous and instantaneous measurement of volume and pressure, affording at the same time the global ventricular as well as the intrinsic myocardial function properties. The conductance technology has been developed for cardiac function determination by Baan et al. [3]. The principle is based on the measurement of the electrical

conductance of blood in the ventricular cavity, differentiating the effect of blood as a good electrical conductor and myocardial tissue as a poor conductor. The catheter consists of several electrodes, producing an electrical field, and at each electrode, the measured volume of blood is considered as a cylinder of which the boundaries are defined by the inner cardiac wall. The total volume of blood within the ventricular cavity corresponds to the sum of the included segmental blood cylinders, distributed at equal distances over the catheter. Through an alternating current between both outermost electrodes, a homogenous intracavitary field of conductance is generated. Conductance is defined as the applied current divided by the potential difference between adjacent electrodes.

Figure. Intraventricular conductance catheter with electrodes measuring the intracavitary blood volume as a cylinder at each segment S. The total blood volume is the sum of all included segments.



Adjustment for interfering effects includes calibration for (1) the dimensionless slope factor α (correction coefficient between the conductance-derived volume and the true volume obtained by a validated alternative technique as thermodilution or ultrasonic flow probe) and for (2) parallel conductance (subtraction of the conductivity measured in structures extrinsic to the intraventricular blood pool as myocardial tissue, the atria and LV, based on the dilution through injecting a hypertonic solution). Accounting for the individual resistivity of blood to the electrical current, the time-varying measured volume by the conductance catheter in the ventricle is calculated by the formula:

$$Vt = 1/\alpha(L2/\rho)(Vc - Vp)$$

with Vt = total intraventricular segmental volume, α = dimensionless slope factor, L = interelectrode distance, ρ = blood resistivity, Vc = measured segmental conductance volume and Vp = parallel conductance.

This technique has been widely validated in the homogeneous LV, and has been introduced to study the RV function in a later phase [4]. Due to the complex geometry of the RV and the dense trabeculation structure, the exact quantification of the absolute RV volume by this method has long been questioned. Further study has demonstrated that, through proper calibration, the conductance-derived RV volumes are equally reliable as with CMRI [5]. The normal pressure-volume relationship of the RV appears as a triangular- or trapezoidal-shaped loop [6]. Subsequent to its relation with the low-resistant pulmonary system, the isovolumic periods, relaxation rather than contraction, are usually ill-defined. In contrast to the LV, the RV ejection continues well beyond the end-systolic point, during pressure decline, reducing or eliminating hereby the isovolumic relaxation phase [7].

The major advantage of this method is related to the quantification of the real-time intrinsic systolic and diastolic myocardial properties of the studied ventricle, during modulation of loading conditions through occlusion of inferior vena cava inflow. In consequence, the obtained load-independent indices represent the systolic function - or contractility - and the diastolic function of the global ventricle, including the contribution of regional dysfunction.

The systolic function of the RV has been validated by the end-systolic pressure-volume relationship (ESPVR), using preferably the maximal elastance – defined as the instantaneous maximal pressure-to-volume ratio – instead of the end-systolic elastance as a load-independent marker of contractility [8, 9]. Together with the slope of the linear ESPVR, the intercept with the volume axis is an important covariate of contractility.

Karunanithi et al. later reported that the slope of the linear regression of stroke work in function to changing end-diastolic volume – the preload recruitable stroke work (PRSW) – is a more reproducible linear marker of contractile function, and more reliable than the ESPVR because of its afterload insensitivity [10]. In addition, the PRSW-slope does not depend on the definition of the exact end-systolic point at the right ventricular pressure-volume loop.

Diastolic function is analyzed by the end-diastolic pressure-volume relationship (EDPVR), showing an exponential curve as volume increase is paired with a steeper pressure raise, for higher end-diastolic volumes. After linearization of the exponential fit $P = Ce^{\beta V}$ into $dP/dV = \beta P$, the slope of the EDPVR is defined as the chamber stiffness coefficient β, addressing the passive compliance of the ventricle [11, 12]. In contrast to the LV, determination of early relaxation in the RV is hampered by the poorly delineated period of isovolumic relaxation. Furthermore, the peak rate of pressure decay (min dP/dT) and the time constant of pressure decay τ (tau) as measure of early diastolic function are strongly load-dependent and therefore less reliable [13].

This method has been validated for evaluation of RV function in several pathological conditions in both the clinical and experimental setting, such as RV pressure-overload [14, 15], RV volume overload [16, 17] and ischemic RV disease [18]. A similar methodological approach was used in our animal experiments to study the RV in relation to the surgically induced anomalies at the RVOT level, according to the

pathophysiological features of repaired TOF. The conductance catheter was uniformly positioned in the RV, from the outflow tract to the apex. Correction for cardiac output was obtained by use of the ultrasonic flow probe, or by the thermo-dilution method with pulmonary artery catheter, or by instantaneous arterial pulse wave contour analysis. RV performance was based on the analysis of the pressure-volume loops, including the measurement of pre-load independent systolic and diastolic indices during transient inferior vena cava occlusion. Assessment of RV function was done at two time episodes : an acute phase to evaluate the postoperative effect, and a chronic phase, set at 3 months of survival, to define the midterm effect, according to the rapid organ maturation and growth of the used animals [19, 20].

Figure. Intra-operative picture of the experiment with the conductance catheter in the RV from the PA (black arrow), and the flow probe around the pulmonary artery (white arrow), after surgical performance of a transannular patch of the RVOT through thoracotomy

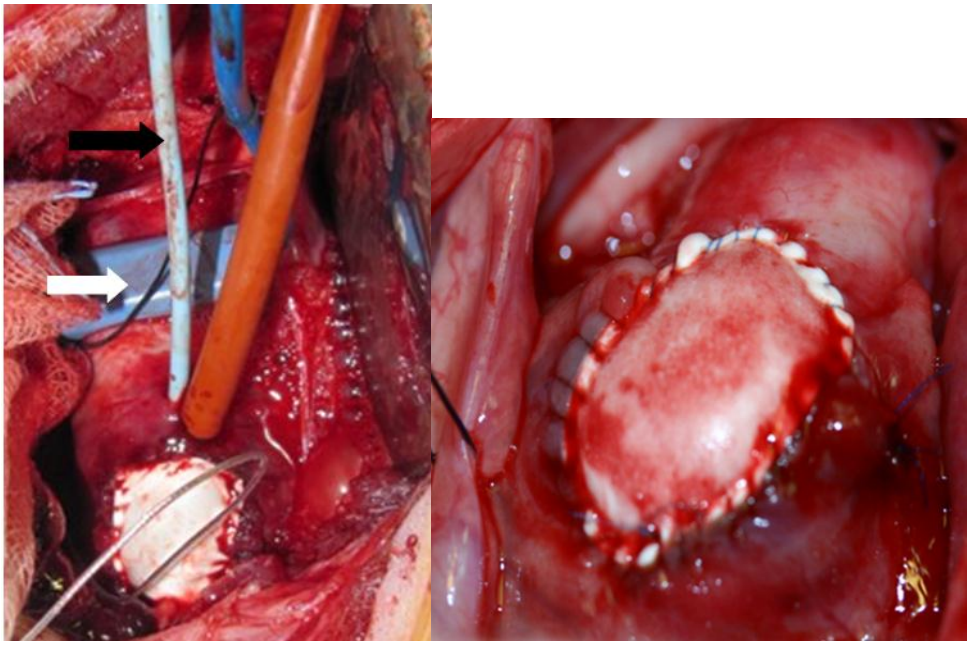
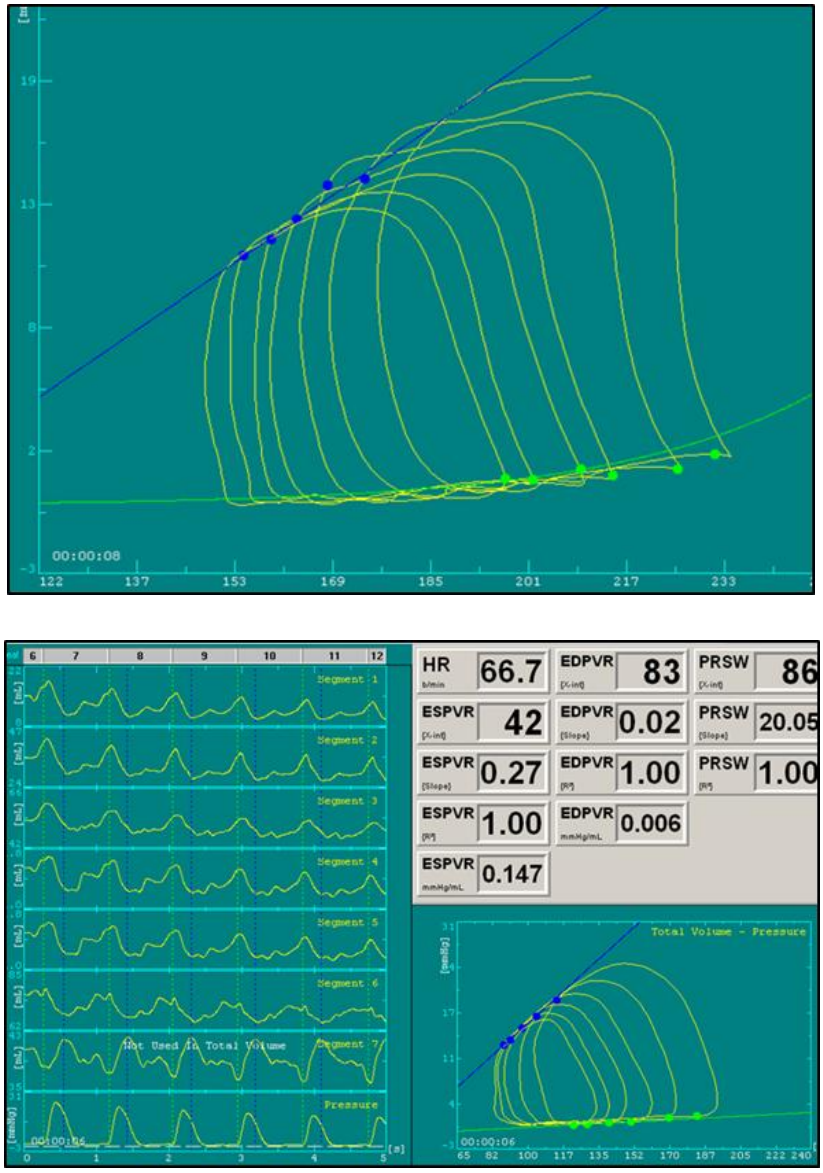


Figure. Regression of PV-loops during occlusion of inferior vena cava (Blue line = ESPVR – Green line = EDPVR)



1.2. Comparison with clinical tools for assessment of RV performance

The conductance technology is the standard technique for correct assessment of the pure systolic and diastolic ventricular performance, by giving simultaneous information on the pressure-volume relationship, independent of the loading conditions. The measurements are reflecting the functional state of the global RV, regardless of the complex RV geometry, and it incorporates thereby the functional effect of eventual regional deformations. But since it is an invasive catheter-based technique, it is mostly applied for academic purposes.

In clinical practice, echocardiography and CMRI are the cornerstone for the evaluation of RV structure and function. Echocardiography offers the advantage of greater availability and versatility, whereas CMRI is increasingly advanced as the golden standard for accurate assessment of RV volumes and its derived variables. Moreover, both imaging tools give relevant information on structures adjacent to the RV as the pulmonary arteries, and abnormalities of inflow and/or outflow valve function. However, a major shortcoming of both techniques to study ventricular function is the lack of instantaneous pressure information.

Echocardiography for assessment of the RV function

Two-dimensional echocardiography is currently used as the first line imaging modality for assessment of RV function. RV size is often qualitatively compared to the LV size, in both the short- and long-axis views, to define eventual RV dilation. Quantitative evaluation of RV function can be obtained by endocardial border contouring during the cardiac cycle, and subtracting the end-systolic volume from the end-diastolic volume to determine RV ejection fraction, following the Simpsons' rule. However, the volume-based estimation of RV by 2-D echocardiography is globally less precise. The development of 3-D imaging technology has certainly opened perspective for more accurate RV volume assessment, including the exact attrition of the outlet part [21].
The change of fractional area between the systolic and diastolic phase in the 4-chamber view by echocardiography probably approximates the RVEF best [22]. Other usable indices of systolic RV function are the tricuspid annular plane systolic excursion as a marker of longitudinal RV function [23, 24], and the RV myocardial performance index as the ratio of isovolumic time interval to ejection time [25]. Tissue Doppler imaging allows quantification of the RV systolic and diastolic function, based on the measurement of myocardial velocities. Pulsed Doppler and color coded techniques are applicable for estimation of RV function, usually taken from the RV free wall at the level of the tricuspid annulus [26]. Myocardial isovolumic acceleration time (IVA) has been advanced as an index of contractility, less dependent on loading conditions. This parameter is calculated as the ratio of the maximal isovolumic myocardial velocity to the time to peak velocity. Vogel et al. demonstrated the reliability of this index in comparison with the conductance-derived ventricular elastance [27]. However, beside to the time-consuming off-line analysis, the reproducibility of the results is often a concern due to the large inter-observer variability and proper accuracy of ultrasound positioning. Recently, strain and strain rate are increasingly studied in the RV. In contrast to radial strain, longitudinal strain is determined more reliably, correlating best with changes in stroke volume. Longitudinal strain rate is however representing better local contractile function [28]. However, most of these parameters are reflecting the regional contractile function at the location of echocardiographic tissue sampling, and do not always correspond with the true systolic function, especially considering the complex geometry of the RV.

Diastolic function by echocardiography is based on the tricuspid inflow signals, including E-wave and A-wave velocity and E-wave deceleration time. Simultaneously, this has to be correlated with distension and flow wave reversal in the inferior caval vein and hepatic veins. The use of Tei-index as time constant of pressure decay, and minimal dP/dT are controversial in assessing specifically the RV diastolic function [13]. Increased deceleration of early rapid filling has been proposed as index of decreased compliance, but this may be difficult to measure correctly in the RV with poorly defined early rapid filling and atrial systolic phases as well as in presence of fast heart rates like in children. Hence, correlation between the RV filling profiles and diastolic ventricular characteristics are not clearly established. Compared to the method of conductance, only the demonstration of antegrade end-diastolic flow into the pulmonary artery by both echocardiography and CMRI has been validated as a marker of restrictive RV physiology.

In summary, the echocardiographic quantification of the RV function is hampered by the complex geometry of the RV, with inconsistent windowing of specifically the RVOT in older children and adults. Moreover, identifying accurate and reliable parameters for the functional study of the RV still remains a challenge [29]

RV function by Cardiac Magnetic Resonance Imaging

Considering the complex anatomy of the RV and its functional inter-relationship with the LV, CMRI has become nowadays the standard method to reflect RV function. Optimal imaging results are obtained using fast breath-hold real-time acquisition, affording accurate volume determination by endocardial contour delineation [30]. RV volume calculation equally includes the contribution of regional deformities of RV morphology. In the clinical setting, the systolic RV function is still frequently based on determination of RVEF, knowing that this parameter is highly load-dependent and therefore elusive with regard to its relevance for contractile performance. Hence, by accurate determination of pulmonary or tricuspid regurgitation volume, CMRI allows correction of stroke volume and so RVEF, in presence of important volume-overload.

CMRI is also used for measurement of flow velocities by phase contrast mapping, giving essential information on valve function and cardiac output. According to echocardiography, diastolic function can be evaluated by analysis of transvalvular time-varying flow wave patterns. Recent pre-clinical investigation has opened perspective on the assessment of diastolic and systolic ventricular function, through constructing single-beat pressure-volume curves, by integration of instantaneous intraventricular pressure recording, CMRI-derived volume and real-time blood flow measurement.[31]

A main advantage of CMRI through the method of contrast enhancement, is related to the possibility to study the intrinsic myocardial tissue characteristics, by differentiating between muscular tissue with preserved contractility and fibrosis or scar tissue.

Despite the excellent image quality and reproducibility, CMRI includes the inconvenience of time-consuming data acquisition and analysis, and limited environmental accessibility. Moreover, its application needs consideration in small children, requiring anesthesia because of inadequate breathing cooperation, and in patients with intra-corporeal devices such as pacemakers [32].

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Chapter IV

Acute and chronic effects of dysfunction of right ventricular outflow tract components on right ventricular performance in a porcine model : implications for primary repair of tetralogy of Fallot (J Am Coll Cardiol 2012; 60:64-71)

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Abstract

Objective: This study investigates the contribution of infundibular versus pulmonary valve (PV) dysfunction on right ventricular (RV) function in a porcine model.

Background : Clinical outcome after repair of tetralogy of Fallot is determined by the adaptation of the RV to the physiological sequelae of the right ventricular outflow tract reconstruction. Recent surgical techniques are pursuing a PV versus infundibulum-sparing approach.

Methods and Results : In a porcine model, 3 types of RVOT dysfunction were created and compared to sham-operated controls : infundibular dysfunction (INF), PV insufficiency (PI) and combined infundibular-PV dysfunction (TAP). Both acute and chronic effects on RV function were studied with conductance technology.
In animals with PI, pulmonary regurgitant fraction progressed more in presence of concomitant infundibular dysfunction (+54 % in TAP versus +14 % in PI ; p = 0.03). Subsequently, RV end-systolic and end-diastolic volume increased more in both groups, resulting in decreased ejection fraction after 3 months. Preload-independent systolic indices showed acute impairment of RV contractility in all treatment groups but most in animals with infundibular scarring (INF and TAP). Further chronic deterioration was observed in animals of group TAP. RV compliance improved proportionally most in groups PI and TAP, in relation to the extent of RV dilation.

Conclusion : Surgical RVOT dysfunction, whether it includes the infundibulum and/or the PV, has an immediate effect on RV performance. While impaired RV contractility is due to intrinsic myocardial damage by infundibular distortion, it is chronically furthered by PI-related RV dilation. These findings support the adoption of a RVOT-sparing strategy to treat tetralogy of Fallot.

Introduction

Surgical RVOT reconstruction during repair of TOF often results in PV insufficiency and in the long-term, progressive RV dysfunction due to chronic volume-overload [1]. Most clinical studies focusing on the sequelae of TOF repair have been incriminating the use of a TAP as major determinant of late RV dilation [2]. Its detrimental role is even more pronounced by the additional development of extended RVOT akinesia or aneurysm, often occurring in patients operated in former eras, when a large ventriculotomy was used for closure of the ventricular septal defect and relief of the infundibular obstruction [3]. To overcome these late effects, recent surgical management of TOF is pursuing a RVOT-sparing approach, including maximal preservation of PV function and/or minimal infundibular scarring [4-6]. However, the long-term results of either strategy preference are unknown.
The chronic effects of PI-related volume-overload on RV function have already been studied in animal models [7-9]. Kuehne et al. demonstrated impaired biventricular systolic function and decreased RV contractility in growing swine, in relation to PI through transcatheter stent implantation across the pulmonary valve [8]. Hence, in contrast with the usual clinical setting, the impact of the commonly associated surgically-induced infundibular dysfunction on RV function has rarely been studied.
We developed an experimental model in growing pigs, to investigate the differential contribution of dysfunction of each RVOT component on RV function, in order to mimic properly the acute and chronic physiological effects of surgical RVOT reconstruction. Hemodynamic assessment was performed using the conductance catheter technology for quantification of RV volumes and indices of systolic and diastolic RV performance.

Material and Methods

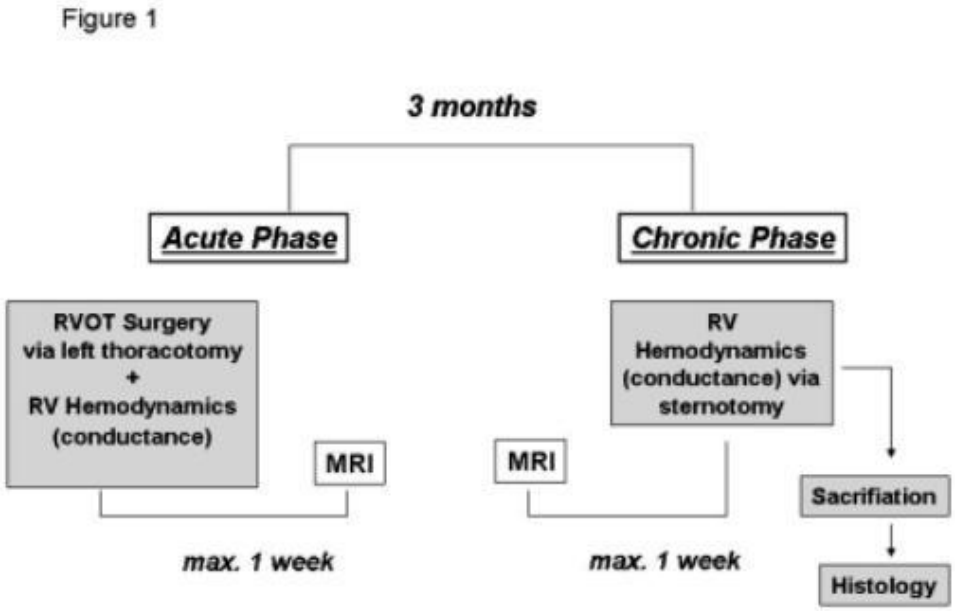
The study protocol was performed according to the standards of "The guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (publication 85-23, revised 1996) and approved by the local ethical committee of the University Hospital of Ghent (ECD 08/30)

Study protocol

The experimental model included 16 land-race pigs (Rattlerow Seghers, Lebbeke, Belgium). Three groups with each 4 pigs underwent a surgical RVOT dysfunction. In group PI, an isolated pulmonary valve insufficiency was created by excision of one anterior PV leaflet through a transverse pulmonary arteriotomy. In group INF, infundibular dysfunction was obtained by infundibulotomy and closure with a polytetrafluorethylene (PTFE) patch of 30 by 20 mm (GORE-TEX, Gore & ass, Delaware, USA). The third group TAP combined a PV insufficiency by excision of 1 leaflet and infundibular dysfunction by using a transannular plasty with a 40 mm long PTFE patch. In both groups INF and

TAP, the length of infundibular incision was made equal at 25-30 mm. Four animals served as control group and were sham-operated (SHAM). None of the animals comprised any RVOT obstruction. The conduct of the study protocol is depicted in figure 1.

Figure 1. Time course of the experimental protocol



In the acute phase, surgical RVOT dysfunction was induced via left thoracotomy. The hemodynamic effect was assessed by conductance technique, followed by MRI study of the RV within a week. The chronic phase was determined at 3 months, and included first MRI and then hemodynamic evaluation through sternotomy. Subsequently the animal was euthanized for heart harvesting and histological RV analysis.

Operative procedure

Following pre-medication with intramuscular tiletamine and zolazepam, in a combined solution with xylazine 2% (0.2 ml/kg), anesthesia was induced with intravenous propofol 3 mg/kg, sufentanil 0.005 mg/kg and rocuronium bromide 1 mg/kg. After endotracheal intubation, the animals were mechanically ventilated with FiO_2 40% and tidal volume of 0.1-0.15 l/kg. Anesthesia was maintained with continuous sevoflurane ET 2.5% administered through the AnaConda® system (Sedana Medical, Sundbyberg, Sweden), and eventually additional boluses of sufentanil 0.005 mg/kg. Basic monitoring included electrocardiogram, body temperature and ventilatory CO_2 emission through capnography. Oxygenation was controlled by arterial blood gas sampling. Hemodynamic monitoring included continuous arterial pressure through a 8.5-F catheter into the left carotid artery, and central venous pressure through a 7.5-F catheter into the right atrium via external jugular vein puncture.

Through a left thoracotomy, the different types of RVOT dysfunction as previously described, were performed with the use of right heart bypass and partial clamping of the RVOT. In sham-operated animals, only right heart bypass was installed during an equal time period. At the end of the procedure, the animals were extubated and treated with intramuscular buprenorphine 0.03 ml/kg and intercostal bloc with levobupivacaine 5 mg/ml.
A follow-up interval of 3 months was used to determine the chronic phase, according to the rapid organ maturation and growth of these animals [8,10]. At that time, hemodynamic effects were assessed in a way similar to the acute phase, but cardiac exposure was obtained through median sternotomy.

Hemodynamical study with conductance catheter

In the acute, post-surgical phase, a 7-F dual field pressure-volume catheter (CD Leycom, Zoetermeer, Netherlands) was introduced into the RV from the RVOT directed towards the apex. Correct catheter positioning was confirmed by radioscopy. The conductance catheter was connected to a Sigma M module and digitized at 250 Hz for on-line computer analysis with the Conduct NT CFL-512 software (CD Leycom). A 16 or 20-mm perivascular flow probe (Transonic Systems, Ithaca, NY, USA) was placed around the pulmonary trunk for cardiac output measurement. Pre-load modulation was achieved by radioscopically guided placement of a pulmonary artery balloon catheter (PTS-303 NUMED , Heart Medical, Best, Netherlands) into the inferior vena cava, via puncture of the right jugular vein. In the chronic phase, conduction of the conductance catheter measurements was similar, but inferior vena cava occlusion was done surgically by a tourniquet.
Acquisition of pressure and volume data was obtained at end-expiration. Volume calibration was performed by integration of slope factor α for cardiac output, and by parallel conductance during injection of 0.02 ml/kg hypertonic saline. Baseline measurements included end-systolic and end-diastolic RV volumes with subsequent calculation of stroke volume (SV), ejection fraction (EF) and cardiac output (CO). In order to correct for growth variability between the animals over the groups, volume-dependent variables were indexed to body surface area (BSA), following Kelley's equation for swine [11] : BSA (cm^2) = 734 x weight $(kg)^{0.656}$
Based on the instantaneous pressure-volume relationship changes during transient occlusions of the inferior vena cava, RV contractile function was quantified by the slope (M_w) of the PRSW and the slope (E_{max}) of the ESPVR. In addition, the volume intercept of the ESPVR was determined at the pressure level of 25 mmHg. Only recordings with less than 10 % change of heart rate and a correlation coefficient of the linear regression line $r^2 > 0,90$ were considered eligible.
Evaluation of diastolic RV function was based solely on passive ventricular compliance, as active isovolumic relaxation (τ) was not reliable in the groups with PI. RV compliance was expressed as chamber stiffness constant β, derived from the exponential fit of the EDPVR.

MRI study

MRI was performed with a 1.5 Tesla imager system (Siemens Avanto, Erlangen, Germany) with maximum gradient strength of 200 mT/m and slew rate of 45 mT/m/ms. Under anesthesia with intravenous propofol 1%, 3 mg/kg and manual-hold ventilation via endotracheal intubation, the animals were positioned on the MRI table in right lateral position. The MRI protocol consisted of ECG-triggered TrueFISP images in 3 orthogonal planes, ECG-gated trueFISP cine imaging of long and short cardiac axes, and phase-contrast acquisition through plane flow mapping perpendicular to the blood flow in the aorta and in the pulmonary artery. If TrueFISP images were artefacted by vivid aortic flow, a spoiled gradient echo sequence was used instead. All images were taken during end-expiratory ventilation stop. LV and RV volume measurements on the short axis stack, as well as post-processing of phase-contrast images were performed by a single investigator, with the use of the Argus software package (Siemens). MRI allowed validation of the RV volumes obtained by the conductance technique as well as determination of the PI grade. Pulmonary regurgitation fraction was calculated as the ratio of pulmonary retrograde to antegrade flow volume, expressed as percentage.

Euthanasia and Histopathology

At the end of the study, the animals were euthanized with an intravenous solution of embutramide 200 mg, mebenzoniumiodide 200 mg, tetracaine hydrochloride 5 mg, dimethylformamide 1 mg (T61) at a dose of 0.3 ml/kg. The heart was harvested and tissue samples of the basal and free wall of RV and LV, and a papillary muscle of tricuspid valve were excised for histological analysis. Hematoxylin-eosine and Masson's trichrome staining were used for delineation of interstitial collagen extent.

Statistical Analysis

All data are expressed as mean ± SD. Data distribution was tested for normality by Shapiro-Wilks testing. Normal distributed data are compared between groups by one-way ANOVA, with Tukey or Dunnett-T3 correction for multiple comparisons, depending on homogeneity of variance. The change of each variable per individual animal between acute and chronic phase is expressed as the proportional change between both variables in percentage. This calculated variable was also analyzed by one-way ANOVA with post-hoc Tukey correction. For not normally distributed data, group comparisons were made with Kruskal-Wallis analysis and subsequent Mann-Whitney testing, with adjustment for multiple comparisons, for defining inter-group differences. Evolution of RV function variables for individual animals between the first and second phase was evaluated with paired t-test or Wilcoxon-signed rank test. Bland-Altman processing was used for validation of agreement of volume

measurement between MRI and conductance technique [12]. Statistical analysis was done with SPSS 19.0 software (SPSS Inc., Chicago, Illinois). A $p < 0.05$ was considered significant.

Results

At the start, all pigs had a comparable weight and BSA, according to their age of 8-9 weeks. After 3 months, some growth variability resulted in a relative BSA increase of respectively 95 ± 28 % in group SHAM, 105 ± 12 % in group INF, 117 ± 6 % in group PI and 121 ± 8 % in group TAP ($p = 0.15$). Although these differences were not significant, the use of indexed RV volumes seemed more appropriate to differentiate growth versus dilation. In addition, the extent of surgical infundibulotomy was identical in group INF and TAP, shown by an indexed incision length of respectively 47.2 ± 1.6 mm/m² and 46.6 ± 2.3 mm/m² ($p = 0.65$).

Determination of RV volumes and global RV function variables (table 1)

Measurement of RV volumes showed a close reliability between the conductance method and MRI, with a correlation coefficient of respectively 0.93 ($p < 0.0001$) and 0.85 ($p < 0.0001$) for EDV and ESV. Bland-Altman analysis confirmed agreement between both methods, with a bias of 8 ml and limits of agreement (-13;31 ml) for ESV, and a bias of 7 ml and agreement limits (-17;36) for EDV. Post-surgical PI was only present in group PI and TAP (PRF 29 ± 4 % and 22 ± 9 %, $p = 0.14$). After 3 months, PRF changed respectively to 34 ± 5 % and 36 ± 13 %, resulting in significantly greater PRF progression in presence of concomitant infundibular dysfunction (14 ± 2 % versus 54 ± 24 %, $p = 0.03$). Isolated infundibuloplasty did not induce PV dysfunction.

The PI in groups PI and TAP induced a direct significant increase of mainly EDVi, and furthered RV dilation in the chronic phase, as evident from the significant increase of ESVi and EDVi, in comparison to the SHAM group and to their own postoperative volumes. Late ESVi was even significantly larger in group TAP than in group PI ($p = 0.004$). RV volumes of the INF group evolved similarly to the control group. Although stroke volume was increased in group TAP versus SHAM ($p = 0.03$), the relative SVi increase was not statistically different between groups. Conversely, RVEF decreased significantly with respectively 6 ± 3 % and 9 ± 6 % compared to their baseline value in group PI and TAP, while EF remained unchanged in both other groups. RV cardiac output decreased in both groups with PI, achieving nearly significant difference in group TAP (16 ± 6 %, $p = 0.05$), mainly due to physiological adoption of lower heart rates.

RV pressures decreased significantly between the acute and chronic phase in all groups, and was more pronounced for diastolic pressures (ESP: $p = 0.015$; EDP: $p < 0.0001$).

Table 1. Global RV volumes and hemodynamics

	SHAM	INF	PI	TAP	ANOVA p-value
Weight (kg)					
acute	23 ± 5	24 ± 4	22 ± 5	24 ± 1	0,12
chronic	63 ± 15	73 ± 17	72 ± 14	81 ± 7	0,86
% Δ	175 ± 56	199 ± 27	229 ± 30	235 ± 19	0,37
BSA (m²)					
acute	0,57 ± 0,08	0,59 ± 0,06	0,54 ± 0,08	0,59 ± 0,01	0,85
chronic	1,10 ± 0,18	1,21 ± 0,18	1,19 ± 0,19	1,30 ± 0,07	0,35
% Δ	95 ± 28	105 ± 12	117 ± 6	121 ± 8	0,11
Heart rate (bpm)					
acute	102 ± 19	89 ± 4	94 ±4	97± 9	0,34
chronic	89 ± 5	88 ± 8	67 ± 7 [c]	65 ± 2 [c]	< 0,0001
% Δ	- 14 ± 18	- 6 ± 4	- 19 ± 6	- 26 ± 10	0,13
PRF (%)					
acute	0	0	29 ± 4	22 ± 9	0,14
chronic	0	0	34 ± 5	36 ± 13	0,74
% Δ	0	0	14 ± 2	54 ± 24 [b]	0,03
ESP (mmHg)					
acute	26 ± 10	23 ± 4	24 ± 6	26 ± 5	0,94
chronic	20 ± 5	21 ± 9	17 ± 4	20 ± 6	0,86
% Δ	- 18 ± 26	- 4 ± 62	- 29 ± 21	- 21 ± 24	0,82
EDP (mmHg)					
acute	16 ± 9	12 ± 3	13 ± 2	13 ± 0,8	0,78
chronic	7 ± 6	6 ± 5	4 ± 1	7 ± 5	0,53
% Δ	- 53 ± 25	- 50 ± 39	- 70 ± 9	- 47 ± 30	0,45
ESVi (ml/m²)					
acute	55 ± 13	54 ± 7	66 ± 9	71 ± 6	0,06
chronic	57 ± 9	59 ± 7	87 ± 9 [c]	109 ± 6 [b]	< 0,0001
% Δ	7 ± 19	9 ± 5	31 ± 16 [c]	46 ± 10 [c]	< 0,0001
EDVi (ml/m²)					
acute	99 ± 17	104 ± 5	126 ± 13 [c]	129 ± 10 [c]	0,01
chronic	113 ± 12	111 ± 4	158 ± 20 [c]	181 ± 15 [b]	< 0,0001
% Δ	14 ± 21	11 ± 6	28 ± 14 [c]	41 ± 15 [c]	0,01
SVi (ml/m²)					
acute	44 ± 6	51 ± 3	54 ± 7	57 ± 4 [a]	0,03
chronic	56 ± 11	53 ± 4	66 ± 13	78 ± 10 [a]	0,03
% Δ	12 ± 24	4 ± 10	16 ± 14	25 ± 23	0,12
SWi (ml.mmHg/m²)					
acute	700 ± 283	741 ± 64	822 ± 213	948 ± 154	0,34
chronic	794 ± 285	842 ± 181	949 ± 298	1198 ± 431	0,31
% Δ	11 ± 29	14 ± 37	29 ± 41	26 ± 40	0,91
EF (%)					
acute	45 ± 5	51 ± 4	46 ± 3	44 ± 2	0,12
chronic	50 ± 7	49 ± 4	42 ± 4	38 ± 3 [a]	0,007
% Δ	9 ± 7	- 3 ± 5	- 6 ± 3 [c]	- 9 ± 6 [c]	0,003
Effective CI (L/min/m²)					
acute	4,5 ± 0,6	4,6 ± 0,3	5,3 ± 0,8	5,2 ± 0,3	0,11
chronic	4,9 ± 0,7	4,5 ± 0,3	4,4 ± 0,5	4,2 ± 0,5	0,52
% Δ	4 ± 8	- 2 ± 4	- 11 ± 6	- 16 ± 6 [a]	0,05

Post-hoc Tukey correction for multiple comparisons
[a] p<0.05 between TAP and SHAM
[b] p<0.05 between TAP and PI
[c] p<0.05 between TAP - PI and SHAM

Legend :
BSA = body surface area ; PRF = pulmonary regurgitation fraction ; ESP = end-systolic RV pressure ; EDP = end-diastolic RV pressure ; ESVi = indexed end-systolic RV volume ; EDVi = indexed end-diastolic RV volume ; SVi = indexed stroke volume ; SWi = indexed stroke work ; EF = RV ejection fraction ; CI = cardiac index

Assessment of load-independent systolic and diastolic RV performance (table 2)

Surgical RVOT dysfunction induced acute impairment of RV contractile function as shown by the decreased E_{max} - and M_w - slope, with regards to the SHAM group. In comparison with isolated PI, infundibular dysfunction in groups INF and TAP resulted in a lower E_{max} and M_w at the early stage, but the difference with group PI was not significant. RV contractility decreased further after 3 months, and was proportionally most significant in group TAP as E_{max} and M_w decreased respectively 64 ± 22 % and 37 ± 4 % , in relation to its previous value. According to the decrease of ESPVR slopes, V_{25}-intercepts shifted to the right, consistent with progressive deterioration of contractility in all treatment groups. In the chronic phase, group PI showed less impaired contractility in comparison with group TAP, as evidenced by a significantly steeper E_{max} (0.47 ± 0.12 versus 0.20 ± 0.05, p = 0.02) and M_w – slope (13.3 ± 1.6 versus 8.9 ± 1.4, p = 0.01). The lower M_w – and E_{max} –slope of groups INF and TAP illustrated the significant impact of surgical infundibular injury on RV contractile function in comparison with the reference group SHAM. Despite absence of secondary volume remodeling process, both contractility indices were still lower after 3 months, compared to group PI.
RV compliance improved in all groups after 3 months (table 2). However, RV chamber stiffness decreased relatively more in groups PI and TAP (84 ± 6 % and 91 ± 5 % respectively) compared to group SHAM, in relation to the extent of secondary RV dilation and increasing PRF in both groups.

Table 2. Pre-load independent indices of systolic and diastolic RV function

	SHAM	**INF**	**PI**	**TAP**	**ANOVA**
Emax (mmHg.ml^{-1})					**p value**
acute	1,63 ± 0,22 [a]	0,71 ± 0,38	0,96 ± 0,23	0,66 ± 0,24	0,001
chronic	1,34 ± 0,18 [a]	0,33 ± 0,05	0,47 ± 0,12	0,20 ± 0,05 [c]	< 0,001
% Δ	- 17 ± 11	- 43 ± 29	- 46 ± 17	- 64 ± 22 [b]	0,05
V_{25} (ml)					
acute	16 ± 3	21 ± 4	18 ± 4	30 ± 7 [b]	0,005
chronic	36 ± 12	48 ± 10	43 ± 10	79 ± 17 [b]	0,002
% Δ	120 ± 50	132 ± 29	145 ± 26	164 ± 26	0,36
Mw (mW.s.ml^{-1})					
acute	23,4 ± 2,9 [a]	13,8 ± 1,9	17,8 ± 2,4	14,2 ± 3,0	0,001
chronic	22,5 ± 3,1 [a]	10,6 ± 1,3	13,3 ± 1,6	8,9 ± 1,4 [c]	< 0,001
% Δ	- 2 ± 12	- 23 ± 3	- 24 ± 14	- 37 ± 4 [b]	0,03
β (ml^{-1})					
acute	0,37 ± 0,21	0,42 ± 0,15	0,33 ± 0,03	0,62 ± 0,27	0,18
chronic	0,12 ± 0,02	0,10 ± 0,08	0,05 ± 0,02	0,05 ± 0,02	0,09
% Δ	- 61 ± 12	- 77 ± 13	- 84 ± 6 [d]	- 91 ± 5 [d]	0,006

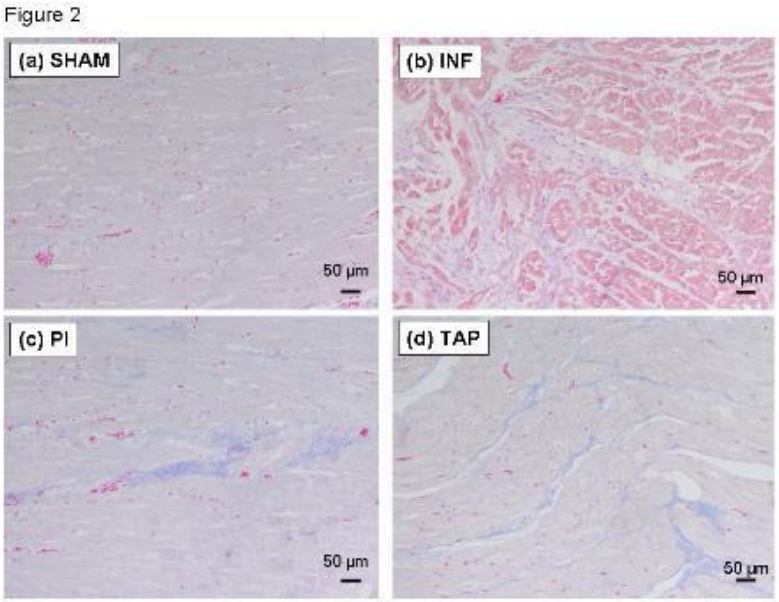
Post-hoc correction for multiple comparisons
[a] p<0.05 between SHAM and other groups
[b] p<0.05 between TAP and SHAM
[c] p<0.05 between TAP and PI
[d] p<0.05 between TAP-PI and SHAM

Legend :
E_{max} = maximal elastance ; V_{25} = volume intercept of end-systolic pressure-volume relationship at RV pressure of 25 mmHg ; M_w = slope of preload recruitable stroke work relationship ; β = chamber stiffness constant of end-diastolic pressure-volume relationship

Histopathological results

Macroscopic evaluation after 3 months showed a patent RVOT in all animals, with only scar fibrosis around the patched area in groups INF and TAP. In animals with PI, the most anterior PV leaflet was lacking, and was associated with effective PV annulus disruption in the group TAP. Both posterior leaflets were intact. The PV was anatomically and functionally normal in groups SHAM and INF. Microscopy revealed normal myocyte architecture and absence of interstitial fibrosis in group SHAM. However, increased interstitial collagen proliferation and enhanced myocardial bundle disarray were seen in groups INF and TAP, while these changes were only mildly present in group PI. Tissue samples are illustrated in figure 2.

Figure 2. RV tissue histology



Masson's trichrome stained tissue samples of the right ventricular wall showing the extent of myocardial bundle disarray and interstitial fibrosis in the different groups (magnification x 10) : (a) SHAM, (b) INF, (c) PI, (d) TAP

Discussion

In this study on a growing swine model, RV function was assessed in relation to dysfunction of the different anatomical components of the RVOT. Effective surgically induced PI resulted in secondary RV remodeling, affecting mainly the end-diastolic volume in the acute phase. After 3 months, RV dilation was associated with regression of RVEF by the higher ratio of end-systolic to end-diastolic volume increase. The presence of infundibular dysfunction concomitant to PI, promoted the RV dilation process, merely by increasing the PRF. As isolated infundibular dysfunction had no effect on RV geometry, and as RV remodeling was less pronounced in isolated chronic PI, the role of the preserved structural integrity of the infundibulum in sustaining the PI-related volume overload is suggestive. These data are in accordance with Kuehne et al. who found identical changes in RV size along with impaired pump function [8]. In his model, isolated PI was created by pulmonary valve stenting, which resulted in 33 % PRF. This acute PI was higher compared to the one in our series as well as to the usual early clinical observation. Moreover, PRF increased to 49 % after 3 months, corresponding to 50 % PRF progression in their experiment. This was only seen in our study by adding infundibular dysfunction, which renders the comparison with the physiological sequelae of TOF after TAP repair more consistent.

Based on the analysis of indices as PRSW and ESPVR, any RVOT dysfunction resulted in instant impairment of RV contractile performance. Contractile function seemed particularly more attenuated through infundibular dysfunction, certainly due to intrinsic myocardial damage of that part of the RV. Even though further deterioration was enhanced by PI-related volume load, in correlation with the extent of the secondary RV remodeling process, contractility still appeared to be superior by preserving infundibular function. At last, systolic RV performance was worst after TAP reconstruction. This observation is currently in line with the clinical findings of Frigiola et al, who demonstrated reduced RV contractility in relation to the degree of PR and subsequent RV dilation, occurring mainly after TAP repair of tetralogy patients [13]. Here, they used isovolumic myocardial acceleration, a tissue Doppler based parameter, which was previously validated as a load-insensitive marker of contractility, comparable to the conductance-derived slopes E_{max} and M_w [14].

In contrast with other animal models addressing the RV properties after chronic PI [8,9], we noticed already a decreased RV contractile state after isolated PI at baseline conditions. Although contractility indices were lower at rest, contractile reserve only appeared to be impaired during dobutamine stress testing in these studies. This distinct finding might be attributed to differences in experiment conduction. First, the placement of the conductance catheter - which was aligned from the RV inlet to the apex in their studies - might have underestimated the real contribution of the infundibulum when challenged by the volume overload. Previous reports examined the effect of catheter position in the inhomogeneous RV and demonstrated that a larger part of the ventricular cavity is assessed by placing the catheter in the RV apex from the RVOT [15-16]. From this point of view, the measurements in our

study are probably reflecting more adequately the functional changes at the level of interest, namely the RVOT. Secondly, the technical way of achieving PV dysfunction in our experiment might have been more detrimental for RV function. However, the use of mechanical right heart support could not be incriminated for its influence on RV contractility, since the indices were significantly altered in comparison with the sham-operated animals, which were also subjected to the myocardial effects of partial circulatory assistance.

Regarding diastolic performance, RV compliance increased proportionally the most in correlation with increasing PI-related volume overload and RV dilation. This is in accordance to Pasipoularides et al.[17], who demonstrated improved passive myocardial compliance in a canine model of volume overload, due to significant tricuspid regurgitation. Also the experiment of Kuehne et al. confirmed the transition of a non-compliant restrictive RV to a compliant non-restrictive RV as a natural adaptation mechanism to volume overload [8]. Nonetheless, the impact of cardiopulmonary bypass on diastolic RV properties must be assumed in our model, as the stiffness coefficient decreased also in the control group, equally to the decreased end-diastolic RV pressures at 3 months.

The functional RV properties of the different groups are globally corresponding to the histological alterations after 3 months. The impaired contractility observed in the 3 groups of RVOT dysfunction correlated with the increased presence of myocardial bundle disarray and interstitial fibrosis, suggesting already some secondary remodeling at cellular level. Similarly, modest increase in collagen concentration, with preserved diastolic compliance, was noticed in a pig model of volume overload through an A-V fistula [18]. Our results further support the clinical findings of Babu-Narayan et al. that the extent of late cellular RV remodeling, indicated by fibrosis, is adversely related to the systolic RV function after TOF repair. Moreover, this process seemed to be advanced by the magnitude of the surgical RVOT insult as by progressive ventricular dilatation [19].

Clinical implications

In clinical practice, the kind of applied RVOT reconstruction is mainly determined by the RVOT morphological features including the degree of RV hypertrophy. Hence, a TAP with its subsequent deleterious long-term expectations, is still clinically used in many patients [20].

The current study confirms that a transannular patch affects the RV performance the most by combining the adverse early effect on myocardial contractility by infundibular dysfunction and, on top of this, the gradual RV volume remodeling due to chronic and progressive PI. Our data support therefore the adoption of a RVOT-sparing approach, although it remains open whether this should be achieved by pursuing a PV- versus infundibulum-sparing technique. Protagonists of the PV-sparing repair admit that the major advantage is merely related to preservation of the pulmonary annulus, as more than one third of the patients experience PI at midterm follow-up. Besides, in more than 25 % of

the cases, an infundibular patch is associated for adequate relief of the infundibular hypertrophic stenosis [4].

The role of the infundibulum after TOF repair has currently been studied on patient cohorts operated in former eras, with the use of extensive RV incisions closed with liberal patches [21]. Two MRI studies on the functional analysis of the RV components in TOF patients demonstrated that the decreased ejection performance of the RV outlet portion was related to the extent of post-surgical scarring. RV dysfunction was only evident once the adaptive response of the larger trabecular part of the RV to PI became insufficient [22-23]. Our experimental findings indirectly underscore the importance to maintain the infundibular function because : (1) large infundibular scarring negatively affects the RV contractile function, and (2) the preserved infundibular integrity resists to progression of associated PR and delays the secondary dilation process. Meanwhile, early clinical data on the use of an infundibulum-sparing RVOT repair are promising in those infants with severe pulmonary valve hypoplasia, in whom relief of the PV annulus is deemed necessary at the cost of a minimal infundibular incision [5-6].

Study limitations

Even though the induced RVOT dysfunctions are clinically relevant and the hemodynamic measurements are homogeneous, extrapolation of these animal data to the clinical setting of TOF patients needs careful consideration. Confounding effects on RV function by factors as cyanosis and RV hypertrophy were not taken into account. The investigation of infundibular dysfunction was solely based on the complete surgical incision of the infundibulum. Consequently, the effect of a more conservative infundibular surgery, appropriate to actual techniques, was not fully ascertained. In addition, this model did not include the contribution of some residual low-gradient RVOT stenosis, with its beneficial effect on the PI-related RV dysfunction [24].

The chronic phase in this porcine model has been determined by a 3-months time interval, corresponding approximately to midterm follow-up in humans. However, it remains debatable whether longer follow-up in these animals is desired for clearer discrimination of the effects of RVOT component dysfunction.

Due to several peri-procedural incidents, the sample size of each group is limited, which might undermine the power of the intentional study sample. Nonetheless, we feel confident with the conclusions on our data as the differences between the hemodynamic effects among the groups were indicative within an acceptable range of variance.

Conclusion

In a juvenile chronic pig model, RV function was assessed in relation to dysfunction of the main components of the RVOT, based on analysis of pressure-volume loops. Although RV performance

was significantly affected by any surgical-induced RVOT dysfunction, involving the infundibulum and/or the pulmonary valve, the most detrimental effect was observed by combined dysfunction of both components through TAP repair. RV contractility was immediately impaired by infundibular distortion, due to intrinsic myocardial damage, while it was chronically furthered by PI-related RV dilation. Preservation of the structural and functional integrity of the infundibulum appears to delay the extent of the volume load-dependent secondary RV remodeling by impeding PR progression. Based on these findings, the adoption of a RVOT-sparing strategy for repair of TOF seems justified.

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Chapter V

The role of myocardial hypertrophy on acute and chronic right ventricular performance in relation to chronic volume-overload in a porcine model : relevance for the surgical management of tetralogy of Fallot (J Thorac Cardiovasc Surg, in press)

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Abstract

Aims: The age for repair of tetralogy of Fallot has progressively declined to the postnatal period, often at the cost of an increased rate of transannular RVOT repair. The long-term effect of premature exposure to chronic PI-related volume-overload on a less hypertrophied RV has to be awaited. This study aims to investigate the role of hypertrophy on RV performance after chronic volume-overload in a growing animal model.

Methods and Results: RV hypertrophy, induced by PA-banding, was studied in animals with (RVH+PI) and without subsequent PR (RVH). The effect of volume-overload was compared to animals without RV hypertrophy (PI) and to controls (SHAM). Both acute and chronic effects on RV function were studied with conductance technology, and validated by echocardiography.
After chronic volume-overload, end-systolic and end-diastolic volumes were smaller in group RVH+PI compared to group PI, including a lower PRF (25±5% versus 35±5%, p=0.002). RV hypertrophy preserved better systolic function, confirmed by increased PRSW-slope (14.7±1.8 versus 9.3±1.3 Mw.s/ml, p=0.025) and higher RVEF (51±3 versus 45±4%, p=0.05). Myocardial stiffness was impaired in group RVH+PI versus PI (β: 0.19±0.03 versus 0.12±0.02 ml^{-1}, p=0.001), presenting a restrictive physiology only in the condition associating hypertrophy and volume-overload at the acute and chronic phase.

Conclusion: This study demonstrated that RV hypertrophy attenuates the RV remodeling process related to chronic volume-overload by pulmonary insufficiency. It enables better preservation of contractility, but at the cost of sustained diastolic impairment. These findings might help to conduct timing and strategy for repair of tetralogy of Fallot when RVOT morphology indicates a definite need for transannular reconstruction.

Introduction

Despite more than 50 years experience with the surgical management of tetralogy of Fallot (TOF), the optimal timing as well as the surgical approach are still a matter of debate. Over the past decade primary repair has been advanced to the first months of life and even the neonatal age, without compromising the surgical outcome in terms of mortality [1-3]. Besides avoiding the use of a palliative shunt and its potential complications, protagonists claimed the physiological benefit of early elimination of hypoxemia with its adverse effects on organ maturation, improved pulmonary angiogenesis and alveologenesis, and reduced RV hypertrophy (RVH). A major concern is the high frequency of transannular patch (TAP) reconstruction of the RVOT, subjecting these young children prematurely to the physiological consequences of pulmonary insufficiency (PI). Hence, the long-term effects on RV function need to be seen.

Pressure-overload usually results in compensatory myocardial hypertrophy. Previous work has shown improved contractile performance of the RV by gradual and chronic afterload increase, but at the cost of impaired diastolic function [4,5]. This ambivalent phenomenon has to be considered for its effect on RV performance when challenged by acute and chronic PI-related volume-overload as a common sequel of TOF repair. Since there is a direct relationship between age of the patient and extent of RV hypertrophy, insight in this process might help the decision-making concerning the timing of surgical therapy with regards to the RVOT morphology.

The purpose of this study was to mimic the physiological condition of TOF repair with postoperative PI in a growing swine model, with first inducing RV pressure-overload to have RVH, followed by chronic volume-overload by surgical TAP reconstruction of the RVOT . The impact of RVH on RV remodeling and function was hemodynamically assessed with the conductance technique for quantification of RV volumes and pre-load independent indices of systolic and diastolic function.

Material and Methods

The study protocol was performed according to the standards of "The guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (publication 85-23, revised 1996) and approved by the ethical committee for animal research of the Ghent University Hospital (ECD 11/27)

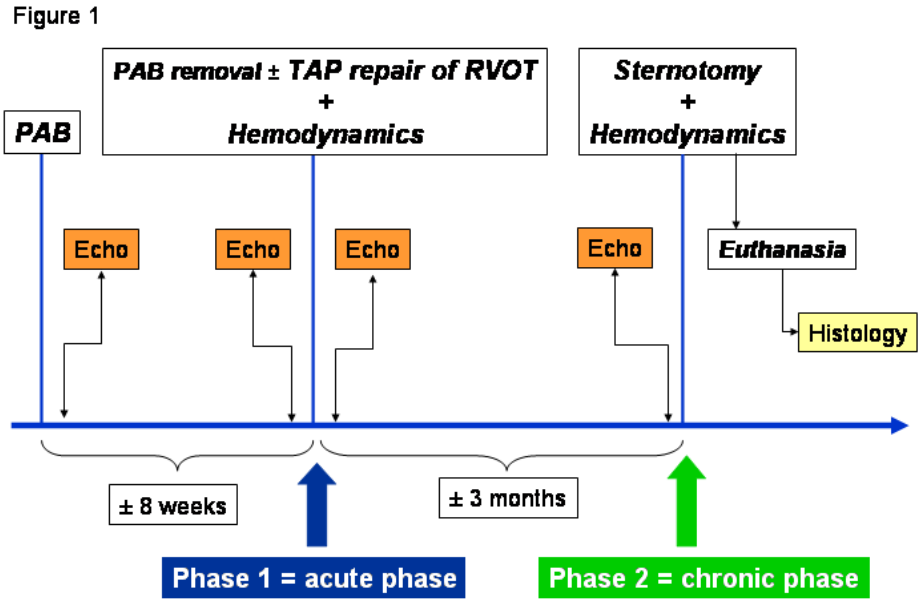
Study protocol

Twenty-eight landrace pigs entered the study protocol. These were divided into 4 groups: (1) group RVH+PI (n=7) with pressure-overload induced RVH and subsequent PI-related volume-overload by TAP, (2) group RVH (n=7) underwent isolated pressure-overload by PAB, with secondary relief of

pulmonary artery obstruction, (3) group PI (n=7) was subjected only to volume-overload by TAP-mediated PI, and (4) group SHAM (n=7) as control group, without exposure to any pathophysiological loading condition.

Fourteen animals were submitted to gradual pressure-overload by fixed PAB at the age of 6-7 weeks (mean weight 17.9±1.8 kg). Follow-up by transthoracic echocardiography (TTE) was done for serial evaluation of RV function and PAB gradient. After ca. 8 weeks, they were equally and at random, divided into group RVH+PI and group RVH. One pig out of each group died during the study period and was excluded. All animals underwent evaluation of RV function with the conductance catheter, respectively at the acute, postoperative phase and at the late, chronic phase, respecting a time interval of ca. 3 months (mean 13.1±1.4 weeks) according to previous work [6,7]. Animals of group PI and SHAM were age-matched to the former groups at the time of the first hemodynamic assessment. TTE was performed within the same week of hemodynamic investigation for assessment of the procedural effect on the RV. The conduct of the study protocol is shown in figure 1.

Figure 1. Time course and conduct of the study



Operative procedures

The anesthesia protocol and basic hemodynamic monitoring of all surgical procedures was identical to the one used in previous study [6].

PAB was performed through a small left thoracotomy, by encircling the pulmonary artery with a 5 mm large band of silicone elastomere (Perthese, Bornel, France), to obtain a gradient of at least 10 mmHg,

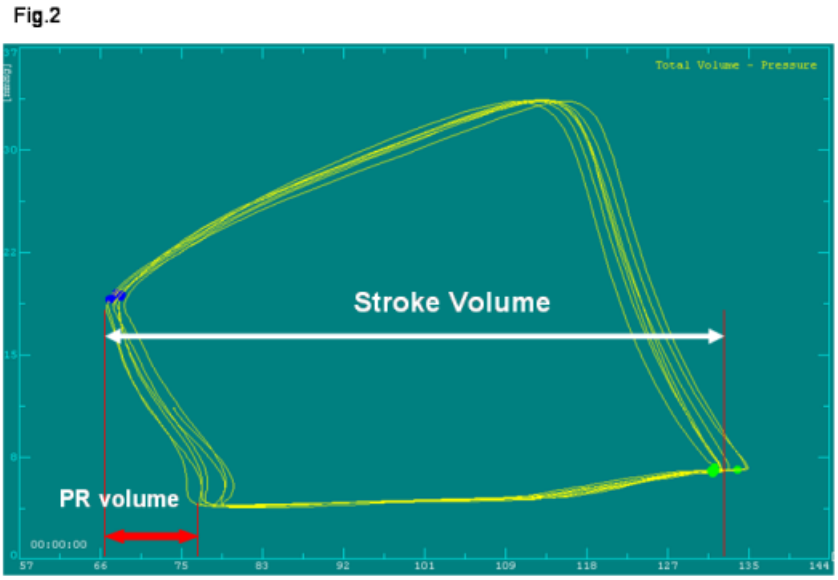
while systemic blood pressure remained stable. Further growth of the animal should result in progressive afterload increase. The hemodynamical effect of PAB was assessed by direct measurement of RV pressure in relation to aortic pressure and distal PA pressure.
The second surgical step, done at phase 1, comprised a redo-thoracotomy for removal of the banding and resection of the surrounding fibrous tissue, which mostly relieved the obstruction effectively. In 3 pigs, an additional patch plasty of the pulmonary trunk was needed to obtain a residual target gradient of less than 10 mmHg. To create significant PI, a longitudinal incision across the ventriculo-arterial junction was made under partial clamping of the RVOT, the anterior PV leaflet was excised and a transannular polytetrafluorethylene patch (GORE-TEX, Gore&ass, Delaware, USA) of 30 by 20 mm was inserted. In group RVH, no further surgery than band removal was done. In group PI, PI was obtained as first procedure likewise to group RVH+PI. SHAM-operated animals underwent a left thoracotomy for hemodynamical testing, without RV surgery.
At the end of each procedure, the animals were extubated and treated with intramuscular buprenorphine 0.03 ml/kg and intercostal bloc with levobupivacaine 5 mg/kg.
Finally, at the last phase, cardiac exposure was obtained for solely hemodynamic testing through median sternotomy, with release of pericardial adhesions.

Hemodynamical study with conductance catheter

In the acute phase, a 7-F dual field pressure-volume catheter (CD Leycom, Zoetermeer, Netherlands) was introduced into the RV from the RVOT directed towards the apex. Correct catheter positioning was confirmed by fluoroscopy. The catheter was connected to a Sigma M module and digitized at 250 Hz for on-line computer analysis with the Conduct NT CFL-512 software (CD Leycom). Pre-load modulation at phase 1 was achieved by radioscopically guided placement of a pulmonary artery balloon catheter (PTS-303 NUMED , Heart Medical, Best, Netherlands) into the inferior vena cava, via puncture of the right jugular vein. During phase 2, work-out of conductance measurements was similar, but inferior vena cava occlusion was done surgically by a tourniquet.
Acquisition of pressure and volume data was obtained at end-expiration. Volume calibration was performed by integration of slope factor α for cardiac output, verified by effective cardiac output measurement based on pulse-pressure waveform analysis of the aortic pressure signal (Vigileo, Edwards Lifesciences, Irvine, USA). Calibration for parallel conductance was acquired during injection of 0.02 ml/kg hypertonic saline. Baseline measurements included end-systolic and end-diastolic RV volumes with subsequent calculation of stroke volume and ejection fraction. In order to correct for growth variability between animals over the groups, volume-dependent variables were indexed to body surface area (BSA), following the equation for swine [8]: $BSA(cm^2)=734 \times weight\ (kg)^{0.656}$

As described previously [9], PRF was quantified as the ratio of the amount volume increase during pressure decline to stroke volume during a cardiac cycle at baseline (figure 2).

Figure 2. Baseline P-V loop of RV in animal of group RVH+PI, showing the method of PRF calculation



Based on the instantaneous pressure-volume relationship changes during transient occlusions of the inferior vena cava, RV contractility was quantified by the slope (M_w) of PRSW and the slope (E_{max}) of ESPVR. The volume intercept of ESPVR was determined at pressure level 25 mmHg and indexed to BSA (V_{25}-I). Only recordings with less than 10% change of heart rate and a correlation coefficient of the linear regression >0,90 were considered eligible. Evaluation of diastolic RV function was based solely on passive ventricular compliance, as active isovolumetric relaxation was not reliable in the groups with PI. RV compliance was expressed as chamber stiffness constant β, derived from the EDPVR relationship.

Echocardiography

Transthoracic echocardiography was performed with the portable Vivid-I ultrasound system (General Electrics Healthcare, Buckinghamshire, UK) and a 3MHz transducer, by one single observer (KVDK) blinded for the invasive hemodynamical results. The primary goal of TTE was directed to validate the functional effect of each surgical procedure. The timing of each examination is indicated in figure1. Echocardiography included two-dimensional anatomical imaging of the RV for size estimation at the basal, mid-ventricular and RVOT level. RVH was quantified by measurement of RV free wall(FWT) and interventricular septal thickness(IVST), adjusted for BSA. The tricuspid and pulmonary valve were evaluated by color-flow mapping and the degree of regurgitation was semi-quantitatively nominated as grade 1 to 4, according to standard criteria. Tricuspid inflow signal

analysis included determination of E-wave and A-wave velocity, E-to-A-wave velocity ratio, E-wave deceleration time and E-wave deceleration slope. Pulse-wave Doppler analysis of the main pulmonary flow was performed to (1) estimate the flow velocity over the RVOT to follow the gradient during PAB, and to exclude residual obstruction after de-banding, and to (2) calculate the duration of diastolic regurgitant jet in presence of PI. The presence of an A-wave at late diastole throughout the respiratory cycle was categorized as a restrictive pattern. Estimation of systolic RV function was based on tricuspid annulus plane systolic excursion (TAPSE) and fractional shortening (FS) measurement at mid-ventricular level on M-mode.

Euthanasia and Histopathology

At the end of the study, the animals were euthanized with an intravenous solution of embutramide 200mg, mebenzoniumiodide 200mg, tetracaine hydrochloride 5mg, dimethylformamide 1mg (T61) at a dose of 0.3 ml/kg. The heart was harvested and discarded from atria and great vessels; the ventricles were divided into the free wall of RV and LV and the interventricular septum. Each component was weighed separately to calculate the RV-to-heart ratio and RV mass/end-diastolic volume ratio, adjusted for BSA. Tissue samples of RV and LV were taken for histological analysis, with hematoxylin-eosine and Masson's trichrome staining for delineation of interstitial collagen extent. Myocyte cell area was counted for defining hypertrophy, including presence of cell apoptosis.

Statistical analysis

All data are expressed as mean ± SD. Data distribution was tested for normality by Shapiro-Wilks testing. Normal distributed data are compared between groups by one-way ANOVA, with Tukey or Dunnett-T3 correction for multiple comparisons, depending on homogeneity of variance. For non-parametric data, group comparisons were made with Kruskal-Wallis analysis and subsequent Mann-Whitney testing with Bonferroni correction. Evolution of RV function variables for individual animals between phase 1 and 2 was evaluated with paired t-test or Wilcoxon-signed rank test.
Correlation between conductance-related and echocardiographic observations was based on Pearson or Spearman rank test as appropriate. Statistical analysis was done with SPSS 19.0 software(SPSS Inc., Chicago, Illinois).A $p<0.05$ was considered significant.

Results

Validation of RV hypertrophy by PAB-induced pressure overload

PAB caused a comparable postoperative gradient and RV/LV-pressure ratio in groups RVH+PI and RVH, respectively 12.5±2.0 versus 14.1±6.1 mmHg (p=0.57) and 51±6 versus 52±5 % (p=0.64). This corresponded to an echocardiographic gradient of 26.5±10.1 and 26.3±15.4 mmHg (p=0.97). After 8 weeks, the echo-gradient increased to respectively 63.9±14.4 and 52.8±18.8 mmHg (p=0.28). RVH was confirmed by a significant and comparable increase of RV wall thickness in both groups (FWT: 5.9±1.2 to 9.3±1.7 mm, p=0.005 and IVST: 6.8±1.4 to 10.2±2.5 mm, p=0.007). Additionally, both PAB groups had increased FWT in comparison with the non-PAB groups, shown by TTE at phase 1 (RVH+PI: 11.0±1.4 mm and RVH: 10.8±1.8 mm versus SHAM: 7.6±0.6 mm and PI: 7.0±0.4 mm, p=0.002).

RV volume- and pressure-related results (table 1)

PRF was greater in group PI than in group RVH+PI at the acute stage. Because the PRF had increased proportionally after 3 months in both groups, the late difference in PRF remained significant.
This had an immediate effect on the RV volumes, resulting in smaller indexed RV end-systolic and end-diastolic volume in group RVH+PI compared with group PI in the acute phase. This was equally reflected in the chronic phase, with a less dilated RV in group RVH+PI than in group PI. Both volume-overloaded groups had a larger RV than the RVH and SHAM groups.
RV pump function was globally preserved in all groups at phase 1, reaching only a small significant difference of RVEF between group PI and RVH (62 ± 3 % versus 69 ± 5%, p=0.009). After 3 months, RVEF had worsened significantly in group PI than in the other groups, whereas group RVH+PI also had a lower RVEF than group SHAM (mean difference 8 ± 2%, p=0.008). Global RV function was comparable between groups RVH and SHAM regarding RVEF at both phases, but included a smaller ESVI and EDVI for group RVH in the acute phase.
The groups with previous pressure-overload had higher RV end-systolic and end-diastolic pressure at phase 1. At the chronic stage, only the RVEDP remained significantly elevated in these groups, while RVESP had equalized. Pulmonary valve dysfunction resulted in lower PAEDP in group PI, while PAEDP remained comparable between group RVH+PI and the groups RVH and SHAM in the acute phase, despite significant PI. This phenomenon was identical after 3 months, indicating then also a significantly lower PAEDP in group RVH+PI. Finally, the stroke work was significantly increased in all study groups in comparison with group SHAM at phase 1. Three months later, no difference was found in SW between group SHAM and RVH, probably owing to regression of RVESP. Chronic volume-overload led to increased SW in group RVH+PI and even more in group PI, in comparison with group SHAM.

Table 1. RV volume and pressure data

	RVH+PI	RVH	PI	SHAM	ANOVA p-value
Weight (kg)					
acute	39 ± 8	44 ± 4	32 ± 4	31 ± 12[*]	0.02
chronic	102 ± 16	109 ± 4	89 ± 11	77 ± 19[*]	0,002
BSA (m²)					
acute	0,81 ± 0,11	0,88 ± 0,05	0,71 ± 0,06	0,69 ± 0,17[*]	0,02
chronic	1,52 ± 0,16	1,60 ± 0,03	1,39 ± 0,12	1,26 ± 0,21[*]	0,002
Heart rate (bpm)					
acute	96 ± 7	93 ± 6	96 ± 4	90 ± 4	0,11
chronic	78 ± 3	81 ± 3	78 ± 9	79 ± 5	0.77
PRF (%)					
acute	19 ± 4	-	26 ± 4	-	0,02
chronic	25 ± 5	-	35 ± 5	-	0,002
% Δ	29 ± 4	-	39 ± 21	-	0,3
RVESP (mmHg)					
acute	33 ± 4	32 ± 3	26 ± 4	24 ± 5	0,001[#]
chronic	25 ± 3	27 ± 5	19 ± 5	21 ± 6	0,05
RVEDP (mmHg)					
acute	14 ± 0,9	15 ± 3	10 ± 2	8 ± 3	<0.001[#]
chronic	11 ± 1	12 ± 1	6 ± 2	7 ± 3	<0.001[#]
PAESP (mmHg)					
acute	29 ± 4	28 ± 4	27 ± 4	24 ± 5	0.16
chronic	25 ± 3	25 ± 5	19 ± 5	22 ± 7	0.17
PAEDP (mmHg)					
acute	18 ± 3	18 ± 2	10 ± 2[**]	17 ± 5	<0.001
chronic	11 ± 2	15 ± 2	8 ± 1[**]	14 ± 3	<0.001
ESVI (ml/m²)					
acute	40 ± 3	27 ± 5	46 ± 4	34 ± 4	<0.001[†]
chronic	62 ± 5	51 ± 4	76 ± 7	43 ± 6	<0,001[‡]
EDVI (ml/m²)					
acute	111 ± 4	88 ± 8	123 ± 9	101 ± 5	<0.001[†]
chronic	127 ± 3	111 ± 5	140 ± 7	103 ± 9	<0.001[‡]
SVI (ml/m²)					
acute	71 ± 4	61 ± 7	76 ± 8[§]	66 ± 5	0.001
chronic	65 ± 4	60 ± 3	64 ± 7	61 ± 6	0.38
SWI (ml.mmHg/m²)					
acute	1244 ± 207	1032 ± 370	1004 ± 192	777 ± 148[¶]	0.02
chronic	1090 ± 87	752 ± 110	1222 ± 214	813 ± 147	<0.001[‖]
EF (%)					
acute	64 ± 3	69 ± 5	62 ± 3[***]	66 ± 3	0.01
chronic	51 ± 3	54 ± 3	45 ± 4	59 ± 4	<0.001[‖]
Effective CI (L/min/m²)					
acute	6.1 ± 0.4	5.0 ± 0.7	6.2 ± 0.6	5.1 ± 0,6	<0.001[‖]
chronic	3.8 ± 0.2	4.0 ± 0.3	3.7 ± 0.4	3.5 ± 0.8	0.45

Post-hoc Tukey correction for multiple comparisons :

*p<0.05 between RVH and SHAM
† p<0.05 for all comparisons excepted SHAM – RVH+PI
‡ p<0.05 for all comparisons excepted SHAM - RVH
§ p<0.05 between PI and SHAM - RVH
‖ p<0.05 for all comparisons excepted SHAM-RVH and PI-RVH+PI

¶ p<0.05 between SHAM and RVH+PI
# p<0.05 for all comparisons excepted RVH-RVH+PI and PI-SHAM
** p<0.05 between PI and other groups
***p<0.05 between PI and RVH

Legend :

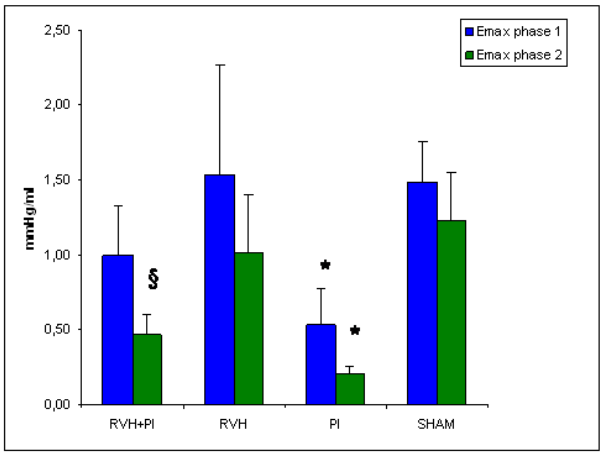
BSA=body surface area; PRF=pulmonary regurgitation fraction; RVESP=end-systolic RVpressure; RVEDP=end-diastolic RVpressure; PAESP=pulmonary artery end-systolic pressure; PAEDP=pulmonary artery end-diastolic pressure; ESVI=indexed end-systolic RVvolume; EDVI=indexed end-diastolic RVvolume; SVI=indexed stroke volume; SWI=indexed stroke work; EF=RV ejection fraction; CI=cardiac index

Assessment of load-independent systolic and diastolic RV performance

Contractile function was mainly impaired in group PI, illustrated by lower E_{max} and M_w-slope at phase 1, although the difference with group RVH+PI was not significant. At phase 2, both indices evolved in disadvantages to both groups with volume-overload. The PRSW-slope was significantly lower in group PI than in other groups, and was also significantly decreased in comparison with group RVH+PI. Analysis of the E_{max} and volume-intercept V_{25}-I showed a similar trend; however, the difference between groups PI and RVH+PI at phase 2 did not reach statistical significance ($p = 0.09$). Contractility was comparable between groups RVH and SHAM in the acute and chronic phases. RV compliance was significantly altered by hypertrophy, with a significantly increased stiffness coefficient β in group RVH+PI and RVH at phase 1, that persisted after 3 months. However, diastolic compliance coefficient appeared to be lower in all groups at phase 2. This could be explained by the different measurement conditions, minimizing the effect of pericardial restraint by using sternotomy for cardiac exposure. Pre-load independent RV function indices are depicted in figures 3 and 4.

Figure 3A. Bar-plot of E_{max} derived from ESPVR at both study phases

Fig. 3A

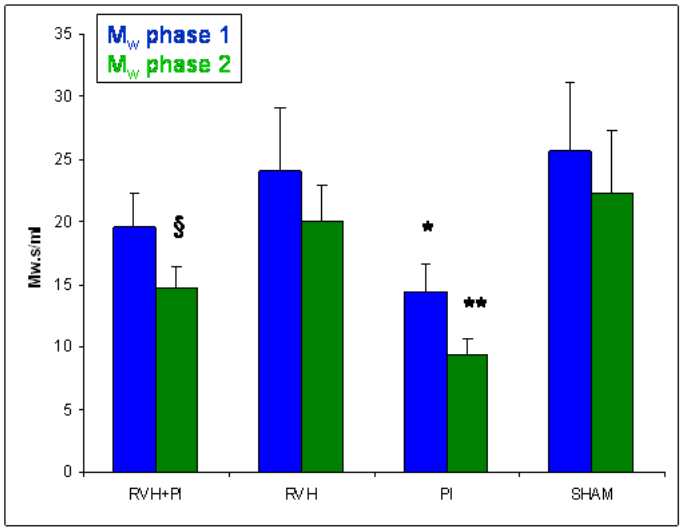


	RVH+PI	RVH	PI	SHAM	p-value
Emax (mmHg/ml)					
acute	1.00 ± 0.33	1.54 ± 0.72	0.53 ± 0.24*	1.49 ± 0.27	0.001
chronic	0.47 ± 0.13§	1.02 ± 0.39	0.21 ± 0.04*	1.23 ± 0.33	<0.001
V25-I (ml/m²)					
acute	42 ± 11	31 ± 10	46 ± 9*	34 ± 9	0.03
chronic	52 ± 15§	45 ± 12	61 ± 13*	31 ± 5	0.001

*p<0.05 between PI and SHAM – RVH
§p<0.05 between RVH+PI and SHAM - RVH

Figure 3B. Bar-plot of M_w derived from Preload-Recruitable Stroke Work at both study phases

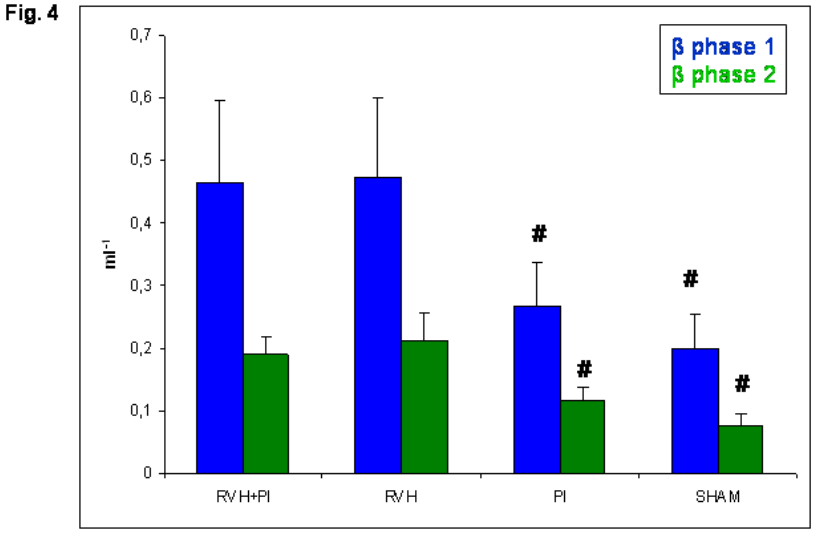
Fig. 3B



	RVH+PI	RVH	PI	SHAM	p-value
PRSW slope (Mw.s/ml)					
acute	19.5 ± 2.8	24.1 ± 5.1	14.4 ± 2.2*	25.7 ± 5.6	<0.001
chronic	14.7 ± 1.8§	20.0 ± 2.9	9.3 ± 1.3**	22.4 ± 4.9	<0.001

*p<0.05 between PI and SHAM – RVH
**p<0.05 between PI and all other groups
§p<0.05 between RVH+PI and SHAM – RVH

Figure 4. Bar-plot of β-stiffness coefficient derived from EDPVR at both study phases



	RVH+PI	RVH	PI	SHAM	p-value
β (ml-1)					
acute	0.47 ± 0.13#	0.48 ± 0.12#	0.27 ± 0.07	0.20 ± 0.06	<0.001
chronic	0.19 ± 0.03#	0.21 ± 0.04#	0.12 ± 0.02	0.08 ± 0.02	<0.001

#p<0.05 between RVH – RVH+PI and SHAM - PI

Echocardiographic data (table 2)

Echocardiography at phase 1 confirmed the presence of significant PI in groups RVH+PI and PI, with a shorter PI duration (respectively 256±14 and 291±10 msec, p=0.01) in group RVH+PI. After 3 months, both groups showed a larger RV size at the subpulmonary level, but differences at the basal and midventricular level were less pronounced. Again, the PI duration was significantly shorter in group RVH+PI, compared to group PI (263±19 versus 293±9 msec, p=0.047).

A restrictive physiology was seen mainly in group RVH+PI, in respectively 4 of the 6 animals at phase 1, and in 5 animals at phase 2. This was only noticed at phase 1 in one animal of group RVH, which disappeared at phase 2. Regarding diastolic function, RVH was only associated with a significant decrease of the E-wave deceleration slope, compared to group SHAM. This parameter correlated inversely with the stiffness coefficient β (ρ -0.70; p=0.001) and RVEDP (ρ -0.53; p=0.026) at the chronic phase. In contrast, echocardiographic determinants of systolic RV function as FS (ρ 0.05; p=0.84) and TAPSE (ρ 0.16; p=0.52) were poorly associated with systolic indices obtained by the conductance technique. Echocardiographic RV size estimation showed a good correlation between RVEDVI and RV size at basal level (ρ 0.49; p=0.04), midventricular level (ρ 0.34; p=0.07) and RVOT level (ρ 0.55; p=0.02).

Table 2. Basic echocardiographic data

	RVH+PI	RVH	PI	SHAM	ANOVA p-value
TV E-wave (m/sec)					
acute	0.67 ± 0.27	0.80 ± 0.12	0.92 ± 0.16	0.83 ± 0.16	0.40
chronic	0.73 ± 0.15	0.67 ± 0.10	0.81 ± 0.06	0.89 ± 0.15	0.10
TV A-wave (m/sec)					
acute	0.63 ± 0,22	0.53 ± 0,16	0,64 ± 0.08	0,43 ± 0.07	0.30
chronic	0.56 ± 0.06	0.55 ± 0.15	0.66 ± 0.09	0.56 ± 0.	0.47
TV E/A ratio					
acute	1.11 ± 0.39	1.66 ± 0.64	1.42 ± 0.17	1.95 ± 0.23	0.13
chronic	1.33 ± 0.34	1.27 ± 0.32	1.23 ± 0.07	1.60 ± 0.26	0.41
TV E-wave DCT (msec)					
acute	257 ±50	192 ± 17	178 ± 45	181 ± 15	0.05
chronic	254 ± 47	200 ± 43	202 ± 64	179 ± 10	0.11
TV E-wave DC slope					
acute	2.7 ± 1.3	4.1 ± 0.7	5.5 ± 2.3	4.7 ± 1.2	0.12
chronic	2.9 ± 0.7	3.4 ± 0.7	4.2 ± 1.1	5.0 ± 0.7	0.01¶
Restrictive Pattern (n)					
acute	4/6	1/6	0	0	0.04
chronic	5/6	0	0	0	0.001
TAPSE (mm)					
acute	13.0 ± 1.4	13.0 ± 3.7	13.7 ± 2.1	15.4 ± 2.5	0.67
chronic	17.4 ± 4.3	18.0 ± 4.5	14.3 ± 2.9	18.0 ± 1.7	0.58
FS (%)					
acute	37.3 ± 5.6	38.8 ± 5.7	37.5 ± 0.5	33.1 ± 6.6	0.55
chronic	33.0 ± 10.5	37.8 ± 6.1	30.7 ± 4.2	38.9 ± 7.2	0.38
PI grade					
acute	3.4 ± 0.5	0.8 ± 0.8	3.7 ± 0.6	0	<0.0001‖
chronic	3.5 ± 0.8	0.6 ± 0.8	3.7 ± 0.6	0	<0.0001‖
PI duration (msec)					
acute	256 ± 14	0	291 ± 10	0	0.01
chronic	265 ± 19	0	293 ± 9	0	0.05
RV Size (mm/m²)					
Basal level					
acute	43.6 ± 9.1	41.3 ± 4.7	46.1 ± 3.5	34.7 ± 2.6	0.14
chronic	31.0 ± 3.8	29.3 ± 4.4	34.6 ± 5.4††	24.0 ± 3.8	0.04
Mid-ventricular level					
acute	35.4 ± 7.8	32.0 ± 2.9	39.8 ± 3.5	32.9 ± 0.6	0.19
chronic	26.2 ± 4.6	24.6 ± 2.8	33.2 ± 7.1	23.4 ± 5.3	0.06
RVOT level					
acute	28.9 ± 5.8	26.7 ± 6.7	29.9 ± 5.0	27.5 ± 5.4	0.88
chronic	21.3 ± 3.4	18.1 ± 2.9	26.2 ± 3.6§	19.8 ± 4.5	0.008
FWTI (mm/m²)					
acute	13.2 ± 1.9	12.5 ± 2.8	9.1 ± 0.2	8.9 ± 1.4	0.02#
chronic	9.5 ± 1.0	8.0 ± 0.6	7.0 ± 0.6	5.6 ± 0.6	<0.0001#
IVST (mm/m²)					
acute	16.1 ± 5.5	13.6 ± 3.4	11.2 ± 0.6	8.2 ± 0.8	0.07
chronic	9.8 ± 1.2	8.0 ± 1.3	6.3 ± 0.7	7.0 ± 0.9	0.003#

Post-hoc Tukey correction for multiple comparisons

¶ p<0.05 between SHAM – RVH+PI
‖ p<0.05 for all comparisons excepted SHAM-RVH and PI-RVH+PI
†† p<0.05 between SHAM – PI
§ p<0.05 between PI and SHAM - RVH
# p<0.05 for all comparisons excepted RVH-RVH+PI and PI-SHAM

Legend:
TV=tricuspid valve; DCT=deceleration time; TAPSE=tricuspid annular plane systolic excursion; FS=fractional shortening; FWTI=indexed free wall thickness; IVSTI=indexed interventricular septum thickness

Histopathological results

A significant difference of RV mass was found between all groups (RVH+PI: 99±10 g/m²; PI: 87±5 g/m²; RVH: 72±3 g/m²; SHAM 50±1 g/m²; p<0.03). The RV mass-to-total heart weight ratio was higher in the volume-overloaded groups (RVH+PI: 36±5%; PI: 38±2%; RVH: 29±1%; SHAM 26±2%; p=0.001). The RV mass-to-volume ratio was particularly increased in group RVH+PI (0.77±0.08 g/ml) compared to group PI (0.62±0.07 g/ml, p=0.003) and RVH (0.64±0.04 g/ml, p=0.012), whereas group SHAM had the lowest ratio (0.51±0.05 g/ml, p<0.001), also lower than group PI (p=0.05) and group RVH (p=0.03). Microscopy of the RV revealed evident cellular hypertrophy and focal apoptosis in groups RVH+PI and RVH, more than in group PI. Interstitial fibrosis and myocardial disarray were equally observed in all treatment groups, but to a greater extent in group RVH+PI. Microscopy was normal in group SHAM.

Discussion

In the present study, a physiological model was established to investigate the role of RVH, initiated by previous pressure-overload, on RV performance during acute and chronic exposure to PI-related volume-overload in growing swine. To our knowledge, such an experimental animal model likely mimicking the presentation of TOF with its inherent physiological variability in pressure- and volume-overload sequences, has not yet been elaborated.

According to our previous work, volume-overload by TAP reconstruction of the RVOT affected immediately the systolic RV function, with impaired myocardial contractility through surgical damage of the infundibulum [6]. Progression of PI involved significant RV dilation, with further deterioration of the systolic function.

Pre-existing RVH appeared to alter this process in several ways. Previous pressure-overload is known to initiate improved contractile performance by increasing the myocardial cell mass, merely by cell hyperplasia, such as has been shown in younger animals [4,9]. In this study, RVH yielded a contractile RV function comparable to that of the control animals, despite significant PI in the acute phase.

However, loss of contractile function was observed in relation to chronic volume-overload, owing to secondary RV dilation. RVH appeared to attenuate this phenomenon only partially. In contrast, when the RV with hypertrophy was not physiologically challenged after relief of the obstruction, contractility was maintained.

RVH also influenced the remodeling secondary to chronic volume-overload, by retarding the RV dilatation. This might have been related to the lower amount and shorter diastolic duration of PI, even though the surgically created TAP was similar. Hence, it seemed more valid that both latter features are rather a consequence of the altered mechanical RV properties by hypertrophy, than the primary cause. Kuehne et al.[10] also stipulated the beneficial effect of RVH on the degree of PI. They found in analogy, less RV dilation and enhanced myocardial contractility in an animal study, by combining a component of stenosis to pulmonary insufficiency. Although they attributed RVH to be responsible for this effect, their experimental design involved at the same time a reduction of the regurgitant pulmonary orifice. But it underscores the advantage of leaving an acceptable residual obstruction during relief of the RVOT, to prolong the beneficial contribution of RVH on RV performance [11].

In contrast to the favorable effect on myocardial contractility, hypertrophy has commonly been associated with decreased diastolic function, by impaired early relaxation and passive compliance[12]. In this model, the determinants of early relaxation such as the minimal pressure-versus-time decline (dP/dTmin) and time-constant of pressure decay (τ) were not included because these are known to be load dependent and poorly reliable in the context of PI-related disturbance of isovolumetric relaxation. However, RV compliance was significantly worse in both groups with RVH at both the acute and chronic stage, and was simultaneously associated with increased end-diastolic RV-pressure.

A restrictive RV physiology was noted only in the group combining RVH and significant PI, already present in the acute setting and persisting chronically. This finding highlights the mechanism of primary restriction, advancing the role of hypertrophy as its main substrate, and subsequently furthered by the volume-overload, through decreasing the diastolic pressure gradient between the stiff RV and the pulmonary artery in presence of significant pulmonary regurgitation.

Considering the histologic changes after 3 months, including microscopically prominent myocyte hypertrophy as well as interstitial fibrosis, and macroscopically an increased mass/volume ratio, the advantage of RVH on RV remodeling after chronic volume-overload might eventually be the combined result of sustained systolic performance and impaired diastolic properties of the RV. One can assume that a stiffer hypertrophic ventricle, but with preserved contractility, would accommodate better to the PI and consequently resist longer to the dilation process. This issue evokes the ambivalent role of a primary restrictive RV physiology in the clinical setting of TOF repair, with its detrimental effect on the early postoperative course, but its potentially favorable influence on late RV dilation[13,14].

Clinical implications

The present study has demonstrated that RVH entails a benefit on RV remodeling by chronic PI-related volume-overload by affecting both systolic and diastolic RV performance. In TOF, a direct relationship exists between the extent of RVH and the duration of pressure-overload and thus, the age of the patient. During the past decade, the age of TOF repair has been decreasing to even the neonatal age. Hence, this early repair policy has been accompanied by a frequent use of TAP, subjecting a RV with less hypertrophy to chronic volume overload [2,3]. This clinical situation corresponds to that of the PI group in our experiment, showing the worst outcomes in terms of systolic function and RV dilation. Munkhammar et al. revealed an inverse relationship between the presence of restrictive RV physiology and patient age at repair, irrespective of the type of RVOT reconstruction. A restrictive physiology was observed in only 10% of the patients less than 6 months of age[15]. In agreement with their doubts on the late effect of early repair, our study supports the execution of primary repair beyond the neonatal age, to take advantage of some degree of RVH, particularly in the patient whose RVOT morphology will require TAP repair for effective RVOT relief. Considering the risk of increased perioperative morbidity after repair in infants < 3 months old [16], judiciously choosing a palliative shunt in order to postpone complete correction for a few months might be justified. However, the design of our experiment could not allow more precise advise on the optimal age for repair, by lacking variability in the quantification of RVH.
Otherwise, if RVOT morphology permits salvage of its functional integrity, early correction might be pursued as shown in group RVH, to overcome incomplete recovery of impaired diastolic compliance. Therefore, the ultimate answer to this conflicting problem concerning the timing and strategy of TOF repair, requires an an individualized approach to each patient, taking into account the specific RV-dependent characteristics such as RVOT morphology and RVH.

Study limitations

Although this experimental model is relevant for its hemodynamical effects, extrapolation of these data to the clinical setting needs careful consideration by lack of confounding interaction with specifically cyanosis. This factor is often advanced by the duration and severity of RV pressure-overload and thus, the age of the TOF patient, and might additionally impact RV performance by enhancing some histologic alterations. Secondly, RVH was induced as a fixed component and precluded investigation of varying degrees of RVH on RV function. Further study on this issue should include a wider time span of previous pressure-overload exposure; however, this would be at the cost of a larger sample size of animals. Echocardiography was primarily used to validate the surgical result, comprising mainly basic measurements. The addition of tissue Doppler data might have allowed more subtle examination of the systolic and diastolic RV function, albeit its exact contribution remains vague in the setting of TOF.

Conclusion

In a model of juvenile growing swine, the role of RVH was studied for its effect on RV function and remodeling after acute and chronic PI-related volume-overload. RVH initiated improved contractile function, which preserved global RV function longer in relation to chronic PI. However, it entailed decreased diastolic compliance, responsible for a restrictive RV physiology when simultaneously challenged by significant PI. Both alterations in RV performance affected secondary RV remodeling by retarding the dilation process and restricting the amount and duration of PI. From these findings, primary repair of TOF during the early postnatal period should not be favored, when RVOT reconstruction is definitely deemed to result in significant PI, prematurely loading a less hypertrophied RV. These insights on the influence of RVH on chronic PI might help in the decision-making process on the timing and surgical strategy as an individualized process for each patient with TOF.

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Disclosures

The authors have no conflict of interest to disclose.

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Chapter VI

Assessment of a right ventricular infundibulum-sparing approach in transatrial-transpulmonary repair of Tetralogy of Fallot (Eur J Cardio-Thorac Surg 2012;41:126-133)

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Abstract

Objective : to evaluate the outcome of transatrial-transpulmonary repair of tetralogy of Fallot in relation to a right ventricular outflow tract (RVOT)-sparing surgery

Methods :
Based on the surgical management of RVOTO at repair of tetralogy of Fallot, 140 children were retrospectively divided into 3 groups : (1) pulmonary valve (PV)-sparing, (2) infundibulum-sparing and (3) extended transanular patch (TAP). Clinical and echocardiographic outcome was assessed with regards to 3 equally divided study time eras between January 1994 and June 2010.

Results :
Over a 15-year study period, median age decreased from 11 (2 – 101) to 5 (1 – 11) months ($p < 0.001$), while type of RVOT repair changed significantly between the first and the last era (group 1: 18 to 40 %, group 2: 25 to 40 % versus group 3: 57 to 20 % ($p = 0.002$)).
Mortality was 0 %. Complications were mainly related to clinical restrictive RV physiology (27 %) and arrhythmia (10%). This cardiac morbidity remained constant over the eras and was associated with younger age ($p = 0,04$), increased postoperative RV/LV pressure ratio ($p = 0,01$) and type of RVOT repair at the cost of TAP ($p = 0,03$).
Median follow-up of 8 years (1-16 y) showed an overall freedom from RVOT reoperation of 84 % and 73 % respectively at 5 and 10 years. Most reoperations were for residual/recurrent RVOTO (12 %) occurring more frequently in the latter era : 16 % versus 7 % in era 1 ($p = 0,08$).
Late echocardiographic evaluation revealed a strong correlation between severity of pulmonary regurgitation and increased RV/LV size ratio, which was mainly determined by increased TAP length ($p < 0,001$) and duration of follow-up ($p = 0,06$).

Conclusion :

In a 15-year's experience with transatrial-transpulmonary correction of Tetralogy of Fallot, a valve- and infundibulum-sparing approach has been advanced by lowering the age for elective repair. This change has been performed without compromising immediate clinical outcome, despite an increased early reoperation rate for residual obstruction. However, longer follow-up will disclose whether this approach is protective against progressive and late RV dysfunction.

1. Introduction

More than 50 years experience with surgical treatment of tetralogy of Fallot (ToF) has revealed that the physiological sequelae of the formerly performed transventricular repair with a large transannular patch are not benign on the long-term [1-3]. Over the past decades, two issues have been addressed in order to optimize the surgical outcome : the type of right ventricular outflow tract (RVOT) correction and the timing for complete repair.

Regarding the first issue, the transatrial-transpulmonary approach has gained a lot of popularity by minimizing transmural myocardial scarring of the right ventricle [4,5]. Even though a transannular enlargement is required in 60 to 70 % of the patients, leading to pulmonary valve incompetence, preservation of the RVOT integrity is often pursued by limiting the infundibular incision, considered as a right ventricle infundibulum-sparing procedure [6]. Some authors have also advocated a pulmonary valve or annulus-sparing strategy in selected cases of severe pulmonary annulus hypoplasia, eventually associated with a separate transventricular patch plasty for adequate relief of the infundibular stenosis [7,8].

The second debate concerns the optimal time of primary repair. Protagonists of early corrective heart surgery have introduced complete repair of tetralogy of Fallot in the neonatal period to overcome the potentially morbid effects of cyanosis and advanced right ventricular hypertrophy, as well as the complications related to prior shunt palliation [9,10]. Opponents of this early repair have used the argument of increased morbidity and even mortality in these neonates, to strengthen their preference for a two-stage approach in infants with symptomatic tetralogy of Fallot. In accordance with the ideas claimed by Fraser et al. [11], we have been adopting an individualized strategy in the surgical therapy of children with tetralogy of Fallot. This included the use of modified Blalock-Taussig shunt (BTS) in the symptomatic neonate, particularly with ductal dependent pulmonary flow, and in presence of small native pulmonary branches. Complete repair has consistently been performed by a transatrial-transpulmonary approach within the first year of life. However, during this 15-years experience, we have gradually introduced a more RVOT-sparing approach, while lowering the age of repair simultaneously. The purpose of this study is to report on the early and late effects of both changes on

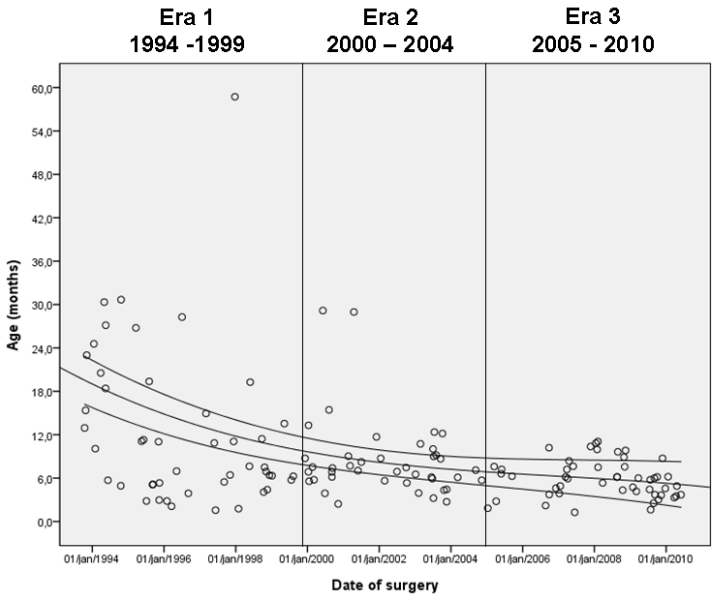
clinical outcome, and to assess specifically the usefulness of an infundibulum-sparing approach in comparison with more extensive transannular patch plasty.

2. Patients and Methods

2.1 Patients

This study has been approved by the Ethical Committee of the University Hospital of Gent (registration number B67020109388) and informed consent was waived for its retrospective design. The medical records of all patients who underwent complete repair of ToF between January 1994 and June 2010 were reviewed and consisted of 140 patients (84 males and 56 females). Patients with absent pulmonary valve syndrome and pulmonary atresia requiring insertion of a valved conduit for primary correction were excluded.
During the study period, the age at the time of complete repair progressively decreased as depicted in figure 1. Based on this graphical analysis, 3 equally divided time periods were differentiated as era 1 for period 1994-1999, era 2 for period 2000-2004, and era 3 for period 2005-2010.

Figure 1. Evolution of age at repair over study period



2.2 Surgical policy

During the whole study period, the operative management of children with ToF remained constant. Using standard cardiopulmonary bypass with moderate systemic hypothermia and cold crystalloid

cardioplegia, complete repair entailed consistently transatrial closure of the ventricular septal defect with a 0.4 mm PTFE patch (Gore-Tex, WL Gore & associates, Flagstaff, AZ) through the tricuspid valve, and excision/transsection of obstructive parietal and septal bundles in the infundibulum. Intra-atrial communications were closed routinely. Via a longitudinal arteriotomy of the pulmonary trunk, the size of the pulmonary branches was measured with Hegar dilators. After commissurotomy of the pulmonary valve, the adequacy of the pulmonary annulus size was compared to the minimal acceptable pulmonary size from Rowlatt's tables [12]. If the pulmonary annulus was found appropriate within the lower limits of the expected normalized z-value and relief of the infundibular stenosis seemed satisfactory after further transpulmonary resection, the arteriotomy was closed with an autologous pericardial patch. When the pulmonary annulus was deemed too small, the pulmonary arteriotomy was extended across the annulus, by preference through the most anterior commissure, into the infundibulum. Based on this approach, we defined 3 types of RVOT repair : (group 1) a pulmonary valve-sparing procedure with preservation of the pulmonary valve annulus after commissurotomy, (group 2) an infundibulum-sparing procedure with a transannular incision limited to the first 5 mm of the RVOT, and (group 3) an extended transannular patch plasty, where the RVOT incision was extended beyond the first 5 mm, to cross the level of the hypertrophic infundibular septum.

At the end of the procedure, peak RV/LV pressure (P) ratio determination and transesophageal echocardiography were performed in all patients. The RVOT repair was judged adequate when RV/LVP ratio was lower than 0.8 and echocardiography excluded residual anatomic obstruction. When RV/LVP ratio was initially higher than 0.8, the decision on the appropriateness of RVOT relief was made by echocardiography to differentiate between anatomic versus dynamic obstruction, after intra-operative optimization of hemodynamics and withdrawal of inotropics.

The approximate length of the transannular incision, the Hegar size defining the final z-value of the RVOT and the intra-operative RV/LV pressure ratio were noted in the operative record. In addition, the length of transannular incision was indexed to body surface area of each patient, in order to allow proper comparison of TAP length in function to age at repair.

2.3 Postoperative follow-up

Endpoints of early outcome were mortality, ventilation support time, duration of intensive care and hospital stay, and morbidity defined by complications affecting one of the former endpoints. In particular, cardiac complications were related to RV dysfunction with clinical signs of restrictive RV physiology and temporarily increased need for inotropic support, and/or arrhythmia, mainly defined as junctional ectopic tachycardia.

Median follow-up was 7.7 years (range 6 months – 16 years), and complete clinical data were available for at least 1 year since the closing date of this study in 85 % of the patients. Follow-up

focused on clinical evolution and need for late reoperation and/or reintervention for RVOT-related issues. Clinical data were obtained from routine medical records, QRS duration from the last electrocardiogram and parameters as residual RVOT gradient, grade of pulmonary valve regurgitation and RV/LV size ratio by measuring the maximal diameter of both ventricles on 4-chamber view on the latest trans-thoracic echocardiography.

2.4 Statistical analysis

Continuous data are expressed as mean value ± standard deviation or median value and range. Categorical data are expressed as frequencies. Comparison of continuous data between different time periods or types of RVOT procedure has been done by one way-ANOVA analysis with Tukey correction for multiple comparisons, in case of normally distributed data with equal variance. Kruskal-Wallis analysis followed by Mann-Whitney analysis for post-hoc subgroup differences, was used for non-normally distributed data. Between group differences of categorical data were compared by Chi-square or Fisher's exact test.

Risk factor analysis of categorical outcome was performed by multivariate logistic regression in a backward likelihood-ratio model. A multivariate stepwise linear regression model was used to identify risk factors for increased RV/LV size ratio at the last echocardiography, after exclusion of patients who underwent late pulmonary valve implantation. Additional data exploration with the classification tree method has been carried out to determine a significant cut-off value for continuous variables reaching statistical significant influence in a multivariate model.

Freedom from time-related events was calculated with the Kaplan-Meier method with log-rank test for univariate analysis. Multivariate Cox regression analysis was used to define independent predictors for late reoperation. Statistical analysis was performed with SPSS 18 – PASW software version (SPSS Inc, Chicago IL).

3. Results

3.1 Demographic and operative results

Demographic data of the study population are depicted in table 1. In the first era, patients were significantly older, having a median age of 11 months at the time of complete correction ($p < 0.001$). Although there was no significant age difference between era 2 and era 3, graphic 1 shows a greater variability of age in era 2, whereas the children in era 3 were consistently operated between 3 and 6 months of age. This evolution involved a higher proportion of children in era 1, that was operated in a symptomatic status (66 % in era 1 versus 40 % in era 2 versus 28 % in era 3, $p = 0.001$), which was reflected by the lower arterial saturation ($p = 0.03$). However, the percentage of patients treated

previously by a shunt, as well as the frequency of associated genetic disorders like microdeletion 22q11 (n = 16) and trisomy 21 (n = 8) were equal over eras.

Table 1. Demographic patient data over study eras

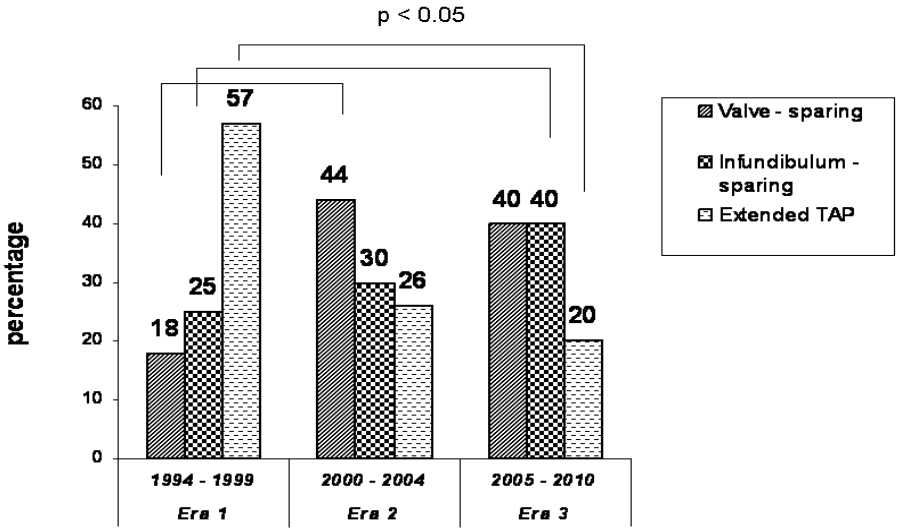
	Overall	**Era 1**	**Era 2**	**Era 3**	**p-value**
		1994-1999	**2000-2004**	**2005-2010**	
Number patients	140	44	43	53	0.48
Median age (m)	6.6	11 [a]	7	5	< 0.001
Weight (kg)	7.2 ± 2.3	8.1 ± 3.2 [a]	7.3 ± 1.9	6.5 ± 1.4	0.003
Gender (m/f)	84/56	22/22	28/15	24/19	0.26
Genetic disorder	24 %	18 %	28 %	25 %	0.55
Previous shunt	19 %	14 %	26 %	17 %	0.33
Symptoms	44 %	66 % [b]	40 %	28 %	0.001
Median SaO2	87 %	84 % [b]	86 %	88 %	0.03
Preop PV z-value	-2.32 ± 1.43	-2.40 ± 1.40	-2.08 ± 1.60	-2.47 ± 1.30	0.41

[a] $p < 0.05$ between era 1 and era 2-3
[b] $p < 0.05$ between era 1 and era 3

Within the study period, the morphologic features of ToF remained unchanged. Associated malformations were a persistent left superior caval vein (n = 8), a right-sided aortic arch (n = 18), atrial septal defect or patent foramen ovale (n = 67), aberrant coronary anatomy (n = 3) and atrioventricular septal defect (n = 6). RVOT characteristics showed no significant differences between the eras, as shown by the preoperative z-value of the pulmonary annulus. The mean size of the pulmonary branches was respectively 6.8 ± 1.1 mm for the right pulmonary artery, and 6.7 ± 1.2 mm for the left pulmonary artery.

The evolution of the surgical approach of the RVOTO is reflecting a significant higher proportion of extended transannular patch plasty in era 1, moving progressively to a more frequent valve- or infundibulum-sparing approach in era 2 and 3 ($p = 0.002$) (figure 2).

Figure 2. Evolution of type of RVOT repair over study period



At the same time, the length of the transannular incision, indexed to the patient's body surface area, decreased significantly from era 1 to era 2 and 3 : 19.9 ± 12.9 mm/cm² in era 1 versus 11.5 ± 13.5 mm/cm² in era 2 and 11.9 ± 12.8 mm/cm² in era 3 (p = 0.005). In 21 (15 %) patients a pericardial patch plasty of a pulmonary artery stenosis was performed. The immediate operative result over the different time periods indicated a significant difference of the postoperative RVOT z-value between era 1 and era 3 (0.40 ± 0.81 in era 1, 0.22 ± 0.83 in era 2 and - 0.11 ± 0.72 in era 3)(p = 0.007), whereas the intra-operative peak RV/LVP ratio remained equal (0.76 ± 0.17 in era 1, 0.74 ± 0.17 in era 2 and 0.69 ± 0.18 in era 3)(p = 0.16). In 6 (4%) patients, adjacent surgical revision by extending the transannular patch was required due to unacceptable residual RVOTO and suprasystemic RV pressures.

When comparing the 3 RVOT treatment categories, some important differences in anatomic and physiologic characteristics were observed (table 2). Patients in whom the pulmonary valve was preserved, had a better pre-operative arterial saturation, a larger native pulmonary annulus and a more favorable RV/LVP ratio at the end of the procedure. However, patients undergoing an infundibulum-sparing repair or a more extended transannular incision had similar pre- and peri-operative characteristics, unless a higher proportion of prior shunt use in the latter group (34 % in group 3 versus 10 % in group 2, p = 0.004).

Table 2. Demographic and operative data between types of RVOT repair

	Group 1	Group 2	Group 3	p-value
	Valve-sparing	**Infundibulum-sparing**	**TAP**	
Number patients	48	45	47	0.66
Median age (m)	7	6	7.5	0.21
Median SaO2	91 % [b]	87 %	85 %	0.03
Previous shunt	10 %	11 %	34 % [c]	0.004
Preop PV z-value	-0.86 ± 1.15 [a]	-2.84 ± 0.75	-3.26 ± 0.95	< 0.001
TAP length/BSA - (mm/cm²)		13.2 ± 3.6	30.2 ± 8.1 [d]	< 0.001
Postop PV z-value	0.34 ± 0.94	0.0 ± 0.61	0.12 ± 0.84	0.13
Postop RV/LVP	0.65 ± 0.17 [a]	0.74 ± 0.16	0.79 ± 0.16	< 0.001

[a] $p < 0.05$ between group 1 and 2-3
[b] $p < 0.05$ between group 1 and 3
[c] $p < 0.05$ between group 3 and 1-2
[d] $p < 0.05$ between group 2 and 3

3.2 Early outcome

There was no operative mortality. The median ventilation time was 6 h (range 3 – 336). Median ICU and hospital stay were respectively 2 d (range 1 - 21) and 9 d (range 7 - 42).

Two third of the patients (68 %) had an uneventful postoperative course. Major morbidity was mainly related to temporary RV dysfunction (27 %) and arrhythmia (10 %) such as junctional ectopic tachycardia. Other complications were pulmonary problems (pneumonia, chylothorax) (n = 8), renal failure requiring peritoneal dialysis (n = 5) and seizures (n = 4). Four patients needed early reoperation during the same hospital period, within 2 – 15 days after repair, because of residual RVOTO and subsequent RV dysfunction.

Table 3 shows an overview of the early results in perspective of the different eras and the type of RVOT repair. There were no significant differences between the 3 eras, and regarding the type of RVOT procedure, only the patients undergoing a PV-sparing surgery, had less post-operative cardiac events. Multivariate analysis revealed 3 independent predictors for increased cardiac-related morbidity : higher RV/LV pressure ratio at the end of repair (OR 29.7, 95% CI 2.3-384.5, p = 0.01), type of RVOT repair at the cost of an extended transannular patch (OR 3.1, 95% CI 1.1-9.1, p = 0.03) and lower age at the time of correction (OR 0.93, 95 % CI 0.86-0.99, p = 0.04), indicating a cut-off value at the age of 3 months.

Table 3. Early outcome over study eras and between types of RVOT repair

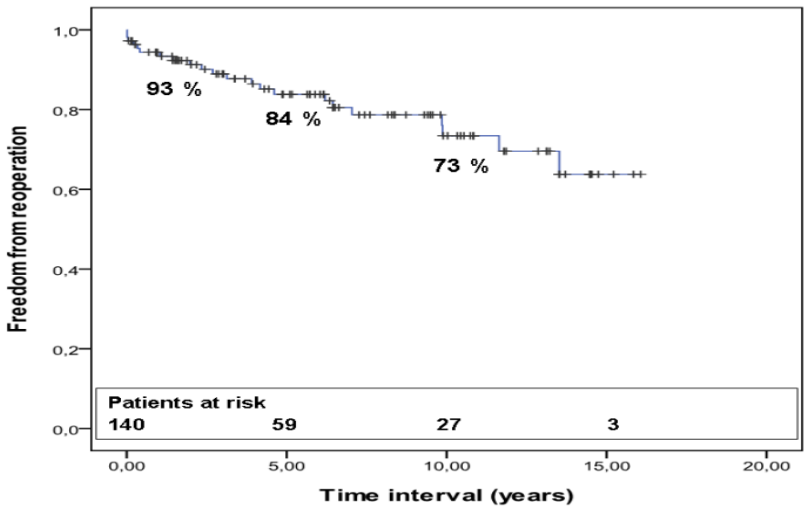
	Era 1 1994-1999	Era 2 2000-2004	Era 3 2005-2010	p-value
All complications	27 %	37 %	32 %	0.61
Cardiac complications	23 %	33 %	26 %	0.58
Median ventilation time (h)	8	5	5	0.62
Median ICU stay (d)	3	2	2	0.48
Early 30 d-reoperation	0 %	2 %	6 %	0.26
	Group 1 PV-sparing	**Group 2 Infund-sparing**	**Group 3 TAP**	**p-value**
All complications	23 %	31 %	43 %	0.12
Cardiac complications	15 % [a]	29 %	38 %	0.03
Median ventilation time (h)	4	7	8	0.63
Median ICU stay (d)	2	2	3	0.20
Early 30 d-reoperation	0 %	2 %	6 %	0.17

[a] $p < 0.05$ between group 1 and 3

3.3 Late outcome and reoperations

Within the mean follow-up of 7.5 ± 4.7 y (range 6 m – 16 y), there was one late death, occurring during a reoperation for recurrent RVOTO 4 months after the primary repair. All patients in follow-up were doing well, with only 3 patients necessitating medication for cardiac reasons. Freedom from reoperation and/or reintervention was 93 ± 2 % at 1 year, 84 ± 3 % at 5 years and 73 ± 4 % at 10 years (figure 3).

Figure 3. Actuarial freedom curve from all reoperations

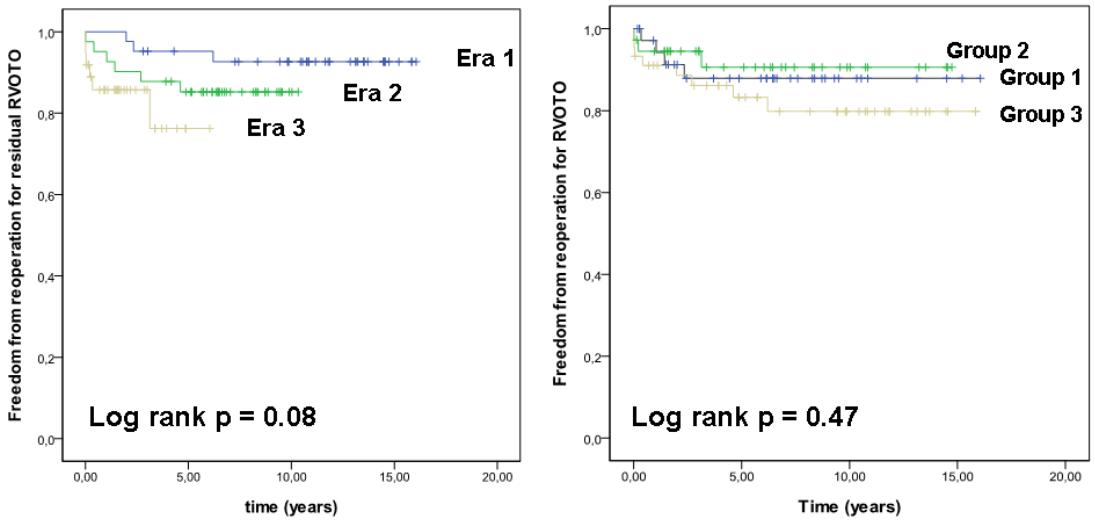


Recurrent RVOTO (n = 16, 12%) was the major cause for reintervention, treated by pulmonary artery stenting (n = 1), infundibular patch plasty (n = 2), extension of the transannular patch (n = 2), resection of residual infundibular muscle (n = 5). In 6 patients with recurrent RVOTO, a pulmonary valve homograft was implanted together with resection of obstructing bundles, to treat simultaneously pulmonary regurgitation. Valvulation using a pulmonary homograft (n = 8) or a bovine jugular vein conduit (n = 1) was performed in 9 (7%) patients for progressive RV dilation due to isolated pulmonary insufficiency. Finally, 1 patient required a pacemaker for atrioventricular bloc.
Univariate log-rank analysis for late reintervention for recurrent RVOTO or pure PI was not influenced by the type of RVOT repair (p-value 0.47 and 0.34 respectively). However, there was a trend for a higher rate of late reoperation for recurrent RVOTO during the latter era of the study period (p = 0.08) (figure 4).

Figure 4. Actuarial freedom from reoperation for RVOTO recurrence

(a) comparison between study eras

(b) comparison between types of RVOT repair



Multivariate Cox-regression analysis revealed the following independent risk factors for any reoperation : type of RVOT repair, determined by extended transannular patch plasty (HR 12.3, 95% CI 2.6-58.7, p = 0.004) and era of surgery (era 3 versus era 1, HR 37.4 , 95 % CI 1.5-913.8, p = 0.005) However, concerning specifically reoperation for recurrent RVOTO, only increased RV/LVP ratio at the end of repair (HR 111.7, 95 % CI 6.1-2059.9, p = 0.002) was predictive, indicated by a significant cut-off value of 0.84 (p = 0.006). Era of surgery achieved statistical significance only regarding the comparison of era 3 versus era 1 (HR 5.4, 95 % CI 1.3-22.8, p = 0.02). Considering the late need for

PV implantation, type of repair (only group 3 versus group 1) (HR 39.7, 95% CI 3.1-501.1, p = 0.004) and increased RV/LV size ratio at echo (HR 2.1, 95 % CI 1.2-4.6, p = 0.03) were relevant risk factors.

3.4 Last echocardiographic assessment

Complementary investigation during follow-up was routinely based on 12-lead electrocardiogram and transthoracic echocardiography. Table 4 shows the commonly available measurements in most patients by both examinations. Univariate analysis demonstrated a significant higher RV/LV diameter ratio ($p < 0.001$) in group 3, while patients of group 1 had significantly less pulmonary regurgitation ($p < 0.001$). Linear regression analysis revealed one major independent predictor for late RV dilation as indicated by increased RV/LV size ratio : length of transannular incision (unstandardized β coeff. 0.16 , 95 % CI 0.009-0.897, $p < 0.001$). Duration of follow-up reached nearly statistical significance (unstandardized β coeff. 0.008, 95% CI 0.000-0.17, p = 0.06).

Table 4. Late echocardiographic results and QRS duration between types of RVOT repair

	All	Group 1 PV-sparing	Group 2 Infund-sparing	Group 3 TAP	p-value
Late RV/LV size ratio	0.96 ± 0.20	0.88 ± 0.18	0.90 ± 0.15	1.15 ± 0.16 [b]	< 0.001
Late PI grade	2.4 ± 0.9	1.9 ± 0.9 [a]	2.5 ± 0.7	3.0 ± 0.9	< 0.001
Late RVOTO (mm Hg)	15 ± 14	14 ± 14	16 ± 13	17 ± 15	0.62
Late QRS (msec)	120 ± 19	115 ± 21	122 ± 18	123 ± 17	0.26

[a] $p < 0.05$ between group 1 and 3
[b] $p < 0.05$ between group 3 and 1-2

4. Discussion

This study actually reviews a single-center experience with the surgical treatment of tetralogy of Fallot over the past 15 years. This included a management individualized to the patient by using a two-stage approach in symptomatic neonates with duct-dependent pulmonary flow, with first palliation by a modified Blalock-Taussig shunt, followed by complete repair in infancy. A one-stage approach was adopted beyond the neonatal age, independent of their clinical status, and preferably within the first year of life. Complete correction has consistently been achieved by a transatrial-transpulmonary technique. According to Fraser et al. [11], our strategy has focused primarily on the type of RVOT repair,

preserving by preference the ventricle and then the valve. During the study period, we have gradually lowered the age at repair, which facilitated simultaneously a RVOT-sparing approach.

Implications on early outcome

Although the morphology of the RVOTO in tetralogy patients has not changed substantially over time, this conceptual change allowed to decrease significantly the extent of the transannular incision, especially in patients with pulmonary annulus hypoplasia, and favored the use of an infundibulum-sparing repair in stead of the more extensive transannular patch relief.

Advancing the timing of surgery has been an important issue to improve the surgical outcome of ToF. Neonatal repair has been favored to avoid the physiological consequences of hypoxemia and right ventricular hypertrophy as well as the problems associated to prior shunting. But, even in experienced institutions, this approach is associated with increased morbidity, leading to significantly longer ventilation times and intensive care stay, and eventual mortality [9,10]. However, it remains uncertain if such early repair is really advantageous to the right ventricle on the long term, considering the high proportion of transannular patches and the decreased benefit of restrictive RV physiology. In a study of 227 patients reviewing a local change of practice lowering the age for primary repair, Van Arsdell and colleagues found that the optimal age for repair, in terms of physiological tolerance, is probably between 3 and 11 months of age [13]. Our results have shown that decreasing the age at repair – at least to the age of 3 months - while adapting a RVOT-sparing policy, did not affect the early clinical outcome. Postoperative morbidity was mainly related to transient RV function impairment and arrhythmia, which were independently promoted by age younger than 3 months, use of an extended transannular patch but especially an increased RV/LV pressure ratio at the end of repair. Both last factors are the direct effect of the interaction between repair type and the severity of RV hypertrophy, which in se is also age-related. The group of Great Ormond Street and Brompton Hospital have first demonstrated that impaired diastolic RV function was determined by the type of repair, in particular by transannular patch plasty [14]. But in a later study, younger age at repair appeared to prevent the development of early restrictive RV physiology, as 80 % of their patients aging less than 6 months, underwent a TAP repair. Hence, TAP repair was not an independent predictor for later restriction [15]. Subsequently, one can assume that the degree of RV hypertrophy is the main substrate for a restrictive RV pattern, certainly when the ventricle is challenged by the volume load due to variable pulmonary valve insufficiency. Based on the knowledge that a restrictive RV physiology has a beneficial long-term effect on RV function [14,16], this RVOT-sparing surgery seems justified in the attempt to maintain the functional advantage of RV hypertrophy against late RV dilation by pursuing some residual restrictive effective opening – as depicted by a lower pulmonary z-value in the last versus the first era. Presently, we are proposing elective complete correction between 3 and 6 months of age, irrespective of symptomatic status or even previous palliation. To our belief, this age range enhances the

opportunity to relief the hypoplastic RVOTO with minimal transannular incision and less infundibular resection to deal with the balance between the postoperative adverse, but long-term protective effect of a restrictive physiology on right ventricular function.

A side-effect of the adoption of a RVOT-sparing policy in our series is a higher reoperation rate for residual or recurrent RVOTO. At 3 years, the freedom from reoperation was respectively 95 ± 3 % in era 1, 88 ± 5 % in era 3 and 86 ± 6 % in era 3. Previous reports have already pointed to the higher residual outflow gradients after transatrial correction [4,17]. Based on a disturbing increased incidence of recurrent RVOTO, Alexiou et al. even went back to a transventricular repair in tetralogy patients with severe infundibular stenosis [18]. According to Kaushal et al. [19], we have been using the addition of transesophageal echocardiography to differentiate between a fixed anatomical obstruction and a dynamic obstruction, when systemic or even suprasystemic RV pressures were recorded. On-site revision for inadequate RVOTO relief was 12 % in their commonly older population, and noticeably higher than the 4 % in our cohort. As a peak RV/LV pressure ratio above 0.84 was the strongest predictor of reoperation for recurrent RVOTO in our experience, we should question whether we had wrongly appreciated the first surgical result. Therefore, in the pursuit of the optimal equilibrium between adequate relief of pressure load and the potential inconvenience of pulmonary insufficiency-related volume load, the benefit of a RVOT-sparing procedure has to be outweighed against the risk of incomplete RVOT relief and subsequent reoperation, by respecting more rigorously the recommended threshold of 0.8 for intra-operative RV/LV pressure ratio.

Considerations on late outcome

Since the evidence is growing that the deleterious long-term complications of tetralogy of Fallot repair are the result of the interaction between surgical induced RVOT dysfunction and the mode of RV compliance, our surgical strategy is aimed to minimize the insult to the RV. Undeniably the infants in whom a valve-sparing technique was carried out, are belonging to the better part of the tetralogy spectrum, with intrinsically an adequate sized pulmonary valve and less RV hypertrophy. The most interesting comparison in this series concerns the patients with the narrowest outflow tract, treated by an infundibulum-sparing approach versus a more extensive transannular patch. Basic measurements on routine echocardiography at last follow-up, indicated a close relationship between RV dilation and the extent of transannular patch repair. Moreover, the time span the RV is subjected to the PI-related volume load, is an additional factor for increased RV dilation. These results are not surprising as the use of TAP has currently a negative impact on both late clinical outcome and RV function. In a study of 59 patients who were evaluated 14 years after contemporary transatrial-transpulmonary repair, Van den Berg et al. found impaired functional capacity and moderate RV dysfunction in relation to the use of TAP [20].

However, the question remains whether an infundibulum-sparing repair will ultimately delay this physiological post-PI dilation process, as actually the follow-up of these RVOT-sparing procedures is too short to be conclusive. The exact role of the infundibulum on the RV function is controversial. In a study concerning systolic RV function in young individuals without heart disease, Geva et al. demonstrated that the infundibulum contributed for only 13 % of the total RV stroke volume [21]. Otherwise, d'Udekem and colleagues found that patching the subvalvular outflow tract affected both PV and RV function equal to transannular patch repair, and subsequently pointed out the peculiar function of this anatomic substrate as a kind of contractile support of the pulmonary valve [22,23]. We believe that the main advantage of the infundibulum-sparing technique is related to (1) the proper absorptive support to important pulmonary regurgitation and (2) the controlled restriction that helps to sustain the long-term benefit of RV hypertrophy.

Study limitations

There are some obvious shortcomings of this study, primarily because of its retrospective design. It covers a considerable time span, during which two of the utmost important variables of surgical outcome changed, i.e. age at repair and type of RVOT reconstruction. Therefore, it is not easy to evaluate the clear effect of each change as the result of the confounding interference between both variables on the final results. Moreover, the number of patients in each era and repair group is small, perhaps limiting the strength of some interpretations.
In addition, the differentiation into 3 groups of RVOT repair is subjected to bias. Tetralogy of Fallot is known by a wide spectrum of RVOTO morphology. Children treated by a PV-sparing procedure, have definitely a more friendly RVOT anatomy, resulting in better functional outcome and prognosis. Although it was retrospectively impossible to delineate the features of the infundibular stenosis such as the infundibular length and the degree of infundibular septal hypertrophy and malalignment, we feel confident that the morphological RVOT differences between group 2 and 3 are negligible. The conclusions on the comparison between both repair groups are thereby valid, but need further follow-up to prove consistency.
Finally, the echocardiographic analyses are only based on measurements of some rude parameters, as afforded by routine ambulatory echocardiographies performed beyond study purposes. More in-depth elaboration of parameters of systolic as well as diastolic RV performance, using echocardiography and/or magnetic resonance, will probably better clarify the exact contribution of each type of repair.

In conclusion, a valve- and infundibulum-sparing reconstruction of the right ventricular outflow tract has been advanced reciprocally through and together with lowering the age at repair during transatrial-transpulmonary correction of tetralogy of Fallot. This change has been achieved without compromising the immediate clinical outcome, but at the cost of an increased early reoperation rate for

residual and/or recurrent obstruction. As the length of the transannular relief of the RVOT is, with time, the main determinant of right ventricular dilation, further long-term follow-up is needed to disclose whether such infundibulum-sparing approach is more protective against progressive right ventricular dysfunction.

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Chapter VII

Functional analysis of the anatomical right ventricular components : should assessment of right ventricular function after repair of tetralogy of Fallot be refined ? (Eur J Cardio-Thorac Surg, in press)

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Abstract

Objective : Follow-up after Tetralogy of Fallot repair is directed to detect timely RV dysfunction by following pulmonary regurgitation and global RV size, with little attention for the effective contribution of regional RV dysfunction. This study investigates the contribution of regional RV dysfunction on exercise capacity after ToF repair.

Methods : 42 patients were investigated with cardiac magnetic resonance imaging for regional RV dysfunction in relation to global RV function by functional quantification of sinus and outflow part of the RV. Impact of regional and global RV dysfunction on clinical status was studied by exercise testing.

Results : Global RV function was lower than sinus function (EF 52 ± 12 % versus 58 ± 10 %, $p<0.001$), attributable to the adverse influence of RVOT dysfunction (EF 34 ± 17 %). Percent predicted peak VO_2 correlated better with RV sinus EF compared to global RVEF ($r=0.51$, $p=0.001$ versus $r=0.44$, $p=0.004$). Multivariate analysis revealed EF of RV sinus ($\beta = 0.34$, 95% CI 0.07-0.61, $p=0.013$) and extent of RVOT akinesia ($\beta = -0.28$, 95% CI -0.50; -0.06, $p=0.015$) as significant determinants of exercise capacity. Impaired exercise performance occurred in 43 % of the patients, and was independently determined by type of repair (transventricular versus transatrial : OR. 6.0, 95% CI 1.31-17.3, $p=0.02$) by associating greater sinus and RVOT dysfunction.

Conclusion : Functional analysis of the RV components shows that exercise capacity after repair of tetralogy of Fallot is better predicted by systolic function of the RV sinus as the extent of RVOT dysfunction commonly leads to underestimation of global RV function. This method of differential quantification of regional RV function might be more appropriate than assessment of global RV function during long-term follow up of repaired tetralogy of Fallot patients.

Introduction

The long-term outcome of ToF is commonly determined by the adaptive response of the RV to the physiological sequelae after RVOT reconstruction [1,2]. The advent of CMRI has certainly increased our insights into the pathophysiological development of RV dysfunction resulting from the chronic volume overload by pulmonary valve regurgitation. Usually the RV has been analyzed as one entity, irrespective of its natural complex geometry, which is further distorted after surgical repair. Otherwise, the impact of regional RV dysfunction on clinical outcome has predominantly been based on qualitative measures of the RV, such as the presence of a RVOT aneurysm [3].

However, recent reports have indicated that the functional evaluation of the global RV does not necessarily reflect the true function when the RV components are considered separately. Lytrivi et al. observed that patients after ToF repair had reduced global RV systolic function, merely by decreased function of the infundibulum, while the ejection fraction of the sinus part was preserved and equal to that of normal control subjects [4]. A similar study on the comparison between ToF patients and healthy peers, confirmed that the function of the trabecular part of the RV was maintained, albeit this component absorbed the largest part of the volume overload, and this finding was independent of the surgical technique for RVOT restoration [5].

In this study, we sought to investigate the effect of the functional contribution of the main anatomical components of the RV on global RV function, quantified by CMRI, and to determine its influence on the clinical status of patients after ToF repair, based on their exercise performance.

Methods

Study subjects

Out of the cohort of repaired ToF patients currently in follow-up at the department of Pediatric and Adult Congenital Cardiology, patients were retrospectively included in the study if they had a complete CMRI examination and a clinical evaluation including a reliable exercise test within a 1-year time span. Patients were excluded when (1) they were treated primarily with a valved RVOT conduit, (2) previous pulmonary valve implantation was performed, (3) they had a significant residual RVOT obstruction > 30 mmHg at last echocardiography and (4) the time between CMRI and exercise test exceeded 1 year.

Patient data were retrospectively obtained from medical reports including demographic characteristics, surgical details of the primary repair and routine echocardiographic assessment at the approximate date of the CMRI and exercise test in order to exclude significant residual RV pressure load. The study was approved by the ethical committee of the University Hospital of Ghent (registration B670201110922), and informed consent was waived by the retrospective study design.

Cardiac MRI protocol

CMRI was performed with a 1.5-T imager system (Siemens Avanto, Erlangen, Germany). A complete CMRI protocol consisted of ECG-triggered HASTE sequence of images in 3 orthogonal planes, and balanced field echo cine-imaging of long and short axis stack from base to apex for volumetric analysis of the right ventricle in 2-chamber view, the RVOT and pulmonary arteries. Phase-contrast flow-mapping was acquired in-plane for the RVOT view, and through-plane over the pulmonary and aortic valve.

Post-processing volumetric analysis was done with the use of the Argus software (Siemens, Erlangen, Germany) on the short axis stack, by semi-automated endocardial delineation of left and right ventricular wall at end-diastole and end-systole. In a second phase, the RV sinus and RVOT were traced separately, using the septo-parietal bands as anatomical landmark [4,5]. The sinus component comprised the tricuspid inlet and the trabeculated apical part to the septo-parietal muscles distally. The RVOT component extended from the defined landmark to the position of the pulmonary valve remnants or the presumed transition to the native pulmonary root (figure 1). Accordingly, the end-diastolic and end-systolic volume of both components were determined, with subsequent calculation of stroke volume and ejection fraction. All volume data were indexed to body surface area. The volume measurements were done by two investigators blinded to the clinical outcome.

Figure 1. CMRI : endocardial contouring of Sinus and RVOT component of the RV, on the end-diastolic and end-systolic short axis sequence after respectively (A) transventricular repair with TAP and (B) transatrial-transpulmonary repair with TAP. Both figures reflect the different functional properties of the RVOT, with preservation of the end-systolic excursion of sinus component.

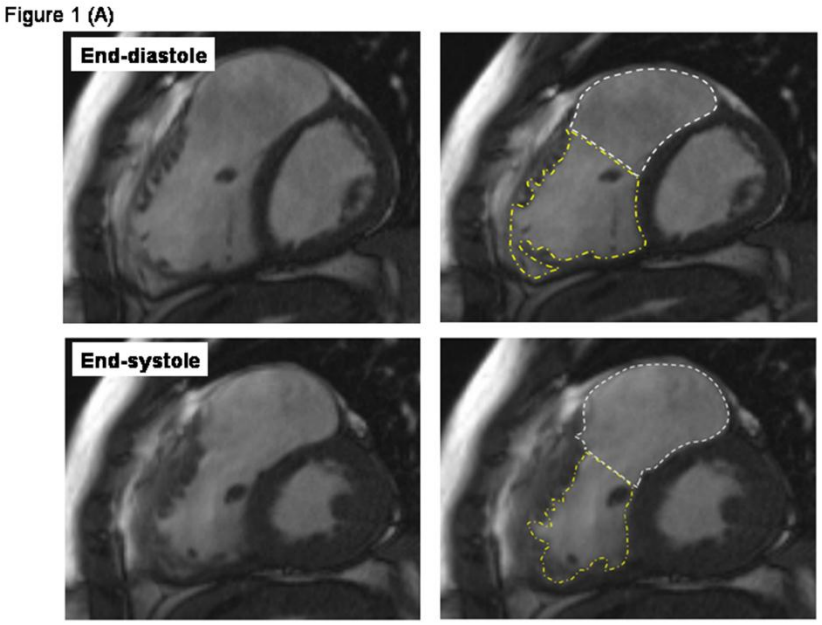
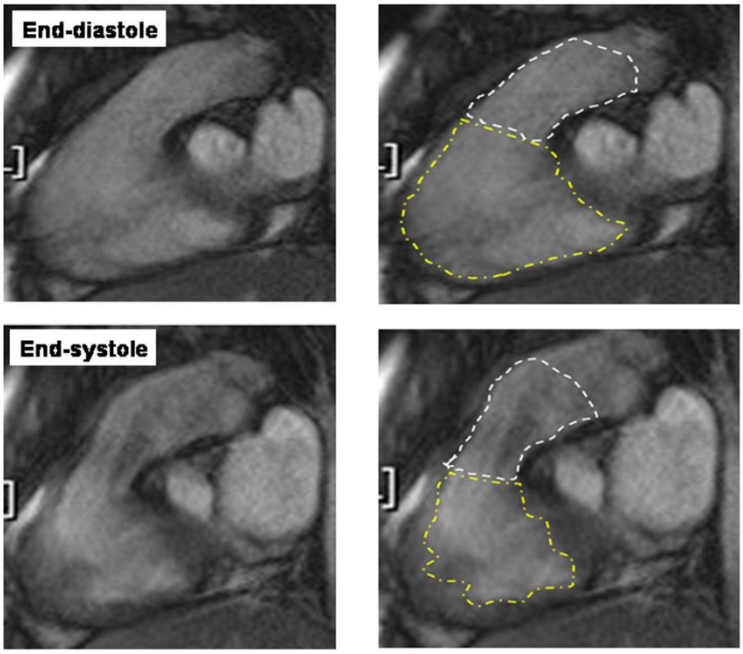


Figure 1 (B)



Assessment of the PRF was based on the ratio of pulmonary retrograde to antegrade flow volume, expressed as percentage. Based on the fast field cine images with alignment to the RVOT and pulmonary trunk, dynamic evaluation of the RVOT allowed to define the extent of the RVOT akinesia as the curvilinear distance from the contractile muscular free wall of the RV sinus to the end of the fibrotic patch at the RVOT. The posterior part of the pulmonary valve annulus remnant was identified unequivocally as a small indentation between RVOT and pulmonary trunk, often at the origin of the regurgitant jet. In none of the patients, major calcifications of the RVOT patch were observed.
All subtracted and native angiographic images as well as the 3D-whole heart dataset are viewed and evaluated in a 3D-image analysis tool.

Cardiopulmonary exercise testing

Cardiopulmonary exercise test was performed on an electronically braked cycle ergometer (Ergoselect 100K, Ergoline, Germany) with a continuous gradual increment of workload adjusted for each patient according to the method of Wasserman et al. [6]. All subjects were encouraged to exercise until exhaustion or notice of any adverse event. A 12-lead ECG (ECG, Marquette, GE Healthcare, UK) and pulse oximetry (Radical, Masimo Corp., US or Accutor Plus, Masimo Corp., US) were recorded continuously throughout the test. Cuff blood pressure was measured every 3 min (Tango, SunTech Medical, US). A breath-by-breath gas-exchange analysis was made using a calibrated expiratory gas analysis system (Oxycon Pro, Jaeger, CareFusion Corporation, US). With this method, the highest 30 second average of oxygen consumption during the last phase of exercise was defined as the peak VO_2.

Predicted values were obtained from established values from age- and sex-matched controls, and expressed as percentage of the predicted peak VO_2 [6]. A % predicted peak VO_2 < 85 % was identified as subnormal exercise capacity. Minute ventilation (VE, y-axis) and carbon dioxide production (VCO_2, x-axis) were plotted in a curve and its slope VE/VCO_2 was defined as index of gas exchange efficiency during exercise. Heart rate variation was obtained from ECG recordings. HR at recovery was defined as the HR at 5 min after cessation of exercise. HR reserve was calculated as the difference between maximal HR and HR at rest. HR recovery represented the difference between maximal HR and HR at the determined recovery time point. Using the formula of Astrand to define the predicted maximum HR, the chronotropic index was calculated as (peak HR-baseline HR)/(220-age-baseline HR) [7,8].

Statistical analysis

Data distribution was tested for normality by the Kolmogorov-Smirnov test. Continuous data are presented as mean ± SD or median (range) for respectively parametric and non-parametric distributed variables. Categorical data are expressed as number and frequency. The relationship between indices of exercise function and CMRI-derived cardiac function variables was assessed by Pearson or Spearman rank correlation analysis. Multivariate linear regression analysis was used to evaluate the independent effect of patient- and procedure-related factors and cardiac function parameters on exercise capacity. Based on the heterogenous distribution of the time interval between date of primary correction and date of CMRI examination, this variable was entered into a stepwise linear regression model after adjustment by the weighted least squares method. Accordingly, risk factor analysis of impaired exercise capacity was achieved by binary logistic regression (backward likelihood-ratio method), with correction for time interval variability.
Comparison of continuous data between groups with normal and impaired exercise performance was done by unpaired t-test or Mann-Whitney test as appropriate. Between-group comparison of dichotomous parameters was done by Fisher's exact test. Validation of the inter-observer agreement between CMRI-derived global RV volume and the summation of regional RV volumes was based on the method of Bland-Altmann.
Statistical analysis was performed with SPSS 20.0 software (SPSS Inc., Chicago, Illinois). A two-sided p-value < 0.05 was considered significant.

Results

Patient population

Forty-two patients fullfilled the inclusion criteria and were entered into the study. The study cohort yielded a time span for inclusion from may 2003 to june 2012. The patient characteristics are shown in table 1. As the study population covered the transition era between a transventricular repair performed before 1990 and a transatrial-transpulmonary repair used routinely since 1993, the follow-up interval of the former group at the time of study inclusion was significantly higher compared to the latter group: 29.0 ± 7.0 versus 11.5 ± 3.6 y ($p<0.001$).

Table 1. Patient characteristics

Number of patients	42
Male gender (n, %)	27 (64)
Median age at repair (y)	1.9 (0.13 – 16.6)
Median age at MRI study (y)	17.9 (8.2 – 56.0)
Median time interval between TOF repair and MRI (y)	17.6 (9.1 – 45.5)
Type of TOF repair (n, %)	
Transventricular repair	20 (48)
With TAP	15
With PV commissurotomy	5
Transatrial repair	22 (52)
With TAP	18
With PV commissurotomy	4
Clinical symptoms (n, %)	13 (31)
Dyspnoea	9
Ventricular/supraventricular arrhythmia	4
NYHA functional class	
NYHA I	29 (69)
NYHA II	11 (26)
NYHA III	2 (5)
NYHA IV	0
Medication	
No medication	37 (88)
B-blockers	3 (7)
Ca+ - antagonist	2 (5)
Mean QRS duration (msec)	145 ± 22

Exercise performance

The results of exercise testing are depicted in table 2. Correlation analysis showed a consistent association between the achieved % of predicted capacity based on peak VO_2 measurement and the VE/VCO_2 slope ($r = -0.54$, $p=0.001$), the maximal HR ($r = 0.64$, $p<0.001$), the HR reserve ($r = 0.32$, $p=0.04$), the chronotropic index ($r = 0.38$, $p=0.02$) and the HR recovery ($r = 0.47$, $p=0.002$). Consequently, patients with subnormal exercise function had prominent chronotropic incompetence, with a lower maximal HR (155 ± 18 bpm versus 175 ± 12 bpm, $p=0.001$), decreased HR reserve (77 ±

16 bpm versus 88 ± 15 bpm, p=0.03) and lower chronotropic index (0.70 ± 0.13 versus 0.78 ± 0.11, p=0.05). The difference in HR recovery was not significant (52 ± 18 bpm versus 60 ± 23 bpm, p=0.22).

Ten out of the 17 patients with impaired exercise testing were also clinically symptomatic, and were later referred for pulmonary valve implantation.

Table 2. Exercise test results

Mean peak VO_2 ($ml.kg^{-1}.min^{-1}$)	19.6 ± 5.9
Mean % of predicted peak VO_2 (%)	85.9 ± 17.1
Number of patients with % predicted peak VO_2 < 85 %	17 (43)
Mean VE/VCO2 slope	30.6 ± 4.6
HR at rest (beats/min)	83 ± 15
Maximal HR (b/min)	166 ± 18
HR at recovery (b/min)	110 ± 19
HR reserve (b/min)	83 ± 16
Chronotropic index	0.74 ± 0.12
HR recovery (b/min)	56 ± 21

Assessment of regional dysfunction in relation to global systolic RV function

Measurement of the RV volume by summation of the sinus and RVOT component correlated closely with the standard global RV volume calculation (RVEDV: r = 0.98, p<0.0001 and RVESV: r = 0.97, p<0.0001), with good inter-observer agreement on both measurements for RVEDV (mean bias: 2.89 ± 16.88 ml) and RVESV (mean bias: -0.91 ± 13.50 ml).

Table 3. CMRI data of global and regional RV and LV

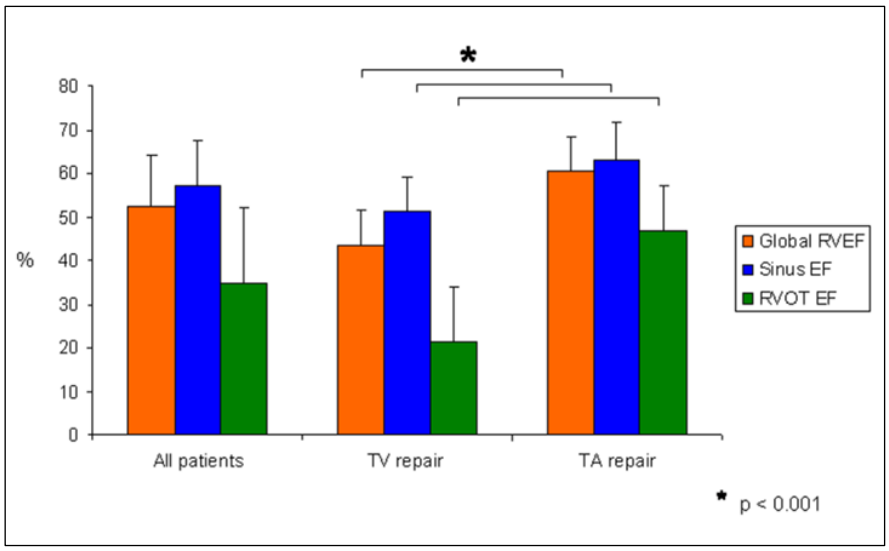
	All patients	**Normal exercise function**	**Subnormal exercise function**	**p-value**
	n = 42	n = 25	n = 17	
Global RV data				
RVEDVi (ml/m²)	141 ± 38	145 ± 41	139 ± 36	0.96
RVESVi (ml/m²)	67 ± 31	64 ± 27	77 ± 34	0.18
RVSVi (ml/m²)	70 ± 19	77 ± 20	64 ± 16	0.03
RVEF (%)	52 ± 12	56 ±11	47 ± 11	0.02
PRF (%)	37 ± 11	37 ± 10	38 ± 12	0.97
RV akinesia (mm)	33 ± 23	29 ± 23	42 ± 20	0.07

Regional RV data				
SinusEDVi (ml/m²)	111 ± 30	115 ± 30	107 ± 30	0.33
SinusESVi (ml/m²)	48 ± 20	47 ± 19	51 ± 21	0.64
SinusSVi (ml/m²)	62 ± 18	67 ± 16	57 ± 18	0.02
SinusEF (%)	58 ± 10	60 ± 10	54 ± 9	0.05
RVOTEDVi (ml/m²)	29 ± 16	26 ± 14	36 ± 17	0.05
RVOTESVi (ml/m²)	20 ± 15	17 ± 13	27 ± 17	0.03
RVOTSVi (ml/m²)	9 ± 5	9 ± 5	9 ± 6	0.87
RVOTEF (%)	35 ± 17	38 ± 15	28 ± 17	0.04
LV data				
LVEDVi (ml/m²)	77 ± 14	79 ± 15	74 ± 14	0.29
LVESVi (ml/m²)	27 ± 9	26 ± 9	29 ± 9	0.37
LVSVi (ml/m²)	50 ± 11	52 ± 10	44 ± 10	0.02
LVEF (%)	65 ± 9	67 ± 8	61 ± 10	0.05

All CMRI-derived RV and LV function data are given in table 3. The global RV systolic function is lower in comparison with the RVsinus function (RVEF: 52 ± 12 % versus SinusEF: 58 ± 10 %, $p<0.001$), due to the negative effect of commonly decreased RVOT function (RVOTEF: 35 ± 17 %). For the whole population, the sinus and RVOT volume attributed respectively 79 ± 8 % and 21 ± 8 % to the global RVEDV, and 72 ± 11 % and 28 ± 11 % to the global RVESV. Regardless of the type of surgical repair, the systolic function of the sinus component was significantly better than the global RV function (mean difference of 8 ± 4 %, $p<0.001$ and 3 ± 2 %, $p<0.001$ for respectively TV and TA repair). Hence, the decreased global RVEF after TV repair was due to both worse RVOT function (TV repair: 22 ± 13 % versus TA repair: 47 ± 10 %, $p<0.001$) and worse sinus function (TV repair: 51 ± 8 % versus TA repair: 63 ± 9 %, $p< 0.001$).(figure 2)

Figure 2. Bar-plot representing the contribution of Sinus and RVOT component on global RV function in all patients and by type of ToF repair

(Each bar represents the mean ± SD)



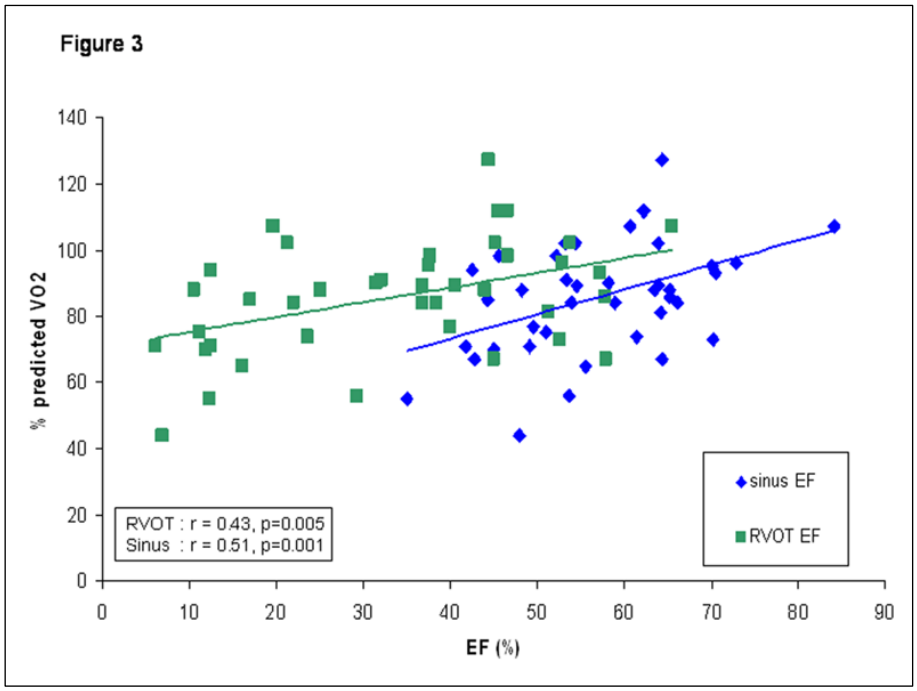
Increased PRF was significantly associated with dilatation of both sinus (EDVi: r = 0.58, p<0.001 and ESVi: r = 0.50, p<0.001) and RVOT component (EDVi: r = 0.56, p<0.001 and ESVi: r = 0.51, p<0.001), but not with systolic function of the components : sinusEF (r = -0.23, p=0.14) and RVOTEF (r = -0.26, p=0.10). In contrast, the extent of RVOT akinesia correlated negatively with both sinusEF (r = -0.48, p=0.001) and RVOTEF (r = -0.70, p<0.0001), but did not correlate with PRF (r = 0.29, p=0.06).

Regarding the LV function, LVEF was significantly associated with decreased RV function (sinusEF: r = 0.43, p=0.005 and RVOTEF: r = 0.56, p<0.0001 and global RVEF: r = 0.54, p<0.0001).

Effects of regional RV dysfunction on exercise performance

Percentage predicted peak VO_2 correlated better with sinusEF (r = 0.51, p=0.001) than with RVOTEF (r = 0.43, p=0.005) and global RVEF (r = 0.45, p=0.004) (figure 3).

Figure 3. Relation between exercise capacity and RV component function



Based on the use of end-diastolic volume for size of the RV components, a significant association was only found with the RVOT size (EDVi: r = -0.39, p=0.013), but not with the size of the sinus component (EDVi: r = -0.13, p=0.43) nor global RV dilation (EDVi: r = -0.06, p=0.71). There was no relationship between % predicted peak VO_2 and PRF (r = -0.047, p=0.39). The correlation between exercise capacity and LV function (LVEF: r = 0.30, p=0.06) was not significant. Multivariate stepwise linear regression analysis with adjustment for differences in follow-up interval, revealed sinus EF and extent of RVOT akinesia as main determinants of % predicted peak VO_2 (table 4).

Table 4. Linear regression analysis of % predicted peak VO2 in relation to RV and LV function variables

	Univariate analysis		**Multivariate analysis**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**
Global RV Data				
RVEDVi	-0.03 (-0.17;0.12)	0.71		
RVESVi	-0.18 (-0.35;-.007)	0.04		
RVEF	0.70 (0.25;1.23)	0.04		
PRF	-0.08 (-0.62;0.46)	0.77		
RV akinesia	-0.33 (-0.55; -0.1)	0.005	-0.28 (-0.5;-0.06)	0.015
Regional RV Data				
Sinus EDVi	0.07 (-0.11; 0.26)	0.43		
Sinus ESVi	0.15 (.13;0.43)	0.17		
Sinus EF	0.74 (0.31;1.14)	0.001	0.34 (0.07;0.61)	0.013
RVOT EDVi	-0.42 (-0.74;-0.09)	0.01		
RVOT ESVi	-0.47 (-0.81;-0.15)	0.006		
RVOT EF	0.45 (0.14;0.75)	0.005		
LV Data				
LVEDVi	0.13 (-0.27;0.52)	0.52		
LVESVi	-0.36 (-0.99;0.28)	0.26		
LVEF	0.56 (-0.03;1.14)	0.07		

Seventeen patients (43 %) had subnormal exercise performance, in respectively 13(65 %) and 4(20 %) patients after TV and TA repair (p=0.01). Compared to patients with normal exercise capacity, they had worse global RVEF by both decreased RVOTEF and sinusEF as well as lower LVEF (table 3). Multivariate logistic regression analysis with adjustment for time interval variability, demonstrated only TV type of repair as main determinant of poor exercise performance (OR. 6.0, 95 %CI 1.31-17.3, p=0.02), by combining lower sinusEF (TV repair: 51 ± 8 % versus TA repair: 63 ± 9 %, p< 0.001) and lower RVOTEF (TV repair: 22 ± 13 % versus TA repair: 47 ± 10 %, p< 0.001), as well as impaired LVEF (TV repair: 60 ± 9 versus TA repair: 69 ± 7 %, p< 0.001).

Discussion

Longterm surveillance after repair of ToF is focused on the timely detection of RV dysfunction to indicate the need for pulmonary valve implantation, and is usually based on the measurement of severity of PR and global RV size by echocardiography and CMRI, assessment of clinical functional status by exercise testing and follow-up of pro-arrhythmogenic indicators such as increased QRS duration [9,10].

In order to clarify the discrepancy between the residual hemodynamic abnormalities of the RV and the clinical performance in these patients, the relation between CMRI parameters and exercise capacity has been examined in only a few studies [11-13]. Assessing global RV function, RV ejection fraction was the strongest predictor of percentage of predicted peak VO_2, independent of RV size, pulmonary regurgitation fraction and systolic LV function[11,12]. The Boston group also demonstrated that greater regional dysfunction of the RVOT adversely affected both global RV function and exercise function[13]. Through separate quantitative functional analysis of the anatomical RV components, i.e. sinus and outflow parts, our study has shown that this conceptual approach reflects more appropriately the real RV function after ToF repair, as the commonly depressed or even absent contractile function of the RVOT usually results in underestimation of global RV function. In addition, the systolic function of the RV sinus component appears to be a better predictor of the exercise performance of these patients, supporting the usefulness of such more refined analysis of the RV during late follow-up of ToF patients.

Lytrivi et al. revealed an equivalent conclusion in a ToF population with a wider age variation of 2-42 years, as they found globally a preserved sinusEF of 43-64 %, in a range comparable to healthy control subjects [4]. Moreover, the relevance of the sinus component on clinical performance is certainly pertinent and corresponds to the findings of Bodhey et al. on the functional analysis of the tripartite RV in ToF patients, showing that the trabecular part constitutes the major driving force of the RV and provides most accomodation to the chronic PR-related volume overload [5].

Otherwise, greater regional dysfunction at the RVOT, quantified by both EF as well as by extent and displacement of dyskinetic area, was the predominant factor affecting exercise capacity in the series of Wald et al [13]. According to their results, the extent of RVOT akinesia was another independent but negative predictor of exercise tolerance in our study. Here, the technique of primary ToF repair has indirectly interfered as a transventricular approach induced worse RVOT function by use of larger RVOT patches, in comparison with the more contemporary operated patients. However, since the time from ToF repair to study inclusion was indentical to their study, ranging between 8 and 45 years, it remains questionable whether this technical issue was underestimated in their analysis by including patients with probably different physiological loading conditions, as these treated with a RV-PA conduit or with a minimal PRF of 3 %.

Our data revealed a poor correlation between exercise function and size of the RV, excepted for the RVOT component. The latter is comprehensible as the end-diastolic and end-systolic volume are approximating, depending on the extent of the RVOT patch. However, the systolic function of the RV, and in particular the sinus component, seems more reliable than the degree of dilatation and the severity of pulmonary insufficiency. This additionally subscribes the superior value of the end-systolic volume over the end-diastolic volume for the serial follow-up of RV function.

Specific subgroup analysis concerning exercise capacity demonstrated that the type of ToF repair was the main determinant of subnormal exercise performance, indicated by a predicted peak $VO_2 < 85$ %.

In relation to the CMRI data, this group had worse RV function by both depressed sinusEF and RVOTEF. Although this patient cohort had also inferior LV function, it is difficult to assume that a LVEF averaging 60 %, is responsible for the decreased exercise tolerance. Besides the potential influence of the interventricular functional dependency, other discriminants have to be considered such as the proven time-related deterioration of exercise capacity and the reciprocal interactive effect of chronotropic incompetence [8,14].

Clinical implications

Unless evidence of heart failure symptoms or malignant arrhythmia, current management to restore RV function by implantation of a pulmonary valve in patients with repaired ToF is based on determination of global RV volumes. However, several studies have reported conflicting results from complete normalization of RV size to lack of improvement of RV function, still keeping up the debate on the timing of RVOT valvulation [15-17]. Perhaps, one of the reasons for these inconsistent results is related to the fact that most studies have been performed on patients treated in former eras, including a variety of surgical techniques for RVOT relief – from pulmonary valvotomy to extensive RV patches and RVOT conduits – and different gradations of combined volume- and/or pressure overload sequelae. In addition, investigation of the RV remodeling in these studies has usually been based on the whole RV as one anatomical entity. However, it is obvious to assume the prognostic difference in recovery of RV function after pulmonary valve implantation between two equally volume-sized RV's with equal degree of PR, whereas in the first case the RVOT component is aneurysmal and contributes strongly to the global RV volume, while in the second case, most of the dilatation process has involved already the sinus part, but preserved RVOT function. By individual functional quantification of the main RV components, our method might be more appropriate to further elucidate this decision-making process. The large akinetic RVOT commonly increases the global RV volume, inducing underestimation of the real RV function, as it probably also affects the contractile properties of the adjacent segments involved in the remodeling process. Hence, the function of the sinus part might represent a more reliable determination of the intrinsic RV function, and correlates best with the clinical functional status. The relevance of this contribution has recently been confirmed by Alghamdi et al. who identified that the longitudinal strain at the base of the RV, remoted from the RVOT, was a stronger predictor of exercise performance than other echocardiographic or CMRI-derived measurements [18]. The precise role of this specific assessment has yet to be confirmed as CMRI is still indispensable in the work-out of the repaired ToF patient, for delineation of global RV volume and function as well as of RVOT morphology. Basically, there are some similarities with the concept and management of the post-infarction LV remodeling. The extent of the scarred aneurysm adversely affects LV size and function, and is certainly useful to guide the decision for surgical therapy [19,20]. But it is the contractile performance of the remote, intrinsically undiseased myocardium that best predicts

the functional outcome after surgical ventricular restoration, and so helps to improve the patient selection [21].

Our data also underscore the statements of Wald et al. on the therapeutical implications, that extensive resection of the akinetic RVOT segments should be performed in addition to pulmonary valve insertion, for maximal functional recovery of the RV [13]. Subsequently, it is conceivable that the particular patients with a prominent post-surgically scarred RVOT will benefit more from a surgical approach with additional operative RVOT remodeling than from isolated transcatheter valve implantation.

Study limitations

As a consequence of the retrospective design, the studied patient cohort is subjected to bias. It is plausible that merely these patients were included, who had a specific indication, either by clinical, electrophysiological or echocardiographic examination, to perform CMRI. Hence, the patient characteristics of our study are comparable to others, and incorporates a cohort of ToF patients treated within a time span including the transition of surgical eras from a transventricular to the more actual transatrial-transpulmonary correction [5,11-13]. Although the type of surgical approach was entered as study variable, it remains difficult to differentiate the effect of the repair technique from the time effect that the RV has been exposed to the pathological loading conditions. However, potential confounders were minimized by correlating the CMRI-derived RV parameters with the individual age-adjusted exercise function. Nonetheless, we feel confident that the sinus part of the RV corresponds best to the intrinsic RV function, irrespective of the kind of RVOT repair, emphasizing the usefulness of a differential and more refined functional analysis of the RV.

In this study, only the effect of purely chronic volume-overload after ToF repair was analyzed, and might not be completely representative for the ToF spectrum by excluding patients with significant residual obstruction at both ventricular and/or pulmonary arterial level.

Conclusion

After repair of ToF, the RV is challenged by the kind of RVOT reconstruction and its subsequent longterm physiological effects. Through separate functional analysis of the anatomical RV components, this study has demonstrated that the global RV function is commonly underestimated, depending on the extent of RVOT dysfunction. The systolic function of the RV sinus appears to be a more reliable determinant of the intrinsic RV performance, by better predicting the exercise capacity of the individual patient. Further validation in larger scale studies is needed to postulate whether this method of RV analysis is more appropriate than assessment of global RV volumes for timely detection

of early RV dysfunction in order to initiate subsequent pulmonary valve implantation with eventual associated surgical RVOT remodeling.

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Chapter VIII : Discussion

Contemporary surgical repair of TOF consists of a transatrial-transpulmonary approach for closure of the VSD and relief of the RVOTO. The increasing knowledge on the detrimental long-term sequelae of severe PI, acquired in TOF patients operated on in former eras, has stimulated a change in the management of TOF on two fronts.

First, there has been a competitive search to minimize the surgical insult to the RVOT, pursuing maximal preservation of pulmonary valve function. Successful valve-sparing RVOT repair has been reported in selected TOF patients with moderate hypoplasia of the pulmonary valve annulus [1, 2]. Recently, adepts of this valve-sparing approach started with intra-operative dilatation of the pulmonary valve. However, in a substantial number of patients, relief of the infundibular obstruction is performed through a separate subvalvular infundibulotomy followed by patch closure, resulting in elimination of infundibular function. Moreover, more than half of these patients developed PI at short-term [3]. In order to maintain some pulmonary valve function, reconstruction of the RVOT with a monocusp patch in the patients necessitating transannular relief, has been proposed as a valid alternative. Despite encouraging short-term results, its long-term advantage has never been proven [4, 5]. Others however have focused on an infundibulum-sparing approach in order to spare preferentially the RV [6].

Secondly, to avoid some of the inconvenient physiological features as cyanosis and RV hypertrophy , and to get rid of the potential shunt-related complications, complete repair has been advanced as a primary therapy in younger aged children with TOF. Presently, experience with TOF repair in neonates or within the first months of life has demonstrated the feasibility of this surgery, resulting in acceptable mortality but at the cost of prolonged ventilation times and intensive care stay. Moreover, RVOTO relief necessitated a TAP in 60 to even 100 % of the patients [7-10].

However, the long-term effects of this two-sided change - decreasing the age for repair and pursuing a RVOT-sparing correction – remain to be seen.

1) Regarding the RVOT-sparing strategy, the role of the infundibulum versus the pulmonary valve on RV performance has been investigated occasionally. Based on the history of the treatment of isolated pulmonary valve stenosis, it has been shown that chronic PI with preservation of infundibular integrity, unlikely resulted in severe impairment of clinical status before the third decade [11]. In contrast, the effect of PI is accelerated in the setting of TOF, after repair of the RVOT with TAP. d'Udekem et al. observed that a large RV patch had a similar effect on the clinical outcome as a transannular patch, even though the pulmonary annulus was anatomically kept intact [12]. However, this analysis concerned patients operated on by the former transventricular approach, and in all cases the pulmonary valve needed at least concomitant commissurotomy.

Since Geva et al. demonstrated that the infundibulum contributed to only 15% of the total RV stroke volume in healthy individuals [13], hereby minimizing its participation in RV function, the dilemma on the differential contribution of infundibulum versus pulmonary valve in the condition of TOF was further clarified in an experimental model, as described in **chapter IV**.

In a model of growing swine, RV performance was studied in relation to isolated PI versus isolated infundibular dysfunction, and compared to the effect of combined PI and infundibular dysfunction by a TAP. Both the acute postoperative effect and the chronic effect after 3 months were assessed with the conductance catheter, with additional validation by CMRI. We found increasing PRF in animals with isolated PI after 3 months, but this PRF progression was significantly enhanced by concomitant infundibular dysfunction. Subsequently, RV dilation with progressive decrease of RVEF was noticed more extensively in animals with TAP repair compared to those with isolated PI. Increasing PRF was also found in a similar experiment, where PI was created by stent implantation at the level of the pulmonary valve [14]. In that study, PRF was already high due to the study design, and increased with 50 % after 3 months, a result that was only seen in our experiment by adding infundibular dysfunction. Of interest, isolated infundibular dysfunction did not result in secondary RV remodeling, but induced immediate decrease of contractile function due to intrinsic surgical damage of the ventricle. After 3 months, contractility had decreased in all study groups, with the worst result in animals with TAP repair. Although isolated PI also initiated progressive decrease of contractile function, the contractility indices were still superior in the animals with preserved infundibular function. The physiological effects in terms of RV dilation and contractility, were similar to those observed in other animal studies, albeit in one study the infundibular effect was not integrated [14], whereas in the other, only the effect of the classical transannular patch was examined [15]. From a clinical point of view, our animal study confirmed that TAP reconstruction of the RVOT affected the RV performance most by combining the adverse effect on myocardial contractility due to the infundibular dysfunction, and on top of this, the gradual RV dilation by progressive PI. The importance of sparing the infundibulum was underscored by its impact on RV contractile function, even though it represents only a small part of the global RV, and by the enhanced accommodation on progression of PI. In consequence, the results of this study certainly supported the actual adoption of a RVOT-sparing strategy for repair of TOF.

2) The policy to perform primary complete repair of TOF in infants at early postnatal age, has been addressed by the second experimental study, reported in **chapter V**.

In TOF, one might assume that the degree of RV hypertrophy before correction is related to the severity of RV pressure-overload – which is depending on the morphology of RVOTO – and to the duration of pressure-overload exposure – which relates to the age of the patient at the time of surgery. In a model of growing swine, the effect of RV hypertrophy, first induced by pulmonary artery banding, was investigated in function of chronic PI-related volume overload, induced by TAP reconstruction of the RVOT. The acute and chronic effects after 3 months were evaluated with the conductance catheter

method, and verified with echocardiography. In this experiment,, volume-overload was only created by TAP, as it revealed to have the most detrimental effect on RV performance in our previous study. The results demonstrated that RV hypertrophy is associated with alterations of intrinsic myocardial properties of both systolic and diastolic function. RVH initiates better contractility in comparison with animals without RV hypertrophy, and it enables better preservation of systolic function 3 months after exposure to PI. However, it entails sustained impairment of RV compliance, in relation to an increased mass-to-volume ratio of the RV. In addition, RVH attenuated the amount of PI as well as the duration of pulmonary regurgitation time. Subsequently, the RV remodeling in relation to chronic volume-overload appeared to be significantly less extensive.

The investigation of the sequential effect of pressure-overload preceding volume-overload has never been addressed in animal models. In contrast, RV adaptation to chronic isolated pressure-overload has been studied frequently, confirming the positive effect on contractile function and the negative effect on diastolic performance [16, 17]. Although dissimilar to our study design, Kuehne et al. evaluated the chronic effect of combined volume- and pressure-overload on RV dynamics [18]. They found that the addition of pulmonary stenosis improved the systolic RV function, at the cost of decreased diastolic RV function in relation to PI. Nonetheless, concluding that the resultant RVH acted protective against progression of PI in their study, seemed blunted to us as the method to create combined PI-PS was based on the insertion of a partially obstructive stent into the pulmonary valve, with an obviously restrictive regurgitant orifice.

Interestingly, we found a characteristic pulmonary artery flow pattern at echocardiography suggestive for restrictive RV physiology, only in animals with RVH and PI, both in the acute as in the chronic phase. Precluding other confounding factors thought interacting with this phenomenon [19-21], our findings revealed that probably RVH is the culprit substrate, promoted specifically by severe PI, through decreasing the diastolic pressure gradient between the stiff RV and the pulmonary artery. Although the clinical meaning of restrictive RV physiology on the long-term is controversial, it was associated with a propitious effect on the late RV remodeling after volume-overload in our animal model.

The clinical consequence of this study is that repair of TOF in a neonate might compromise RV performance prematurely, in particular when TAP reconstruction is deemed necessary, by subjecting a poorly hypertrophied RV to the acute and chronic effects of PI-related volume-overload. Therefore, adapting the strategy to choose for a shunt in a symptomatic neonate, and postponing elective primary repair for a few months, might here be justified. However, a neonate or young infant presenting with a favorable RVOT morphology in whom the pulmonary valve might be kept functional at the time of repair, should benefit from early repair to enhance the reversal of the RVH-related diastolic dysfunction.

Otherwise, this model did not allow speculation on the optimal age for TOF repair by lacking variability in RVH quantity. In contrast to the real-time physiology in TOF, affording overload

decompression through the VSD, longer exposure to RV pressure-overload in these animals would have resulted in a decompensated state of the RV. In addition, the rate of reversibility of RVH has to be considered in long-standing pressure-overload, entailing an adverse effect on RV function rather by interstitial fibrosis than by myocyte hypertrophy [22, 23]. Based on clinically-oriented studies focusing on the impact of age on late functional outcome, one might accept that complete repair of TOF should ideally be performed before the age of 1 year [24, 25].

The link between the findings of the experimental studies and clinical observations is reported in **chapter VI**. In this study, we reviewed our 15-years experience with surgical treatment of TOF, using consistently a transatrial-transpulmonary approach in 140 children. During the study period, surgical practice evolved from the application of an extended TAP (57% in the first era) towards a valve- or infundibulum-sparing RVOT repair (40% valve-sparing and 40 % infundibulum-sparing in the recent era). At the same time, the median age decreased from 11 months to 5 months. We concluded that the adoption of RVOT-sparing surgery was advanced reciprocally through and together with lowering the age for repair. This change was performed without compromising the immediate clinical outcome, however entailing an increased rate of early reoperation (14%) due to residual/recurrent obstruction. Echocardiographic assessment confirmed that RVOT-sparing techniques provided a lesser degree of PI and lower RV/LV size ratio, revealing that the length of transannular incision was the strongest predictor of RV dilation within a mean follow-up of 7.5 ± 4.7 years.
The advantages on RV remodeling, by attempting preservation of the pulmonary valve or at least the infundibular function, have been shown by the data of the first experimental study (chapter IV). Of course, as the main objective in the treatment of TOF is the adequate relief of the RVOTO, the extent of RVOT reconstruction is largely dictated by the morphology of the RVOT. Pulmonary valve preservation is facilitated in TOF patients belonging to the better range of the spectrum with appropriately sized pulmonary annulus, whereas extended TAP repair was used rather in the anatomically less favorable patients. In the endeavor to limit the surgical damage of the RVOT, the immediate operative result is challenged by the risk of early reoperation. Here, critical intra-operative appraisal of the RVOT by transoesophageal echocardiography is of utmost importance, to differentiate between a fixed anatomical stenosis and a dynamic obstruction, in case of elevated RV/LV pressure ratio at the end of repair. According to Uebing et al. [26], tailoring the pulmonary annulus by sizing the transannular patch to the lower acceptable limit of z-value for each individual patient, might perhaps be the ideal compromise concerning a 'too much, too little' policy for relief of the RVOTO.

Lowering the age of primary repair of TOF, as shown in the retrospective clinical study, might be in conflict with the findings of the second animal study (chapter VI), relying on the beneficial contribution of RVH on late RV remodeling by chronic volume-overload. However, an RVOT-sparing repair of TOF was facilitated partially through the less extensive hypertrophy in these

younger infants, assuming that the magnitude of transannular relief is greater in the condition of a more hypertrophied and cumbersome outflow tract. Based on the positive effect of some low-grade residual obstruction on late RV performance [27, 28], resulting in a reduced need for late PVR [29], we feel confident that minimizing the surgical aggression on the RVOT, might swing the pendulum slightly in favor of the surgical technique above the physiological feature.

Nevertheless, our experimental and clinical findings are in agreement regarding the issue of repairing TOF at a too young age. Our strategy of TOF repair is to preclude primary correction in the symptomatic neonate or infant less than 2-3 months old. Instead, an intermediate Blalock-Taussig shunt is preferred in order to perform complete elective repair at a later age. However, it is likely that, in the symptomatic neonate, the anatomical substrate would trend towards a smaller RVOT, explaining the high frequency of TAP in most series [9, 10, 30]. Such two-stage strategy evokes the question on the natural growth of the pulmonary annulus, to predict the potential of performing a valve-sparing procedure later. The opinions on this subject are discussable [31, 32], but in practice, the use of a TAP is avoided in a substantial number of patients who were initially treated with a shunt [33, 34]. Furthermore, if RVOT repair inevitably includes pulmonary valve dysfunction, an infundibulum-sparing approach is still valid with the additional benefit of already distinct RVH at a slightly older age.

Recently, stenting of the narrow RVOT has been proposed as another alternative to overcome the early symptomatic neonatal course. Removal of the stent imbedded in the infundibulum, resulted in the later requirement of a TAP in 86 % [35], and compromised certainly the possibility of an infundibulum-sparing approach.

Finally, besides associated comorbidities as genetic disease or extra-cardiac malformations, the decision on the surgical management of TOF should be based on an individualized approach, taking into account of the specific cardiac-related factors as RVOT characteristics and associated intra-cardiac anomalies, to minimize the risk of the early surgery, while assuring the optimal cardiac condition for the future.

The concerns on the long-term outcome of TOF are related to the adaptation of the RV to the chronic PI-related volume-overload. There is no doubt that PVR is indicated in the patient with evident symptoms assigned to the RV dilation and significant PI. In the majority of TOF patients however, the relation between RV dysfunction and clinical status is less clear.

Currently, PVR is advised in the asymptomatic patient, based on a QRS duration > 140 msec and the determination of the critical end-diastolic volume of 150-180 ml/m² [36-38]. Geva et al. also validated the importance of end-systolic volume in the judgment for PVR [39]. However, the question raises whether these absolute volumes have a similar significance for the one RV in which one third of the volume is comprised in a RVOT aneurysm, versus the other RV accumulating most of that volume in the body of the ventricle.

In **chapter VII**, a study on the contribution of the main anatomical components of the RV, i.e. the sinus and the RVOT, on global RV function by CMRI, was designed in 42 repaired TOF patients. The RV data were related to their exercise capacity as an objective parameter of clinical status.
Independent of the type of surgical repair, the global RV function, expressed as RVEF, was commonly underestimated, due to the usually decreased function of the akinetic RVOT. This effect was more pronounced in the group that underwent transventricular repair. Additional analysis showed that the magnitude of PRF correlated significantly with the RV size, but not with the RV function. The pump function of the sinus part of the RV correlated best with the exercise performance, based on the determination of predicted peak VO_2, adjusted for age and gender. Multivariate analysis identified RV sinus EF as a positive predictor, and extent of RV akinesia as a negative predictor of exercise performance.
Applying an identical method of analysis comparing TOF patients with healthy peers, other authors found that the sinus part of the RV in TOF usually had a preserved function [40, 41]. In a CMRI-mediated study based on the evaluation of the RV as a whole, exercise function appeared to correlate mainly with RVEF. Wald et al. demonstrated later that the extent of RVOT dysfunction was the main determinant of worse exercise tolerance. In agreement with the similar finding on the qualitative assessment of a RVOT aneurysm [42], they quantified RVOT function by spatial extent of dyskinesia, via the method of late gadolinium enhancement [43].
The relevance of the systolic function of the RV sinus to the functional capacity is further supported by the recent report of Alghamdi et al., showing that the common echocardiographic and CMRI-related indices of global systolic function are at least weak predictors of exercise performance in TOF patients with common RVOT dysfunction. They advanced the longitudinal function of the RV by tissue-Doppler echocardiography, measured remotely from the RVOT, as the most reliable determinant of exercise performance [44]. Therefore, as the RV sinus reflects more properly the intrinsic contractile reserve of the RV, it is conceivable that the analysis of this RV component should be considered separately for its potentially stronger predictive value for post-PVR functional recovery.
This largely underscores the method of RV analysis through separate estimation of the contribution of sinus part versus RVOT part during the late follow-up of TOF, instead of the integral analysis of the RV as one global entity. This might not only contribute to the timing for PVR, but also to the technique of PVR. If decreased exercise tolerance is related to large RVOT akinesia with preserved RV sinus function, PVR should include additional surgical remodeling of the RVOT in an attempt to optimize the global RV performance. In contrast, if exercise intolerance is due to merely impairment of sinus function, earlier valvulation of the RV should be proposed, which can be achieved equally effective by transcatheter valve implantation in case of adequate RVOT anatomy.
However, validation in larger scale studies is needed to postulate whether this refined method of RV analysis is more appropriate than assessment of global RV volumes for timely detection of early RV dysfunction in order to point out the ideal timing of subsequent pulmonary valve implantation.

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Chapter IX : Future Perspectives

At the time of presentation of this thesis, some studies have already been initiated, while other ideas for further research on topics specifically related to this subject are maturing.

1. Experimental research

The experimental animal model as described in chapter III, included already the investigation of electrophysiological changes of the RV in relation to chronic volume-overload. The methodology was based on the evaluation of locale RV myocardial electrical depolarization properties through measurement of epicardial mapping of monophasic action potentials (MAP), measurement of intra-ventricular conduction propagation of the RV in two axes, and a protocol of induction of malignant tachy-arrhythmia. The execution and analysis of this additional study has been done in close collaboration with some members of the clinical electrophysiology staff. However, preliminary analysis of the data showed inconclusive results in view of the small sampled animal series.
After modification of the technical application of MAP recording with the use of the more stable endocardial MAP-electrode, the study was further elaborated during the second animal experiment, reported in chapter IV. The analysis of these data are currently in process.
Nonetheless, it is conceivable that the premised period of 3 months to determine the 'chronic phase' in this animal model, might be relevant for the mechanical changes of the RV, but not for the electrical ones. According to a similar study design [1, 2], significant electrical disturbances have been found after at least 5 to 6 months of chronic volume-overload. Presuming that 3 months in the growing immature swine corresponds to a mid-term follow-up span of approximately 10 to 12 years, a preliminary conclusion on our data might be that the mechano-electrical feedback mechanism did not yet induce important electrophysiological changes, such that the risk of malignant ventricular arrhythmia in the TOF patient is negligible at mid-term follow-up.
Consequently, the intention to extent the experiment by adding a group of animals, subjected to chronic PI-related volume-overload for at least 6 months, has already been decided for evaluation of the electrical characteristics in relation to the hemodynamical effects.

The future of the history of TOF should probably have a different scenario, once the advent of a tissue-engineered valve substitute will lead to a consistent and reproducible result. Besides promising initiatives elaborated in our laboratory regarding engineering of tissue valves, we already started a first step towards the development of a pericardial patch with contractile properties. Based on the successful method of myocyte cultures derived from atrial appendage progenitor cells [3], myocyte isolation from atrial appendage samples has been performed for an early trial of cell culture in a bio-reactor. The idea should be to seed a decellularized pericardial patch with living myocytes, in order to

obtain a patch with some preserved contractile performance. The hemodynamic contribution of such contractile patch might be further examined by the conductance technique and CMRI.
As the data of our experiment in chapter III emphasized the importance of preserved functional integrity of the infundibulum in the process of chronic volume-overload, this alternative approach might be of interest for further research in the setting of TOF.

2. Clinical studies

In cardiac surgery there is a growing trend for application of hybrid approaches, gathering the best of two techniques to optimize the outcome of a procedure. Convinced by the benefit of the RVOT-sparing repair techniques in TOF on the long-term, the introduction of intra-operative balloon dilatation of the pulmonary annulus has yet been discussed. So far, the technique has already been applied successfully in one patient. The feasibility and effectiveness of this approach will be put in a prospective pilot study, focusing on selected TOF patients with a hypoplastic pulmonary annulus including a z-value ranging between – 1 to – 4.

Confronted with an increasing number of patients with congenital heart disease, reaching adult age, a protocol of prospective disease-oriented follow-up has already been discussed in our department of pediatric and adult cardiology in collaboration with the members of cardiac surgery, involved in that field. Regarding TOF, this includes the serial follow-up of RV function by echocardiography and yearly exercise testing. Additional CMRI investigation is performed on a prospective basis, first as a baseline evaluation and then every 2-3 years, depending on particular indices suggesting deterioration on echocardiography or exercise tests in asymptomatic patients.
This protocol was partly the fundament of the clinical study reported in chapter VI, concerning here the inclusion of the younger aged patients of the cohort. Further elaboration of this protocol with time should not only benefit the follow-up of the individual TOF patient, but using the proposed methodology of RV assessment by separate analysis of the sinus versus the RVOT, might be of help to increase our insight into the specific adaptation of each RV component in function of the contemporary surgical treatment. Moreover, confirmation of the validity of this method definitely should be based on larger sample-sized patient groups, in order to derive clear cut-off points for decision on timing and type of subsequent surgery.

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Chapter X : Summary

The surgical treatment of tetralogy of Fallot is one of the success stories in the history of congenital heart diseases. Over the years, the operative mortality has decreased to less than 2 % and the long-term survival is excellent, affording the majority of these patients an acceptable quality of life. However, late attrition has increasingly been recognized in relation to progressive RV dysfunction due to chronic and severe PI.

To cope with the deleterious long-term sequelae of the originally extensive relief of the RVOTO, the focus has moved to the currently performed transatrial-transpulmonary repair of TOF. Moreover, during the past decade, surgical management yielded a two-sided change through pursuing RVOT-sparing techniques on one hand, and through performing primary complete repair in infants during their first months of life on the other hand. The late impact of these adaptations are however unknown.

Over the past 15-years, the surgical management of TOF in our center involved a gradual and mutual change, that included a trend towards a RVOT preserving policy and lowering the age of repair (chapter VI). This policy change was performed without major impact on the clinical outcome but at the cost of an increased frequency of early reoperation for residual or recurrent RVOTO. Although the midterm effect on RV remodeling appears promising, the controversy whether the protection of the pulmonary valve function or the function of the RV should be the primary focus at repair remains open.

In chapter IV, this issue was addressed in an animal study, investigating the differential contribution of the infundibulum versus the pulmonary valve on RV performance after chronic volume-overload. This study learned us that preservation of the pulmonary valve function prevents progressive remodeling of the RV, with its adverse effect on pump function and finally contractile performance. However, as in these cases with pulmonary annulus hypoplasia, a valve-sparing technique might not appropriately address the obstruction, maximal preservation of the infundibulum is encouraged because surgical damage of the infundibulum not only is associated with immediate decrease of RV contractility, but also further loss of accommodation capacity to progression of PI. Based on these findings, we feel confident with the pursuit of a RVOT-sparing strategy during complete correction of TOF.

The other issue regarding the age at the time of primary repair, was indirectly addressed in chapter V, by analyzing the effect of RVH on the RV performance after chronic volume-overload. The alterations of intrinsic myocardial properties in terms of systolic and diastolic function, induced by RVH, appeared to affect significantly the physiological effect of PI and so, the RV remodeling process. The clinical consequence relies on the beneficial effect of reversible RVH through discouraging primary repair of TOF at the neonatal age, in particular when RVOTO relief would implicate a transannular patch resulting in early severe PI. It additionally strengthens the idea that an intermediate shunt before

complete elective repair at a later age, is still a valid option without necessarily compromising the child's RV by a TAP-induced PI. Meanwhile, there is strong evidence that leaving some mild residual obstruction might be the best protection against chronic PI, supporting the surgeon's search for the optimal equilibrium between residual pressure-overload and minimal volume-overload, for the benefit of the RV.

Once severe RV dilation due to PI has occurred during late follow-up, the decision for PVR to prevent irreversible RV dysfunction, is usually based on the determination of global RV volumes, even in asymptomatic patients. Classically, an end-diastolic volume of global RV that exceeds 150-170 ml/m² already indicates a threshold for PVR, irrespective of the post-surgical RVOT morphology. In chapter VII, we proposed another method of RV analysis by separate functional assessment of sinus and RVOT component of the RV, using CMRI. Despite severe PI, the sinus function of the RV in TOF patients remains usually well preserved, in contrast to the negative influence of the akinetic RVOT. Using exercise testing as objective estimate of clinical status, the percentage of predicted peak VO_2 was independently determined by the sinus function as well as by the RVOT function, in an opposite way. Consequently, integration of the sinus function in the choice for PVR might better predict the chance of post-PVR recovery of RV function. We suggest that this more refined method of analyzing the RV in relation to the contribution of its main components on the global RV function, is more appropriate to the decision-making process for eventual PVR in TOF patients.

In summary, through assessment of the RV performance in relation to RVOT dysfunction in experimental and clinical studies, we have increased the understanding on the contribution of specific components of the RV, from an anatomical standpoint (infundibulum versus pulmonary valve – RVOT versus sinus) as well as from a physiological standpoint (right ventricular hypertrophy – myocardial dysfunction versus PI). The results of this research have consolidated a surgical strategy of repair of TOF in favour of a RVOT-sparing approach, best performed in infants beyond the postnatal age, to provide the perspective on an optimal longstanding RV performance. Further insight into the pathophysiological adaptations of the main components of the RV after repair of TOF might also help in the decision to timely detect and reverse RV dysfunction by appropriate valvulation of the RVOT.

Chapter XI : Samenvatting

De heelkundige behandeling van tetralogie van Fallot behoort ontegensprekelijk tot de succesverhalen van de chirurgie in het domein van aangeboren hartziekten. Over de voorbije 50 jaren, is de operatieve mortaliteit gedaald tot minder dan 2 % , terwijl de overleving op lange termijn uitstekend is, met een aanvaardbare levenskwaliteit voor de meeste patienten. Toch zijn deze patienten niet vrij van laattijdige problemen, door het optreden van progressief functieverlies van het RV door chronische pulmonalisklepinsufficientie. De chirurgie van TOF was in eerste instantie vooral gericht op het maximaal wegnemen van de RV-uitstroomobstructie, waarvoor vaak een uitgebreide chirurgische uitruiming werd aangewend. Geconfronteerd met de ernstige sequelen van deze techniek, werd overgegaan naar een transatriale-transpulmonale benadering, die minder agressief is voor het rechter ventrikel. Gedurende het voorbije decennium onderging deze benadering bovendien 2 wijzigingen: enerzijds werd gestreefd naar technieken om de functionele componenten van de RV-uitstroomtractus zoveel mogelijk te sparen, en anderzijds werd een volledige correctie van de hartkwaal voorgesteld aan kinderen op steeds jongere leeftijd, zelfs bij pasgeborenen. De laattijdige gevolgen van beide wijzigingen zijn echter onbekend.

Tijdens onze 15-jarige ervaring met de chirurgische behandeling van TOF, hebben wij een graduele wijziging in het beleid ingevoerd, gebaseerd op toepassing van RVOT -sparende technieken en verlaging van de leeftijd voor operatie. In een retrospectief overzicht (Hoofdstuk V) hebben wij aangetoond dat deze beleidsaanpassing geen invloed had op morbiditeit en mortaliteit, doch werd een verhoogde incidentie van vroegtijdige reoperatie voor recidief van RV-uitstroomobstructie vastgesteld. Hoewel deze verandering op het eerste zicht gunstig lijkt voor de RV functie op termijn, is het onduidelijk of men eerder de voorkeur moet bieden aan behoud van de pulmonalisklepfunctie, dan wel aan de maximale bescherming van het RV.
Deze vraagstelling werd uitgewerkt in een dierproefmodel (Hoofdstuk III), waar het differentieel effect van infundibulaire versus valvulaire disfunctie op de RV functie na chronische volume-overbelasting werd onderzocht. Deze studie liet ons toe om vast te stellen dat behoud van pulmonalisklepfunctie de graduele volume-toename van het RV, welke verantwoordelijk is voor laattijdig verlies van effectieve RV pompfunctie en contractiliteit, voorkomt. Vermits een klepsparende behandeling obsoleet is bij ernstige hypoplasie van de pulmonalisklepring, spreken onze data in het voordeel van een infundibulum-sparende techniek in vergelijking met een klassieke transannulaire patch. Beschadiging van het infundibulum door chirurgische therapie leidt immers tot een onmiddellijke aantasting van het contractiele vermogen van het RV, en bovendien gaat hierdoor ook de bufferfunctie van het RV tegenover de pulmonalisklepinsufficientie verloren. Dit dieronderzoek bevestigt hiermee dat de chirurgische behandeling van TOF, die berust op maximaal

behoud van de functionele integriteit van de RV-uitstroomtractus, gerechtvaardigd is met het oog op het gunstige laattijdige effect op de RV functie.
Het andere heikele punt betreffende de toepasselijke leeftijd voor heelkundige correctie van TOF, werd bestudeerd in een analoog diermodel (Hoofdstuk IV), waarbij de invloed van RV hypertrofie op de RV functie na chronische volume-overbelasting werd onderzocht. RV hypertrofie gaat gepaard met specifieke myocardiale wijzigingen met invloed op de systolische en diastolische ventrikelfunctie. Hierdoor wordt het progressieve dilatatieproces door pulmonalisklepinsufficientie op voordelige wijze beïnvloed. Als men rekening houdt met een rechtstreeks verband tussen RV hypertrofie en de leeftijd bij operatie, impliceert dit dat vroegtijdig herstel van TOF op pasgeboren leeftijd niet aan te raden is, voornamelijk niet wanneer de chirurgie ter hoogte van de RV-uitstroomtractus onvermijdelijk zal leiden tot ernstige pulmonalisklepinsufficientie. Daarom lijkt de strategie om deze TOF patienten eerst te behandelen met een tijdelijke shunt in afwachting van een electief herstel op wat oudere leeftijd zeker een valabele oplossing. Bovendien sluit deze houding een RVOT-sparende techniek op later tijdstip niet uit. Inmiddels wordt deze strategie gesterkt door recente gegevens die aantonen dat een beperkte residuele obstructie de beste garantie biedt tegen de nadelige effecten van chronische pulmonalisklepinsufficientie, wat de ijver van de chirurg ondersteunt in zijn zoektocht naar het optimale evenwicht tussen maximaal opheffen van de obstructie en achterlaten van een minimale insufficientie.
Wanneer ernstige RV dilatatie door pulmonalisklepinsufficientie wordt vastgesteld tijdens de opvolging, wordt de beslissing tot pulmonalisklepvervanging meestal genomen op basis van het globale RV volume om irreversibele RV disfunctie te voorkomen, ook bij asymptomatische patienten. Heden wordt een eind-diastolisch RV volume van 150-170 ml/m² weerhouden als indicatie voor pulmonalisklepimplantatie, zonder rekening te houden met de vaak vervormde RV-uitstroomtractus na chirurgie. Wij stellen een alternatieve analyse van het RV voor (Hoofdstuk VI) die steunt op de afzonderlijke functionele evaluatie van de sinus en van de RV-uitstroomtractus, door middel van cardiale magnetische resonantie. Deze studie heeft aangetoond dat de RV sinus functie bij TOF patienten meestal bewaard is ten opzichte van de globale RV functie, als gevolg van de varierende graad van disfunctie van het uitstroomgebied. Via inspanningstesten bleek de voorspelde inspanningscapaciteit – uitgedrukt door maximale zuurstofcomsumptie – positief gerelateerd te zijn aan de RV sinus functie en negatief aan de functie van de RV-uitstroomtractus. Bijgevolg zijn wij van mening dat de RV sinus functie een betere indicator voor pulmonalisklepvervanging kan zijn, met een grotere voorspellende waarde inzake kans op herstel van de RV functie na klepvervanging. Wij zijn dan ook van mening dat deze meer subtiele analyse van het RV via zijn deelcomponenten, een plaats verdient binnen de beslissingsboom voor pulmonalisklepimplantatie bij TOF patienten.

Dankzij de evaluatie van het RV in relatie tot disfunctie van de uitstroomtractus via experimentele en klinische studies, hebben wij getracht om een beter inzicht te verkrijgen in het specifieke aandeel van

elke anatomische deelcomponent die bij het pathologisch proces van TOF betrokken is, dit zowel vanuit anatomisch oogpunt (infundibulum versus pulmonaalklep, RV uitstroom versus RV sinus) als vanuit fysiologisch oogpunt (RV hypertrofie, intrinsieke myocarddisfunctie versus klepdisfunctie). De resultaten van dit onderzoek hebben ons gesterkt in de toepassing van een heelkundig beleid voor TOF dat gericht is op het maximaal behoud van de functie van de RV-uitstroomtractus, en dat een volledige correctie bij voorkeur verricht wordt bij kinderen van minstens enkele maanden oud, met het oog op langdurig behoud van een optimale RV functie. Bijkomend inzicht in de pathofysiologische aanpassing van de deelcomponenten van het RV na chirurgisch herstel van TOF, kan een rol spelen bij de beslissing tot pulmonalisklepvervanging ter preventie van RV dysfunctie.

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