Arterial switch operation for transposition of great arteries: late results in adult patients

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Introduction

Complete transposition of the great arteries (TGA) accounts for 5% to 7% of congenital cardiac anomalies, and represents the second most common cyanotic heart defect 1, 2. Successful surgery, allowing the majority of patients to survive to adulthood, can either involve a physiologic or anatomic “correction”. The former (i.e. atrial switch), introduced in 1958 by Senning and later modified by Mustard, corrects the physiologic abnormality of the TGA by creating an atrial baffle to direct the venous return to the contralateral atrioventricular valve and ventricle3, 4. Although mid-term clinical results are excellent, this procedure leaves the RV supporting the systemic circulation. Hence, complications such as progressive RV dysfunction, ensuing tricuspid regurgitation, frequent arrhythmias, heart failure and early mortality may arise in the long-term5-7.

Several attempts were made to perform an “anatomical correction” of TGA by an arterial switch operation (ASO) even before the Mustard and Senning procedures were introduced. However, it was not until 1975 that Jatene reported a method for switching the great arteries and re-implanting the coronary arteries8. This technique, with subsequent modifications, has nowadays become the method of choice for TGA repair as it, compared to atrial switch, offers the advantage of restoring the left ventricle as the systemic pumping chamber. Although the results of early and mid-term follow-up have been excellent, uncertainty and some concerns about long-term complications in adulthood remain.

The aim of this present study was to review the literatures on the long-term outcomes in early survivors of the ASO and to analyse the rate of cardiopulmonary complications, cardiac function, cardio-pulmonary performance and rate of re-intervention and re-operations. Special attention has been paid for the usefulness of different imaging techniques in detecting residual anatomic and haemodynamic lesions.

Technical aspects

The ASO consists of the transection of the aorta and pulmonary trunk above their sinuses. The coronary arteries are detached from the aorta with a surrounding “button” of aortic wall and sutured in the “neo-aorta”. In the first interventions, RV to pulmonary artery (PA) continuity was frequently established by a prosthetic conduit, due to the excessive distance between the pulmonary trunk, located posterior to the aorta, and the anterior RV9 (Figure 1).

Afterwards, the introduction of the Lecompte manoeuvre allowed translating the pulmonary bifurcation forward anterior to the ascending aorta. Both switched great arteries are then anastomosed into place, with pericardial patches placed into the neopulmonary trunk to fill the defects left by the coronary buttons10. Subsequent technical modifications in coronary translocation and PA reconstruction have further improved the surgical outcome11, 12. The procedure is usually performed within the first 2 weeks of life and should be undertaken no later than the 6th week. Later than this, patients with TGA and intact ventricular septum will have experienced significant regression of LV mass owing to low afterload in the pulmonary circulation. This phenomenon will increase the surgical risk and the occurrence of post-operative LV failure. Coronary pattern is quite variable in patients with TGA. Several methods have been proposed to classify the different patterns of coronary origin and course in this population, as this can significantly affect the surgical approach for the coronary transfer and the long-term outcome13, 14 (Figure 2).

Survival

With increased surgical experience, ASO has demonstrated excellent surgical results and low mortality rate in paediatric cohorts. Consequently, a growing number of such patients are

Figure 1: Schematic view of ASO intervention. A. Great artery configuration in TGA before surgical repair.

The procedure involves:
1. Transection of the aorta above the sinotubular junction and the pulmonary trunk above the pulmonary root (B)
2. Translocation of the coronary arteries into the root of the pulmonary trunk (C)
3. Switching of the aorta and pulmonary trunk with anterior positioning of the pulmonary trunk (Lecompte maneuver), and subsequent reconstruction of the former aortic root with a pericardial patch (D).
4. The former pulmonary root has now become the neo-aortic root.
now reaching the adulthood and recent studies are beginning to define the characteristics and the outcome of this emerging adult cohort. 

Table 1

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<tr>
<th>Diagnostic Projection</th>
<th>Frontal View</th>
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<td>Single RCA</td>
<td>Inverted RCA and Circumflex</td>
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Figure 2: Coronary artery patterns in TGA.

1. Leiden classification. Upper panels show coronary artery distribution as visualized by 2D echocardiography and caudally angulated aortography. Lower panels show same coronary artery distribution as viewed from front. Ant indicates anterior; Post, posterior; R, right; L, left; Sup, superior; Inf, inferior; LAD, left anterior descending artery; and Cx, circumflex coronary artery. Reproduced with permission from Wernovsky and Sanders.

2. Yacoub classification. Reproduced with permission from Yacoub and Radley-Smith.

Coronary complications and ventricular function

Epidemiology

The prevalence of coronary complications in ASO patients and its prognostic significance remain unknown. Survival free of coronary events has been estimated as 92.7, 91, and 88.2% at 1, 10, and 15 years, respectively, while asymptomatic occlusion of the coronary arteries has been reported in up to 2% of hospital survivors. Coronary events most often occur immediately after the ASO and are mainly related to coronary anatomy and to surgical technique difficulties. Late coronary events are rare, with an estimated prevalence of less than 2%, and are supposed to be related to progressive fibrocellular intimal thickening or stretching of the coronary arteries with growth.

In a retrospective study by Legendre et al. among 324 paediatric and adolescent patients who underwent a coronary angiography during the follow-up, coronary obstruction was found in 6.8% of cases, and, at multivariate analysis, it significantly correlated with abnormal coronary patterns (B and
C according to Yacoub and Radley-Smith classification) 21. In this study, non-invasive ischemia tests, i.e. treadmill exercise test and myocardial scintigraphy, demonstrated low sensitivity, even when used in conjunction, in the diagnosis of a potentially severe disease, such as coronary obstruction, and, therefore, the authors recommended periodical coronary angiograms.

Noninvasive assessment of myocardial ischemia
Further studies have been conducted in asymptomatic paediatric and adolescent populations by different non-invasive techniques, but the best means for assessing the coronary circulation in ASO are still controversial.

Nuclear techniques
Positron emission tomography (PET) with N-13 ammonia analysis in asymptomatic children showed an increase of myocardial blood flow (MBF) at rest and, consequently, a significant impairment of coronary flow reserve (CFR) when compared to healthy controls. Visual analysis of the PET images revealed adenosine induced reversible perfusion defects in 24% of patients after ASO 25. These abnormalities were confirmed by a reduced vasoreactivity of the translocated coronary arteries after ASO when studied with quantitative angiographic analysis and intracoronary Doppler flow wire velocimetry 26. Vasoreactivity was reduced not only in the proximal segment, but also in the mid and distal tracts of the coronary arteries. This could be, at least partially, a consequence of translocation of the coronary arteries, which may result in partial myocardial sympathetic denervation, with a potential influence on MBF, as sympathetic system is thought to play a relevant role in modulating the ability of the coronary vasculature to dilate and thus increase the myocardial blood flow during exercise. On the other hand, coronary explantation from the aortic root could account for scar formation around the proximal segment of the vessel with subsequent progressive negative remodeling even in the more distal vessels. Even when myocardial ischemia was assessed using scintigraphy, perfusion abnormalities were extremely common after ASO, with a prevalence of 95.6% at rest. Interestingly, in contrast to what occurs in adults with atherosclerotic coronary disease, in ASO myocardial perfusion defects tended to be stable or improve with exercise, a finding which may possibly reflect a microcirculatory involvement, with recruitment of additional collateral vessels in response to the increased metabolic demands of exercise 27.

Echocardiography
Compared with nuclear techniques, echocardiography offers the advantage to simultaneously assess both myocardial ischemia and ventricular contractile reserve during stress. This is an important issue in ASO patients, as adequacy of the left ventricle is vital to ensure suitability for anatomic repair of TGA. Previous studies have shown a good mid-term prognosis, with the majority of patients having a normal left ventricular ejection fraction (LVEF) at echocardiogram and/or MRI 9, 28. However, it is known that EF, even if a powerful predicting prognostic factor, is not a very sensitive index of early subclinical systolic dysfunction. In a retrospective analysis by Kempny et al in adult ASO patients, among the echocardiographic parameters only mitral anular plane systolic excursion (MAPSE) was found to correlate with exercise tolerance parameters and longitudinal LV function was found to be reduced in a higher proportion of patients compared to LV-EF (15.0% vs. 9.6%). It has been argued that minor changes in myocardial perfusion may affect the subendocardial myocardial layer, whose fibers are mainly longitudinally arranged, and, thus may explain longitudinal LV dysfunction 15.

This was also confirmed by a speckle-tracking echocardiography study showing a normal EF but a significant, even though slight, reduction of global LV longitudinal strain in ASO patients when compared to healthy controls 29. New echocardiographic parameters, as aforementioned, are also useful for the assessment of the LV contractile reserve. Non invasive determination of LV force-frequency relationship (FFR) during exercise showed a reduced LV contractile reserve in adolescents and young adults after ASO, particularly in patients with variant coronary arterial anatomy 30.

Computed tomography angiography
Multislice computed tomography (CT) angiography offers a non-invasive visualization of the coronary artery lumen, and the course of the vessels in the topographic context of the adjacent structures. Its results in ASO patients are very promising. In a child cohort, 64-slice CT correctly identified all patients in whom significant stenoses were shown at coronary angiography 31. Furthermore, due to its capability to show the surrounding structures, it can potentially be more useful than invasive angiography to elucidate the underlying mechanisms of a
luminal narrowing, which in ASO patients is often subsequent to stretching, kinking or compression of the vessel.

### RVOT complications

#### Epidemiology

PA stenosis is by far the most common sequela reported in adults after ASO, with an estimated prevalence ranging from 17% to 55% [12, 32, 37]. It is haemodynamically significant in approximately 10-25% of cases, irrespective of the type of repair. In the first series, before the Lecompte manoeuvre was routinely performed, RV to PA connection was maintained by a conduit. These patients showed high prevalence of significant RVOT obstruction since childhood and, as a consequence, were at highest risk for cardiac reintervention as adults [9, 15, 34]. After the introduction of the Lecompte manoeuvre and despite evolution of PA surgical reconstruction of the PA, RVOT stenosis continued to be the most frequent long-term complication, with the obstruction mostly located in the main trunk or proximal branches, although valvular and subvalvular stenoses, as well as combined obstructions at various levels, are also described.

#### Mechanisms

Although the cause of RVOT obstruction is unknown, scar tissue formation at the anastomosis site, inadequate somatic growth of the PA, and inadequate mobilization of both the neopulmonic root and PA, resulting in tension at the anastomosis site have been invoked as potential mechanisms. Tension may create excessive collagen formation at the anastomosis site and, especially in the low-pressure pulmonary vasculature, this may have a critical role in the outcome of the operation [12]. Compression of the proximal pulmonary branches may also occur in these patients because of the close anatomical relation with the posteriorly located ascending aorta. In particular, left PA stretching and tethering over the neoaoorta can occur after the Lecompte maneuver if the great arteries have a more oblique relationship as opposed to a direct anterior-posterior relationship [30, 37]. Other mechanisms for pulmonary stenosis include abnormal coronary artery anatomy requiring unusual reconstructive techniques used to avoid compression of the coronary artery during translocation, a rapid somatic growth and remnant ductal tissue causing left PA coarctation [30, 37].

Nowadays, RVOT obstruction after ASO is observed more frequently in patients with Taussig-Bing anomaly and coarctation, which are associated with small RVOTs [38].

### Diagnosis

#### Echocardiography

Echocardiography represents the first-line tool in the diagnostic evaluation and grading of PA stenosis. Assessment of peak and mean outflow tract gradient should be accomplished by continuous wave Doppler interrogation. Sometimes, from a high parasternal window, it is possible to visualize the pulmonary branches straddling the ascending aorta in patients after Lecompte procedure. In these cases Color Doppler interrogation can show stenoses of the proximal branches. In the few adults with RV to PA conduit, this is best visualized from the parasternal view (Figure 3). However, Doppler analysis may not accurately define the actual degree of stenosis because of the known limitations of the simplified Bernoulli equation use in long stenotic segments. The objective limitations of echocardiography for adequate assessment of the pulmonary arteries, and the frequently inadequate acoustic windowing to the typical retrosternal location of PA and its main branches, often requires further evaluation with computed tomography (CT) and magnetic resonance imaging (MRI).

#### Computed tomography

CT offers an accurate assessment of the central and peripheral pulmonary arteries. Pulmonary arterial narrowing can be accurately and non-invasively characterized with CT, which provides accurate measurements of luminal diameter of the PA that correlates highly with findings at cardiac catheterization [39].

#### Magnetic resonance imaging

MRI is regarded superior to echocardiography in the assessment of great arteries and for detection of a stenosis in the PA and its primary branches. For a comprehensive evaluation of the pulmonary arteries, cine views are usually obtained in several planes, focused primarily on RVOT, pulmonary trunk and its branches. Parallel RVOT cines allow for dynamic assessment surrounding the sites of surgical anastomoses. A cine view of the pulmonary bifurcation is also recommended. Volumetric coverage in more than one imaging plane allows for identification of regions of flow acceleration and anatomical narrowing and guide the acquisition of phase contrast images which provide useful information about velocities and pressure gradients across the stenoses.

### Treatment

As PA stenosis is the most frequent complication after ASO, it also represents the most common reason for re-operation, being responsible for about 75% of the re-interventions [42]. The majority of patients who undergo relief of RVOT/PA stenosis during adulthood had already undergone a first re-intervention in childhood [15]. Patients who had undergone a 2-stage repair had a trend towards a higher risk of subsequent interventions compared to those with a one stage repair. In a multivariable analysis, only the type of PA reconstruction technique has been identified as a significant risk factor for reintervention. In fact, most of PS are located at the pericardial patch site, as consequence of its distortion or retraction, and their occurrence seems to be less frequent when an autologous pericardial patch is used [13]. The several types of lesions responsible for PA stenosis respond differently to various treatments, including surgery or balloon angioplasty. When weakness of the main PA and involvement of the valve is present, e.g. whenever the suture line is too close to the pulmonary valve, the stenosis is difficult to relieve with balloon angioplasty and frequently requires enlargement of the complete RV outflow tract with a transannular patch. In general, balloon dilatation combined with intravascular stent deployment is more effective in the management of branch PA narrowing but not in supravalvar neopulmonary artery stenosis [33, 36].

### Aortic regurgitation

#### Epidemiology

Dilatation of the pulmonary root in the aortic position and development of neoarotic regurgitation (AR) are well-known in the long-term follow-up after ASO. Occurrence of AR was observed early in the ASO experience and reported in 30% to 55% of the patients with a two-stage intervention in whom ASO was preceded by PA banding [41, 42]. Later, when primary repair or rapid two-stage operation was the rule, AR prevalence decreased and ranged between 5% and 22% [43-45]. In most of the recent reports with a longer follow-up, AR prevalence was between 0.3% and 15% significantly lower than that of...
pulmonary stenosis or coronary stenosis. In 172 patients, freedom from AR was 93.0% at 1 year, 85.2% at 5 years, and 77.9% at 10 years. The hazard function for AR showed an initial rapid declining phase after the intervention followed by a slower decrease and a late slow increase, with new cases of AR observed up to 16 years. In adults AR is usually mild. The incidence of haemodynamically significant AR ranges between 1 and 15% and about 2.3% of patients require aortic valve replacement with freedom from reoperation of 99.3%, 97.7%, and 96.8% at 5, 10, and 15 years, respectively.

Mechanisms

Several factors have been hypothesized to contribute to the development of ASO-related AR. Presence of a VSD has been found to be closely related to occurrence of AR in several studies. It has been speculated that a VSD can increase PA pressure and flow through the pulmonary valve and, thus, predispose to AR development by promoting pulmonary root dilatation. This hypothesis is also supported by the higher prevalence of AR in patients with a previous PA banding, which increases PA pressure. Further surgical issues, such as VSD closure through the pulmonary valve in Tausig-Bing anomaly or some methods of coronary artery reimplantation as VsD closure through the pulmonary valve in Taussig-Bing heart syndrome. The presence of left ventricular outflow tract obstruction (LVOTO) has also been identified as an independent risk factor for AR. Although the mechanism of interaction between the occurrence of AR and the presence of LVOTO is unclear, it has been suggested that a native pulmonary valve, which had been protected in low-pressure circumstances by the presence of LVOTO, exposed to high pressure might lead to dilatation. In addition, turbulent flow at the left ventricle (LV) outflow may distort the neo-aortic valve in the long term.

Aortic root dilatation

Epidemiology

Dilatation of the aortic annulus and neoaortic root has been found in more than half of patients during the follow-up. In particular, dilatation of the neoaortic root over time appears to be a progressive process, with an increase in size that is disproportionate to somatic growth, and no evidence of stabilization by 15 to 20 years postoperatively. Further surgical issues, such as arterial hypertension.

Mechanisms

Aortic wall abnormalities in TGA have been related to abnormal aorto-pulmonary septation, damage to the vasa vasorum, and surgical manipulations during the ASO, predisposing patients to aortic dilatation, aneurysm formation, and even aortic dissection. In addition, aortic distensibility may be reduced by impaired aortic elastogenesis, as well as by scar formation at the site of anastomosis. Both aortic distensibility and aortic dimensions are crucial for aortic valve dynamics. Aortic valve opening occurs in concert with root expansion during the beginning of systole. Decreased distensibility of the aortic root increases leaflet stress and therefore predisposes for aortic valve dysfunction. Aortic dilatation contributes to aortic valve dysfunction through loss of coaptation of the aortic valve leaflets.

A higher degree of dilatation occurs at the level of the sinus of Valsalva, whereas diameters at the level of the ascending aorta are usually within normal limits. Both root dilatation and reduced elasticity of the proximal aorta are related to the degree of AR. The risk for native pulmonary dilatation when in the aortic position may reflect the mentioned histologic differences in the vessel walls of the pulmonary and aortic arteries. Analogously to normal hearts, post-mortem specimens from unoperated TGA exhibit a native PA wall with a less dense structure, a decreased number of smooth muscle cells and a down regulation of all smooth muscle cell markers, in comparison to the aortic wall. When after ASO, this pulmonary autograft is exposed to a systemic afterload, its less compact and muscular wall may be more prone to weaken and dilate. This hypothesis is supported by the evidence of neoaortic root dilatation after repair of other congenital heart conditions where the pulmonary root is placed in the systemic position, such as after the Fross procedure and after palliation for hypoplastic left heart syndrome. The significance of AR and neoaortic root dilatation after ASO remains unclear. Further follow-up is needed to evaluate whether aortic valve regurgitation and aortic root dilatation are likely to progress in later adulthood, specifically when patients start to develop acquired adult onset disease such as arterial hypertension.

Functional Status and Exercise Test

Most adult patients report a normal exercise tolerance late after ASO, with more than 90% steadily in New York Heart Association Class I. Compared to age-matched patients undergone atrial switch operation, ASO patients show a superior cardiorespiratory performance, as expressed by a significantly higher peak oxygen consumption (peak VO2), which is a surrogate marker of the functional status of the pulmonary, cardiocirculatory, and muscular systems.

Further exercise parameters reflecting the superiority of ASO than atrial switch

The higher increase in O2 pulse, which is the amount of oxygen transported by the circulatory system in a single heartbeat, which is considered a surrogate variable for peak stroke volume after ASO confirms that patients after atrial redirection cannot increase stroke volume under exercise, as they suffer not only from the burden of a systemic RV, but also from a reduced preload reserve due to stiff atrial baffle. In addition, ASO patients have better blood pressure response to exercise compared to patients after atrial redirection. This
also can be explained by the normal preload of the systemic ventricle in patients after ASO. VE/VO2 slope, a marker of ventilatory efficiency, is also improved in the ASO group compared to the atrial switch procedure. This suggests a more adequate ventilation/perfusion matching in ASO group and correlates with the better functional outcome during daily life these patients have compared to those with the atrial switch procedure who tend to tire sooner 1). 2).

**ASO vs general population**

When analyzed in an absolute fashion and/or compared to healthy peers, exercise parameters remain abnormal. In the largest series of 161 ASO patients with cardiopulmonary exercise, the peak VO2 was 35.1±7.6 mL/kg/min, corresponding to 86.1% of predicted values 16. In 45 young adults, 82% showed an abnormal exercise capacity, defined by a peak VO2 less than 80% of predicted, with lower values in complex TGA and adults with a reoperation in childhood 9.

**Mechanisms**

Several factors, including sympathetic denervation, abnormal coronary flow reserve, reduced levels of physical activity, haemodinamic sequelae and, longer follow-up have all been suggested to reduce exercise capacity after ASO. It has been hypothesized that after ASO, a residual sympathetic denervation might contribute to a blunted exercise performance either through a chronotropic incompetence, which has been found in more than one third of patients, that caused an inappropriate contractile response to exercise, in a similar way to that observed after cardiac transplantation. An abnormal heart rate response to exercise has prognostic implications, as it is known to be associated with increased mortality in adults with congenital heart disease 14, 15. A residual RVOT obstruction has also been related to a reduced peak VO2, likely because this causes the RV to cope with excessive pressure load, which, in turn, hampers the physiologic increase in cardiac output during exercise 14. Furthermore, in patients with more peripheral obstruction of the pulmonary branches, in addition to a reduced peak VO2, an increased ventilatory response has been reported. This exercise parameter has been observed in many patients with different underlying congenital heart defects and has been demonstrated to be associated with an adverse prognosis. In ASO patients with branches stenosis it can reflect a perfusion/ventilation mismatch, due to an abnormal right/left pulmonary blood flow distribution, which has been identified as a cause of increased ventilatory drive. This finding has also therapeutic implications, as it has been observed that improvement in the pulmonary blood flow distribution by effective PA stenting leads to a reduced ventilatory drive during exercise 16.

**Arrhythmias**

While cardiac arrhythmias represent common sequelae of the atrial switch procedure, their incidence after ASO is remarkably low 17. Studies on the electrophysiologic properties of the conduction system after ASO support this findings, as they show the absence of inducible arrhythmias and no evidence of injury to the AV node or His bundle 18. In a large series of adults ASO patients, arrhythmias, namely supraventricular tachycardias such as atrial fibrillation and atrial flutter, and bradyarrhythmias requiring pacemaker, accounted for 2.4% of late cardiac events, with an arrhythmia-free survival of 98.4% at 10 years and 96.6% at 25 years 18. However an increase in the incidence of infrequent supraventricular and ventricular premature beats has been observed with increased duration of follow-up, which may reflect the natural history of arrhythmias after ASO.

**Conclusion**

Arterial switch operation for transposition of great arteries results in better preservation of cardiac structure and function compared with atrial switch. However, important residual lesions are increasingly recognised including supravalvar pulmonary stenosis, aortic valve regurgitation and aortic root dilatation and...
coronary complications, with a proportion of them requiring re-operations or interventions. As a result, these patients remain with subnormal exercise capacity and need closer long term follow-up and monitoring of their haemodynamics.

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