The aorta in transposition of the great arteries

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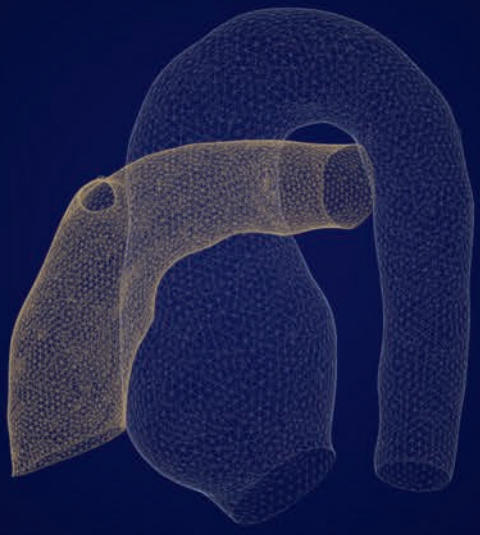

CHAPTER 1

General introduction

Transposition of the great arteries

Transposition of the great arteries (TGA) is a congenital heart disease characterised by atrioventricular concordance and ventriculoarterial discordance: the right atrium is connected to the right ventricle from which the entire or most of the aorta originates; the left atrium is connected to the left ventricle from which the pulmonary artery arises. This results in a circulation in which the pulmonary and systemic circulation are running in parallel rather than in series. Postnatally, the blood with high oxygen content, coming from the lungs enters the left atrium, passes the left ventricle and is redirected to the lungs again; blood with low oxygen content returning from the body enters the right atrium and is redirected to the body again via the right ventricle, without passing the lungs. Cyanosis is often present directly after birth and survival is dependent on the presence of adequate communications between the two circulations (i.e. presence of an atrial septal defect or ventricular septal defect (VSD)). When these communications are too small or absent, neonates will deteriorate clinically with systemic acidosis, hypoxia and eventually leading to death. Neonates can be stabilized hemodynamically in the first days after birth by administration of prostaglandin E1, to maintain patency of the arterial duct ensuring sufficient pulmonary venous flow for mixing. In addition, a balloon atrial septostomy may be necessary to create an unrestrictive interatrial communication allowing adequate mixing between the systemic and pulmonary circulation.

Prenatal detection of TGA is of paramount importance as it may prevent hypoxia and acidosis early after birth thereby improving preoperative morbidity and mortality rates.[1] Ultimately, children with TGA need corrective cardiac surgery as only option for survival. A natural history study performed in California (1957-1964) showed that without intervention life expectancy in children with TGA is short and dependent on associated lesions: about 30% and 52% of the patients die within the first week and first month after birth respectively, 86% within 6 months and 89% within the first year of life.[2]

The arterial switch operation – Leiden history

The current surgery of choice is the arterial switch operation (ASO). Before mid-eighties, children with TGA were treated by the *atrial* switch operation (according to dr. W.T. (William) Mustard or dr. A. (Åke) Senning). This surgical approach is based on an *atrial* rerooting of the systemic and pulmonary venous blood, by constructing an intraatrial baffle, leaving the right ventricle in the position to sustain the systemic circulation and the left ventricle in the position to sustain the pulmonary circulation. However, the systemic right ventricle is not developed to pump against high systemic arterial vascular resistance for many years and will fail sooner or later causing heart failure and ventricular arrhythmias.[3, 4] Furthermore, the complex intraatrial surgery of the *atrial* switch procedure is also complicated by sinus node dysfunction, atrial arrhythmias, baffle stenosis[5] and baffle leakages during early-,

mid- and long-term follow-up.[3, 6] These complications contribute to a high risk of reoperations, interventions and a limited life expectancy.[3, 4, 6, 7]

A significant milestone in congenital cardiac surgery was the introduction of a new surgical technique for TGA patients: the arterial switch operation (ASO). In Leiden, the ASO for the correction of TGA already started very early, only two years after the first successful ASO by dr. A.D. (Adib) Jatene in 1975.[8] Leiden's cardiothoracic surgeon prof. dr. A.G. (Gerard) Brom and the South African-born British cardiothoracic surgeon dr. D.N. (Donald) Ross performed the first ASO in a patient with TGA and VSD in May 1977 at the Academic Hospital Leiden. The ASO restores the ventriculoarterial concordance in such way that after repair the left and right ventricle support the systemic and pulmonary circulation respectively. During the ASO, the ascending aorta and pulmonary trunk are transected just above the commissures and relocated, leaving the semilunar valves and native roots in its original position. Consequently, the proximal part of the native pulmonary trunk becomes the neo-aorta and the native aortic root becomes the neo-pulmonary trunk. The coronary arteries are harvested from the native aortic root and are also relocated to the neo-aortic root. In the classical ASO as described by dr. Jatene, the reconstruction of the neo-pulmonary trunk was performed by a conduit.

Since the mid-eighties, after most high-volume surgical centers accomplished low perioperative mortality, the ASO technique replaced *atrial* switch operation worldwide. Leiden has played a role in this achievement, with its cardiothoracic surgeons prof. dr. Brom and prof. dr. J.M. (Jan) Quaegebeur as leading European pioneers and teachers of the ASO and other techniques in pediatric congenital heart surgery.[9]

TGA subtypes and surgical refinements to the ASO

There is a so far unexplained male predominance in TGA patients with a male to female ratio of approximately 2:1. TGA is usually an isolated lesion (65% of the cases) but may be associated with a ventricular septal defect (VSD), left ventricular outflow tract obstruction, and abnormalities related to the pulmonary valve (i.e. bi-leaflet, asymmetrical three-leaflet or stenotic valve) or the aortic arch. A slightly different TGA subtype, also amenable for ASO, is double outlet right ventricle (DORV) with subpulmonary VSD (i.e. Taussig-Bing anomaly), which is frequently associated with an aortic arch abnormality and/or aortic outflow obstruction. Moreover, there is a large variation of coronary artery patterns in TGA patients. The international nomenclature for the structural description of these variants and its course, irrespective of the position of the great arteries, has been simplified by the introduction of the Leiden Convention coronary coding system invented by the Leiden professor of Anatomy and Embryology dr. A.C. (Adriana) Gittenberger-de Groot.[10]

Certain coronary variants necessitate different surgical techniques of coronary artery transfer. These techniques developed over time, as did other refinements that were implemented to optimize ASO. An important improvement was the application of the

Lecompte maneuver developed by dr. Y (Yves) Lecompte and his colleagues.[11] With this maneuver the pulmonary artery bifurcation is transferred to the front of the ascending aorta and made a direct reconstruction of the neo-pulmonary artery possible without the need of prosthetic conduits.[11] As a result, an altered spatial great artery relationship and geometry of the thoracic (neo-)aorta remains after ASO with Lecompte maneuver (Figure 1). Reconstruction of the neo-pulmonary artery after harvesting the coronary arteries is usually performed by using a pantaloon-shaped patch of fresh autologous pericardium.

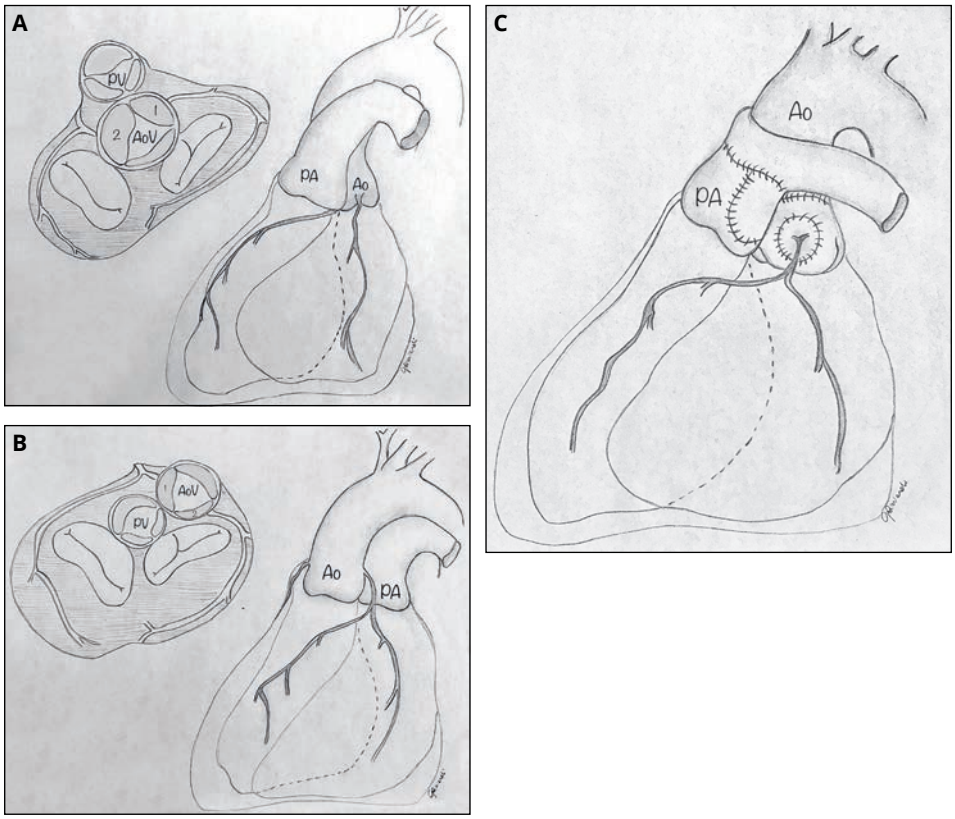

Figure 1. Representation of the great artery anatomy of the normal heart and the heart with transposition of the great arteries before and after the arterial switch operation.
Drawings by Gabriella Ricciardi - adapted and expanded after Prêtre et al. *Lancet* 2001;357:1826–30.
Normal heart (A); Transposition of the great arteries (B); Arterial switch operation (C). Note the anterior position of the pulmonary artery bifurcation over the ascending aorta after arterial switch operation and the translocation of the coronary arteries to the neo-aortic root (C). 1, *sinus 1* or right-hand facing sinus; 2, *sinus 2* or left-hand facing sinus (according to the Leiden Convention coronary coding system); Ao, aorta; AoV, aortic valve; PA, pulmonary artery; PV, pulmonary valve.

Long-term outcome – the neo-aorta

From short- and mid-term follow-up studies after ASO[9, 12-14] and mid- and long-term follow-up studies of the *atrial* switch cohort,[3, 6] we may now conclude that the step towards the ASO technique was a good decision. Over the years, early mortality rates decreased significantly to current rates less than 5% in large international pediatric cardiac surgical centers. The question remains how the long-term cardiovascular status of these patients develops, with the first patients now reaching the age of 40 years post-ASO.

Residual problems are recognized during follow-up. The overall surgical and percutaneous intervention rates for right-sided lesions varies from 11-28% between different studies.[15-17] Less is known about the residual lesions and the need for interventions on the left side of the heart in the long-term. Neo-aortic root pathology plays a central role in the management of patients after ASO. Neo-aortic dilatation has been reported to be present in more than two-third of the patients but data on the progression of neo-aortic dilatation in adulthood are scarce and controversial.[18-21] There are concerns about impairment of neo-aortic valve function over time and whether neo-aortic root dilatation may play a key role in this. Furthermore, aortic expansion also enhances branch pulmonary artery stenosis[22] and is associated with a more acute angulation of the reimplanted coronary arteries possibly increasing the risk of coronary malperfusion, ventricular dysfunction and even sudden cardiac death.[23, 24]

Neo-aortic valve repair with root reconstruction or even valve and/or root replacement is required when aortic complications progress. If valve replacement already needs to be done at very young age, the use of the autologous neo-pulmonary valve (the former aortic valve) is the preferred choice. This procedure for smaller children after ASO was first introduced by the Leiden cardiothoracic surgeon prof. dr. M.G. (Mark) Hazekamp and named this procedure the *switch back Ross operation*.[25] Together with cardiothoracic surgeon dr. D.R. (David) Koolbergen he reported that redo neo-aortic surgery for neo-aortic valve and root pathology can be performed with low risk taking into account the specific technical difficulties.[26] During these reoperations, remarkable thinning of the anterior wall of the ascending aorta was observed in many of these patients, located close to the level of the pulmonary artery embracement over the aorta after Lecompte maneuver.[26]

The course of neo-aortic root pathology in the long run is largely unknown and the contributors leading to neo-aortic valve and root problems are important to identify. In **part I** of this thesis, the unexplored questions regarding the long-term cardiovascular outcome and the fate of the neo-aortic valve and root are investigated. The incidence of adverse cardiovascular outcome, such as late death, presence of arrhythmias, coronary artery issues and the need for reoperations or catheter interventions are assessed in the cohort of the Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL) with current 43-year experience of ASO. Neo-aortic valve function and the course of neo-aortic root dilatation during long-term follow-up for the various morphological subtypes of TGA after ASO are studied longitudinally. Furthermore, fetal growth of the semilunar valves is

investigated in order to understand the origin of the differences between the morphological subtypes of TGA (and with normal fetal semilunar growth), as starting point for the further course of neo-aortic valve and root growth beyond ASO. Finally, questions regarding the critical factor(s) for the neo-aortic root dilatation and impairment of neo-aortic valve function in the long-term are addressed.

Evaluation of thoracic aorta hemodynamics with 4D flow MRI

The etiology of neo-aortic root pathology and anterior aortic wall thinning after ASO is not clear and the pathophysiological mechanisms leading to neo-aortic root dilatation have not been elucidated so far. The pulmonary root in the systemic circulation and the structural cell differences in the neo-aortic root wall itself, as described by the Leiden group,[27, 28] have been reported previously as risk factors for dilatation.

Computational fluid dynamic model studies, simulating patient specific cardiac pathologies, have shown *in vitro* that altered hemodynamics can play a causative role in modelling of the heart and large blood vessels.[29] The concept that altered blood flow patterns with altered local shear stress acting on the vessel wall in a reconstructed neo-aortic root after ASO for TGA may contribute to the development of root dilation is of importance. However, this has not been investigated so far.

Recently, four-dimensional flow magnetic resonance imaging (4D flow MRI) has been introduced as a novel non-invasive imaging tool that can be used for comprehensive *in vivo* assessment of blood flow in the large vessels.[30] It provides information about the spatial and temporal distribution of vascular blood flow and enables the quantification of flow related hemodynamic parameters. Using this technique, it has been shown that altered blood flow hemodynamics like blood flow profile and wall shear stress cause remodelling of the large vessels and dilation of the aorta in patients with bicuspid aortic valve disease.[31, 32] The application of aortic 4D flow MRI can therefore be of great value for the evaluation of aortopathy in patients after ASO for TGA.

Leonardo da Vinci already demonstrated 500 years ago (~1507-1513) the flow patterns within the aortic root by his genius sketches (Figure 2A), presumably based on his observations from blood flow simulations in glass models with grass seeds suspended in water.[33, 34] Da Vinci proposed that these observed vortical flow patterns in the aortic root aid in closure of the aortic valve and postulated that these secondary vortices do not occur more distal in the normal ascending aorta, where the flow is laminar.[33] With the use of the advanced 4D flow MRI technology, we can now prove that the flow phenomena expressed in his sketches show a highly accurate representation of the actual flow patterns in the proximal ascending aorta (Figure 2A and 2B).

4D flow MRI enables us to gain new insights in the contribution of flow dynamics on the development of aortic disease (i.e. pathophysiology) or disease progression in genetic inherited and congenital heart disease related aortopathies. In **part II** of this thesis, the 4D

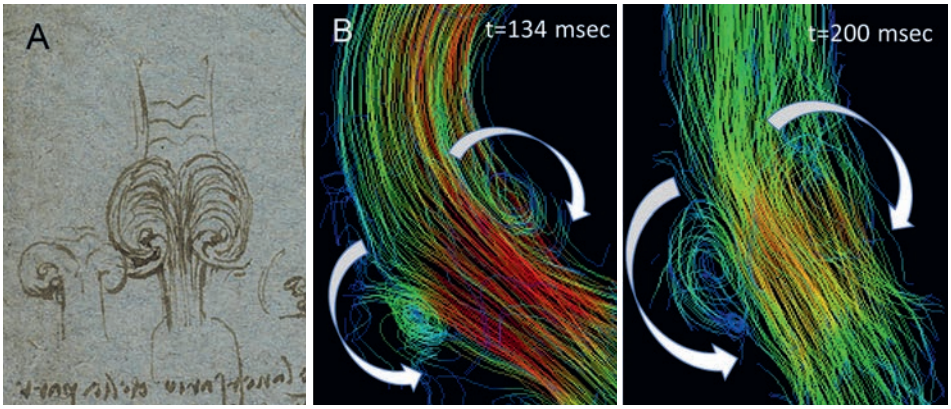

Figure 2. Vortex patterns in the aortic root and the laminar flow downstream the ascending aorta by a schematic sketch from Leonardo da Vinci (A) and by streamline visualization from 4D flow MRI of the proximal part of ascending aorta (B).
Figure 2A. Detail of RL19083 verso, Blood flow through the aortic valve. Leonardo da Vinci, c.1512-13. – Courtesy by Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020; Figure 2B. 4D flow MRI illustration derived from Chapter 9 of this thesis. Altered aortic 3D hemodynamics and geometry in pediatric Marfan syndrome patients. *J Cardiovasc Magn Reson*. 2017;19(1):30.

flow MRI technique is used to study on aortic hemodynamics in healthy volunteers and in TGA patients after ASO. Furthermore, the application of 4D flow MRI to assess aortopathy is explored in patients at risk for aortic problems such as patients with Marfan syndrome. Blood flow patterns and 4D flow MRI-derived parameters, regional aortic wall shear stress and aortic flow displacement, within the thoracic aorta are investigated to unravel aortic flow abnormalities and their relationship with altered aortic geometry which may be indicative for vascular wall remodeling and root dilatation. The aortic flow hemodynamics are evaluated in rest and during dobutamine-induced stress conditions.

Aim and outline of this thesis

The aim of this thesis is to investigate the prevalence and evolution of neo-aortic root pathology and surgical cardiovascular outcomes in patients after ASO for TGA in the long-term. Secondly, thoracic aortic blood flow hemodynamics are investigated in relation to post-ASO geometry and root pathology with advanced non-invasive 4D flow cardiovascular MR imaging techniques.

Part I of the thesis focuses on the fate of the neo-aortic valve and the course of neo-aortic root dimensions during fetal development and long-term post-ASO with echocardiographic imaging. Risk factors for the impairment of the neo-aortic valve function are assessed and long-term cardiovascular outcomes such as the prevalence of late mortality and the need for reoperations and interventions are investigated.

Part II of the thesis describes the thoracic aortic blood flow hemodynamics from 4D flow MR imaging in relation to post-ASO geometry and its potential role in the contribution to neo-aortic root dilatation and aortic wall thinning. Prior to these studies, aortic blood flow in healthy volunteers is investigated to test reproducibility of the 4D flow MRI-derived wall shear stress parameter. In addition, to further explore the use of aortic 4D flow MR imaging in patients with dilative aortopathy, a 4D flow MRI study is performed in patients with Marfan syndrome to assess aortic geometry in relation to aortic wall shear stress.

Part I

Chapter 2 reports the long-term surgical outcomes after ASO for TGA performed in the Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL), based on 43 years of experience and follow-up. Prevalence of reoperations and interventions, arrhythmias and late mortality are described and risk factors for reoperation and intervention are identified.
Chapter 3 addresses fetal semilunar valve growth in conjunction with short-term postoperative neo-aortic root dilatation.
Chapter 4 shows the neo-aortic growth, neo-aortic valve function and the need for reoperations on the neo-aortic valve and/or root during long-term follow-up for the various morphological subtypes of TGA after ASO. Moreover, risk factors for neo-aortic root dilatation and neo-aortic valve regurgitation are determined.
Chapter 5 demonstrates the effect of changing neo-aortic dimensions over time on the risk of neo-aortic valve regurgitation.

Part II

Chapter 6 describes the scan-rescan validation and reproducibility study on the hemodynamic parameter wall shear stress derived from aortic 4D flow MR imaging in healthy volunteers. These data serve as reference data for the knowledge about variability of the hemodynamic parameter and to judge whether differences between patients and healthy volunteers or hemodynamic changes in patients over time or between rest-rest examinations represent true (patho)physiological differences.
Chapter 7 shows the altered ascending aorta hemodynamics in patients after ASO for TGA and the effect of differences in aortic geometry on hemodynamics.
Chapter 8 further delineates the abnormalities in aorta hemodynamics within the entire thoracic aorta after ASO by a rest versus dobutamine-stress comparison.
Chapter 9 describes the altered aorta hemodynamics and geometry in pediatric Marfan syndrome patients.
In **Chapter 10** the results of all studies from this thesis are summarized and clinical perspectives and future directions are discussed.

References

1. van Velzen CL, Haak MC, Reijnders G, Rijlaarsdam ME, Bax CJ, Pajkrt E, Hruda J, Galindo-Garre F, Bilardo CM, de Groot CJ, et al. Prenatal detection of transposition of the great arteries reduces mortality and morbidity. *Ultrasound Obstet Gynecol*. 2015;45(3):320-5.
2. Liebman J, Cullum L, Belloc NB. Natural history of transpositon of the great arteries. Anatomy and birth and death characteristics. *Circulation*. 1969;40(2):237-62.
3. Couperus LE, Vliegen HW, Zandstra TE, Kies P, Jongbloed MRM, Holman ER, Zeppenfeld K, Hazekamp MG, Schalij MJ, Scherptong RWC. Long-term outcome after atrial correction for transposition of the great arteries. *Heart*. 2019;105(10):790-6.
4. Cuypers JA, Eindhoven JA, Slager MA, Opic P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J*. 2014;35(25):1666-74.
5. van der Palen RL, Westenberg JJ, Hazekamp MG, Kuipers IM, Roest AA. Four-dimensional flow cardiovascular magnetic resonance for the evaluation of the atrial baffle after Mustard repair. *Eur Heart J Cardiovasc Imaging*. 2016;17(3):353.
6. Gelatt M, Hamilton RM, McCrindle BW, Connelly M, Davis A, Harris L, Gow RM, Williams WG, Trusler GA, Freedom RM. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. *J Am Coll Cardiol*. 1997;29(1):194-201.
7. Venkatesh P, Evans AT, Maw AM, Pashun RA, Patel A, Kim L, Feldman D, Minutello R, Wong SC, Stribling JC, et al. Predictors of Late Mortality in D-Transposition of the Great Arteries After Atrial Switch Repair: Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2019;8(21):e012932.
8. Jatene AD, Fontes VF, Paulista PP, de Souza LC, Neger F, Galantier M, Souza JE. Successful anatomic correction of transposition of the great vessels. A preliminary report. *Arq Bras Cardiol*. 1975;28(4):461-64.
9. Quaegebeur JM, Rohmer J, Ottenkamp J, Buis T, Kirklin JW, Blackstone EH, Brom AG. The arterial switch operation. An eight-year experience. *J Thorac Cardiovasc Surg*. 1986;92(3 Pt 1):361-84.
10. Gittenberger-de Groot AC, Koenraadt WMC, Bartelings MM, Bokenkamp R, DeRuiter MC, Hazekamp MG, Bogers A, Quaegebeur JM, Schalij MJ, Vliegen HW, et al. Coding of coronary arterial origin and branching in congenital heart disease: The modified Leiden Convention. *J Thorac Cardiovasc Surg*. 2018;156(6):2260-9.
11. Lecompte Y, Neveux JY, Leca F, Zannini L, Tu TV, Duboys Y, Jarreau MM. Reconstruction of the pulmonary outflow tract without prosthetic conduit. *J Thorac Cardiovasc Surg*. 1982;84(5):727-33.
12. Hazekamp MG, Ottenkamp J, Quaegebeur JM, Hardjowijono R, Boot CA, Rohmer J, Huysmans HA. Follow-up of arterial switch operation. *Thorac Cardiovasc Surg*. 1991;39:166-9.
13. Lalezari S, Bruggemans EF, Blom NA, Hazekamp MG. Thirty-year experience with the arterial switch operation. *Ann Thorac Surg*. 2011;92(3):973-9.
14. Pretre R, Tamisier D, Bonhoeffer P, Mauriat P, Pouard P, Sidi D, Vouhe P. Results of the arterial switch operation in neonates with transposed great arteries. *Lancet*. 2001;357(9271):1826-30.
15. Cleuziou J, Vitanova K, Pabst von Ohain J, Ono M, Tanase D, Burri M, Lange R. Incidence and Risk Factors for Right Ventricular Outflow Tract Obstruction after the Arterial Switch Operation. *Thorac Cardiovasc Surg*. 2019;67(1):37-43.
16. Delmo Walter EM, Miera O, Nasseri B, Huebler M, Alexi-Meskishvili V, Berger F, Hetzer R. Onset of pulmonary stenosis after arterial switch operation for transposition of great arteries with intact ventricular septum. *HSR Proc Intensive Care Cardiovasc Anesth*. 2011;3(3):177-87.
17. Nellis JR, Turek JW, Aldoss OT, Atkins DL, Ng BY. Intervention for Supravalvar Pulmonary Stenosis After the Arterial Switch Operation. *Ann Thorac Surg*. 2016;102(1):154-62.

18. Kempny A, Wustmann K, Borgia F, Dimopoulos K, Uebing A, Li W, Chen SS, Piorkowski A, Radley-Smith R, Yacoub MH, et al. Outcome in adult patients after arterial switch operation for transposition of the great arteries. *Int J Cardiol*. 2013;167(6):2588-93.

19. McMahon CJ, Ravekes WJ, Smith EO, Denfield SW, Pignatelli RH, Altman CA, Ayres NA. Risk factors for neo-aortic root enlargement and aortic regurgitation following arterial switch operation. *Pediatr Cardiol*. 2004;25(4):329-35.

20. van der Bom T, van der Palen RL, Bouma BJ, van Veldhuisen SL, Vliegen HW, Konings TC, Zwinderman AH, Blom NA, Koolbergen DR, Hazekamp MG, et al. Persistent neo-aortic growth during adulthood in patients after an arterial switch operation. *Heart*. 2014;100(17):1360-5.

21. Vandekerckhove KD, Blom NA, Lalezari S, Koolbergen DR, Rijlaarsdam ME, Hazekamp MG. Long-term follow-up of arterial switch operation with an emphasis on function and dimensions of left ventricle and aorta. *Eur J Cardiothorac Surg*. 2009;35(4):582-7.

22. Morgan CT, Mertens L, Grotenhuis H, Yoo SJ, Seed M, Grosse-Wortmann L. Understanding the mechanism for branch pulmonary artery stenosis after the arterial switch operation for transposition of the great arteries. *Eur Heart J Cardiovasc Imaging*. 2017;18(2):180-5.

23. Ou P, Khraiche D, Celermajer DS, Agnoletti G, Le Quan Sang KH, Thalabard JC, Quintin M, Raisky O, Vouhe P, Sidi D, et al. Mechanisms of coronary complications after the arterial switch for transposition of the great arteries. *J Thorac Cardiovasc Surg*. 2013;145(5):1263-9.

24. Veltman CE, Beeres SL, Kalkman DN, Kelder TP, Kies P, Vliegen HW, Hazekamp MG, Delgado V, Kroft LJ, van der Wall EE, et al. Variation in coronary anatomy in adult patients late after arterial switch operation: a computed tomography coronary angiography study. *Ann Thorac Surg*. 2013;96(4):1390-7.

25. Hazekamp MG, Schoof PH, Suys BE, Hutter PA, Meijboom EJ, Ottenkamp J, Huysmans HA. Switch back: using the pulmonary autograft to replace the aortic valve after arterial switch operation. *J Thorac Cardiovasc Surg*. 1997;114(5):844-6.

26. Koolbergen DR, Manshanden JS, Yazdanbakhsh AP, Bouma BJ, Blom NA, de Mol BA, Mulder BJ, Hazekamp MG. Reoperation for neoaortic root pathology after the arterial switch operation. *Eur J Cardiothorac Surg*. 2014;46(3):474-9.

27. Lalezari S, Hazekamp MG, Bartelings MM, Schoof PH, Gittenberger-De Groot AC. Pulmonary artery remodeling in transposition of the great arteries: relevance for neoaortic root dilatation. *J Thorac Cardiovasc Surg*. 2003;126(4):1053-60.

28. Lalezari S, Mahtab EA, Bartelings MM, Wisse LJ, Hazekamp MG, Gittenberger-de Groot AC. The outflow tract in transposition of the great arteries: an anatomic and morphologic study. *Ann Thorac Surg*. 2009;88(4):1300-5.

29. Morris PD, Narracott A, von Tengg-Kobligk H, Silva Soto DA, Hsiao S, Lungu A, Evans P, Bressloff NW, Lawford PV, Hose DR, et al. Computational fluid dynamics modelling in cardiovascular medicine. *Heart*. 2016;102(1):18-28.

30. Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carlhall CJ, Ebbers T, Francios CJ, Frydrychowicz A, Geiger J, Giese D, et al. 4D flow cardiovascular magnetic resonance consensus statement. *J Cardiovasc Magn Reson*. 2015;17:72.

31. Guzzardi DG, Barker AJ, van Ooij P, Malaisrie SC, Puthumana JJ, Belke DD, Mewhort HE, Svystonyuk DA, Kang S, Verma S, et al. Valve-Related Hemodynamics Mediate Human Bicuspid Aortopathy: Insights From Wall Shear Stress Mapping. *J Am Coll Cardiol*. 2015;66(8):892-900.

32. Mahadevia R, Barker AJ, Schnell S, Entezari P, Kansal P, Fedak PW, Malaisrie SC, McCarthy P, Collins J, Carr J, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. *Circulation*. 2014;129(6):673-82.

33. Bissell MM, Dall'Armellina E, Choudhury RP. Flow vortices in the aortic root: in vivo 4D-MRI confirms predictions of Leonardo da Vinci. *Eur Heart J*. 2014;35(20):1344.

34. Gharib M, Kremers D, Koochesfahani MM, Kemp M. Leonardo's vision of flow visualization. *Experiments in Fluids*. 2002;33(1):219-23.