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Perspectives in Paediatric Cardiology: Perspektive u pedjatrijskoj kardiologiji

Mesihović Dinarević, Senka

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Editor in Chief
Senka Mesihović-Dinarević

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SARAJEVO 2012

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ABOUT THE CONFERENCE

The Conference is organized by the Academy of Sciences and Arts of Bosnia and Herzegovina (ANUBiH), Vienna General Hospital (AKH Wien) – Department of Paediatric Cardio Surgery, University Medical Centre Ljubljana – Paediatric Clinic-Department of Paediatric Cardiology, within the Academic programme 2011/2012 of the Inter University Center (IUC), Dubrovnik.

The programme consistS of the invited lectures given by distinguished experts with international expertise in their respective fields.

Conference aims and scope

The International Scientific Conference „Perspectives in Paediatric Cardiology" has the aim to highlight the present status of paediatric cardiology with a view of genetics in molecular biology, cardiac anatomy, morfohaemodynamices, sequential segmental analyses, imaging techniques including foetal echocardiography, hypertension, atherosclerosis, electrophysiology and cardiosurgery. Improvements in diagnostic modalities of congenital heart disease, especially imaging techniques, surgical and interventional as well as postoperative intensive cardiac therapy and care have contributed to the significant decrease in mortality and morbidity in congenital heart disease. The understanding of factors that influence heart development and its structure and functional development could produce the information in connection with pathogenesis of congenital heart anomalies and detect early mechanisms of controlling development of acquired cardiovascular disease in adulthood. Keynote speakers on these topics with international expertise in their respective fields are a guarantee of success for this international meeting.

Keynote speakers

Prof. Dr Senka Mesihović-Dinarević, corresponding member of ANUBiH – Academy of Sciences and Arts of Bosnia and Herzegovina; Clinical Center University of Sarajevo, Paediatric Clinic, Sarajevo, BA; **Prof. Dr Gregor Wollenek** – Vienna General Hospital (AKH), Department of Paediatric Cardio Surgery, Vienna, AT; **Prof. Dr Tomaž Podnar** – University Medical Center Ljubljana, Paediatric Clinic, Department of Paediatric Cardiology, Ljubljana, SI; **Professor Sir Magdi H Yacoub**

– National Heart & Lung Institute, Imperial College London, London, GB; **Prof. Dr Sune Johansson** – Pediatric Cardiac Surgical Unit, Children‘s Hospital, Lund University Hospital, Lund, SE; **Prof. Dr Ida Jovanović** – University Children‘s Hospital Belgrade, Belgrade, RS; **Prof. Dr Elma Kučukalić-Selimović** – Clinical Center University of Sarajevo, Clinic for Nuclear Medicine, Sarajevo, BA; **Prof. Dr Max Manfred** – Universitätsklinik für Chirurgie, Abteilung für Herz-u. Kinderherzchirurgie, Vienna, AT; **Prof. Dr Renate Oberhoffer** – Technische Universität München, Fakultät für Sport und Gesundheitswissenschaft, Lehrstuhl für Präventive Pädiatrie, Munich, DE; **Prof. Dr Ettore Pedreti** – Unita sanitaria locale di Piacenza, Presidio Ospedalioero di Fiorenzuola D‘arda, Divisione Pediatrica, Fiorenzola D‘arda, IT; **Prof. Dr Bo Sahlgren** – Karolinska University Hospital, Stockholm, SE; **Asc. Prof. Dr Yusuf Kenan Yalçınbaş** – Kalp Damar Cerrahisi Bölüm Başkani, Acibadem Bakirköy Hastanesi, Istanbul, TR; **Prof. Dr Slavko Simeunović** – Specialist Outpatient Clinic „PROFMEDICA–SIMEUNOVIĆ“, Belgrade, RS; **Prof. Dr Jochen Weil** – Universitares Herzzentrum Hamburg GmbH, Kinderkardiologie, Hamburg, DE; **Doc. Dr Amina Kozarić** – Clinical Center University of Sarajevo, Clinical Pathology and Cytology, Sarajevo, BA; **Doc. Dr Samo Vesel** – University Medical Center Ljubljana, Paediatric Clinic, Ljubljana, SI; **Dr Jens Johansson Ramgren** – Pediatric Cardiac Surgical Unit, Children‘s Hospital, Lund University Hospital, Lund, SE; **Dr Mary N Sheppard** – Royal Brompton Hospital, London, GB; **Dr Janice Till** – Department of Paediatric Cardiology, Royal Brompton Hospital, London, GB.

ABOUT ORGANIZERS

Academy of Sciences and Arts of Bosnia and Herzegovina (ANUBiH)

The Academy of Sciences and Arts of Bosnia and Herzegovina (ANUBiH), arose from the Scientific Society which was established in 1951 by Assembly of the Socialist Republic of Bosnia and Herzegovina, the highest state organ in the country, passing the resolution on foundation of Scientific Society of Bosnia and Herzegovina. Scientific Society as the highest institution in charge of the welfare of scientific life, was functioning until the Assembly of the Socialist Republic of Bosnia and Herzegovina passed the Law on the Academy of Sciences and Arts of Bosnia and Herzegovina. The Academy of Sciences and Arts of Bosnia and Herzegovina was founded by this Law, passed in 1966, as the highest scientific and artistic institution on the territory of the state of Bosnia and Herzegovina. Pursuant to this Law, the Academy of Sciences and Arts of Bosnia and Herzegovina was assigned to take care about the overall development of science and arts, to organize scientific and artistic manifestations, to publish works of its members and Academy's associates, and to take care about the overall condition and development of science and arts in the country. In its work the Academy is entirely independent and autonomous, and it is managed exclusively by the principles and interests of science and free beliefs of its members. ANUBIH is composed of six Departments organized on the basis of selected branches of sciences and arts: *Department of Social Sciences, Department of Humanities, Department of Medical Sciences, Department of Natural Sciences and Mathematics, Department of Technical Sciences, Department of Arts*. Departments are carriers of fundamental activities of the Academy in the domain of science and arts. Departments form Committees and Commissions which tasks are to organize realization of the Academy's scientific projects and programs, and to immediately participate in realization of the programs of some Interacademic Committees. ANUBIH members are chosen from among the most prominent persons actively engaged in different fields of science and art.

www.anubih.ba

Vienna General Hospital (AKH)

The history of the Vienna General Hospital (AKH) goes back more than three hundred years. It came about as the result of the reconstruction of the "Home for the Poor and Invalid", which was founded by Emperor Leopold I in 1693 and was located from 1694 on the site between Alserstrasse, Spitalgasse and Garnisongasse. The home was partly opened in 1695, and in 1696 it housed more than 1,000 poor people. The original "Home for the Poor and Invalid" has developed into one of the most modern and advanced hospitals in Europe. With more than 30 university clinics and clinical institutes, the AKH guarantees extremely high standards and innovative technologies in all medical fields. At the AKH, patient care, instruction and research have been laid down as inseparable and equal elements. The people are always at the centre of the AKH's tasks and objectives. Vienna General Hospital performs all services in accordance with the standard of a university hospital while observing ethical principles and due consideration for the economic environment. Vienna General Hospital regards all institutions, providers and suppliers in the health care system as partners and recognises their services. The guiding principle of the university clinics and university establishments at the Vienna General Hospital is the combination of health care, teaching and research. The wide range and variety of science and teaching, supported by extensive capital investment, permits top-class medicine and training. The methods applied are justifiable, repeatable and verified. The acquired know-how is made available nationally and internationally, and results are continually evaluated. Members of various professions are involved in both research and teaching. They contribute to the reputation of the Vienna General Hospital as an important research and training centre for the medical and health care professions

www.akhwien.at

University Medical Centre Ljubljana

The University Medical Centre Ljubljana (UMCL) is a public health care institution providing medical services at the secondary and tertiary level. Primary care is also offered at the Divison of Gynaecology and Obstetrics. The UMCL is the leading medical institution in Slovenia and one of the largest hospitals in central Europe. It covers all subspecialties that define a hospital as a tertiary care centre (except adult psychiatry), and operates an extensive and successful transplantation programme. As the main training base for the Faculty of Medicine in Ljubljana, the UMCL effectively combines clinical work with education and research. Principal aim is to provide quality care to patients from Slovenia and other European countries. The UMCL's organization and activities are geared at continuous improvement of services, development and introduction of new methods of treatment, and transfer of knowledge to younger generations of health professionals. Major objectives are to acquire European accreditation, implement a comprehensive system of quality assurance, and achieve international quality standards. They have close contacts with

similar institutions in the European Union. Their wish is to create a favourable working environment for their employees and provide quality professional care to their patients.

Activities of the University Medical Centre Ljubljana include: health care services for inpatients, specialist services and other health care activities for outpatients, education, research and experimental development in medicine and natural sciences, pharmacy services and wholesale trade in pharmaceutical products, other activities needed to support the UMCL's basic functions.

www.kclj.si

Inter-University Centre (IUC)

The Inter-University Centre Dubrovnik (IUC) is an independent international institution for advanced studies.

Its objective is to encourage, promote and implement cooperation among students and scholars through projects, study programmes, courses and conferences across a wide range of academic concerns.

Participants come from universities and other scientific institutions worldwide.

Founded in 1971, at the height of the Cold War, the IUC became an important venue for the exchange of ideas across various divides, between East and West, North and South.

Based in Dubrovnik, formerly a self-governing Mediterranean city-state at the crossroads of varying cultural and political concerns, the IUC is building on its achievements and traditions in facing new challenges in a rapidly changing global environment.

Maintaining high standards of free and independent scholarship, the IUC is dedicated to network building for peaceful co-existence and pluralism regionally as well as internationally.

Over the years, more than 65,000 scholars and students have contributed to the work of the IUC.

www.iuc.hr

PROGRAMME

1st DAY

Thursday, September 20, 2012	17:00–19:00	Registration of participants	GRAND HOTEL PARK
	20.00	Reception	International University Centre (IUC) Dubrovnik (transfer form Hotel to IUC is provided)

2nd DAY

Friday, September 21, 2012 GRAND HOTEL PARK

9:00–10:00	**Registration of participants**		
	Chairpersons: Senka Mesihović-Dinarević, Gregor Wollenek, Tomaž Podnar		
10:00–10:10	*President of ANUBiH*		Opening speech
10:10–10:20	*Corresponding member of ANUBiH, Prof. Dr Senka Mesihović-Dinarević*		Academy of Sciences and Arts of Bosnia and Herzegovina (ANUBiH), Sarajevo, BA
10:20–10:30	*Prof. Dr Gregor Wollenek*		Vienna General Hospital (AKH), Department of Paediatric Cardio Surgery, Vienna, AT
10:30–10:40	*Prof. Dr Tomaž Podnar*		University Medical Center Ljubljana, Paediatric Clinic, Department of Paediatric Cardiology, Ljubljana, SI
10:40–11:00	**Prof. Dr Senka Mesihović-Dinarević, corresponding member of ANUBiH**	Academy of Sciences and Arts of Bosnia and Herzegovina (ANUBiH), Sarajevo, BA	***Paediatric Cardiology***
11:00–11:30	**COFFEE BREAK**		
	Chairpersons: Senka Mesihović-Dinarević, Gregor Wollenek, Tomaž Podnar		
11:30–11:50	**Prof. Dr Renate Oberhoffer**	Technische Universität München, Fakultät für Sport- und Gesundheitswissenschaft, Lehrstuhl für Präventive Pädiatrie, Munich, DE	***Preventive Pediatric Cardiology – from the Fetus to the Young Adult***

11:50–12:10	**Prof. Dr Slavko Simeunović**	Faculty of Medicine, University of Belgrade; University Children's' HospitalBelgrade; Specialist Outpatient Clinic "PROFMEDICA–SIMEUNOVIĆ", Belgrade, RS	***Evaluation Cardiovascular Risk Factors in Children – 15 years of Prospective Yusad Study***
12:10–12:30	**Asc. Prof. Dr Yusuf Kenan Yalçınbaş**	Kalp Damar Cerrahisi Bölüm Başkani, Acibadem Bakirköy Hospital, Istanbul, TR	***Arterial Switch Operation for Transposition of Great Arteries with Coronary Anomalies***
12:30–12:50	**Prof. Dr Ettore Pedreti**	Unita sanitaria locale di Piacenza, Presidio Ospedalioero di Fiorenzuola D'arda, Divisione Pediatrica, Fiorenzola D'arda, IT	***Pediatric Age Dilated Cardiomyopathy (DCM): Report on a Few Cases***
13:00–14:00		**LUNCH**	
	Chairpersons: Senka Mesihović-Dinarević, Gregor Wollenek, Tomaž Podnar		
14:00–14:20	**Prof. Dr Gregor Wollenek**	Vienna General Hospital (AKH), Department of Paediatric Cardio Surgery, Vienna, AT	***Paediatric Cardiac Surgery and Europe: Today´s Situation and Future Aspects***
14:20–14:40	**Prof. Dr Tomaž Podnar**	University Medical Center Ljubljana, Paediatric Clinic, Department of Paediatric Cardiology, Ljubljana, SI	***Current Interventional Paediatric Cardiology***
14:40–15:00	**Prof. Dr Ida Jovanović**	University Children's Hospital Belgrade, Belgrade, RS	***Echocardiography Assessment of Systolic Function in Different Left Ventricular Geometries***
15:00–15:20	**Prof. Dr Manfred Marx**	Universitätsklinik für Chirurgie, Abteilung für Herz-u. Kinderherzchirurgie, Vienna, AT	***Paediatric Electrophysiology: Where Do We Go To?***
15:20–15:40	**Prof. Dr Bo Sahlgren**	Karolinska University Hospital, Stockholm, SE	***Sweedish Approach to Interventional Cardiology***
15:40–16:10		**COFFEE BREAK**	
	Chairpersons: Senka Mesihović-Dinarević, Gregor Wollenek, Tomaž Podnar		
16:10–16:30	**Dr Janice Till**	Department of Paediatric Cardiology, Royal Brompton Hospital, London, GB	***The Role of Defibrillators in Channelopathys***
16:30–16:50	**Dr Jens Johansson**	Pediatric Cardiac Surgical Unit, Children's Hospital, Lund University Hospital, Lund, SE	***Surgical Correction of Complete AVSD during the Last 20 Years in Lund***

16:50–17:10	**Prof. Dr Jochen Weil**	Universitares Herzzentrum Hamburg GmbH, Kinderkardiologie, Hamburg, DE	***Changes of the Left Side of the Heart in Patients with Right Ventricular Problems***
17:10–17:30	**Dr Mary N Sheppard**	Royal Brompton Hospital, London, GB	***Sudden Death in Congenital Heart Disease***
20:00	**DINNER at Taverna Marijin Dvorac, Grand Hotel Park**		

3rd DAY

Saturday, September 22, 2012 GRAND HOTEL PARK

9:30–9:50	**Asst. Prof. Dr Amina Kozarić**	Clinical Center University of Sarajevo, Clinical Pathology and Cytology, Sarajevo, BA	***Molecular Genetics in Pediatric Cardiology: Applications and Current Advances***
9:50–10:10	**Asst. Prof. Dr Samo Vesel**	University Medical Center Ljubljana, Paediatric Clinic, Ljubljana, SI	***The Challenge of Foetal Dysrhytmias: Echocardiographic Diagnosis and Clinical Management***
10:10–10:30	**Prof. Dr Elma Kučukalić-Selimović**	Clinical Center University of Sarajevo, Clinic for Nuclear Medicine, Sarajevo, BA	***Diagnostic Value of Nuclear Medicine Techniques in the Diagnosis and Assessment of Pediatric Cardiac Disorders***
10:30–10:50	**Professor Sir Magdi H Yacoub**	National Heart & Lung Institute, Imperial College London, London, GB	***TGA for Developmental Biology to the Clinic***
10:50–11:10	**Prof. Dr Sune Johansson**	Pediatric Cardiac Surgical Unit, Children's Hospital, Lund University Hospital, Lund, SE	***Monitoring Pediatric Cardiac Surgery in Bosnia; Experience fromthe Swedish Medical Program 1995–2012***
11:10–12:00	**DISCUSSION and CLOSING REMARKS**		
12:00	**CERTIFICATES**		

UPDATE ON PAEDIATRIC CARDIOLOGY

Professor Dr. Senka Mesihović-Dinarević

Paediatric clinic, Clinical University Centre of Sarajevo
Bosnia and Herzegovina

Abstract

During the last decade of the 20th century paediatric cardiology was transformed from a field of exceptional curiosity about the diseased heart in infants and children which had been a uniformly fatal disease, and established a clinical discipline that routinely provides effective medical and surgical therapy. The fields of paediatric cardiology and congenital heart disease have experienced considerable progress in the last few years, with advances in new diagnostic and therapeutic techniques that can be applied at all stages of life from the foetus to the adult. Improvements in diagnostic modalities, especially imaging in surgical and interventional techniques and postoperative care and treatment, contributed to significant decrease in mortality and morbidity related to congenital cardiac anomalies. Thanks to progress in paediatric cardiology, surgery and interventional techniques, about 90% of patients born with congenital heart defects now live relatively normal lives, but most of them require specialised medical care, especially during childhood and adolescence. There is a significant trend of an interdisciplinary approach to treatment of congenitally malformed hearts, which includes cardiologists, interventional cardiologists, intensivists and specialized staff working together on diagnosing, treatment and monitoring of these patients. Given the incidence of congenital heart anomalies, today thousands of patients in the world require an experienced team of medical staff during their preoperative and postoperative monitoring. In developing countries, congenital heart disease is becoming increasingly prevalent in nonpaediatric patients, including pregnant women. Actions aimed at preventing coronary heart disease must start early in infancy and should involve the encouragement of a healthy diet and lifestyle. Recent developments in echocardiography include introduction of 3-dimensional echocardiography and new techniques such as 2-dimensional speckle tracking imaging, which can be used for both anatomical and functional investigations in patients with complex heart disease, including a univentricular heart. Progress has also been made in foetal cardiology, with new data on prognosis and prognostic factors and developments in intrauterine interventions, though indications for these interventions are still to be established. Heart transplantation has become a routine procedure, supplemented in some cases by circulatory support devices. Interventional paediatric cardiology is a constantly evolving speciality. In catheter

interventions, new devices have become available for closure of atrial or ventricular septal defects and patent ductus arteriosus as well as for percutaneous pulmonary valve implantation. Surgery is also advancing, in some cases with hybrid techniques, particularly for the treatment of hypoplastic left heart syndrome. Modern treatment of patients with congenital cardiac anomalies consists of: prenatal diagnosis as part of preventive cardiology, paediatric, and foetal echocardiography, optimal preoperative treatment, diagnostic and therapeutic cardiac catheterisation, palliative and corrective surgical approaches, medications, and the monitoring of patients to the adult age.

At the time when *Thomas Aquinas* known as "the angelic doctor" was applying Aristotelian principles on major theological issues, Ramon Lull, known as "the enlightened doctor" was writing about medicine in several of his famous works, such as Ars Magna and Arbour Scientiae. These remarkable monographers interpret Lulls method for acquisition and mapping of knowledge, beautifully illustrated by Tree of Knowledge, which represents the evolution of knowledge starting from the roots, passing through tree, branches and leaves and culminating in fruit, as products of human investigation endeavours. The *Tree of Cardiovascular Knowledge* relates to: haemodynamic, diagnostic cardiology, heart insufficiency, hypertension, ischaemic heart disease, atherosclerosis, electrophysiology, biology, cardio surgery and genetics in molecular biology.

In the ancient world, when clinical observations were interpreted largely in a philosophical context, science had virtually no impact on the patient care. Studies of pathological anatomy that began in 16th century, along with Harve's description of the circulation in 1628, provide some explanations of cardiovascular diseases, but these had virtually no clinical benefits for almost 300 years.

It was not until 20th century that invention of the electrocardiogram, developments in haemodynamic physiology, identification of the role of coronary diseases in myocardial infarction, characterization of hypertension, discoveries in biochemistry and vascular biology, and other advances began to close the gap between bench and bedside. Practical applications included cardio surgery, pharmacological agents created to correct pathophysiologic abnormalities, risk factors modifications and new technology for diagnosis and treatment.

Basic science and clinical medicine moved even closer to one another in the late 1980s, when molecular biology made it possible to identify additional mechanisms of cardiovascular diseases. The rapid pace at which we are learning about cardiovascular diseases and the increasing relevance of basic science to clinical practice continue the historical process described earlier.

Paediatric cardiology is an exact science thanks to embryological knowledge, morphological anatomy and segmental analysis. Developmental biology from conception up to the end of second month, allows the solution of morphogenesis (pathogenesis) and aetiology of heart malformation. Morphological anatomy is necessary for the recognition of heart chambers as well as to define the diagnosis. The language

of „*segmental analyses"* is one of the most important in understanding in paediatric cardiology which is designed on recognition relations on three levels:

1. the relation of visceral organs towards atriums
2. interrelation of the heart chambers and
3. relation of the heart towards great vessels.

On the basis of segmental analyses it is possible to make anatomical and physiological diagnosis. Detailed clinical evaluation is essential for the diagnosis of patients with congenital heart anomalies.

During the *last decade of the 20th century* paediatric cardiology was transformed from a field of exceptional curiosity about the diseased heart in infants and children which had been a uniformly fatal disease, and established a clinical discipline that routinely provides effective medical and surgical therapy. However, cardiac malformations, and continuing trend of the most common birth defects as well as leading causes of infant mortality, twice higher than cancerous in childhood. Researchers, today apply the means of molecular genetics with the aim of understanding cardiac embryogenesis, as well as understanding the causes of cardiac malformations.

In the *21st century*, the field of computer technology, application of information and biology on the integration path, made possible a new and exciting approach to the treatment of congenital heart anomalies. As new information is accumulating, genetic screening of family members will have a clear predictive value for prenatal counselling. Signalling mechanisms for abnormal heart development are defined. Severe forms of cardiac anomalies can be prevented and new therapies can be applied for associated diseases, including acquired: disrythmias, cardiac hypertrophy and pulmonary vascular disease.

Non-invasive cardiac diagnostic capabilities that show the structure and function of the heart are established. The combination of extreme precision and minimal invasiveness made standard echocardiography a noninvasive diagnostic tool in paediatric cardiology. Patients with the most complex cardiac anomalies, based on the findings of echocardiography, are sent directly to the cardiosurgical treatment. Imaging modalities currently applicable in the diagnosis and treatment of congenital heart anomalies are: echocardiography, X-ray angiography, MRI, multislice CT. Radiation safety is a primary consideration in paediatric imaging modalities. Transesophageal echocardiography *(TEE)* has progressed from biplane probe to multiple imaging probe that is used in infants up to 1500 grams of weight. Using TEE, paediatric cardiologists are now able to give information to the surgeon in operating room. *Intracardiac echocardiography* is performed in the catheterization laboratory with the aim of confirming the position of invasive devices. The application of new echocardiographic approach in the evaluation of cardiac function continues to be the subject of research but the gold standard method has not yet been established. Tissue Doppler echocardiography *(TDE)* uses blood flow Doppler technology to speed the ventricular wall, allowing the analysis of motion in systole and diastole. A few studies

indicate that TDE can be used in both preclinical evaluation of cardiomyopathy and right ventricular function in children. Myocardial performance index *(MPI)* is applied in the evaluation of biventricular cardiac function by Doppler flow information with the aim of measuring systolic time intervals. *Radionuclide imaging techniques* have the potential to quantify myocardial abnormalities of glucose and fatty acid metabolism using positron emission tomography / computed tomography and single photon emission computed tomography *(SPECT). Cardiac magnetic resonance* is established as the best modality to define the relationship between the heart and great blood vessels in relation other intrathoracic structures. This is the technique of choice for complex syndromes, coarctation of the aorta, ascending and descending aortic aneurysms (Marfan syndrome and Turner), vascular rings and anatomy of pulmonary veins. It can enable the application of three-dimensional data by time intervals (*4D* imaging techniques) without the usual limitations of echocardiographic window technique. It analyzes the dynamics of cardiac flow, wall motion, ventricular volumes and ventricular function. These new diagnostic imaging techniques bring clinicians closer towards the ultimate goal of medicine in which computerized agents are used for the construction and evaluation of patient-specific anatomic / physiologic model with the aim to plan surgical or cardiac catheter interventions and prediction of clinical outcome of anomalies.

Interventional cardiology was born in 1953 when Rubio Alvarez applied catheter for incision of stenotic pulmonary valve. Then, in 1966, the procedure of balloon atrial septostomy created by Rashkind and Miller revolutionized the treatment of D transposition of great vessels. Interventional diagnosis and therapy has made great achievements in paediatric cardiology in the last two decades. *Balloon atrial septostomy* with *prostaglandins* application, are precondition of *lege artis* treatment of major group of congenital heart anomalies. Modern paediatric cardiology cannot be imaginable without routine application of prostaglandins. Prostaglandins are indicated as palliative, but not definitive therapeutic medicament in neonates with congenital heart duct dependent anomalies. Application of prostaglandins was necessary and crucially indicated for maintaining the life of these patients up to moment of surgical correction of CHD. Transcatheter implantation of coils, umbrella and stents, is routinely done in cardiac centres in Europe and United States of America. The precondition of this application is, of course, the adequate catheterisation laboratory and equipment and capable staff.

Today, *interventional procedures* can be applied in cardiac catheterisation laboratories providing children with cardiac anomalies safe and effective therapeutic alternatives in relation to surgery. Pulmonary or aortic valvuloplasty, recurrent postoperative coarctation of aorta, stenting or balloon angioplasty of stenotic conduit of pulmonary arteries branches are routine procedures today in the world. Systemic to pulmonary collateral arteries, which are frequently observed in cases of pulmonary atresia, may be closed by occluders: coils, or balloons. Interventional cardiologists are welcome in the operating theatres where they are working with surgeons in order

to open stenotic distal pulmonary branches that often cannot be seen from the standard surgical view. In recent years, paediatric cardiosurgeons had to leave some fields to interventional cardiologists.

Transcatheter closing of secundum atrial septal defect (ASD) is a routine procedure as well as coil embolisation of ductus arteriosus persistens (DAP). On the way are also promising opportunities of closing a perimembranous and membranous ventricular septal defect. The new procedures include percutaneous transcatheter insertion of pulmonary and aortic valves, banding of pulmonary artery in some infants with heart decompensation due to large left-right shunts.

Interesting areas of possible *collaboration of interventional cardiologists and cardiovascular surgeons* are in improving the Fontan cavopulmonary connection in catheterisation laboratory. For children who have a "single ventricle" or hypoplastic left heart, a Glenn shunt is created, generally at age of 6 months of life. Glenn shunt consists of connection of vein cava superior and pulmonary artery. Alternative is "Hemi-Fontan", which creates perforated transatrial tunnel that allows blood flow from inferior vena cava to enter the heart. Completing the procedure is performed in the catheterization laboratory by caval redirecting of blood flow into the pulmonary circulation through the placement of the stent inside the tunnel in order to occlude the perforation and open the previously constructed connection tunnel and pulmonary artery. It can be concluded that the enthusiasm is created for interventions performed in the catheterization laboratory because of the obvious benefits such as: avoiding the risk of bypass surgery, reducing the risk of multiple surgical operations in those children with complex cardiac anomalies, reduced length of hospital stay, decreased medical costs and avoidance of scarring. The potential benefit in preserving brain function, especially in those children who require multiple surgeries throughout life, it is very important but still unproved.

Paediatric cardiology was always the core of paediatrics and together with c*ardiosurgery* has made the development of other paediatric branches possible and has directly contributed to the reduction of prenatal morbidity which is one of the major indicators of the state of development of a country. *Surgical techniques,* technologies of cardiopulmonary bypass and postoperative intensive cardiac care have progressed to such degree that primary correction is performed in the neonates with pulmonary atresia, or at the age of 3 months, for those who have open outflow tract with early signs of severe cyanosis. The low operative mortality associated with early correction has led to increased interest in improving the outcome of these anomalies.

The most important breakthrough in the treatment of Tetralogy of Fallot (TOF) has been made in the mid-20th century with the creation of palliative systemic-pulmonary shunts (Blalock-Taussig) that allowed newborns to grow to a size where the use of bypass surgery was possible. It is clear today that traditional surgical procedure for correction of ToF, that created an iatrogenic pulmonary insufficiency with residual outflow tract obstruction of RV, produces pathological substrate for right

ventricular dysfunction, a tendency to lethal arrhythmias and increased risk of sudden death. The current challenge is to develop new diagnostic modality analysis of the anatomy and function of the right ventricle (3D echocardiography, MRI, SPECT or PET scanning) in order to promptly identify preclinical symptoms. Identifying the pathology of RV disease has directed cardiac surgeons to consider the operative techniques, so called "valve sparing" procedures, or limiting the degree of pulmonary insufficiency through the pulmonary valve construction of monocusp pulmonary valve by pericard use. There were different degrees of right bundle branch block in patients with ToF and those who underwent right ventriculotomy. There is evidence that "resynchronisation" of systole of the right and left ventricular using two separate pacemakers (one for each ventricle) can improve the function of RV and increase cardiac output.

Thanks to salvation of different mechanisms at cellular level (cellular patophysiology) great steps in *paediatric rythmology* have been made. Cardiac catheterisation of the heart, with the aim of electrophysiological investigation, allows the recognition of rhythm disorders, and its treatment is better nowadays. In *clinical electrophysiology* in the last decade huge steps were made in understanding and treatment of arrhythmias in children. In institutions with developed paediatric cardiology, starting from 1990 the established techniques are conservative ablation of tachyarrhythmias in children using radiofrequency catheter. Association of Paediatric electrophysiologists in 1997 announced a huge success in the treatment of supraventricular tachycardia in childhood and adolescence with great acceptance and treatment of the patient, taking into account the cost of drug therapy. Recent development of 3D electroanatomic maps of arrhythmias has improved catheter access in cases of atrial flutter and other tachyarrhythmias due to postsurgical incisions. Progress in the treatment of bardiarrhythmias includes small electrical pacing stimulators and thin wires, even in small premature infants. Advanced pacemaker programming allows more efficient use of energy, which increases battery life.

Cases of *sudden unexpected death* in "healthy" athletes who had inherited hypertrophic cardiomyopathy (HCP) as well as dramatic examples of families who are devastated because of the pain of sudden cardiac death due to congenital prolonged QT and Brugada syndrome, have focused considerable attention on the hereditary causes of sudden death. More than 100 gene mutations that cause defects in the structure of the protein myofibrils that relate to the majority of hereditary hypertrophic cardiomyopathy (HCM) were identified. Similarly, seven different mutations that destroy cardiac ion channel in families with Long QT syndrome were identified. Unfortunately, there is no medical treatment that changed the history of the patient with HCM. Inhibition of adrenergic nervous system reduces the risk of sudden death in many patients with prolonged QT syndromes. For some patients who have severe symptoms despite beta-adrenergic blocker therapy, implanted cardioverter defibrillator *(ICD)* significantly decreased mortality risk. Miniature ICD allows implantation in patients even in the age of 1 month. A recent multicentric study demonstrated the efficacy of

ICD in preventing long-term risk of sudden death in adolescents and children with HCM.

During the last decade, several clinical studies on *adolescents with heart failure* determined the validity of the concept of activation of the sympathetic nervous system and other neuroendocrine systems which have crucial role in development and progression of heart failure. In progress are tests that will determine the efficacy of beta-adrenergic blockade and inhibition of angiotensin converting enzyme in infants and children with heart failure.

Clinicians and researchers in the paediatric cardiology have traditionally focused on the care of infants, children and adolescents with heart disease. However, new fields are opening. Modern diagnostic and therapeutic approach in paediatric cardiology means an early application of *foetal echocardiography* from 18th till 20th week of intrauterine life. This approach gives the possibilities of detection of congenital heart anomalies, rhythm disorders as well as transcatheter therapy of individual lesions and disturbances. In the most European centres, the foetal echocardiography is carried out as the part of routine antenatal protection, which should be the aim of health care and protection in years to come. Research from England indicates that stress during *foetal* development has long-term effect. Based on epidemiological studies, it seems that foetal malnutrition predisposes adults for coronary vascular disease. *"Foetal programming"* can lead to hypertension, hypercholesterolemia and type 2 diabetes, which are major risk factors for heart disease development in adulthood. Molecular and cellular basis of these observations is only the beginning of understanding of these processes. Advanced techniques have led to dramatic changes in the diagnosis and possible treatment of foetuses with congenital heart disease or defects. Foetal medicine is a subdiscipline which is focused on the foetus and concentrated on the diagnosis and access to the foetus as a patient.

Prenatal diagnostic methods involve invasive techniques: amniocentesis (the first amniocentesis, in which foetal cells have been successfully analyzed via chromosome, was performed in 1966; applied from 15 weeks of gestation), and chorionic villus sampling (sampling of foetal tissue from chorionic villi in 11th or 12th week of pregnancy). Accurate and early diagnosis is essential for making decisions about continuing the pregnancy, and treatment options, which led to the development of foetal therapy. It can be carried out indirectly via the mother by pharmacological therapy or as medical or surgical intervention applied directly to the foetus.

"Open foetal therapy" as the most extreme type of foetal therapy, pioneered in America, was introduced by Harrison in 1980: intrauterine correction of diaphragmatic hernia. Gene therapy is the subject of extensive research. Progress in medicine and the possibility of foetal therapy poses a challenge to physicians. If the foetus is regarded as a patient, then the patient is in a unique position. In the first place, the foetus is entirely dependent on the mother during the intrauterine life, but at the same time it is impossible to apply any kind of treatment to the foetus, without

compromising the integrity of the mother. Therefore, a balance must be found between the interests of the foetus and those of the mother.

Futuristic therapy protocols of cardiac diseases: in a study from Germany in 2006: basic scientists as well as cardiologists are faced with idea of ischemic diseases treatment by cardial progenitor or steam cells. Having in mind that in infants and children etiology and pathomechanisms criteria of cardial diseases fundamentally differ from those in adults, the study considers whether those young patients should be therapeutically targeted? There is clear evidence that all structures in the heart could be targeted via steam cell therapy. Pacemaker cardiomyocytes, which could be obtained from embryo stem cells, are applied in experimental investigations as a biological pacemaker. Also, steam cells could be the source of bioartificial vessels. Cardiac cell therapy carries the promise to regenerate a heart muscle, not only after myocardial infarct in adults, but also in different paediatric heart diseases. Theoretically, steam cells could be used in generation of bioprosthesis or regeneration of lost myocardial tissue, for example after myocarditis. Up to now, experimental data are focused on treatment of ischemic injury. Clinical data in adults demonstrate moderate effect when basic steam cells are applied. Probable clinical use of either embryo or adult stem cells technology in paediatric cardiology is going to be reality in years to come. The fact is that there is a great potential of stem cells use which justifies intensive stem cell physiology investigation in this therapeutic approach. The development of this and other treatment options are going to need ethical discussion, and practical application should be investigated.

In recent years the *investigations in molecular biology and genetics* provided powerful tools for studying factors which influence heart development and understanding of its structure and functional development. It is possible that understanding of these fundamentals of normal heart development could offer the information in connection with pathogenesis of congenital malformations and could lead to discovery of mechanisms for early controlling of development of acquired cardiovascular diseases in adulthood.

The task of *preventive cardiology* is to conduct: educational program of adequate nutrition from birth, in family, school, living environment, and ways to live optimal life. Cardiovascular disease stays as the predominant cause of mortality and morbidity in developed countries. Preventive strategy for cardiovascular diseases comprises the follow up of subjects in the population by which we identify factors which could effect on cardiovascular risk, as well as the strategy in promotion of cardiovascular health in years to come.

Hypertension process starts in childhood. Etiopathogenetically is multi-factorial, and possible course and repercussions for the health are longstanding and irreversible. Normotension offers important data in contribution to health, and increased blood pressure in childhood represents the call for preventive paediatric action. It is needed to continue with investigations of primary hypertension because the ultimate goal of medicine is to explore the ways of prevention of diseases and to cure them.

Dislipoproteinaemias and repercussions on myocardium and blood vessels in paediatric population represent the imperative of modern investigations. Basic investigations of lipoproteins, apolipoprotein metabolism, biology of ateromatosis process development in cell and role of genetics in development of coronary artery disease, are necessary in the field of preventive cardiology. *Arteriosclerosis* is a process which originates in childhood. Multi-factorial in its etiopathogenesis, course and repercussions, it demands the action of: family doctors, paediatricians, physicians, cardiologists, biochemists, clinical pharmacologists, nutritionists, pathologists and epidemiologists with the aim of early detection and treatment of dislipoproteinemias as well as reduction of development of risk factors for coronary diseases. *Prevention of arteriosclerosis,* as leading cause of death in society, represents the responsibility for paediatricians who should do a screen of lipid levels to all children age two years with positive family history, as well as for children in schools.

Paediatric cardiology in Bosnia and Herzegovina is in intensive progress. Non-invasive imaging techniques including transthoracal and rhythmic (24–72 hrs monitoring of heart rhythm and blood pressure) ergometry tilt table tests are developed at the European level. Invasive cardiology, with foetal and transezofageal, as well as broadening of cardiosurgical spectrum by the local team, represents the imperative strategy in next decade with continuation of investigations in paediatric cardiology.

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INCREASED CAROTID INTIMA-MEDIA THICKNESS AND IMPAIRED SPORT MOTOR FITNESS IN OBESE ADOLESCENTS: WHAT ARE THE EFFECTS OF A SHORT-TERM MULTIDISCIPLINARY INTERVENTION?

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Abstract

Introduction: Early risk screening is important in cardiovascular (CV) atherosclerosis prevention. In overweight and obese children we assessed carotid intima-media thickness (IMT) and sport motor fitness and evaluated the CV effects of a 4-weeks hospitalized intervention program.

Methods: N=212 adolescents, thereof n=89 obese, age 11–15 years, were examined at baseline. The obese patients were re-tested at discharge of the intervention.

The examination integrated anthropometric data, BMI, body fat, blood pressure, resting heart rate and a sonography of IMT. The fitness test battery included the assessment of endurance capacity, strength, coordination and flexibility.

Results: In overweight and obese patients IMT was significantly ($p=0.023$) increased (0.584 ± 0.045 mm) compared to controls (0.532 ± 0.045 mm). IMT was associated with age ($r=0.213$, $p=0.041$), weight ($r=0.225$, $p=0.032$) and BMI ($r=0.263$, $p=0.015$). BMI was shown to be the only predictor for variable (ß=0.263, $p=0.030$) for IMT ($F\ [1.66] = 4.899$, $p=0.030$), adjusted $R^2 = 5.5\%$. However, after IMT was adjusted for sex and age the statistical significance reduced to a level that did not reach the formal level of significance ($r=0.185$, $p=0.065$). BMI, body composition, systolic and diastolic blood pressure could be significantly reduced by the intervention. However, there was no change in IMT. Skill-related physical fitness in overweight and obese adolescents was impaired in all tested components, but could be significantly improved by the intervention.

Conclusion: Increased IMT is present in obese patients. The multidisciplinary intervention enhanced CV factors and fitness. However, pathological vascular wall changes need longer time for their re-adaptation.

Keywords: intima-media thickness, sport motor fitness, intervention, obesity, paediatrics.

INTRODUCTION

Overweight and obesity prevalence are increasing in children worldwide[1-4]. The World Health Organization has declared obesity as a global epidemic. Using international definitions, at least 10% of the school children worldwide are overweight or obese, whereas the Americans are leading (32%), followed by Europe (20%) and after that the Middle East (16%)[3]. In Germany 8.7% of the children and adolescents between 3 and 17 years of age are overweight, 6.3% are obese. One of the main concerns of the rise in paediatric obesity is the possible impact that this will have on adult atherosclerotic disease rates in the future[5].

The main approach to decrease obesity-related cardiovascular risk is to reduce body weight. Previous studies in adults describe that a reduction of BMI of at least 1, over a period of one year leads to a lower rate of morbidity[6]. However in children, the interpretation of studies focusing on the result of reducing BMI is difficult, since BMI increases in healthy normal weight children with increasing age[7,8].

In childhood and adolescents there are only few studies showing that weight reduction leads to improvement of the atherogenetic risk factor profile[9].

Intervention strategies in obese children: The importance of exercise and the role of sport motor fitness in cardiovascular prevention of overweight and obese children

It is now widely accepted that atherosclerosis is a chronic disease, having its origin in childhood. Since the atherosclerotic progression takes a long time before the development of measurable plaques are manifested[10]. It is important to evaluate the arterial health status, by measuring the carotid intima-media thickness (IMT) and further to analyze the role of physical exercise and over all physical fitness in this process. Studies in adults revealed controversial results. Moreau and co-workers[11] found out that training does not typically have an impact on IMT. Contradictory a recent study in elite athletes examined consistently lower carotid wall thickness in athletes versus control subjects[12]. Findings of the Amsterdam Growth and Health Longitudinal Study described that cardiovascular fitness was an independent determinant of arterial stiffness, independently from obesity and the metabolic syndrome[13].

In obese children it has generally been stated that levels of physical activity in childhood have protective effects on body composition and cardiovascular disease[14]. However, overweight and obese children prefer a sedentary lifestyle, which leads to less sport motor ability and physical fitness[15]. Modules in intervention programs are multi-factorial and multi-disciplinary and include both dietary and physical exercise and activity pattern.

Currently it remains unclear, if sport motor fitness components such as cardiorespiratory endurance, muscular strength and muscular endurance, speed, coordination and reaction time have a positive effect on IMT in overweight and obese adolescents.

Furthermore, little is known about the impact of multidisciplinary interventions on these parameters.

OBJECTIVES

The present study aimed to assess the vascular status (IMT) and sport motor fitness in overweight and obese children and adolescents compared to normal weight peers. Secondly, correlations between traditional cardiovascular risk factors (BMI, total percentage of body fat, systolic and diastolic blood pressure), surrogate markers and physical fitness components in overweight and obese adolescents are calculated.

Thirdly, a short-term stationary rehabilitation program was evaluated to examine whether it has an effect on cardiovascular risk factors, including vascular structural changes and sport motor fitness.

Study hypotheses

1. IMT is significantly enlarged in overweight and obese children and adolescents in comparison to normal weight peers.
1. IMT is associated to non-invasively measured traditional cardiovascular risk factors in overweight and obese adolescents.
2. Obese and overweight adolescents have significantly impaired sport motor fitness compared to non-obese peers.
3. IMT and traditional non-invasive cardiovascular risk factors are significantly associated to components of sport motor fitness (speed of limb movements, reactive strengths, coordination and speed, coordination and reaction time, cardiorespiratory fitness, upper trunk muscular endurance strength, abdominal muscular endurance strength).
4. A 4-week hospitalized multidisciplinary intervention reduces cardiovascular risk factors and increases performance in sport motor skills.

METHODS

A total of 212 children and adolescents were examined. Thereof 89 study participants attended a hospitalized intervention at the Rehabilitation Centre/Clinic Gaissach, Bad Tölz/Germany, and were consecutively examined in the first week after admission (baseline). To analyze the effects of the hospitalized intervention program, 85 obese adolescents were measured at baseline and 4-weeks later. The inclusion criteria for participation in the trial were: age 11 to 15 years, no history of cardiovascular disease and no personal history of diabetes mellitus or impaired fastening glucose. Obesity was defined as a BMI > 97th percentile, using population specific data[8]. All patients participated in the intervention according to the National guidelines[16]. The program was multidisciplinary and based on physical exercise, nutrition education (high carbohydrate, fat reduced diet) and behaviour therapy including individual psychological care of the child. An interdisciplinary team of paediatricians, diet

assistants, psychologists and sport scientists were responsible for the interventional training.

The control group consisted of children and adolescents from Munich secondary schools.

The same medical doctors and sport scientists performed the investigation.

The assessment included sonography of the A. carotis communis, distal of the carotid artery bifurcation on a segment ≥ 1 cm length (GE Loqiq Book XP. 10 Mhz linear probe). Further anthropometric data height, weight, BMI, body composition (FUTREX 6100 AL) and resting (15 min.) blood pressure were taken. Both sonography and anthropometric data collection were performed in the mornings before the sport motor fitness tests following a standardized protocol as previously described[17].

Description of the sport motor fitness test

Further a self-assessed health and skill related physical fitness test was conducted by sport scientists and qualified staff. The tests were performed in the sport gymnasium of the Clinic in Gaissach for all hospitalized patients. For the control group the tests were performed on two afternoons in the sport laboratory of the Faculty of Sport and Health Sciences, Technische Universität München.

Both the laboratory and sports gymnasium of the clinic were provided with standardized gymnastic facilities and were complementally equipped with the computer-based test system[18]. Due to a lack of a wall bar in the laboratory the bent-arm hang could not be tested in the control group.

The physical fitness tests were performed in the afternoons starting off with a 10-minute warm-up program, followed by a 9-minute run on the first afternoon. On the next day, the same warm-up program was performed, followed by a pre-set test order (tapping, drop jump, complex coordination and reaction time test, a 10 m coordination run, sit-ups and bent-arm hang).

Tapping – assessment of speed of limb movement

The aim of the test was to perform as many contacts on the force plate as possible with the right and left foot. This tapping frequency was measured 4 times during a time of 3 seconds. The tapping frequency is measured in Hertz [contacts per minute]. From the four test trails a mean value of the two best trails was calculated and used for further analysis[19,20].

Drop jump – assessment of reactive strength

The aim of the test was to jump down from a platform onto a force plate and immediately up on a second landing platform. The contact time on the force platform was measured in milliseconds [msec]. Each subject performed five jumps. In between the

5 jumps a recovery time of at least 10 seconds was integrated in the test. The best jump with the shortest contact time was taken for further analysis[21].

Coordination run – assessment of coordination and speed

Light barriers were set up at the start line and finishing line within a distance of 10 meters. 5 meters in front of the start line was the preparation point for the test person. The coordination run consisted of 6 squares (total lengths 3.30 meters), which were set up in a row, pair wise (one for the left foot and one for the right foot). A second set of 6 squares was set up with an interspace of 2 meters.

The objective of the coordination run was to run through squares as fast as possible without making a step mistake, e. g right foot steps in right square, left foot steps in left square. The subject had three trials; the best trial (run time in seconds) was counted for statistical analysis[18,22].

Complex reaction test – assessment of coordination and reaction time

The computer screen was divided into 4 sections, two sections for the hands (left and right side) and two sections for the feet (left and right side). The hardware consisted of two hand plates and a force plate with two sections for the right and left foot. The hand sensor plates were set up on the table in front of the test person, the force plate was under the table. Similar to the hardware the computer screen was divided. Two white fields on the screen marked for the hand plates and two blue fields marked for the contact area´s for the feet. After the test start, different black signals appeared on the screen in random order. The aim was to touch the hand and feet plates exactly as their combinations appear on the screen. A following image only appears after the correct repetition of the showed combination. 30 different combinations were shown. The time was counted in seconds. Each test person had three trials. The best trial was counted for further analysis[18].

Sit-and-reach test – assessment of hamstring, gluteal and lower back muscle flexibility

One of the most commonly used field tests for hamstring, gluteal and lower back musculature flexibility in children is the sit-and-reach test. It has one of the highest test-retest reliabilities (r=0.89 to 0.97) for measures of flexibility[23]. With legs fully extended and no shoes, the children were asked to reach forward three times and hold position on maximal reach along a ruler which was placed on the top of the box. Research assistance recorded farthest reach to the nearest cm. The differences between the feet and the tip of the longest finger was measured in cm[24,25].

9-minute run – assessment of cardiorespiratory endurance capacity

Cardiorespiratory endurance capacity was assessed in all students using a group administered timed 9-minute run. Standards of performance for youth are well established, and test-retest reliability in third grade students was 0.90. Correlations with more complex measures of fitness were estimated in the pilot phase of the CATCH study[26,27].

Bent-arm hang – assessment of upper trunk muscular endurance strength

The bent-arm hang was tested and instructed as previously described in the Handbook for Eurofit Tests of Physical Fitness[24,25]. The child maintained a bent-arm position while hanging on a bar with a forward grip at shoulder width. The time in tenth of a second was the score.

Sit-ups – assessment of abdominal and endurance strength

The children were instructed to keep arms folded across the chest, place feet about 38 cm from the buttocks, touch the elbows to thighs on the upward position, and touch mid-back to mat on the downward position. For testing purposes the participants' feet were held down by another participant and floor mats were provided for comfort. The test measures abdominal muscular endurance. The maximum number of achieved sit-ups in 30 seconds was counted[24,25,28].

Statistical analysis

All data were analysed in SPSS 16.0. Weight groups were determined by BMI reference values for German children as standardized by the German Obesity Association[8], defining BMI >90th percentile as overweight, >97th percentile as obese.

Normal distribution was tested using Kolmogorov-Smirnov-Test. Since the data show a Gaussian distribution, data are presented as mean and SD for continuous variables. Univariate, unadjusted analyses between obese and control subjects were performed with the independent samples t-test. ANCOVA was used to evaluate the presence of confounding variables in relationship between obesity status and vascular parameters. Models were adjusted for several confounding variables, including sex, age, height, systolic and diastolic blood pressure. Adjusted IMT means and 95% confidence interval (CI) were estimated with the use of Bonferroni method.

For comparisons between baseline and post examination 4-weeks later, the paired sample t-test for paired samples was used.

Unadjusted relationships were assessed with Pearson's correlation analysis. To evaluate the independence of correlates of risk factors and to assess the main predictor for increased IMT, stepwise multiple linear regression analysis was used. IMT

adjusted by sex and age was integrated in the model as dependent variable and BMI, the total percentage of body fat, systolic and diastolic blood pressure values were included as independent variables.

To evaluate the independence of correlations of IMT, cardiovascular risk factors and health- and skill-related physical fitness, and to assess main predictors for increased IMT and cardiovascular risk factors, multiple linear regression analysis (enter method) was used. IMT, BMI, body fat, systolic and diastolic blood pressure (all adjusted by sex and age) were integrated as independent variables and the test components for sport motor fitness were also adjusted by age and sex and integrated in the model as dependent variables.

In all regression analysis it was thoroughly checked for non-collinearity to avoid violations of model assumptions. Residuals were tested and the distribution was normal. All covariates included in the model were tested for interactions with each other. Because the variance inflation factor (VIF) was <5 and condition indices were <15, no correction for collinearity of the data was necessary[29]. A *P* value of less than 0.05 indicated statistical significance.

RESULTS

Table 1 displays an overview of the anthropometric data and IMT of the A. carotis communis in overweight and obese patients compared to normal weight peers.

Table 1. Descriptive data of the studied obese patients compared to normal weight control subjects

	Group	N	Mean	SD	P value
Age [years]	Normal weight	123	12,97	1,33	0,047
	Overweight/ obese	89	13,39	1,68	
Height [m]	Normal weight	123	1,61	0,1	0,019
	Overweight/ obese	89	1,64	0,09	
Weight [kg]	Normal weight	121	51,03	9,94	<0.001
	Overweight/ obese	89	86,93	24,32	
BMI [kg/m^2]	Normal weight	123	19,31	2,03	<0.001
	Overweight/ obese	89	31,76	6,96	
Body fat [%]	Normal weight	116	20,79	7,36	<0.001
	Overweight/ obese	85	37,91	7,47	

Systolic blood pressure [mmHg]	Normal weight	122	111,87	11,08	<0.001
	Overweight/ obese	85	122,56	14,37	
Diastolic blood pressure [mmHg]	Normal weight	122	67,38	9,06	0,002
	Overweight/ obese	85	63,36	8,51	
IMT [mm]	Normal weight	91	0,532	0,045	0,023
	Overweight/obese	74	0,548	0,045	

Values are presented as means +/- SD. Independent sample t-test was performed to investigate group differences. The level of significance vas $P < 0.05$.

In total, the obese and overweight patients were older (p=0.047). They were also significantly taller than their lean peers. Unquestionably the obese and overweight children and adolescents had significantly higher weight, showed a higher BMI and a higher percentage of total body fat compared to the control group (all p<0.001). Systolic blood pressure was significantly (p<0.001) higher in overweight and obese children as well as diastolic blood pressure (p<0.001). The IMT was significantly (p=0.023) thicker in overweight and obese children compared to normal weight children.

Differences between boys and girls are presented in Table 2 and 3 for overweight and obese children compared to normal weight children. The overweight and obese boys were significantly taller (p=0.003), heavier, had a higher BMI and higher percentage of body fat and a higher systolic and diastolic blood pressure (p=0.049). Also the IMT was significantly increased (p=0.033) compared to the control group. There was no significant difference in age (p=0.075) in boys.

Table 2 Descriptive data of the studied obese patients compared to normal weight control subjects for boys

Sex		Group	N	Mean	SD	*P* value
Boys	Age [years]	Normal weight	67	13,01	1,38	0,075
		Overweight/ obese	45	13,51	1,53	
	Height [m]	Normal weight	67	1,62	0,11	0,003
		Overweight/ obese	45	1,68	0,09	

Boys	Weight [kg]	Normal weight	67	51,85	11,13	<0.001
		Overweight/ obese	45	90,81	25,26	
	BMI [kg/m^2]	Normal weight	67	19,46	2,08	<0.001
		Overweight/ obese	45	31,67	6,22	
	Body fat [%]	Normal weight	62	17,48	8,14	<0.001
		Overweight/ obese	43	36,56	8,06	
	Systolic blood pressure [mmHg]	Normal weight	67	113,48	11,15	<0.001
		Overweight/ obese	45	124	15,58	
	Diastolic blood pressure [mmHg]	Normal weight	67	67,91	9,59	0,049
		Overweight/ obese	45	64,31	9,04	
	IMT [mm]	Normal weight	53	0,535	0,045	0,033
		Overweight/obese	32	0,555	0,037	

Values are presented as means +/– SD. Independent sample t-test was performed to investigate group differences. The level of significance vas $P < 0.05$.

Table 3 Descriptive data of the studied obese patients compared to normal weight control subjects for girls

Sex		Group	N	Mean	SD	*P* value
Girls	Age [years]	Normal weight	56	12,92	1,29	0,289
		Overweight / obese	44	13,26	1,83	
	Height [m]	Normal weight	56	1,61	0,08	0,889
		Overweight/ obese	44	1,61	0,08	
	Weight [kg]	Normal weight	56	50,05	8,27	<0.001
		Overweight/ obese	44	82,97	22,92	
	BMI [kg/m^2]	Normal weight	56	19,14	1,96	<0.001
		Overweight/ obese	44	31,86	7,7	

Girls	Body fat [%]	Normal weight	54	24,59	3,72	<0.001
		Overweight/ obese	42	39,3	6,61	
	Systolic blood pressure [mmHg]	Normal weight	56	109,91	10,78	<0.001
		Overweight/ obese	40	120,95	12,87	
	Diastolic blood pressure [mmHg]	Normal weight	56	66,73	8,42	0,011
		Overweight/ obese	40	62,3	7,85	
	IMT [mm]	Normal weight	38	0,528	0,046	0,174
		Overweight/ obese	42	0,543	0,05	
		Overweight/ obese	42	0,543	0,05	

Values are presented as means +/– SD. Independent sample t-test was performed to investigate group differences. The level of significance vas $P < 0.05$.

Overweight and obese girls were heavier, showed a higher BMI, as well as a higher total percentage of body fat (all p<0.001). Further, systolic blood pressure (p<0.001) and diastolic blood pressure (p=0.011) were increased compared to the healthy control group in girls.

Concerning IMT in girls, no significant difference was found in overweight and obese subjects compared to the non-obese controls.

The analysis of carotid IMT in the total study population revealed that, when adjusted for sex, age and height, there was still evidence of statistically significant differences between obese children and adolescents and control subjects. IMT in overweight and obese patients was 0.549 mm (95% CI 0.538 – 0.559) and in healthy control subjects it was 0.532 mm (95% CI 0.523 – 0.542, p=0.022). Adding diastolic blood pressure as a covariate reduced the p-value, but the statistical significance was retained (p=0.037). However, when systolic blood pressure was substituted the statistical significance was further reduced to a level that did not reach the formal level of statistical significance. IMT in obese patients was then 0.547 mm (95% CI 0.536 – 0.558), and IMT in healthy control subjects was 0.533 mm (95% CI 0.524 – 0.543, p=0.076).

Relationships between IMT and traditional cardiovascular risk factors in overweight and obese children and adolescents

The results of the unadjusted correlation analysis of anthropometric parameters, traditional cardiovascular risk factors (BMI, the total percentage of body fat, systolic

and diastolic blood pressure) and IMT are presented in Table 4. Age was found positively correlated to IMT (r=0.213, p=0.041) as well as weight (r=0.225, p=0.032) and BMI (r=0.263, p=0.015).

Table 4 Relationships between non-invasive cardiovascular risk factors in overweight and obese patiens (n = 68)

		IMT [mm]	Age [years]	Height [m]	Weight [kg]	BMI [kg/m^2]	Body fat [%]	SBP [mmHg]	DBP [mmHg]
IMT [mm]	r	1	0,213	0,062	0,225	0,263	0,184	0,173	–0,027
	P value	,	0,041	0,307	0,032	0,015	0,067	0,079	0,414
Age	r	0,213	1	0,513	0,514	0,388	0,335	0,13	–0,131
[years]	*P* value	0,041	,	0	0	0,001	0,003	0,146	0,143
Height [m]	r	0,062	0,513	1	0,718	0,33	0,309	0,4002	0,126
	P value	0,307	0	,	0	0,003	0,005	0	0,153
Weight [kg]	r	0,225	0,514	0,718	1	0,885	0,644	0,402	0,07
	P value	0,32	0	0	,	0	0	0	0,286
BMI	r	0,263	0,388	0,33	0,885	1	0,726	0,291	0,03
[kg/m^2]	*P* value	0,015	0,001	0,003	0	,	0	0,008	0,406
Body fat [%]	r	0,184	0,335	0,309	0,644	0,726	1	0,261	–0,116
	P value	0,067	0,003	0,005	0	0	,	0,016	0,174
SBP [mmHg]	r	0,173	0,13	0,402	0,402	0,291	0,261	1	0,256
	P value	0,079	0,146	0	0	0,008	0,016	,	0,018
DBP [mmHg]	r	–0,027	-0,131	0,126	0,07	0,03	–0,116	0,256	1
	P value	0,414	0,143	0,153	0,286	0,406	0,174	0,018	,

Pearson correlation coefficients and *P* values are describing the relationship. The level of significance was defined as $P < 0.05$.
Abbreviations: IMT – Intima-media thicknessof the A. carotis communis; BMI – Body mass index; SBP – Systolic blood pressure; DBP: Diabolic blood pressure.

In the multiple linear regression analysis BMI was shown to be the only predictor for variable (ß=0.263, p=0.030) for IMT (F [1.66] = 4.899, p=0.030), adjusted R^2 = 5.5%. However, after IMT was adjusted for sex and age the statistical significance reduced to a level that did not reach the formal level of significance (r=0.185, p=0.065).

Further, BMI was positively related to systolic blood pressure (r=0.291, p=0.008). Moreover, the total percentage of body fat was related to systolic blood pressure (r=0.261, p=0.016).

Sport motor fitness

Table 5 presents the results of the sport motor fitness tests in overweight and obese boys compared to normal weight controls.

Table 5 Sport motor fitness test results in overweight and obese boys compared to normal weight peers.

	Group	N	Mean	SD	*P* value
Tapping [Hz]	Normal weight	67	11,04	1,34	<0.001
	Overweight/obese	45	15,58	9,33	
Drop jump [msec]	Normal weight	67	145,92	19,73	<0.001
	Overweight/obese	45	219,38	62,74	
Coordination run [sec]	Normal weight	67	6,04	0,76	0,002
	Overweight/obese	45	8,99	7,34	
Complex reaction test [sec]	Normal weight	67	21,59	3,25	0,045
	Overweight/obese	45	23,66	5,26	
Sit-and-reach [cm]	Normal weight	67	–0,59	7,63	0,017
	Overweight/obese	45	–5,34	11,73	
9-minute run [m]	Normal weight	0	,	,	–
	Overweight/obese	45	1064,2	195,8	
Bent-arm hang [sec]	Normal weight	0	–,	–,	–,
	Overweight/obese	45	1,35	2,45	
Sit-ups [n]	Normal weight	67	24,13	9,65	0,01
	Overweight/obese	45	19,38	7,6	

Pearson correlation coefficients and *P* values are describing the relationship. The level of significance was defined as $P < 0.05$.

Obese and overweight boys show inferior fitness in coordination and speed in comparison to their normal weight peers. Further, coordination and visual reaction time, performed in the complex reaction test, are reduced in overweight and obese children and adolescents compared to the results of normal weight peers. Moreover, obese boys show less flexibility and less abdominal muscular endurance. They ran 1064.2 ± 195.8 m in the 9-minute run. The obese and overweight boys managed to hold themselves in a bent-arm hang for a mean time of 1.35 ± 2.45 sec.

Overweight and obese girls performed less in tapping (speed of limb movement) and drop jumps (reactive strength) compared to their normal weight peers.

Further obese girls were slower in the 10 m coordination run and also slower in the complex reaction test. The obese girls further demonstrate impaired hamstring, gluteal and lower back muscle flexibility. They ran 1062.3 ± 170.7 meters in the 9-minute run and managed to hold themselves in the bent-arm hang for 1.32 ± 2.61 seconds.

Interestingly, overweight and obese girls presented better abdominal muscular endurance compared to their lean peers (Table 6).

Table 6 Sport motor fitness test in overweight and obese girls compared to normal weight peers.

	Group	N	Mean	SD	*P* value
Tapping [Hz]	Normal weight	56	10,41	1,81	0,002
	Overweight/obese	44	14,4	8,91	
Drop jump [msec]	Normal weight	56	150,41	24,8	<0.001
	Overweight/obese	44	207,97	52,88	
Coordination run [sec]	Normal weight	56	6,36	1,11	0,001
	Overweight/obese	44	7,1	0,92	
Complex reaction test [sec]	Normal weight	56	22,09	3,11	0,019
	Overweight/obese	44	24,76	5,82	
Sit-and-reach [cm]	Normal weight	56	6,87	8,58	0,001
	Overweight/obese	44	–0,34	10,45	
9-minute run [m]	Normal weight	0	,	,	-
	Overweight/obese	44	1062,3	170,7	
Bent-arm hang [sec]	Normal weight	0	,	,	–,
	Overweight/obese	44	1,32	2,61	
Sit-ups [n]	Normal weight	56	19,37	6,16	0,121
	Overweight/obese	44	21,98	8,37	

Relationships between IMT and sport motor fitness in overweight and obese children

In the multiple linear regression analysis all sport motor fitness test results were adjusted by age and sex and put into the model (enter) for predictor analysis of IMT, which was also adjusted for age and sex. The regression model did not reach the formal level of significance for IMT_{adj} (F [1.44] = 0.219, p=0.952), adjusted R^2 = 0.2%. No significant relationships were found between IMT_{adj} and the health- and skill-related physical fitness tests (all adjusted for age and sex): $tapping_{adj}$ (r=0.038,

p=0.751); drop $jumps_{adj}$ (r=0.010, p=0.938); coordination run_{adj} (r=0.067, p=0.583); complex reaction $test_{adj}$ (r=0.276, p=0.173); sit-and-$reach_{adj}$ (r=–0.14, p=0.251); 9-minute-run_{adj} (r=–0.056, p=0.716); bent-arm $hang_{adj}$ r=–0.107, p=0.417); sit ups_{adj} (r=–0.42, p=0.730).

However, the results of the physical fitness tests correlate with body composition. A positive relationship revealed between the performed ground contact time in drop $jumps_{adj}$ and BMI (r=0.340, p=0.004). Further a positive relation could be assessed between the reaction time in the complex coordination and reaction $test_{adj}$ and BMI (r=0.313, p=0.03). Further a negative relation revealed between the component of flexibility (sit-and-reach $test_{adj}$) and BMI (r=–0.225, p=0.04). Furthermore the achieved running performance in the 9-minute-run_{adj} negatively correlated to systolic blood $pressure_{adj}$ (r=–0.275, p=0.04).

Effects of the hospitalized intervention for obese adolescents

Table 7 presents an overview of the medical data at baseline and 4 weeks later. Anthropometric measurements revealed significant decrease in weight, BMI, and the total percentage of body fat. After the intervention the systolic blood pressure and diastolic blood pressure were significantly decreased. Further the heart rate decreased significantly. After 4 weeks the IMT did not change significantly.

Table 7 Changes in weight, BMI body composition, blood pressure heart rate and carotid IMT at baseline and 4 weeks after the hospitalized intervention

	N	Baseline	SD	4-weeks later	SD	*P* value
Weight [kg]	85	91,44	22,93	82,52	20,65	<0.001
BMI [kg/m^2]	85	33,52	6,99	30,25	6,35	<0.001
Body fat [%]	85	40,18	5,49	36,17	6,34	<0.001
Systolic blood pressure [mmHg]	85	123,55	14,1	115,09	11,73	<0.001
Diastolic blood pressure [mmHg]	85	64,51	8,61	61,69	7,58	0,037
Heart rate [beats/min]	85	85,43	12,37	70,68	12,08	<0.001
IMT [mm]	85	0,549	0,041	0,543	0,05	0,44

Data presented as mean +/– SD. A *P* value ≤ 0.05 was considered to be significant.

Results in physical fitness revealed in most tests an increase in performance (Table 8). The tapping frequency significantly improved after 4 weeks. The ground contact time assessed by drop jumps also reduced significantly. The complex reaction test revealed a significant better overall coordination, resulting in a faster reaction time. Hamstring, gluteal and lower back muscle flexibility and cardiorespiratory

endurance increased significantly after the 4-week intervention. The running coordination and speed assessed by the coordination run, upper body muscular endurance assessed by bent-arm hang and the abdominal muscular endurance assessed by sit-ups did not improve significantly.

Table 8 Changes in sport motor fitness at baseline and 4 weeks after the hospitalized intervention in obese adolescents

	N	Baseline	SD	4-weeks later	SD	*P* value
Tapping [Hz]	85	16,41	9,89	9,67	1,45	<0.001
Drop Jump [msec]	85	229,31	60,33	205,18	50,76	0,011
Coordination run [sec]	85	8,64	6,71	7,04	1,37	0,121
Complex reaction test [sec]	85	27,67	5,6	21,26	2,77	<0.001
Sit-and-reach [cm]	85	–4,11	12,61	–1,4	8,65	0,048
9-minute run [m]	85	1084,5	150,7	1240,2	195,8	<0.001
Bent-arm hang [sec]	85	1,46	2,42	1,74	4,11	0,519
Sit-ups [n]	85	37,6	8,16	38	8,28	0,781

Data presented as mean +/– SD. A *P* value ≤ 0.05 was considered to be significant.

DISCUSSION

Vascular risk of overweight and obesity in children and adolescents

Although the most severe complications of overweight and obesity do not manifest until later in life, cardiovascular health consequences may already be evident at a young age[30]. Furthermore the period of adolescence has been described as a critical period for the development and expression of obesity-related comorbidities in boys and in girls[31].

Summarizing the results, the present study documented:

1. Carotid IMT was significantly increased in overweight and obese children and adolescents compared to healthy controls.
2. Significant correlations revealed between IMT and age; IMT and weight; IMT and BMI.
3. Impaired sport motor fitness in overweight and obese adolescents in most of the tested components (except abdominal endurance strength in girls, which was not impaired).
4. No significant correlations revealed between IMT and sport motor fitness components.
5. Significant correlations revealed between traditional cardiovascular risk factors and sport motor fitness components.

Effects of the multidisciplinary intervention:

1. Significant reductions of atherosclerotic cardiovascular risk factors such as weight, BMI, the total percentage of body fat, systolic and diastolic blood pressure.
2. Significant improvements in sport motor fitness.
3. Vascular structure (IMT) decreased after the intervention but not significantly.

Vascular status in overweight and obese adolescents and relationships to traditional cardiovascular risk factors

In both sexes, the measured IMT values for overweight and obese adolescents in the present study range between the 50th and 75th percentile for boys and for girls in age group 12/13 years[17]. The overweight and obese children show a significantly larger IMT than the control group.

This result could also be stated in boys, however in girls, no significant differences for IMT in overweight and obese adolescents compared to normal weight peers were found. The apparent discrepancy within the present study could be due to the small sample size in girls (42 obese versus 38 controls).

The increased IMT in overweight and obese adolescents was accompanied by significantly higher values in body weight, body fat, systolic blood pressure and diastolic blood pressure. These facts still revealed when adjusting for sex.

Further the correlation of cardiovascular risk factors such as weight and BMI with IMT as well as BMI and body fat with systolic blood pressure suggests that obesity in adolescents represents a powerful determinant of early manifestations of atherosclerosis and affects structural properties of major vessels[32]. The effect of structural changes appears to be mediated, at least in parts, by BMI and systolic blood pressure.

The results of the present study further confirm findings of several studies that documented the association of hypertension and childhood overweight as well as obesity[33-36]. Furthermore, it has been stated that obese children have a tenfold greater risk of developing hypertension as young adults compared to non-obese children. This result is of notable concern since blood pressure values tend to track from adolescence into adulthood, and especially in those who are overweight or obese[37].

Sport motor fitness in overweight and obese adolescents and the correlations to vascular structure (IMT) and cardiovascular risk factors

It is increasingly recognized that physical activity and exercise in children and adolescents is an essential component of healthy growth and development. The biological mechanisms linking exercise, physical fitness and health in children are multifactorial and of special interest due to an emerging epidemic of paediatric obesity, type 2 diabetes and the metabolic syndrome[38-40].

Some authors found differences in fitness between obese and non-obese children, while others did not[41-43]. In the present study sport motor fitness components in obese compared to normal weight adolescents were impaired. The obese adolescents had

mainly impaired performance on all tests requiring propulsion or lifting of the body mass, such as tapping, running coordination and bent-arm hang. Energy intake exceeding energy expenditure is stored in the body mainly as fat, but also in protein. Stored protein increases fat free and muscle mass[44]. Therefore, overweight and obese subjects usually have more muscle mass compared with normal weight individuals[45]. This is associated with better absolute muscle strength in adolescents[46]. But most of the functional tasks require the lifting of body weight. Relative muscle strength (muscle strength in relation to body mass) may be the key component of muscle strength to comply in daily life[44] and not the absolute muscle strength.

These poorer performances are probably due to the fact that their excess body fat is an extra load and therefore has a negative influence on relative muscle strength and muscular endurance, that needs to be moved or held during weight-bearing tasks[47]. This then leads to lower performance in many tests such as drop jumps, tapping, 10-m coordination run and bent-arm hang.

Interestingly in overweight and obese girls the numbers of performed sit-ups did not differ significantly in comparison to normal weight peers. When comparing the results of the control group to German reference values[48] the test performance in sit-ups was only sufficient on a five grading scale (very good, good, normal, moderately disturbed and severely disturbed).

Obesity[49] and overweight[50] had a strong negative effect on endurance and upper body muscular strength and muscular endurance. The present study is in agreement with the above two studies and further underlines results of Malina and co-workers[51].

Furthermore, the results of the correlation analysis reveal a positive association between anthropometric data and sport motor fitness. This can be demonstrated especially in drop jumps, testing the reactive strength of lower extremities and measuring the ground contact time. The contact time is positively associated to weight and BMI that underlines the above mentioned negative impact of body weight in weight lifting tasks[47].

The performed coordination skill was positively associated to BMI, which underlines a more impaired overall coordination and reaction in obese children. Furthermore, in the present study, the overweight and obese adolescents performed significantly slower in the complex coordination and reaction test. Wagner and co-workers[52] underlined the importance of developmental coordination in overweight and obese children in the context of human development. The authors reinforced that the data are of particular interest since developmental coordination and obesity both track with age. The results of their study made it clear that obese show higher severe risk of developmental coordination disorder in comparison to normal weight adolescents. The complex coordination test in the present study focused more on the coordination and reaction time, demonstrating less coordinative skills of overweight children.

The fact that excess body adiposity also increases the likelihood of poorer trunk fitness has been stated previously[53,54] and could also be demonstrated in this study, whereas a negative correlation between flexibility and BMI was assessed.

On the other hand, in the present study cardiorespiratory endurance tested by the 9-minute run was negatively associated to systolic blood pressure. This result underlines published data of intervention studies that reported an effectively reduced blood pressure in overweight and obese children after an exercise intervention[55]. Further, the present results are in line with reports of the Children and Adolescents Trial for Cardiovascular Health (CATCH) study[27]. Analysis of the CATCH trial demonstrated a greater number of cardiovascular risk factors in heavier children and a lower performance on 9-minute endurance run.

Boreham and co-workers[56] demonstrated that relationships between fatness and coronary risk factors were stronger than between fitness and cardiovascular risk factors in adolescents. Also in this study, no association between skill-related physical fitness and IMT could be stated.

Effects of the intervention program

The sedentary lifestyle, and within that the imbalance of energy intake and expenditure, contributes to the increased obesity prevalence in adolescents. Intervention strategies are multi-disciplinary, including nutritional, exercise and behavioural treatment programs.

The main finding of the study is that a 4-week hospitalized intervention already accounts for a significant reduction of atherosclerotic cardiovascular risk factors such as weight, BMI, the total percentage of body fat, systolic and diastolic blood pressure. These results are in line with previous paediatric intervention studies that demonstrated an improvement of cardiovascular risk factor profile in association with obesity[57-60].

In this context, studies of Meyer and colleagues[61] underlined that cardiovascular fitness plays an important role for the improvement of cardiovascular risk factors and further in cardiovascular health prevention to reverse any atherosclerotic damage.

However, in the present study vascular structure (IMT) did not change significantly after 4-weeks of hospitalized intervention. This result is in line with reports of Woo and co-workers[62] who did not find changes in IMT after 6 weeks of exercise and diet intervention. It is possible that pathological changes need longer time for their adaptation or in this case re-adaptation.

Studies of Wunsch and colleagues[63] described parallel to an improvement of the cardiovascular risk profile with substantial weight loss, a decrease of IMT after a 1-year outpatient intervention program.

Taking traditional non-invasively measured cardiovascular risk factors into account the intervention program revealed a significant reduction of systolic and diastolic blood pressure. Those positive effects of exercise had been previously stated after a 8-months intervention program by McMurray and colleagues[64]. Richter and co-workers[65] explained the reduction of blood pressure firstly due to the enhancement of insulin action and glucose transport by physical exercise. A second explanation could be that the increased capitalization results in increased blood flow and energy supply to muscle tissue, which results in an improved fat metabolism and decreased blood pressure[65-68].

Advances in sport motor fitness

Exercise training was a major component in the intervention, daily activity indoor and outdoor sport programs. The exercise intervention not only improved measures of cardiovascular risk factors, but also improved sport motor fitness. A significant improvement revealed in speed of lower limbs assessed by tapping, reactive strength assessed by drop jumps, complex coordination and reaction test, hamstring, gluteal and lower back muscle flexibility assessed by the sit-and-reach test and in cardiorespiratory endurance which was assessed by the 9-minute run.

Complex sport motor assessments in hospitalized intervention obese children are still rare. Results of a Belgium hospitalized intervention study[69] underlined the importance of coordination and motor skill development in overweight and obese children. Their results demonstrated impaired scores for overweight and obese children and an increase in test scores of the Körperkoordinationstest after a short-term intervention. The authors emphasized the importance of gross motor skills in obese children with regard to a possible increase in physical activity. Sola and colleagues[70] also tested a variety of different basic motor abilities and complex movements in different muscle groups before and after 6 and 12 months of intervention. They stated an improvement in physical fitness and also a reduction of BMI over the intervention time.

CONCLUSIONS

The study underlines that vascular structure changes with increased body weight. It could be proven that an increased IMT is present in overweight and obese adolescents compared to normal weight controls. Furthermore, overweight and obese children demonstrated impaired sport motor fitness in almost all tested components. Therefore the results emphasize the need of an early focus on motor abilities. A better motor fitness might encourage overweight and obese adolescents to more sport activity. This is even more important since physical fitness components are in correlation with traditional risk factors. However a correlation between vascular structure and physical fitness could not be stated in the present study. The awareness of the complex relationships emphasized with the fact that obesity in childhood and adolescence is an important risk factor for cardiovascular disease as well as morbidity

and mortality in later life [71-73] underlines the importance of early prevention. The necessity becomes even clearer with the continuing increase in overweight and obese children.

The alterations of the analyzed cardiovascular risk factors were significantly related to the loss of weight throughout the intervention program. In advantage to invasive diagnostics, the ultrasound measurement can demonstrate the effect of the intervention program on the level of the vascular system since it enables an insight into the health of the blood vessel. No significant reduction of IMT could be measured after 4-weeks of hospitalized intervention. Obviously pathological changes need longer time to be reduced.

The multidisciplinary intervention with a focus on daily physical exercise revealed an enhancement in speed of lower limbs, reactive strength, complex coordination and reaction time, hamstring, gluteal and lower back muscle flexibility and endurance capacity. These positive effects might be beneficial for long-term physical activity and sport motor skill improvement.

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EVALUATION OF CARDIOVASCULAR RISK FACTORS IN CHILDREN – 15 YEARS OF PROSPECTIVE YUSAD STUDY

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Abstract

Atherosclerosis is dynamic process of cholesterol accumulation and other fatty substances in the artery wall over individual's lifetime, leading to the reduction in hemodynamics of blood vessels and atherothrombosis. Yugoslav Study of Atherosclerosis precursors in School Children (YUSAD) presents prospective longitudinal study that included so far 3 examinations on same school children population. First examination was done in 1998 in 15 cohorts including cohorts from Serbia, Bosnia and Herzegovina, Montenegro and Greece, when children were 10 years of age, where the main research is focused on risk factors for atherosclerosis development in school children and youth. The evaluated population was screened every 5 years. On first and second examination there were 4208 participants, 2124 males and 2084 females. On third examination there were 1293 participants, composing of 555 males and 738 females. The YUSAD study is designed through 7 chapters: epidemiological, clinical, anthropometric, biochemical, nutrition, genetics and ECG. Our study demonstrated that majority of tested school children were normotensive for age and gender, close to the half of evaluated population. Further, we have demonstrated that girls are more prone to accumulate body fat versus boys in the YUSAD study. Frequency of metabolic syndrome in school children population included in the YUSAD study was less than frequency reported in the literature. There is increase in mean values of total cholesterol and LDL fractions from E2 to E4 genotype in evaluated population. Triglycerides levels differ in mean values in different apo-E genotypes. School children from YUSAD study are physically active in moderate range, with preference given to those from rural places.

Keywords: Atherosclerosis; Risk factors; YUSAD study; Children

Introduction

Atherosclerosis is dynamic process of cholesterol accumulation and other fatty substances in the artery wall over individual's entire lifetime, leading to the reduction in hemodynamics of blood vessels and to atherothrombosis. According to the pathobiologic findings, atherosclerosis begins in early life and continues to its final stages in later life. The main characteristic of this process is long silent period. Significant reduction of the lumen during the years may lead to the critical reduction of blood flow in the affected part of vessel lumen resulting in ischemic events (1.2). There is increased frequency of atherosclerosis risk factors, particularly reduction in physical activity and obesity worldwide both in developed and developing countries, stressing out necessity of bringing the well developed and accessible educational programs that could be easily implemented.

Yugoslav Study of Atherosclerosis Precursors in School Children (YUSAD) represents a prospective-longitudinal study, where the main research is focused on risk factors for atherosclerosis development in school children and youth (1.2).

YUSAD is one of the largest national studies in Serbia with international character since it included cohorts from Serbia, Montenegro, Bosnia and Herzegovina and Greece as well.

So far, among many, few risk factors for development of atherosclerosis include: obesity in children (obesity), physical inactivity, genetic factors, metabolic syndrome, diabetes mellitus type 2, hypertension, smoking, hyperlipidemia, smoking, stress, risky behaviour in youth, etc. (2).

Study aims

The most important aims of the YUSAD study are (1.2):

1. Evaluation of selected parameters in school children
1. Identification of atherosclerosis precursors in school children population
2. Identification of children at mild, moderate and high risk
3. Estimation of prevalence and incidence of morbidity and mortality in parents and children through long term follow-up

Study material and methods

The YUSAD study as prospective longitudinal study included 3 examination periods performed on a same population. The first examination was done in 1998 in 15 cohorts including cohorts from Serbia, Bosnia and Herzegovina, Montenegro and Greece. The second examination that was conducted in 2003also included 15 cohorts, while the third check-up that was done in 2007 consisted of population from 9 cohorts from Serbia. The age of participants was 10 years on first examination, 15 years on second and 19/20 years on third. The evaluated population was screened every 5 years.

The study was approved by Institutional Review Board of Medical School University of Belgrade and supported by most prominent institutions in Serbia. International Commission in Bologna recognized YUSAD as a project of national interest. Prior to inclusion of eligible participants in the study, parents or legal guardians were informed and consent was obtained.

On first and second examination there were 4208 participants, of which 2124 were males and 2084 females (1). On third examination there were 1293 participants, composing of 555 males and 738 females (2).

The YUSAD study is designed through 7 chapters: epidemiological (65 characteristics), clinical (68 characteristics), anthropometric (14 characteristics), biochemical (17 characteristics), nutrition (19 characteristics), genetics (19 characteristics) and ECG (24 characteristics) (1). The most significant anthropometric parameters included: body mass index (BMI), waist circumference (Wc), hip circumference (Hc), skin fold on arm (SF), subscapular skin fold (SuS) and upper arm circumference (UAc). Anthropometric parameters were analyzed in the morning before meal in light clothes. Cardiovascular parameters included among others: blood pressure (systolic and diastolic), heart rate (pulse) and ECG evaluation. The cut-off values for blood pressure were 90th and 95th percentile for gender, age and height. The genetic parameters: MTHFR and apo-E genotypes.

Study findings of selective parameters

Cardiovascular parameters (2–4):

From the evaluated school children population, over the period of 15 years, we have found that there is less than 1% of those with congenital heart defects, acquired heart defects and/or myocardial and/or pericardial diseases.

There is increase in both systolic and diastolic blood pressure over 15 years of follow-up in evaluated population, but such increase is in correlation with normal physiological development and growth. Our study also demonstrated that majority of school children were normotensive for age and gender, close to the half of evaluated population.

Further, we have demonstrated that changes in diastolic blood pressure are more closely associated with gender and age of participants, contrary to the findings regarding the systolic blood pressure between the age of 10 and 15 years. Furthermore, it is pointed out that diastolic prehypertensive state is more likely to be noticed in younger school children while diastolic hypertensive state is more likely to be found in older school children from evaluated population.

Anthropometric parameters (2.5):

Over the period between 10 and 15 years of age in the group of boys it is noticed that there is significant increase in mean values of evaluated anthropometric parameters (BMI, Wc, Hc, SuS and UAc), while there were no significant changes in the mean values of SF. Significant increase for all parameters was noticed over the 10 years period in the group of boys. Regarding the group of girls, we found same trends over the same periods for same evaluated parameters. When such parameters were compared between genders it was shown that significant differences persist for every parameter except for pelvic diameter on all 3 examinations and UAc for the group of 10 years of age. In the YUSAD study we have demonstrated that girls are more prone to accumulate body fat versus boys. The possible explanation for such claims could be found in reduced physical activity for the female population. Furthermore, it was shown that there is different proportion of overweight and obese children in different centres from YUSAD study. This could lead to the necessity of introduction of preventive and educational programs in whole society for early detection of risk factors and implementation of healthy dietary habits and proper regular physical activity. In YUSAD study, as well as in other studies, we have noticed that risk for cardiovascular disease curve tends to have "J" distribution.

Lipid parameters (2.6):

Result from our study demonstrated that there are significant changes in lipid fractions: total cholesterol, triglycerides and LDL in boys population, while we found no significant change in mean values of HDL over 15 years of follow-up / concerning the girls population, we found significant changes in mean values of HDL also toward higher values over 15 years of follow-up, indicating more favourable lipid profile in term of greater protection for female population at school age. Beside mean values, the results were presented in percentile distribution also for the 5th, 25th, 50th, 75th and 95th percentile, separately for boys and girl. Given the results from observed parameters we have found that frequency of metabolic syndrome in school children population included in the YUSAD study was less than frequency reported in the literature.

Genetic parameters (1.2):

In the YUSAD study we have evaluated the influence of mean values of certain lipid fractions (cholesterol, HDL fraction, LDL fraction and Triglycerides) on apo-E genotype distribution. It was shown that there is increase in mean values of total cholesterol and LDL fractions from E2 genotype to E4 genotype in evaluated population. Concerning triglycerides levels we found that they differ in mean values in different apo-E genotypes. Since there are studies suggesting possible correlation between apo-E polymorphisms and subclinical markers of atherosclerosis (Intima

Media Thickness (IMT), Carotid artery compliance (CAC), further investigations in our study will include evaluation of these parameters as well.

Regarding MTHFR677 genotype, we found that there is joint correlation between MTHFG677 polymorphism and gender on diastolic blood pressure values. Both genders of evaluated population with MTHFR677TT have increased values of LDL, while only boys with TT genotype have significantly increased total cholesterol values.

Physical activity (2.7):

In the YUSAD study we have demonstrated that there is significant increase in proportion of school children that are physically active less than 3 hours a day over 15 years of follow-up, while for those that were physically active far more, we observed negative trend over the 15 years period in the proportion of these participants. Further, we have also found no significant correlation between trends of changes of blood pressure (systolic and diastolic) and lipid parameters with physical activity, inversions in correlation stress out the possible presence of other factors along with physical activity (hormones, metabolism, etc.). Given the fact above, it can be seen that school children from YUSAD study are physically active in moderate range, with preference given to those from rural places.

Future tasks and considerations

The YUSAD study is a longitudinal prospective study, with confirmed further follow-up examination for the 2012/2013 year on same population across Serbia. At the Scientific Board meeting, it was proposed to introduce further parameters in evaluation such as: ITM, inflammatory markers and other.

It is our opinion that the results obtained after the 4th evaluation will give more insights about the multi-factorial influence on atherosclerotic processes in individuals, therefore it is our task to evaluate the observed population. The particular sensitivity of obtained results is reflected by the fact that we have the trends and referential values both from school children period, adolescents and on future 4th follow-up from young adults.

Acknowledgments

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Arterial Switch Operation for TGA with Coronary Artery Anomaly

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Acıbadem University
Istanbul- Turkey

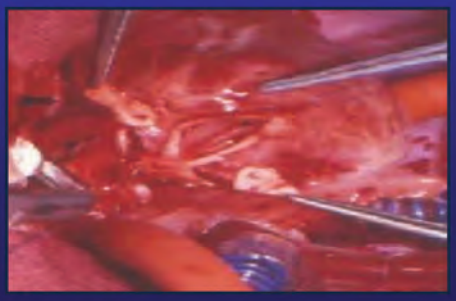
ACIBADEM

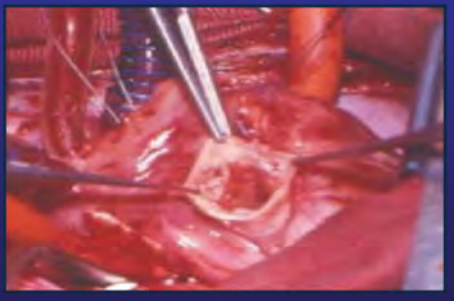


Arterial Switch
TGA & Coronary Patterns

First Neonetal Arterial Switch in
Turkey
October 1990
T.Sarıoglu,T.Paker,O.Bayındır, A.Sarıoglu





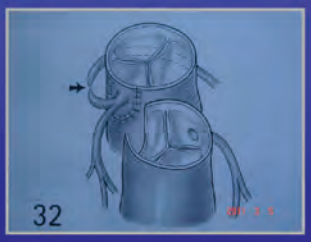


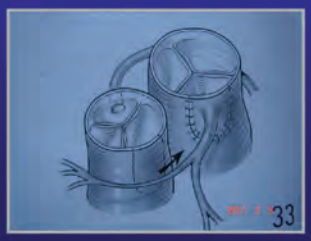
Arterial Switch

TGA & Coronary Patterns

Influences of coronary patterns on coronary translocation:

- Injury
- Torsion-Kinking
- Stretching
- Compression





3

Arterial Switch

TGA & Coronary Patterns

Coronary pattern & possible risks ...

- Inverted coronary artery
- Intramural coronary artery
- Single left (LCA+RCA)
- Single right (RCA+LCA)

* Kirklin JW, Clinical outcomes after ASO Procedural & Institutional risk factors (513 neonates,CHSS). Circulation 1992
* Daebritz, Anatomical risk factors after ASO (312 patients, Aechen,Germany). Ann Thorac Surg., 2000
* Pasquali, Coronary artery pattern and outcome of ASO (Meta analysis of 9 studies, Duke University). Circulation 2002

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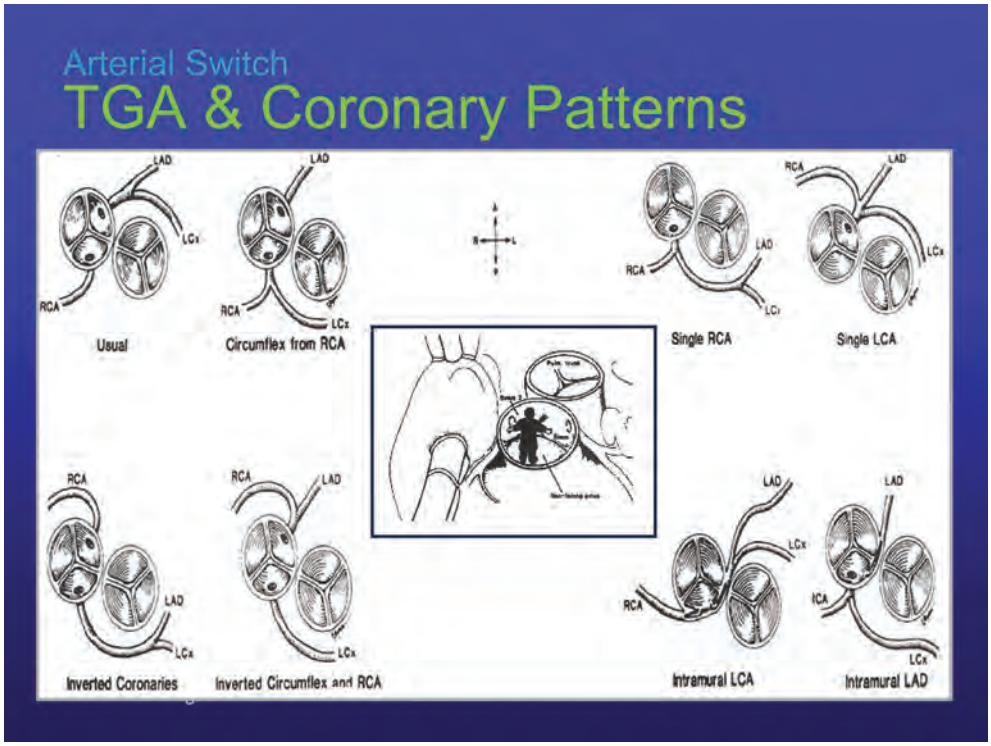
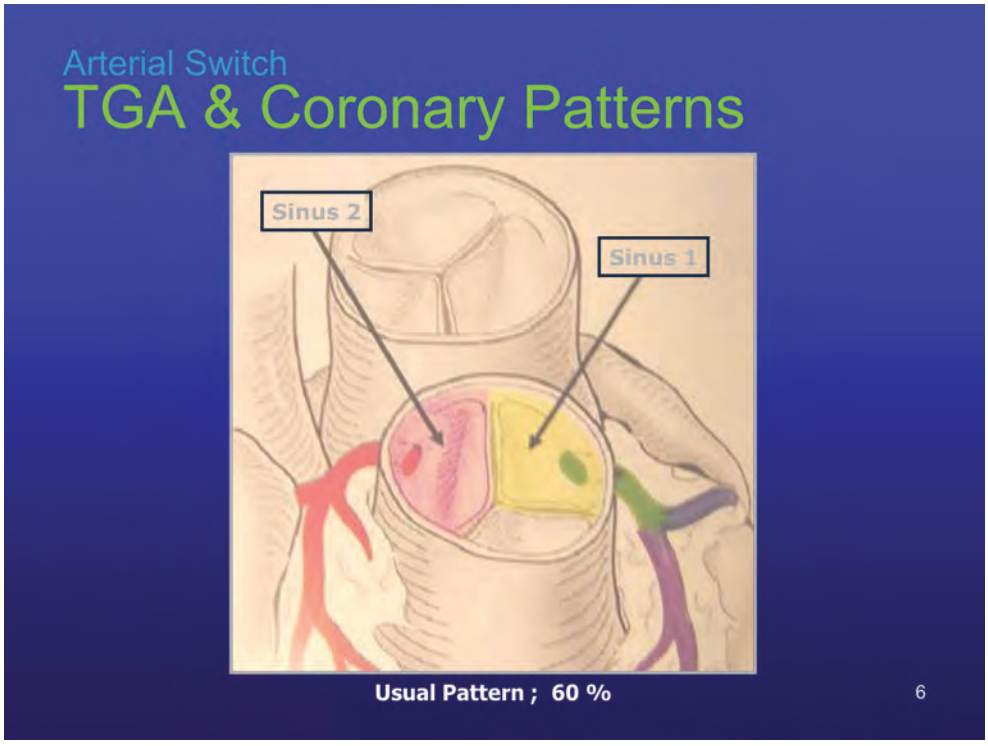
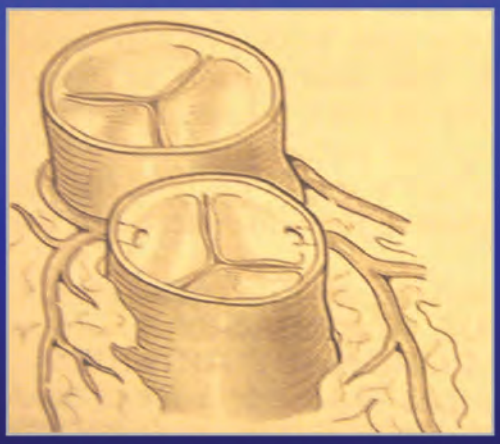

Arterial Switch
TGA & Coronary Patterns
LAD
LCx
RCA
Usual
Circumflex from RCA
Single RCA
Single LCA
Inverted Coronaries
Inverted Circumflex and RCA
Intramural LCA
Intramural LAD


Arterial Switch
TGA & Coronary Patterns
Sinus 2
Sinus 1
Usual Pattern ; 60 %
6

Arterial Switch

TGA & Coronary Patterns

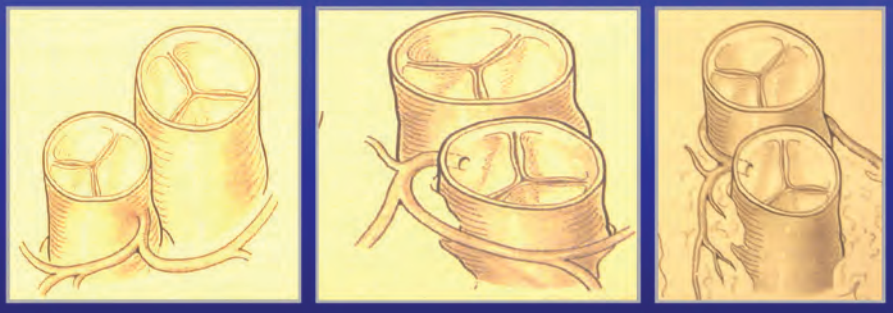


RCA+ CX from sinus-2 & LAD from sinus-1 (Posterior looping); 20 %

7

Arterial Switch

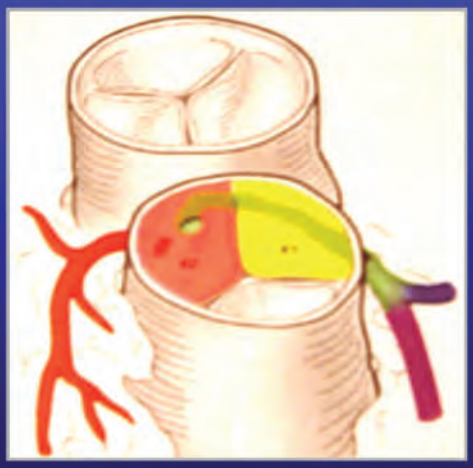
TGA & Coronary Patterns



Single coronary (anterior & posterior looping) 5-6 %

8

Arterial Switch
TGA & Coronary Patterns



Single origin from sinus-2 (RCA+LCA, intramural course); 5 %

9

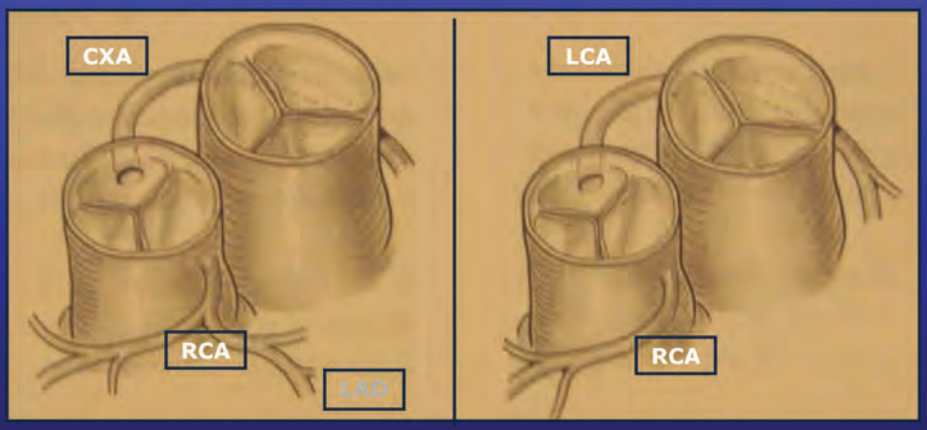
Arterial Switch
TGA & Coronary Patterns



Intramural course; 5 %

10

Arterial Switch
TGA & Coronary Patterns



CXA from sinus-2, RCA+LCA from sinus-1

RCA from sinus-1, LCA from sinus-2

Inverted coronary pattern 8 %

11

Arterial Switch
TGA & Coronary Anomalies

Nomenculture	Sinus 1	Sinus 2	n	%
Usual	LAD, Cx	R	289	61
Circumflex from RCA	LAD	CxR	103	22
Single RCA		LADCxR	21	4
With additional small LAD from sinus 1			2	0,4
Single LCA	RLADCx		10	2
Inverted origins	R	LADCx	13	3
Inverted RCA/Cx	RLAD	Cx	19	4
Intramural LCA		LADCxR	9	2
Intramural LAD		LADCxR	3	0,6
Intramural RCA	LADCxR		1	0,2

CA in 470 patients undergoing ASO at Children's Hospital Boston (1983-1992)

12

Arterial Switch
TGA & Coronary Anomalies

TGA,VSD

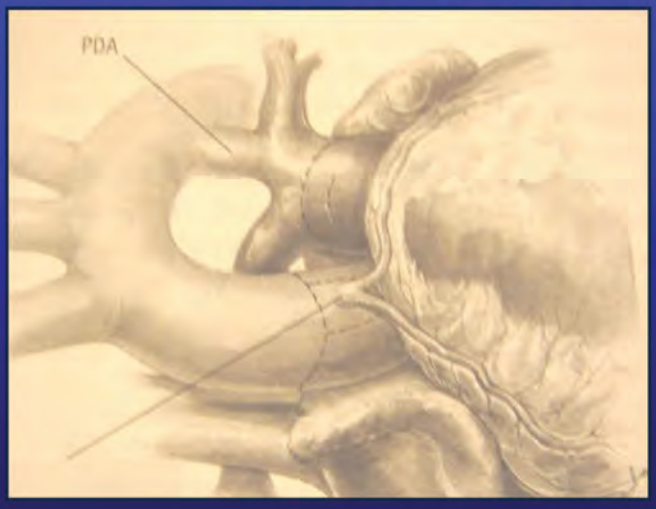






13

Arterial Switch Repair
TGA & Coronary Pattern

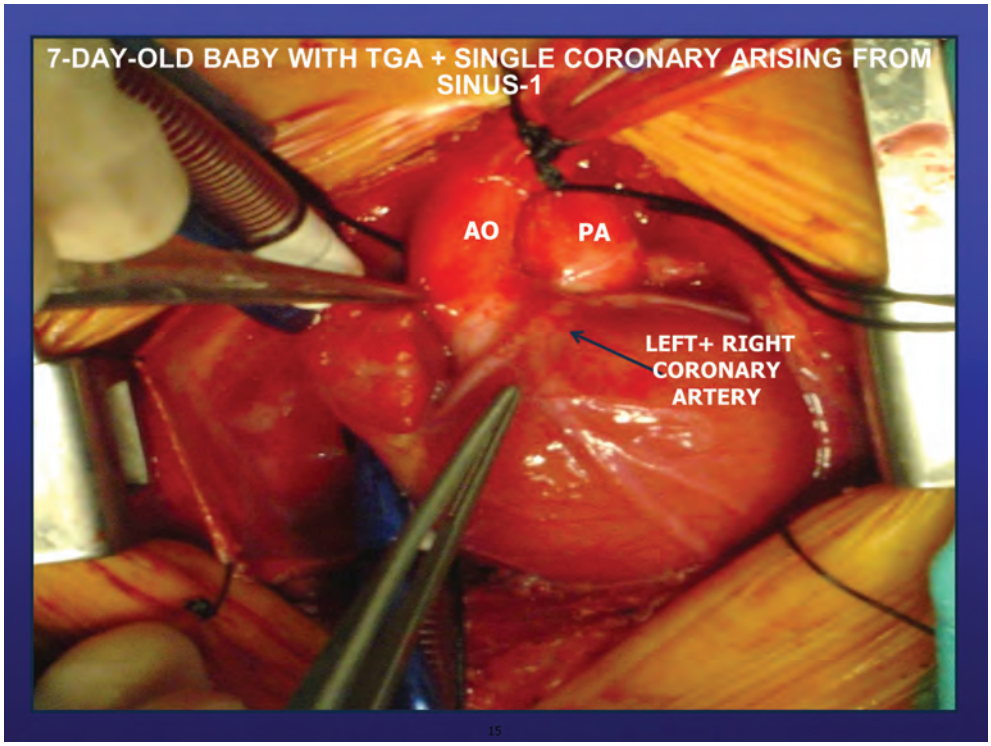


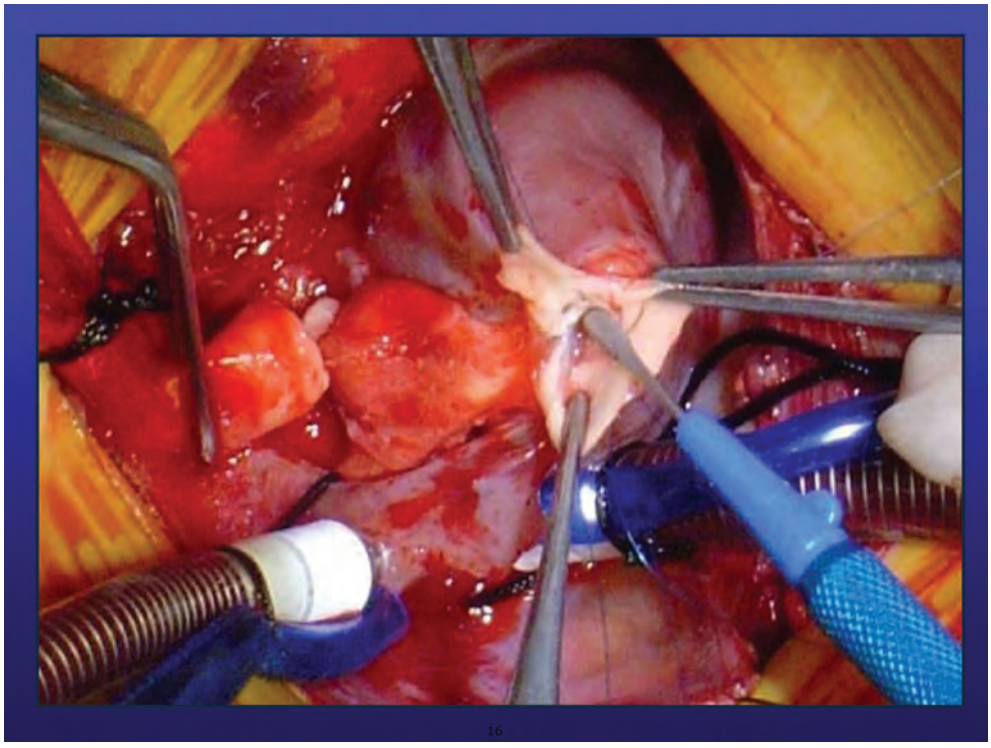




Single origin and translocation methods

14


7-DAY-OLD BABY WITH TGA + SINGLE CORONARY ARISING FROM SINUS-1
AO
PA
LEFT+ RIGHT CORONARY ARTERY
15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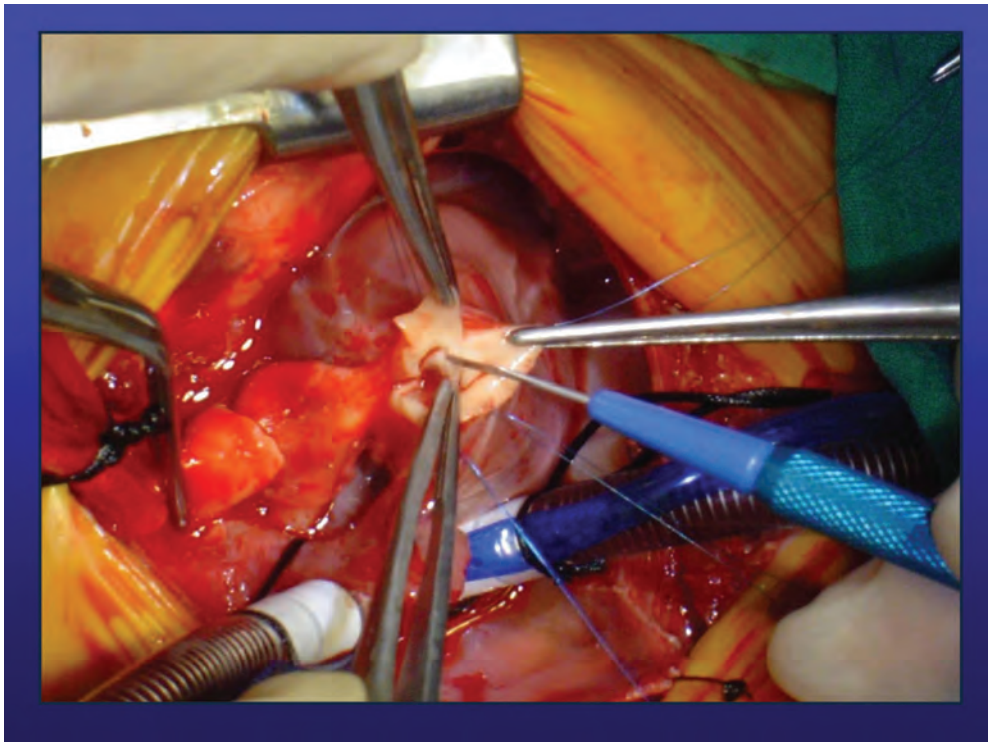
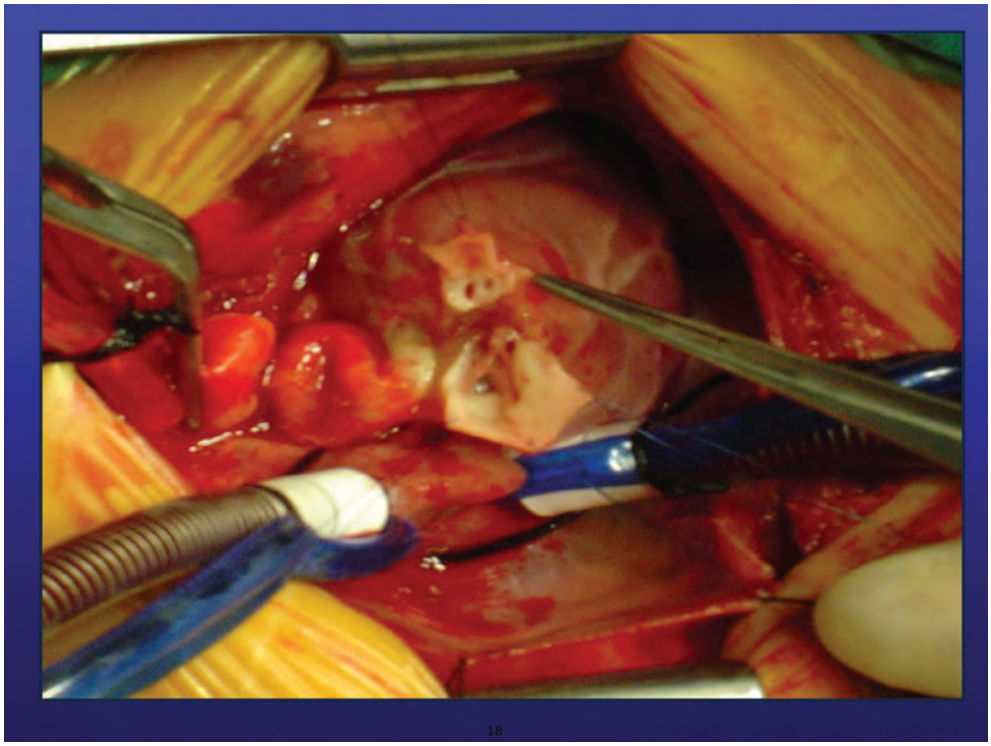
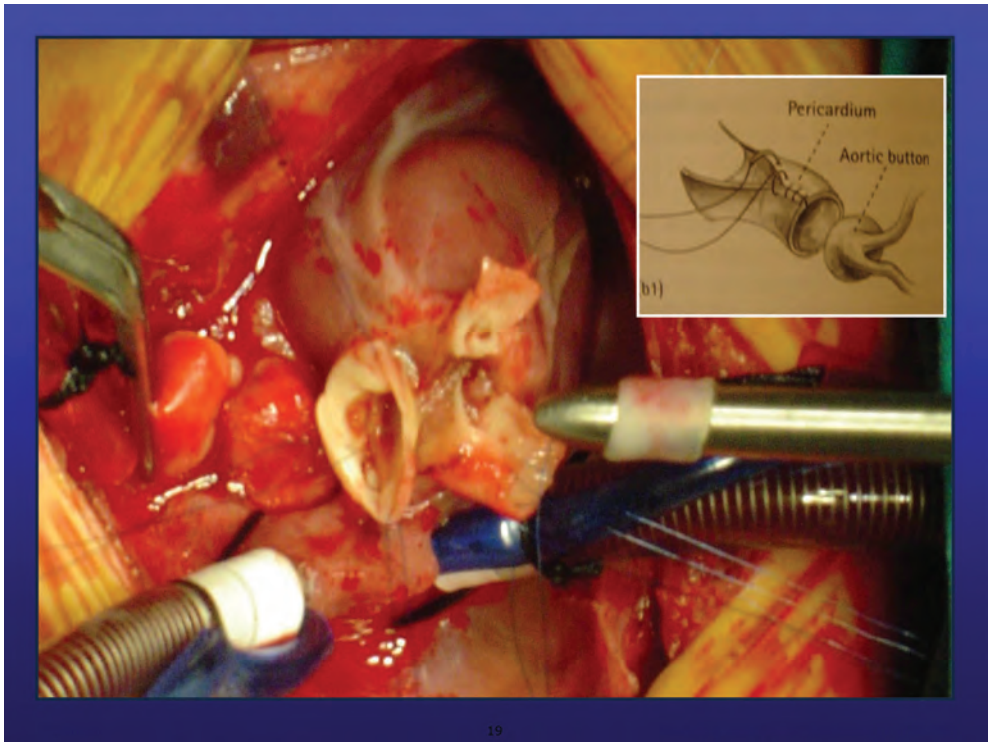
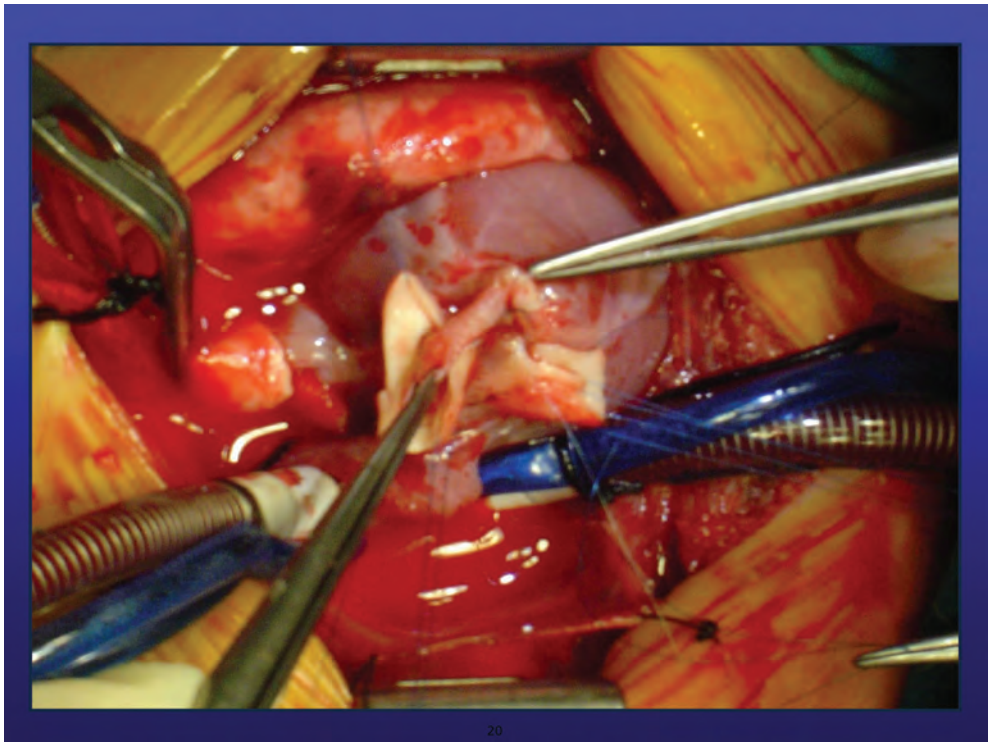





Pericardium
Aortic button
b1)
19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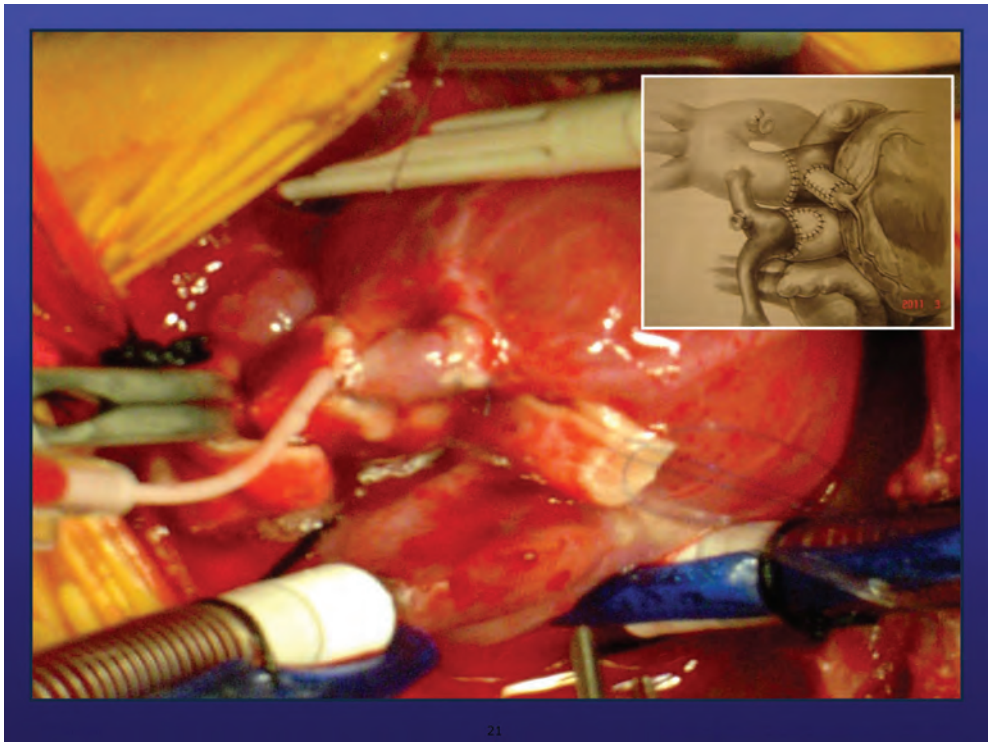
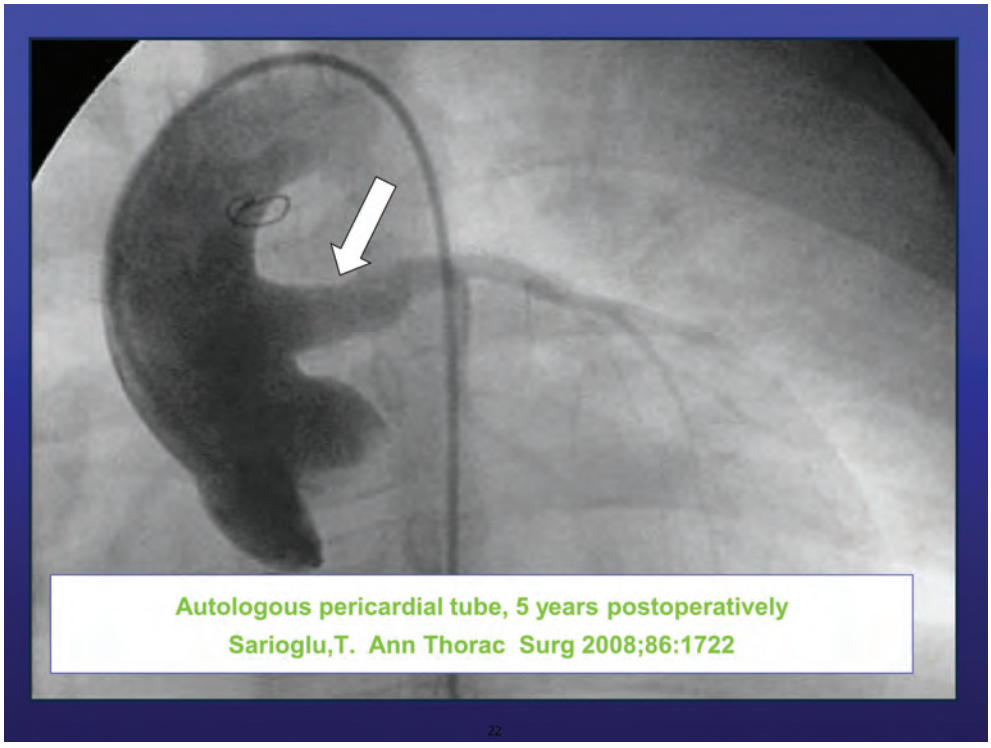
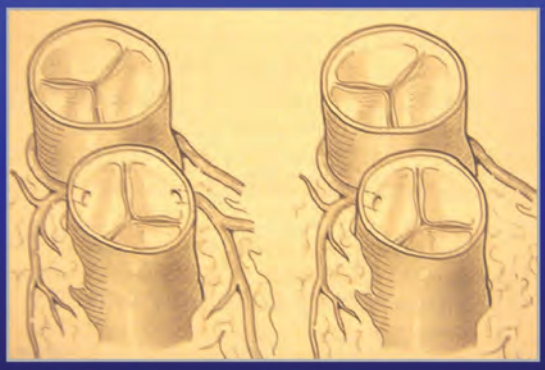
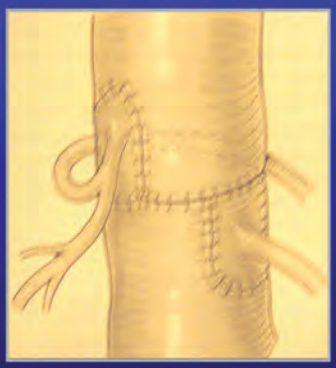



Autologous pericardial tube, 5 years postoperatively
Sarioglu,T. Ann Thorac Surg 2008;86:1722

Arterial Switch
TGA & Coronary Patterns





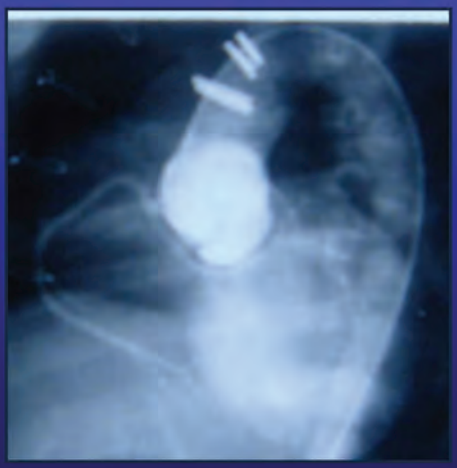
RCA+ CX from sinus-2 & LAD from sinus-1 (Posterior looping); 20 %

23

Arterial Switch
TGA & Coronary Patterns



Single coronary from sinus-2



Coronary angio 1 year postoperatively

24

Arterial Switch

TGA & Coronary Patterns





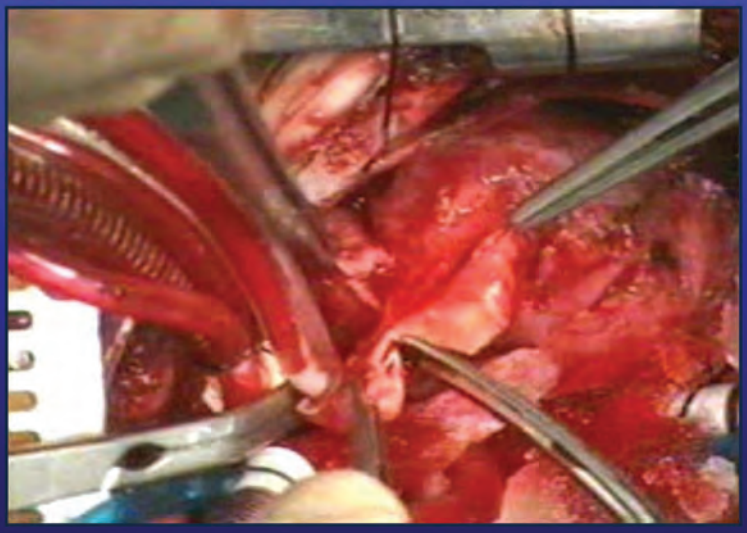


Intramural course; 5 %

25

Arterial Switch

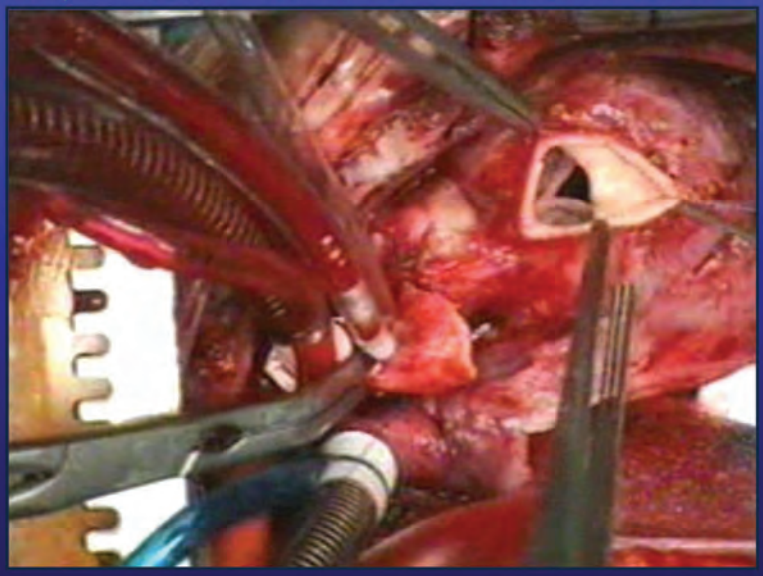
TGA, Intramural LAD from Sinus 2



26

Arterial Switch

TGA, Intramural LAD from Sinus 2



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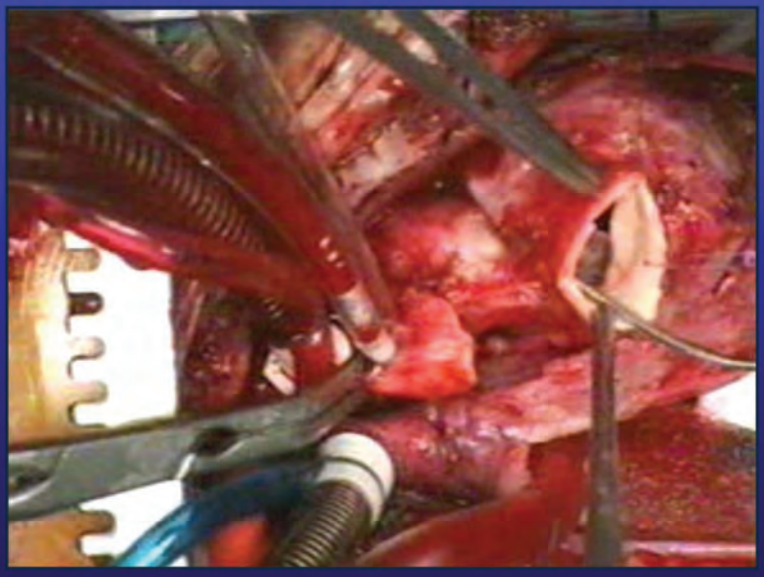
Arterial Switch

TGA, Intramural LAD from Sinus 2



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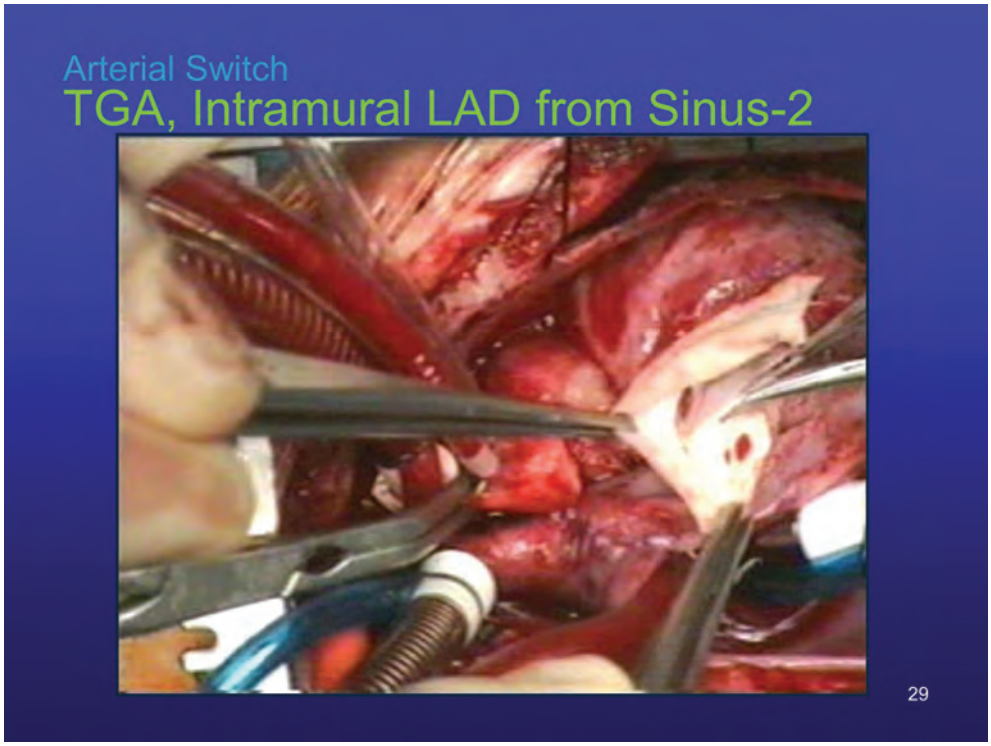
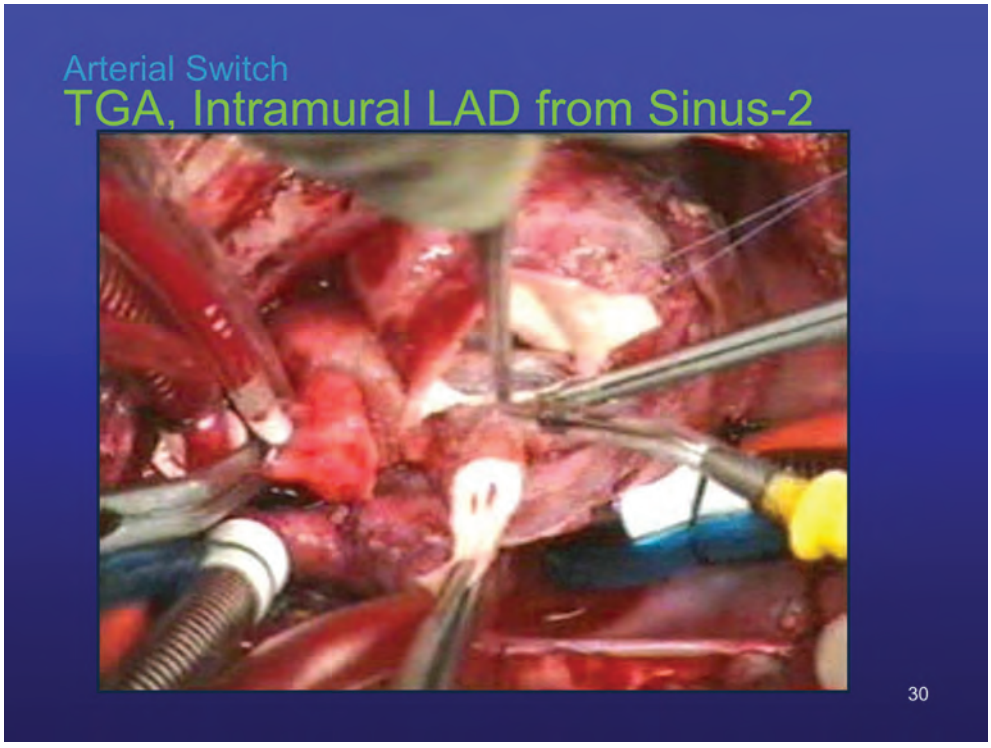

Arterial Switch
TGA, Intramural LAD from Sinus-2
29


Arterial Switch
TGA, Intramural LAD from Sinus-2
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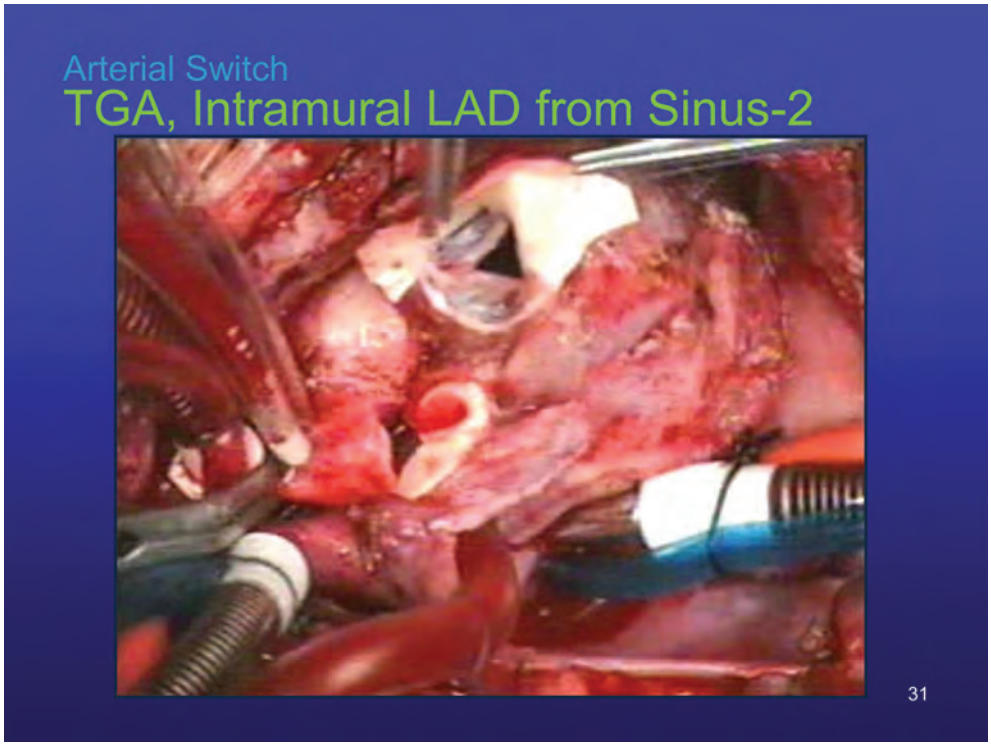
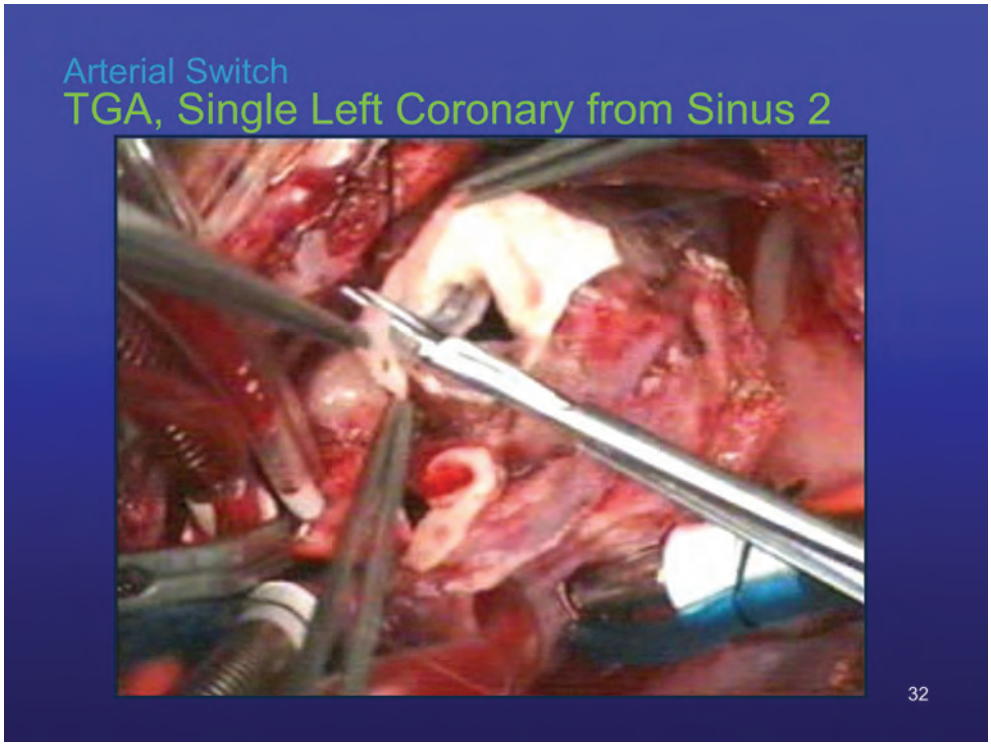
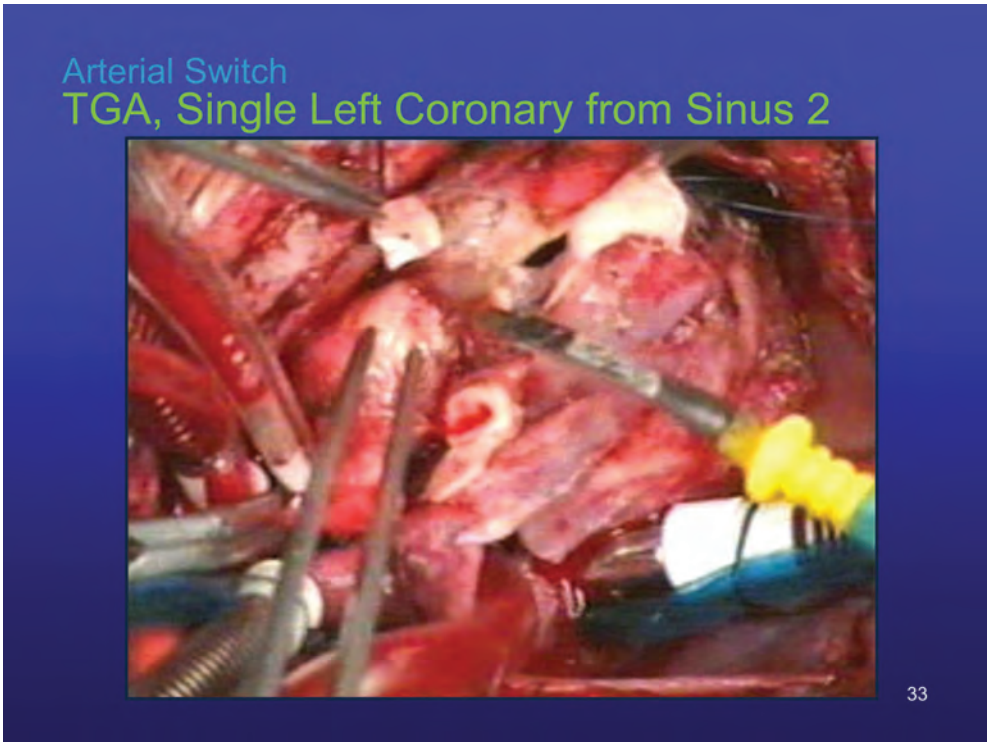

Arterial Switch
TGA, Intramural LAD from Sinus-2
31


Arterial Switch
TGA, Single Left Coronary from Sinus 2
32


Arterial Switch
TGA, Single Left Coronary from Sinus 2
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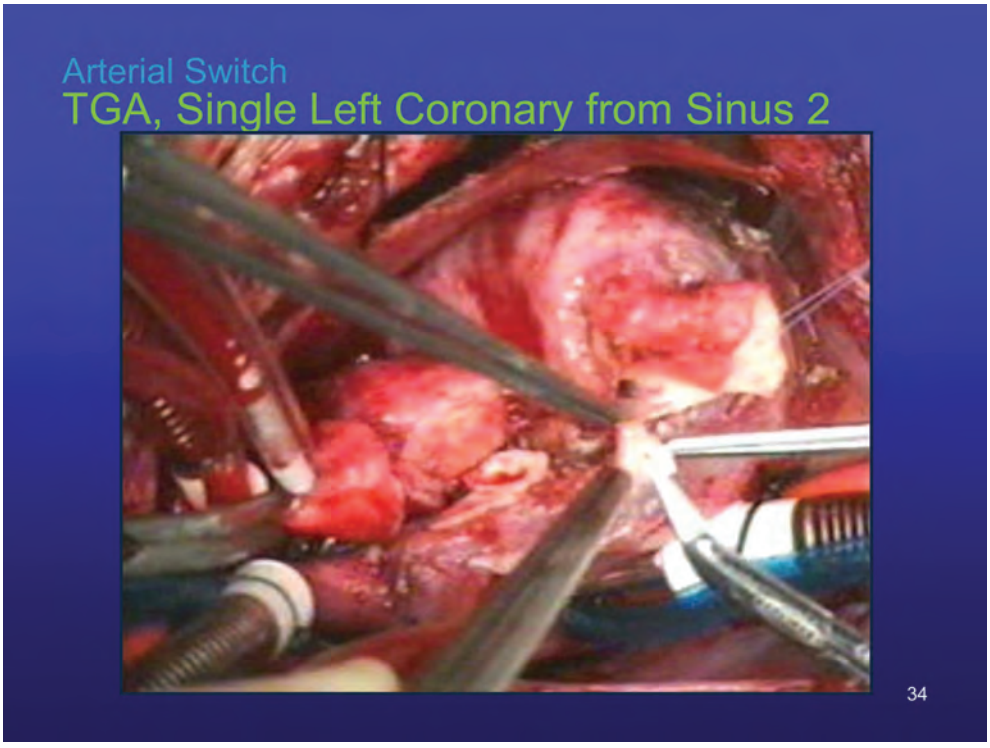
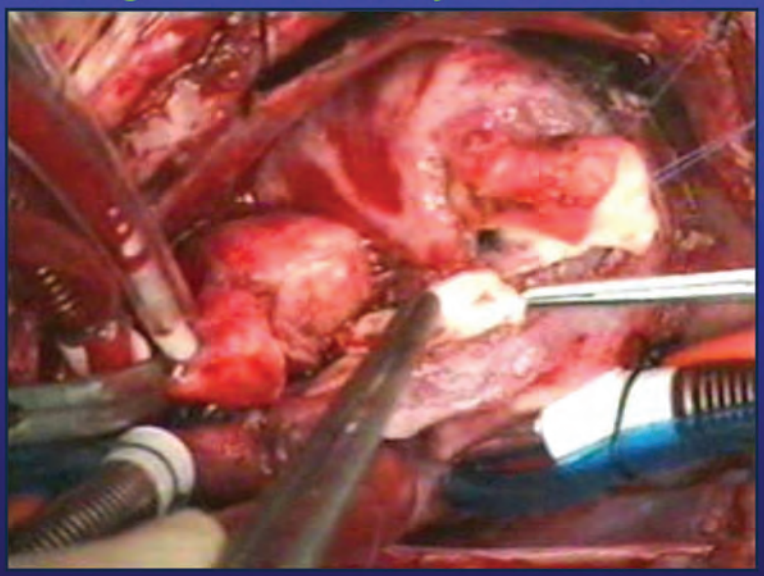

Arterial Switch
TGA, Single Left Coronary from Sinus 2
34

Arterial Switch
TGA, Single Left Coronary from Sinus 2



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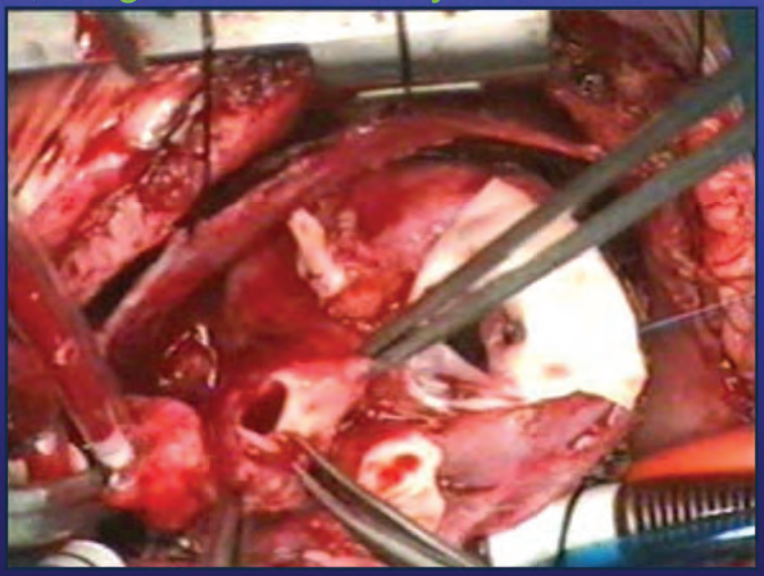
Arterial Switch
TGA, Single Left Coronary from Sinus 2



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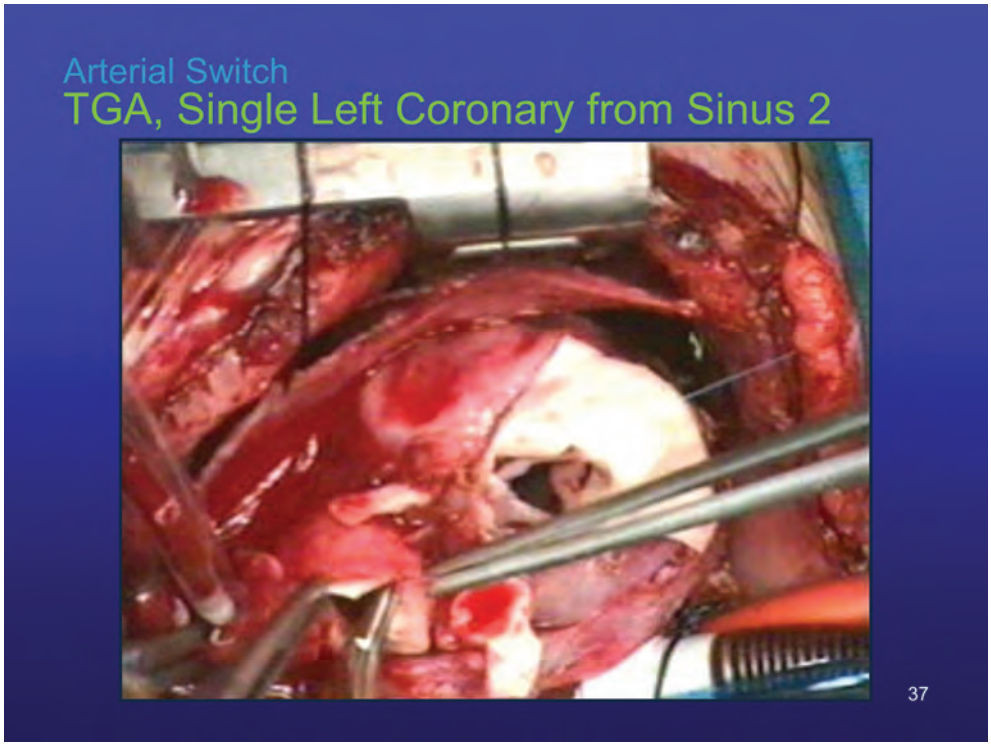
Arterial Switch
TGA, Single Left Coronary from Sinus 2
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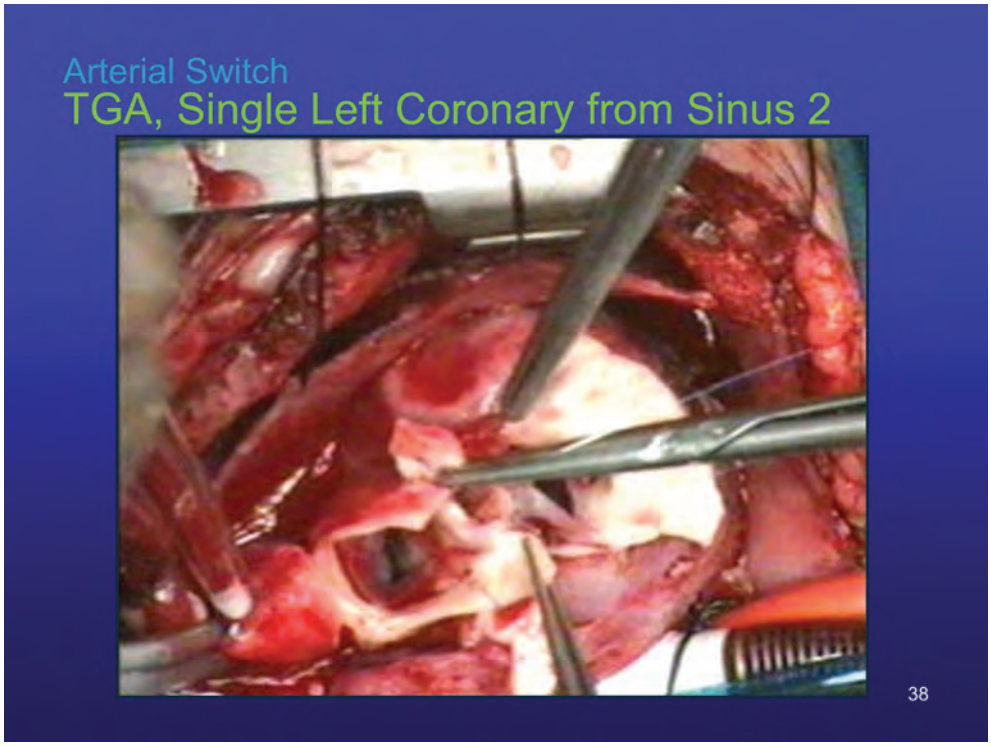
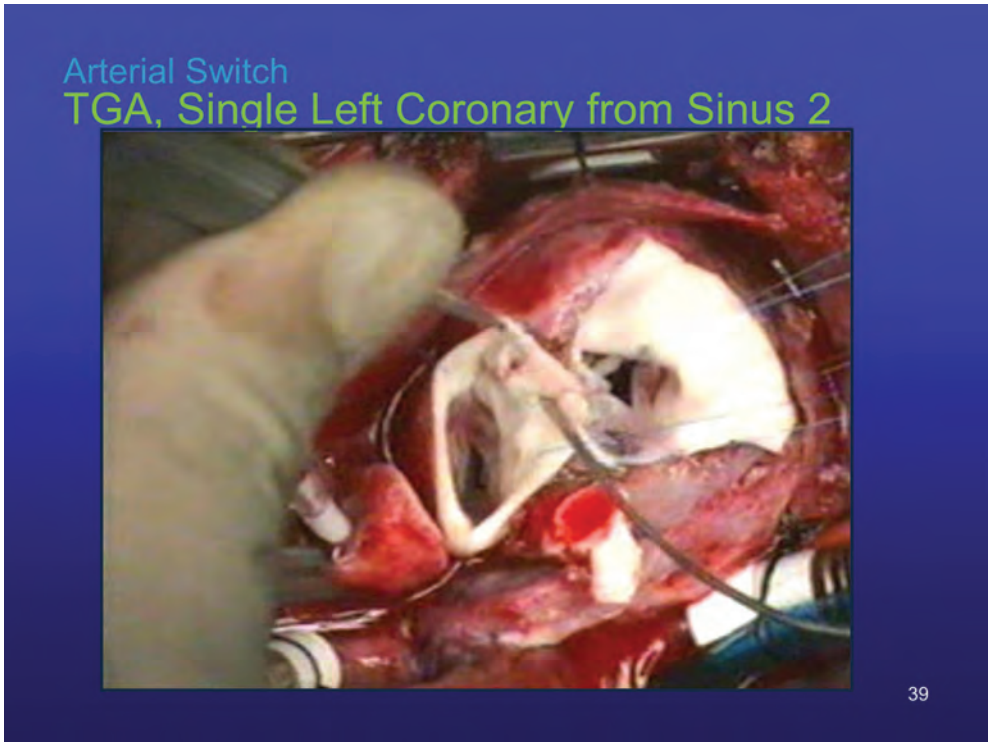
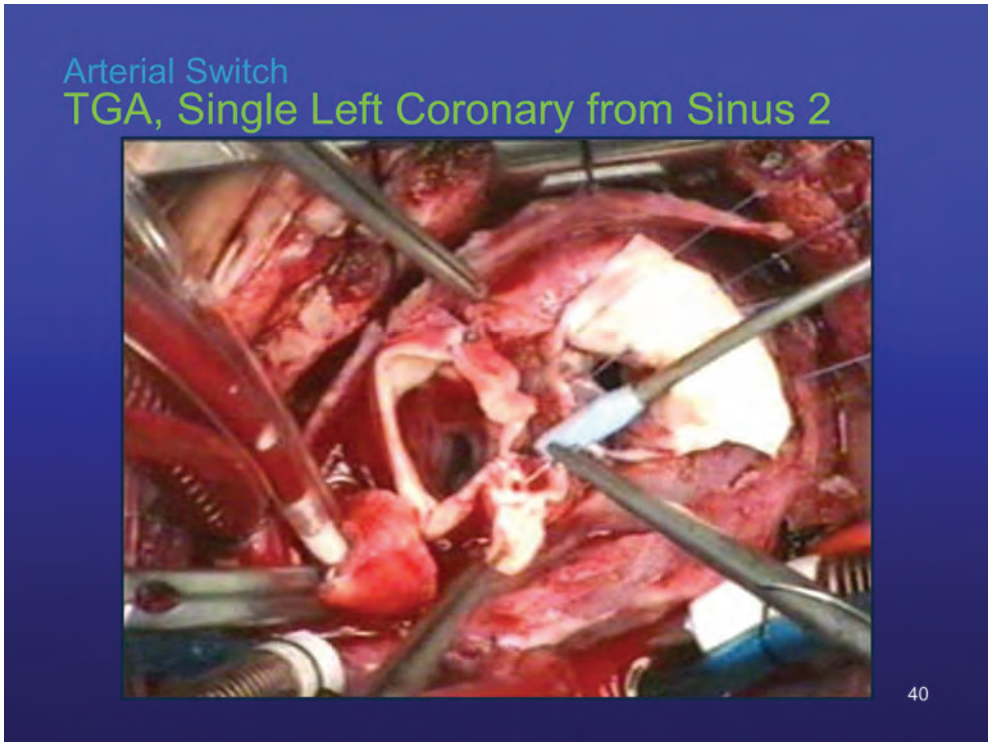
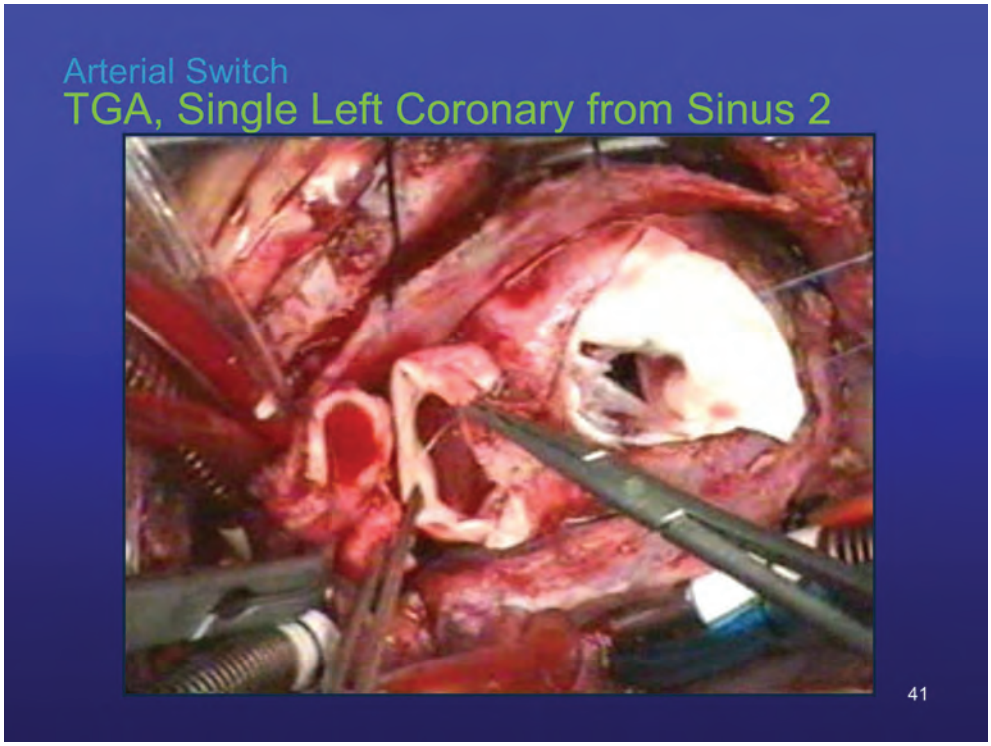
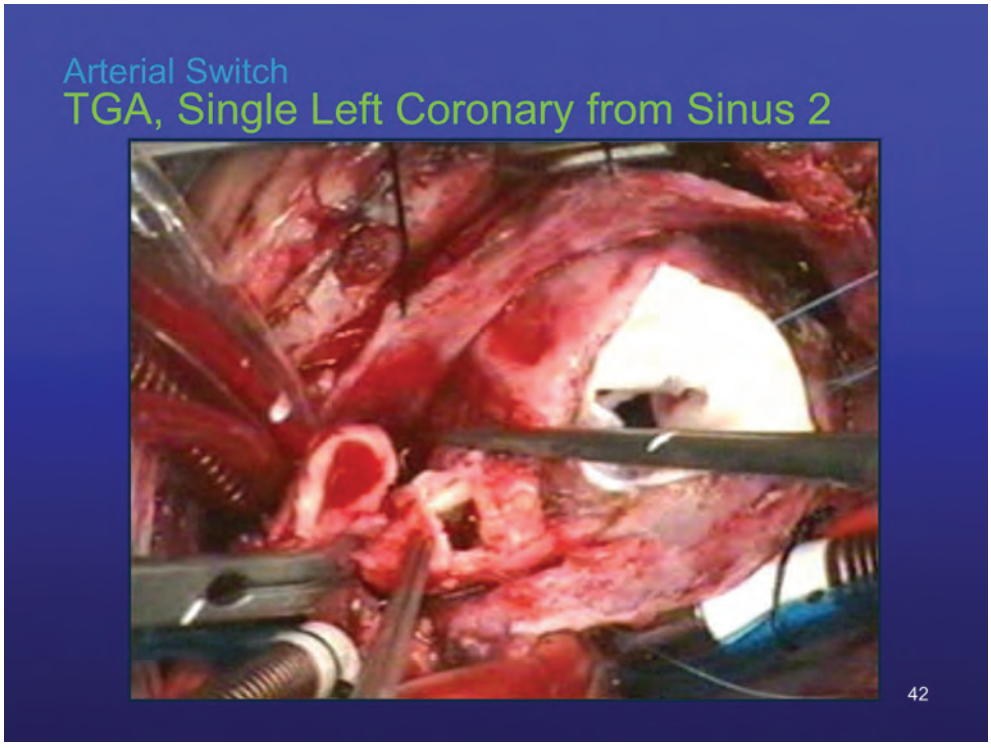

Arterial Switch
TGA, Single Left Coronary from Sinus 2
38

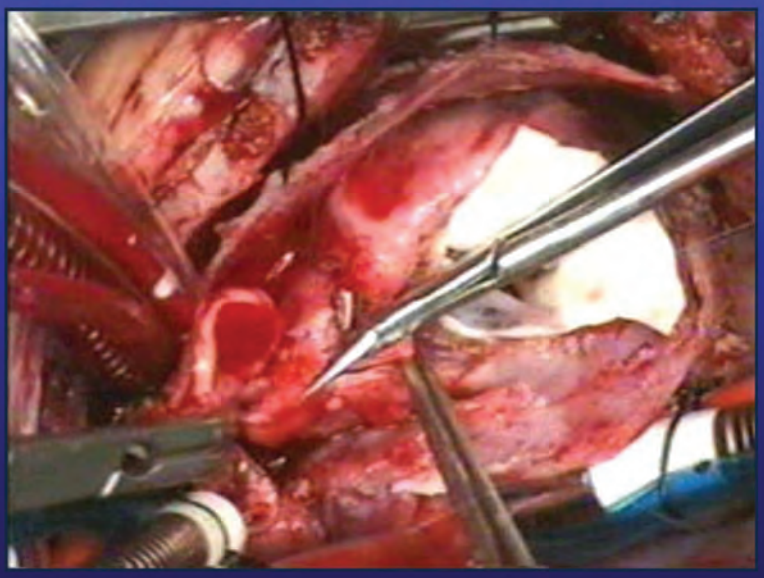

Arterial Switch
TGA, Single Left Coronary from Sinus 2
39


Arterial Switch
TGA, Single Left Coronary from Sinus 2
40


Arterial Switch
TGA, Single Left Coronary from Sinus 2
41


Arterial Switch
TGA, Single Left Coronary from Sinus 2
42

Arterial Switch
TGA, Single Left Coronary from Sinus 2



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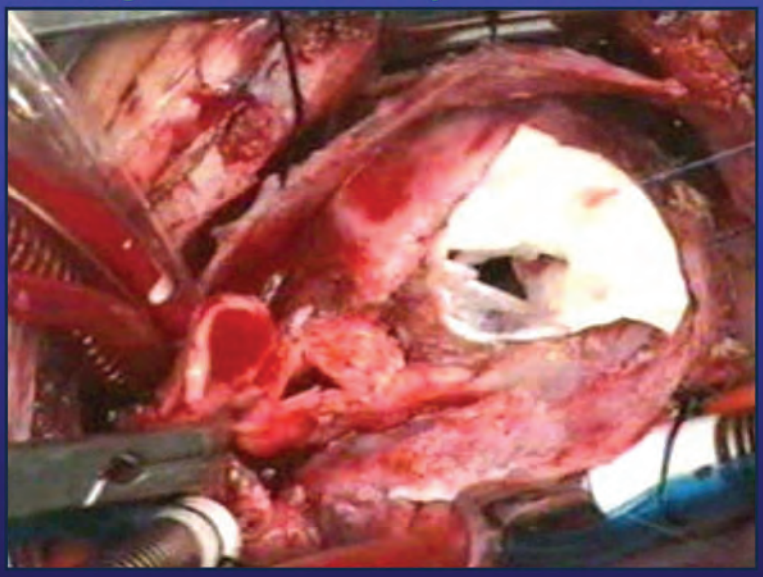
Arterial Switch
TGA, Single Left Coronary from Sinus 2



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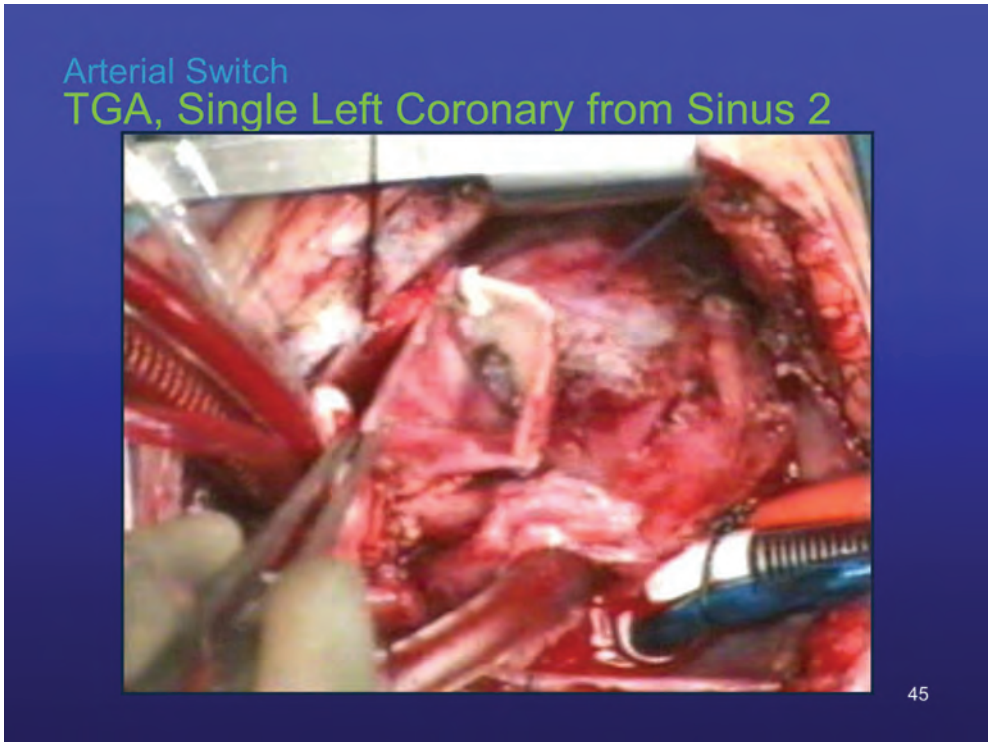
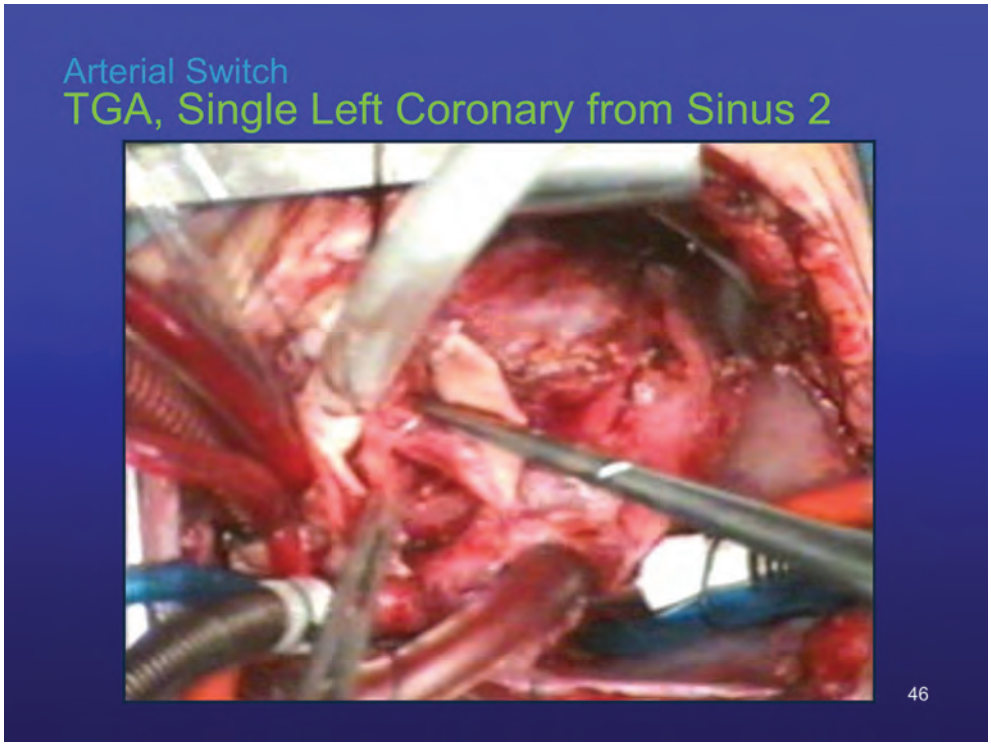
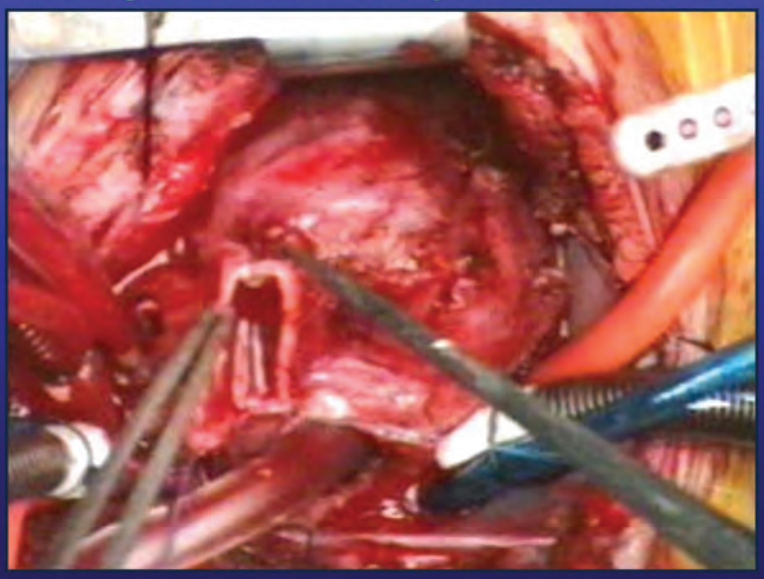

Arterial Switch
TGA, Single Left Coronary from Sinus 2
45


Arterial Switch
TGA, Single Left Coronary from Sinus 2
46

Arterial Switch
TGA, Single Left Coronary from Sinus 2



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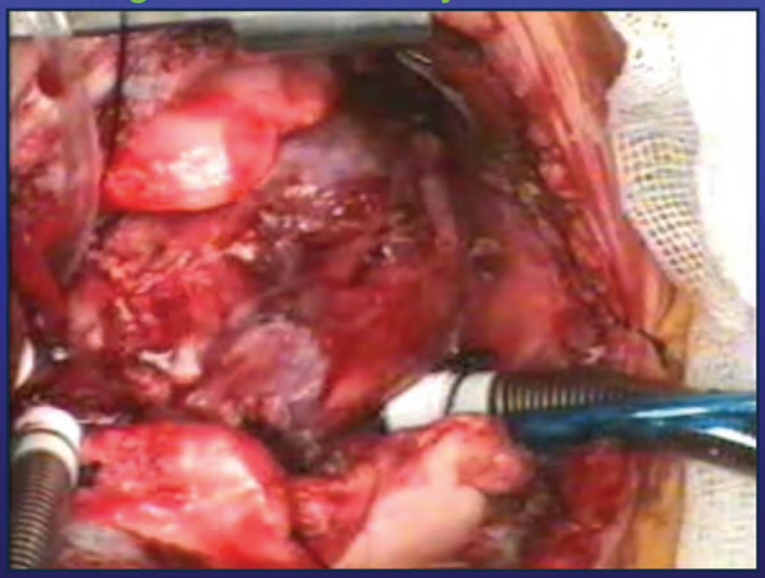
Arterial Switch
TGA, Single Left Coronary from Sinus 2



48

Arterial Switch

TGA, Single Left Coronary from Sinus 2



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Arterial Switch

Results for single coronary artery (1983-2000)

- Analysis of 844 patients, (USA/Boston Children's Hospital)
- 53 had single coronary pattern; (6,3%)
- 7 with single coronary pattern died; (13%)
- Since 1991; 7 patients (13%) was required revision of coronary translocation due to myocardial ischemia
- Single ostium from sinus-2 & side by side GA estimated to have significant risk of mortality; (6-8 fold)

Jonas RA., Transposition of the great arteries, 2004

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Arterial Switch
Coronary artery pattern & Mortality-Morbidity

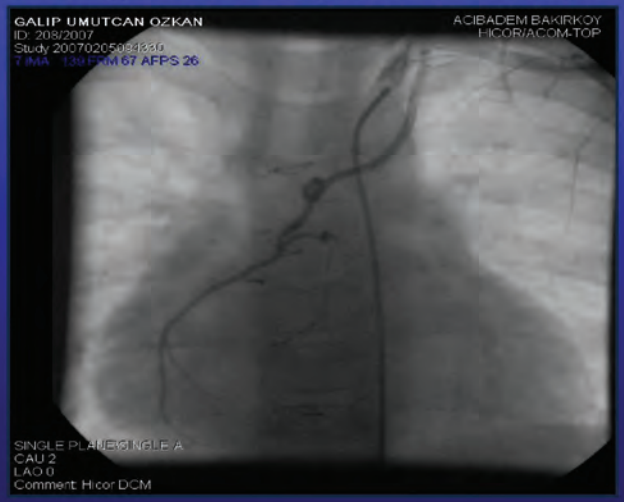
- **Intramural coronary arteries & Outcome of ASO :**
  - ✓ 919 neonates (1987-2008 France/H.Necker)
  - ✓ 48 (5%) had intramural coronary pattern
  - ✓ mortality in intramural group; (28%, 13 pts)
  - ✓ mortality in nonintramural group; (4%)

Vouhe PR, Eur J Thorac Surg, 2010

Conclusion: Intramural coronary pattern remains associated with high risk of morbidity and mortality, even in the current era...

Arterial Switch
TGA & Coronary patterns

6 month old baby, TGA+VSD+Single left from sinus-1, LIMA to RCA



Angiography,12th year postoperatively

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Arterial Switch

TGA & Coronary patterns

Coronary Artery Pattern and Outcome of Arterial Switch Operation for Transposition of the Great Arteries

Duke University,Durham,USA

A Meta-Analysis

Sara K. Pasquali, MD; Vic Hasselblad, PhD; Jennifer S. Li, MD; David F. Kong, MD; Stephen P. Sanders, MD

Background—Prior studies of coronary pattern and outcome after arterial switch operation (ASO) for transposition of the great arteries (TGA) have been hindered by limited statistical power. This meta-analysis assesses the effect of coronary anatomy on post-ASO mortality, both overall and adjusted for time.

Methods and Results—A literature search revealed 9 independent series that reported post-ASO mortality by coronary pattern in a total of 1942 patients. Odds ratios comparing all-cause mortality in patients with usual versus variant coronary patterns were calculated and combined by use of an empirical Bayesian model. Single coronary patterns, both of which loop around the great vessels, were associated with significant mortality (OR 2.9, 95% CI 1.3 to 6.8), whereas looping patterns that arose from 2 separate ostia were not (OR 1.2, 95% CI 0.8 to 1.9). This latter group includes patients with the most common variant, circumflex from right coronary artery. Patients with an intramural coronary artery had the greatest mortality (OR 6.5, 95% CI 2.9 to 14.2). Overall, patients with any variant coronary pattern had nearly twice the mortality seen in those with the usual pattern (OR 1.7, 95% CI 1.3 to 2.4). Single ostium patterns and intramural coronary arteries remained associated with significant added mortality after adjustment for time-trend effects.

Conclusions—Over the past 2 decades, patients with common coronary variants have undergone ASO without added mortality compared with those with the usual coronary pattern. Those with intramural or single coronary arteries have significant added mortality that has persisted over time. (*Circulation*. 2002;106:2575-2580.)

Arterial Switch

Coronary artery pattern & late outcome

- Late coronary insufficiency & reintervention: 3%
- Clinically silent coronary obstruction: 6-8%
- Late pulmonary pulmonary stenosis: 10-20%
  - ✓ Inverted coronary artery
  - ✓ Posterior LCA
  - ✓ Intramural CA

* Late reoperation after neonatal ASO.. Eur J Thorac Surg. 2008;34:32-36
* Predictors of outcome of ASO.. Ann Thorac Surg. 2008;85:1698-1703
* Late complications following the arterial switch operation WJPCHS 2011;2:37-42

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Arterial Switch Repair
TGA+VSD & Coronary anomaly; Late PS

Single left from sinus 1



Supraannular PS, annular hypoplasia, LPA stenosis

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Arterial Switch
Freedom from reoperation

- 1200 patients (mean fu:4,9 y)*. Survival (10-15y); 88%
- Free of reintervention (10 – 15 y); 82%
  - ✓ PS : 3,9 % AI : 3,2 %
  - ✓ Coronary lesions; 8 % (278 angio)
- 514 neonatal**
  - ✓ RVOT obstruction; 62 (83 % free / 10 y)
  - ✓ LVOT obstruction; 6 (98 % free / 10 y)

Planche C, Circulation 2001 ; 104 : 1121

Williams WG, J Thorac Cardiovasc Surg 1997; 114 : 975

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Arterial Switch Repair
Coronary pattern & outcome (n:238 pts)* June,2010

Pattern	n; (%)	Mortality; (%)
Usual pattern	**169 (71)**	**15 (9)**
Unsusual pattern	**69 (29)**	
Cx from RCA	**41 (17)**	**2 (4.8)**
Intramural	**9** (4)	2
Inverted	**6** (2.5) (R:2, L:4)	1
Single left	**8** (3.4)	1
Single right	**5** (2.1)	1

*** Istanbul University, Memorial Hospital, Acıbadem Hospital (1990-2010)**

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Conclusion

- ✓ Coronary anatomy and translocation of coronary arteries are among the major factors that influence the outcome of arterial switch operations for transposition of great arteries
- ✓ Intramural course, single coronary and inverted patterns are particularly important
- ✓ Meticulous preparation of the coronary button and proper translocation are critical steps for intramural coronary arteries
- ✓ Higher implantation and pericardial patch/tube augmentation are useful methods for single coronary and inverted coronary anomaly patterns

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Arterial Switch
All Our Efforts are for the Best Possible Outcomes for Children
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PAEDIATRIC AGE DILATED CARDIOMYOPATHY (DCM): REPORT ON A FEW CASES

C. Olteanu[1]*, G. Privitera, C. Persico, B. Sartori, C. Flori, R. La Fata, M. Falbo, E. Pedretti*

[1]Ospedale "Grigore Alexandrescu" Bucarest Romania
UO Pediatria Fiorenzuola (Piacenza) Italia

Abstract

Dilated Cardiomyopathy in the paediatric patient is a serious condition that asks much of the physician and stresses the family. (1)

We present the following 10 cases for whom, once the precise aetiology and ensuing appropriate therapeutic regimen had been established, conditions improved.

It is of fundamental importance to extensively research all underlying causes for reduced contractility while avoiding the temptation of the panacea of transplant surgery.

INTRODUCTION

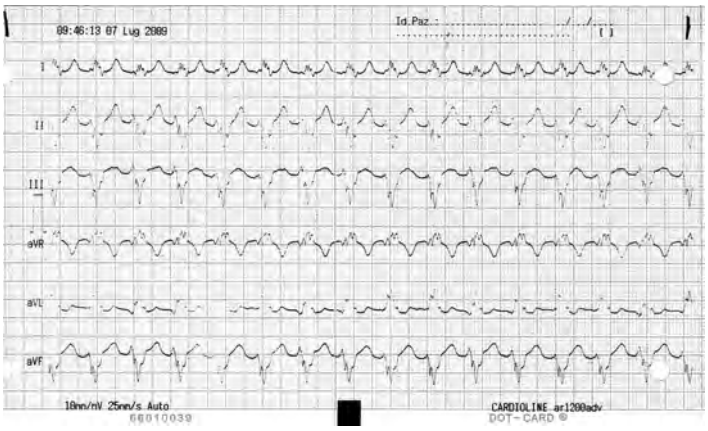
Dilated Cardiomyopathy in the paediatric patient is a life-threatening condition that has a huge impact on the family unit and often poses difficult diagnostic problems with difficult therapeutic and prognostic implications.

All causes of reduced contractility should be evaluated in order to establish the appropriate ensuing therapy.

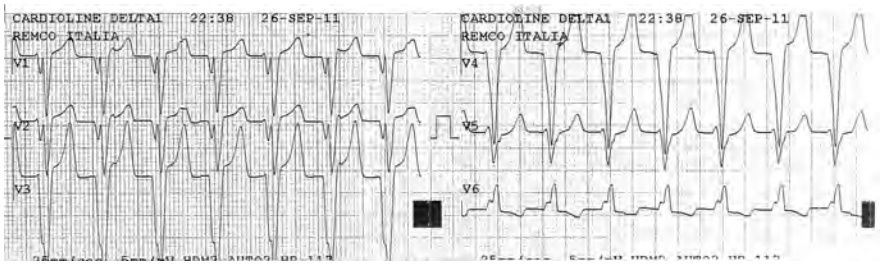
CASES REPORT

Ten cases that evolved favourably (condition reverting to complete normality or bettering of conditions) 4 of the cases, following complete evaluation, were classified as tachycardiomyopathy. (2-3-4)

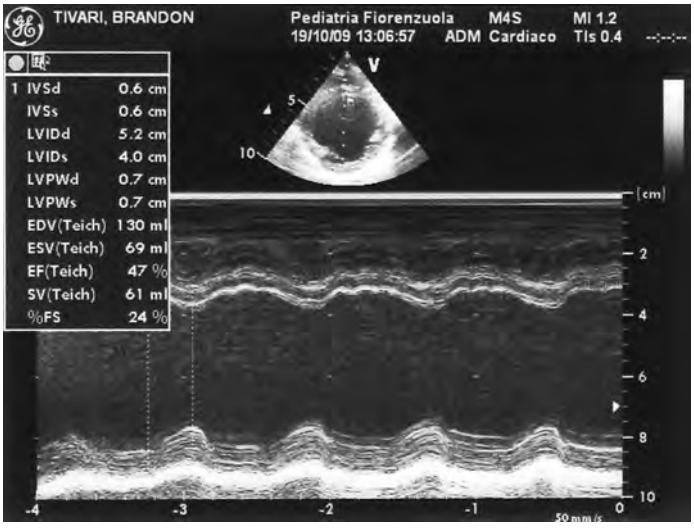
A 5 year old boy who presented incessant ventricular tachycardia (170 bpm) associated with an EF of 10% attained normal contractility following medication and 2 radiofrequency ablations for an ectopic ventricular focus of the right ventricle.



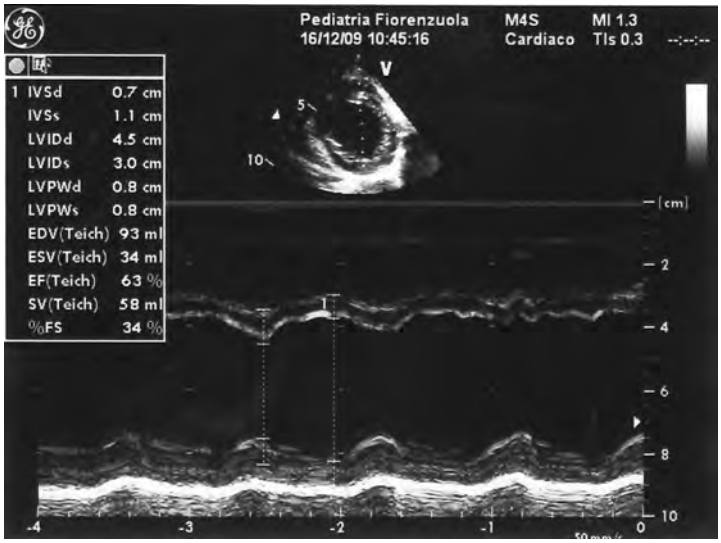
130 bpm ventricular tachycardia



Focus in the right ventricle

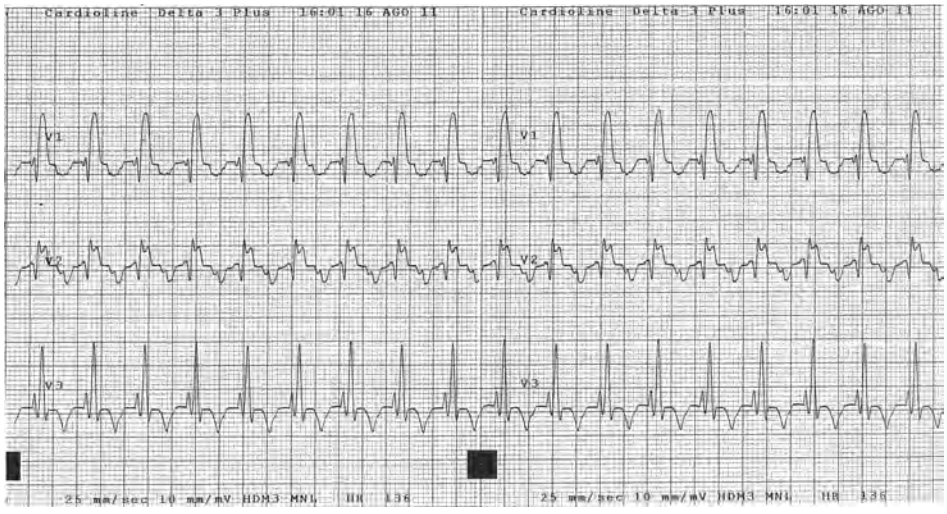


Reduced contractility

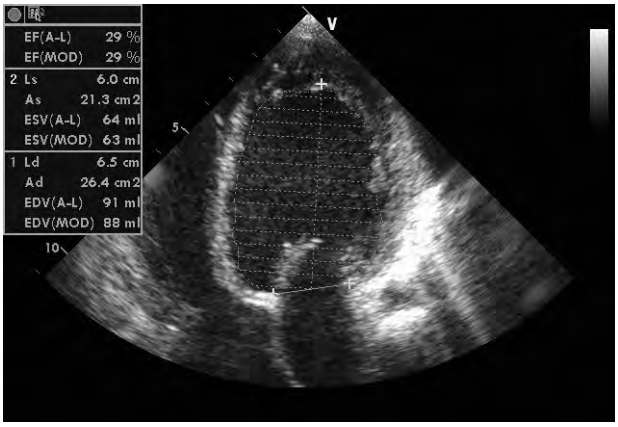


Normal contractility

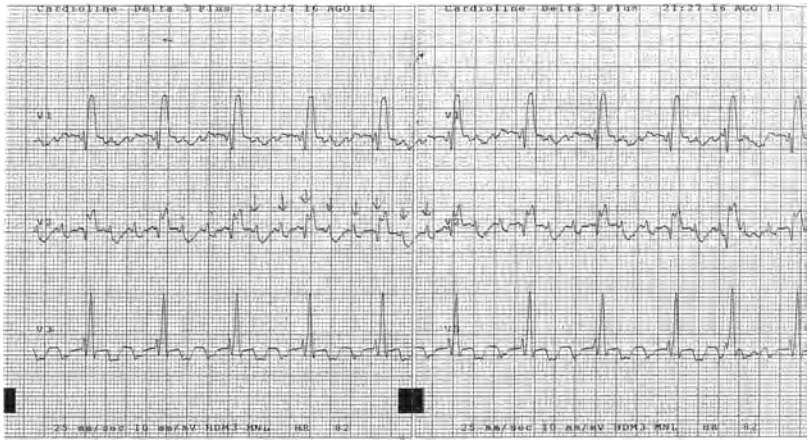
Another 5 year old boy who had previously received surgery for Fallot's tetralogy presenting with an EF of 20% and incessant tachycardia (140 bpm) and for whom transplant had already been suggested elsewhere, received radiofrequency ablation after diagnosis of atrial flutter; ensuing contractility is normal.



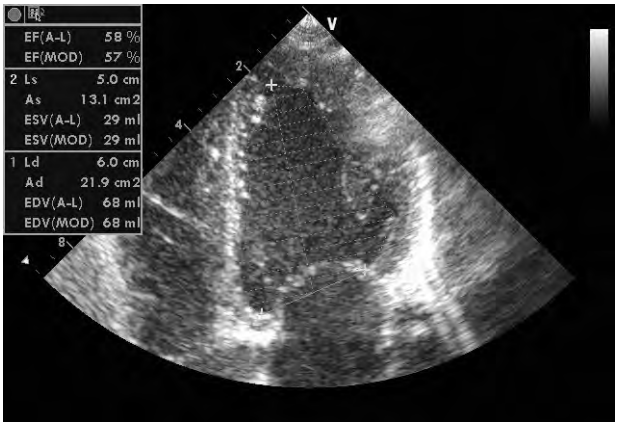
140 bpm fixed rate supraventricular tachycardia



Reduced contractility

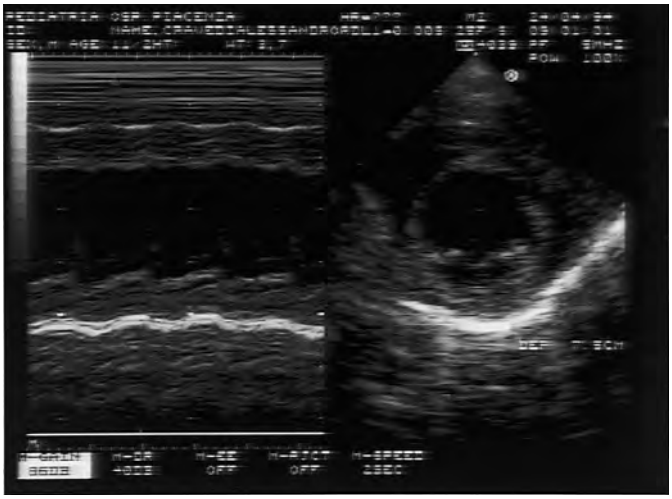


Flutter diagnosis

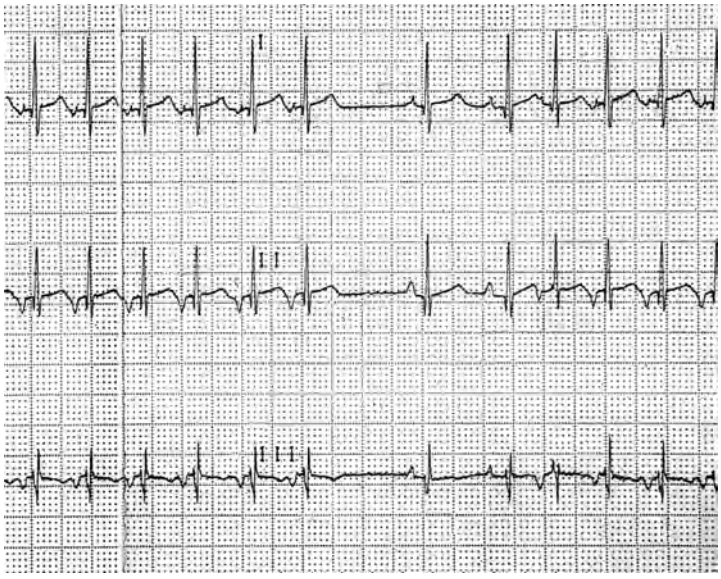


Normal contractility

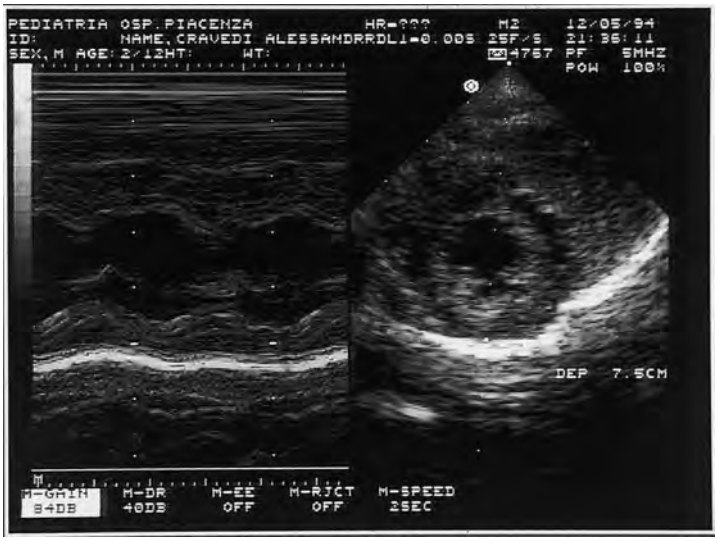
A 30 day old newborn with polypnea, cyanosis and restlessness was admitted to hospital and found to have PJRT - Coumel type supraventricular tachycardia (250 bpm) with an EF of 25%: on the tenth day of medication contractility was normal and sinus rhythm was achieved.



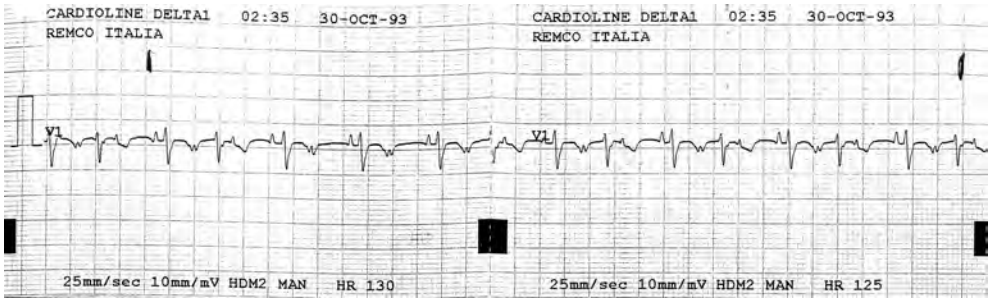
Reduced contractility



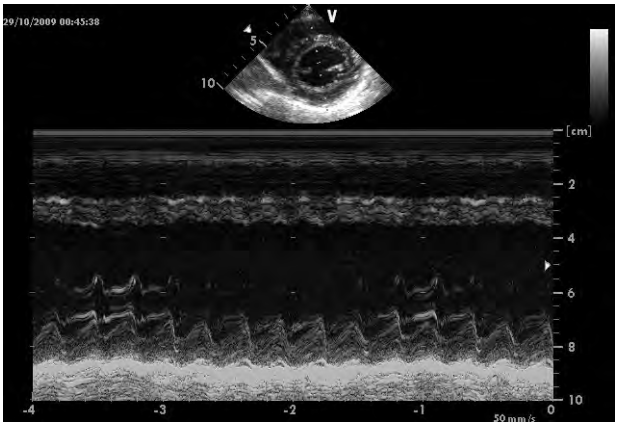
PJRT



Normal contractility

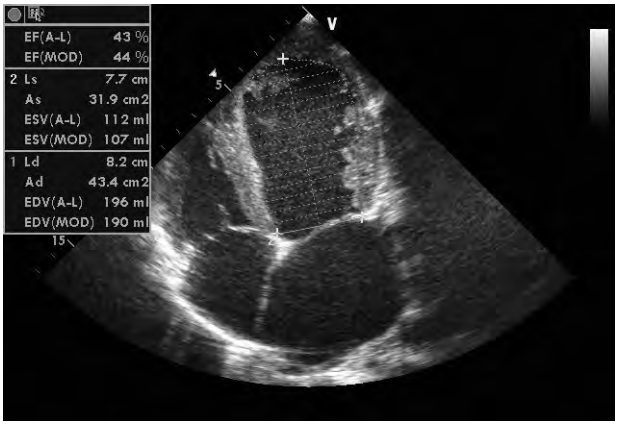


140 bpm atrial tachycardia

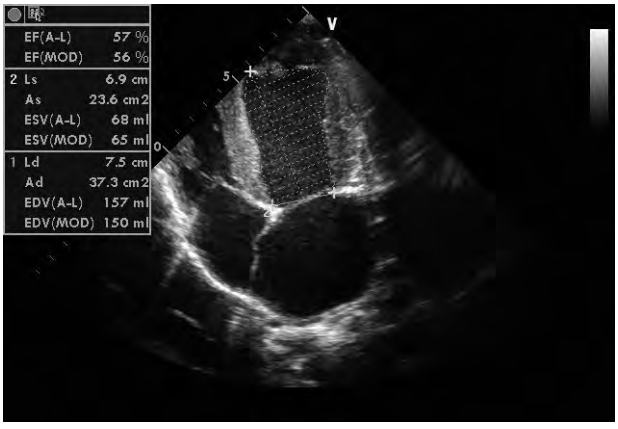


Reduced contractility

A 12 year old who now presents EF of 50%: viral myocarditis at the age of 5 was treated with medical therapy.



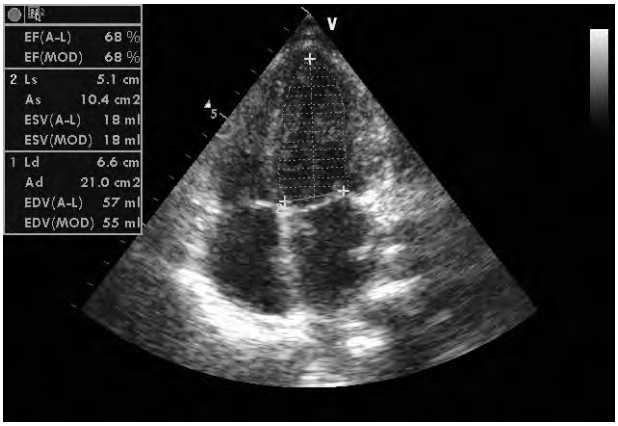
Reduced contractility



Normal contractility

A 6 year old girl who was admitted to hospital with dyspnoea, asthenia and muscle pains was found to have an EF of 45% and extremely low plasma levels of Carnithine: 0,7 micromoli/l (V.N. 21,7– 47,3).

Contractility normalized following administration of L- Carnithine at the dose of 150 mg/Kg/die. (6, 7, 8, 9)

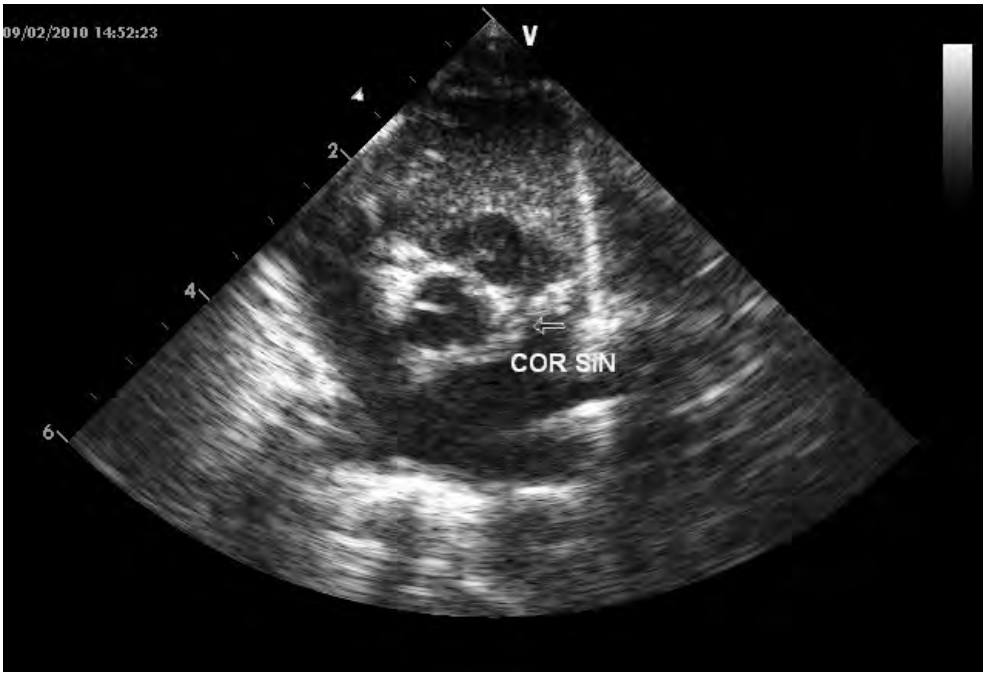


Normal contractility

A 2 year old who is currently asymptomatic was diagnosed, in utero, as having a dilation of the apex of the left ventricle: MR shows partial agenesis of the pericardium and aneurismal thinning of the myocardium.

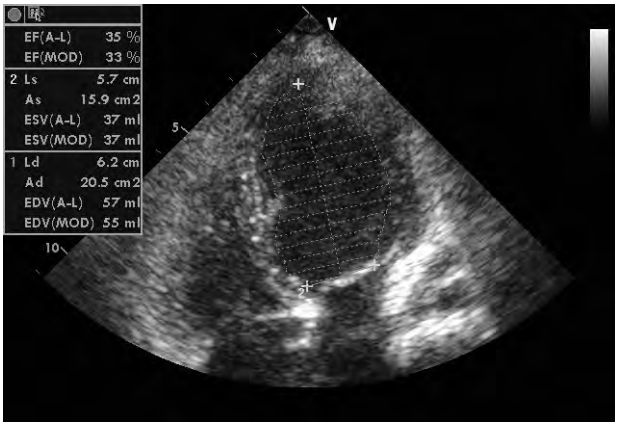


Dilation of the apex of the left ventricle with partial agenesia of the pericardium

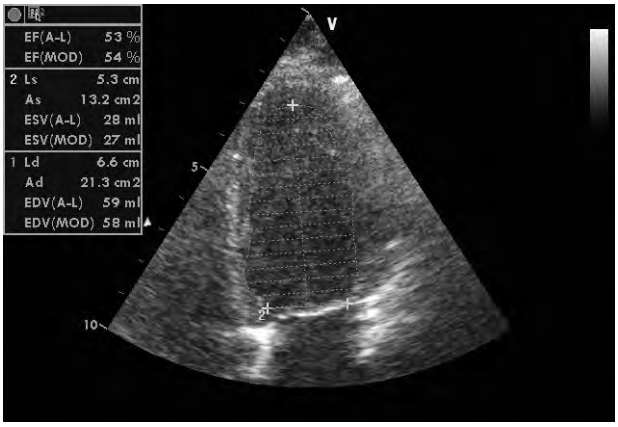


Normal origin of the left coronary artery

A 7 year old boy, with Fallot's disease, underwent two separate surgical procedures: the first operation of radical correction using a trans-annular patch required readmission to surgery following detachment of the inter-ventricular patch. Subsequently ventricular dysfunction and an EF of 20% posed indication for a transplant. He is now on medication and EF is up to 55%.



Reduced contractility



Normal contractility

2 newborns, diagnosed as having ALCAPA after presenting with life-threatening reduction of left ventricle EF, both required emergency surgery.

They are now 5 and 6 years old respectively and both have normal contractility.

DISCUSSION

"Tachycardiomyopathy is an abnormality of systolic or diastolic function of the heart, or both, usually resulting in heart dilatation and ultimately in heart failure caused by a high and/or irregular ventricular rate. This high and/or irregular ventricular rate may result from any type of cardiac arrhythmia." (Brugada P., Andries E.)

Tachycardiomyopathy and reduced contractility are two intertwining aspects that make diagnosis of the primary cause particularly difficult.

If contractility is ameliorated by reducing heart rate the correct diagnosis is Tachycardiomyopathy. One must bear in mind, however, that if tachycardia has been of long duration or of high frequency contractility it may, in these cases, be only partly ameliorated by reducing heart rate.

Tachycardia-induced damage to the myocardium determined reduced number of beta-receptors, reduced blood-flow in the coronary arteries, most notably in the subendocardium, and alteration of Na+ and Ca++ channels that can determine lengthening of repolarisation time and further arrhythmias.

Incessant tachycardia is often paucisymptomatic and drug-resistant; these are cases where transcatheter ablation play an important role.

Pericardial agenesia is a rare malformation (1 case in 10000 – 14000) and is often asymptomatic and underdiagnosed. (10, 11, 12)

It can be partial or complete. In the complete variant the heart is shifted to the left and interposition of lung tissue between heart and diaphragm is found.

The partial variant is more often symptomatic: stress related dyspnoea, precordialgia, ischemia, syncope and sudden death.

It is currently believed that symptoms are due to compression of the coronary arteries arising from the edge of the "hole" in the pericardium.

Another hypothesis is that the deviation of the heart to the left determines angling of the large blood vessels and distortion of the coronary arteries.

Right cavities are falsely enlarged at ultrasound inspection.

Suspicion levels for ALCAPA must be kept high in cases of neonates with important myocardial hypokinesia and in older children with otherwise unexplained severe mitral insufficiency. (13, 14, 15, 16, 17)

CONCLUSIONS

Life-threatening reduction of EF must not impede extensive research into the cause of myocardiopathy in every single case as the precise diagnosis and ensuing correct choice of therapy can achieve normalization of cardiac function.

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PAEDIATRIC CARDIAC SURGERY AND EUROPE: TODAY´S SITUATION AND FUTURE ASPECTS

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Abstract

Depending on the definition as geographical entity, economical or political union or as ethical, philosophical or cultural community referring to the historical Occident, the term "Europe" shows a wide spectrum of varieties. This is even true for regional medical systems and quality and structural availability of medical care and so even true for paediatric cardiac surgery.

In western Europe, after decades of steadily improving performance on the base of an all-inclusive social coverage, nowadays for nearly all CHD optimal treatment is guaranteed with low mortality rates and exceptionally good long term results. In (south)eastern Europe still major differences are present: there are regions with good conditions and – on the other side of reality – areas with no or no local care option. While in western Europe today there are too many surgical centres and surgeons with decreasing numbers of patients of native origin, in some regions in south-eastern Europe there is limitation in centres and trained surgeons for comparably more complex and not everywhere completely recorded children (and adults) with CHD.

This presentation is to deal with options in supporting forced development of paediatric cardiac surgical care, especially in south-eastern Europe. Based on own experiences, the considerations will focus on various activities to improve the situation in Bosnia and Herzegovina and neighbouring countries. This analysis will deal with the evaluation of the reasonability of humanitarian projects, the option of cross-border cooperation and the prerequisites for long lasting care systems including the need for clear strategic political decisions within the health and insurance system.

Keywords: paediatric cardiac surgery – humanitarian programme – development

Introduction

"The evolution of congenital heart surgery has reached a point in time when we should extend care to patients in underserviced emerging countries" (Bill Williams,

1). And indeed, there is an immense demand for logistical and medical support: referring to the ratio between population and number of cardiac centres, a global survey in 1999 outlined a significant regional misdistribution of access to paediatric cardiac care: about 75% of human population has very limited or no access to specified cardiac care including surgery (2, 3). There is no good reason to presume an overwhelming progress over the last years. But in addition to manifold efforts in regions concerned, there are numerous organizations and even more small multidisciplinary groups addressing the problems. Although these activities often may be like a drop of water on a hot stone, step by step regional improvements are achieved. This essay is to deal with topics referring to medical management and logistics of a humanitarian project as well as some of our own experiences.

In paediatric cardiac surgery, the last six decades since implementation of the heart-lung machine have witnessed a steadily ongoing improvement in perioperative management, surgical techniques, mortality rates and functional long-term results. In the privileged part of the world – especially Europe, North America, and Australia – nowadays for nearly all congenital heart diseases optimal treatment is guaranteed, most often on the base of an all-inclusive social coverage.

As in other regions with well-developed cardiac care, after long lasting struggle for progress and finally reaching the best possible quality of sophisticated treatment options, even Europe has to face a decrease in need of paediatric cardiac surgery: beside widespread prenatal diagnosis and consecutive liberal abortion, improved perinatal care, progresses in interventional cardiology, and the policy of single-stage early and complete repair have caused a decrease in children needing cardiac surgery and numbers of procedures per child with congenital heart disease (4, 5, 6). As a consequence, in several countries numbers of surgical institutions have been reduced by fusion (6). But still many paediatric cardiac surgery programmes suffer lack in patients and raise their case load by including significant numbers of patients from abroad. Without a doubt, this approach offers a unique chance for children from less privileged countries, thus treated with highest standards. Although this may be of some short-time benefit for specialized centres in question, on long turn this policy just means delaying unavoidable adaptations in medical infrastructures – and no advantage for the patients' underdeveloped home countries.

In this context, definition of "underdeveloped countries" identifies to regions less privileged in paediatric cardiac surgery. The inability to obtain satisfactory cardiac care for children with congenital heart disease is not limited to 3rd World Countries but is a reality even in Europe, namely in some eastern and south-eastern areas (7).

The reason for poor cardiac care is usually multi-factorial, including economical limitations and widespread poverty, limited access to an insufficient health care, poor and aimless governance, corruption, and other obstacles like lack of resources, scarce specifically trained personnel, combined with inadequate equipment and monitoring (8). In the case of the Balkan conflict, the war 1991-1995 did not only change

the geographical, political, and economical landscape: with gained sovereignty of the post-Yugoslavian constituent republics, for patients from some areas the referral pathways were disrupted, the former allocation centres were found located abroad and charging diagnostics and treatments. With political independence, one of these regions is Bosnia and Herzegovina, self-governing but under the supervision of the international community since 1995.

Concepts for delivering paediatric cardiac care in underserviced emerging countries

There are numerous programmes bringing hundreds of children to countries eager to provide cardiac surgery for free (3, 6). This approach is more frequent after catastrophes or wars, but usually of limited duration: similar problems arise elsewhere and thus the focus of interest is put on other regions. Although this reflects a real humanitarian attitude, it is the least favourable option and creates high costs. This approach is of marginal value for the developing country.

Other medical groups travel around offering their expertise to treat children with cardiac disease at regional sites. Even this is of great value for a small number of children in need but usually without lasting effect for the underserviced country as this approach does not include (systematic) teaching and training. This approach is also very common after some disaster. In principle, we agree with the opinion that surgical tourism is not acceptable unless those visiting are truly interested in building capacities of the local medical and surgical teams (9, 10).

In some places, new centres have been established out of nearly nothing pre-existing. This is usually only possible and successful with a powerful acting institution behind and financial resources guaranteed for long-term service.

In recent years, more and more the policy of humanitarian medicine has shifted away from transferring children to some host countries towards taking care of them in their local environment (11). The majority of donor programmes focus on developing an ongoing relationship with a host programme with the primary goal to improve care and increase the number of children receiving adequate care within the region. This relationship involves teaching, training, collaborative research, and donation of equipment. Basically, this "twinning process" results in transfer of knowledge, ideas, and skills to other people (3, 6). Main part of specialized training may occur either at the site or in the specialized centre (6).

In order to avoid wasting of time, energy and financial resources, in planning a programme it is of decisive benefit to identify places where basic requirements already do exist and hopefully receptive individuals in various sub-specialities are available. Important requirements asked for are a paediatrician (cardiologist), some pre-existing institution (clinical unit including operation room) and postoperative care, access to an echocardiography machine and laboratory as well as blood bank. In

establishing a humanitarian institutional development project, the choice of a partner is critical to the success of the programme. Usually the structures of universities meet requirements best possible (6).

The Viennese project "Kinderherzchirurgie Sarajevo – Hilfe zur Selbsthilfe" (Paediatric cardiac surgery Sarajevo – help to self-help)

After a fact-finding mission in 1999, in March 2000 the Viennese team started the humanitarian activities at the University Clinics of post-war Sarajevo. The aim of our developmental project was to train local partners in all professions with professionalism as well as humility, thus striving for the professional standards but accepting all reasonable differences and limitations of the local environment. The final goal was to establish a regional paediatric cardiac surgical centre. The members of the Viennese team are all active in working process at the General Hospital and Medical University of Vienna. Three to four times per year, missions are performed, usually with a schedule for one week. Many members of the team spend their regular weeks of holidays working in Sarajevo (or other sites like Damascus). Even here it proves true that all humanitarian activity depends on the ideals and spirit of individual medical professionals with the skills, experience and confidence to perform teaching and professional activities safely and efficiently, even in an unknown surrounding with limited resources!

However, a humanitarian mission is not for free. At the beginning of our work, every child treated required financial resources in the range of about € 1.500, to cover all expenses for treatment and the visiting team, including disposables for the heart-lung-machine. This funding was possible due to many private spenders and contributions from medical industry. In exceptions, special materials or drugs were much more expensive and had to be covered in addition. Successively costs were taken over by the University Clinics of Sarajevo, thus reducing the average total costs to about € 300 per patient treated these days.

In addition to the direct commitment in Sarajevo, selected key partners from all professions were invited to spend weeks at the University Clinics in Vienna as visitors thus having the opportunity to take part in everyday life of our home-institution and to observe established procedures. Usually these visits were scheduled immediately before our team went to Sarajevo for the next mission.

During the stay in Sarajevo, intramural training was offered to the local team. Therefore, in recruitment of volunteer medical personnel for the teaching and local team, emphasis was laid on highest possible level of qualification and experience. Over the years the structure of our mission team changed according to requirements: only in the beginning a scrub nurse and a pump technician were part of the team until the local peers soon were able to take over full responsibility. At same short phase an interventional cardiologist was included. But technical equipment proved to be insufficient and monitoring in the catheter lab to be dangerous. Therefore interventional

cardiology was stopped for years until the unit moved into a new and well equipped part of the hospital and a revival of interventional cardiology took place in 2011.

Intervals between humanitarian trips were the reason for prolonged learning curve. This demonstrates that an efficient training requires a continuum, but for the Viennese team this was out of reach. As the local team became more and more proficient, it started to perform less complex operations without us being in Bosnia. Even during our stay nowadays about 80% of all procedures are covered by the local team leaving the Viennese team in the position of a supervisor, not active but all the time available to sort out problems arising. Over time, the local medical professionals, in essence, gradually replace their teaching partners.

In cooperation with our counterparts in Sarajevo, we are now in the process of accumulating and evaluating all data for a reviewing study, analysis and following publication.

As we know, teaching surgery is one of the most important responsibilities of an academic surgeon. So in addition to practical clinical training, one of the aims of the programme was to promote academic education: this goal was not only due to the fact, that the paediatric cardio-surgical program was located within the complex of the University Clinics of Sarajevo. In addition, there is no doubt that this emerging field and persons working in cardiac surgery will only have a prosperous future if there is some integration into academic structures. For this, training included clinical practice, administration, and education, but was even encouraging leadership skills and a high sense of ethics and integrity (12). As a highlight, this focus on academic activities has contributed to the fact of one (paediatric) cardiac surgeon being able to defend his thesis with success...

At the beginning, there were some structural and logistic restrictions (such as missing option to wash hands on the PICU), lack in relevant drugs or implants. But these shortcomings were soon solved by adaptations and at each arrival our team imported everything necessary, including disposables for the operating room and intensive care unit as well as pharmacological products and even hardware. Medical equipment at the site was mostly as good as new and donated by humanitarian groups, mostly international. Over the years we were faced with the fact that these products were without maintenance contracts and after eight years in action, nearly all ventilators and even the heart-lung-machine were outdated and suffered life-threatening malfunction at the same time. Since then, major investments have taken place.

If social and economic problems are not solved, it is difficult to ensure that certain groups are not excluded from society and, as one consequence, from access to cardiac surgery. With regard to the realities in Bosnia, still suffering from the war wounds and being a politically divided multiethnic and multi-religious country, as a maxime we offered our help to children from all regions including the people of Roma population.

Without doubt, if any possible there should be only one level of care, whether it is at home or in another country. The well known attitude of hopefully rare surgeons overestimating their abilities "see one – do one – teach one abroad" is dangerous and exceeding the borders of medical ethics by far; same is true working without being familiar and experienced in the specific field of medicine. But with humanitarian missions, the justified claim to equal approach regardless of situation and geographical location is to be evaluated carefully. But sometimes local circumstances promote the decision for palliation instead of primary repair, as well as performing an operation under suboptimal conditions (for example regarding infectious status) instead of waiting a week or two as would be the case in the home-centre. Other dilemmas relate to failure to comply with standards in care, concerns about coercion and consent as well as reusing disposables or exceeding the date of expiration. These decisions are to be made after conscientious medical and ethical consideration taking into account the waiting time until next mission, uneasiness about how the child in question will develop over the next weeks or months until next chance for treatment, the shortness in intensive care capacity, and the substantial mortality in patients left behind still intubated when the team leaves at the end of the stay. The responsibility for patient´s welfare thus may influence decision-making.

As the main goal of our humanitarian mission was helping to establish a paediatric cardio-surgical unit, most of operative capacity was bound to the fact that operations are selected according to suitability within the stepwise progress of the teaching program. As a consequence, during the short stay of the teaching team only few other operations could be included into the workload. In addition, especially at the beginning of our programme, there was an allocation of the scarce resources to patients who were expected most likely to benefit from cardio-surgical procedures. In the first years, patients with low expectation for satisfactory outcome or less expectation for long-term survival were not listed for operation within the humanitarian mission. The need for some triage - meaning to deny treatment for certain patients - is traumatic for both the families and the whole staff.

In literature, performing operations on the last day of the mission is discussed controversially (9, 10). In our opinion and experience this would mean wasting most valuable time as there are too many children awaiting operations. However, it remains an ethical question evaluating the risk for patients still needing substantial care when the visiting team is leaving, knowing about a very high mortality in complex patients left behind. For this reason, our policy has always been to schedule operations on the last day expected to be easy-going with lowest calculated risk, often non-pump-cases.

But there is one problem, underestimated at the beginning of our programme in Sarajevo. There are patients not treatable in the given surrounding (depending on the situation yet improving significantly over the years of cooperation) due to complexity of the underlying disease, missing special implants necessary, or expected to consume too much postoperative capacity for too long, thus blocking the option to

treat other children. And there are children born or diagnosed in the periods between our mission weeks, urgently in need for cardiac surgery or interventional cardiology. Over many years we were covering the need in Sarajevo alone but not able to offer the optimal solution of monthly visits as a reliably organized structure.

In order to solve the medical, ethical, and structural challenge of required evacuation of children from Bosnia to centres abroad, in 2008 an agreement was found between the insurance company responsible for children from the Bosnian federation and our team: if necessary, an evacuation is feasible within three days aiming for one of the four Austrian centres offering paediatric cardiac care. On the base of this agreement, more than 130 children have been treated, mostly in Vienna. All together, about 500 children have been treated this way, either in Sarajevo or in Austria.

Discussion

Compared to specialized centres, there is a series of differences in less privileged regions. There are some fundamental conditions and prerequisites as well as experiences to be taken into consideration before beginning a project

- countries less privileged in the field of cardiac surgery suffer limited infrastructure, human, and material resources.
- rural areas may be medically underserved, poor infrastructure, long and time consuming distances to clinical centres, poverty of families from secluded areas may make coverage of travelling and housing difficult
- patients often present very late with advanced consequences and effects of complex congenital heart defects. This state may be complicated by malnutrition, inappropriate sanitary conditions, and infections as well as – rarely – parasites.
- patients are more often in poor condition, which contributes to increased perioperative risk (13, 14)
- infectious complications contribute significantly to morbidity and mortality
- in underserviced countries, for children who receive cardiac surgery, perioperative mortality and morbidity remain high (8)
- even in relatively well-established centres, basic systems (such as cardiopulmonary resuscitation, reliable blood services, and constant gas supply) are often absent and adequate supplies are rather the exception than the norm (8, 14)
- there is often a fatalistic approach to problems (8, 14)
- financial limitations do not necessarily imply an insufficient medicine
- well-trained and skilful surgeons, while being able to generate excellent results in children, have difficulties reproducing the same kind of outcomes with neonates and infants (3)
- healthcare professionals trained in adult cardiac care may not be able to provide optimal care for neonates and critically ill small infants – they may be afraid of unused dimensions (16).

- WHO and other international organisations decree that facilities and treatments provided by donors to less privileges countries should correspond to the economic realities of those regions (15)
- parallel to development there is a growing need for trained personnel in all subspecialities. This tendency is increased if there is migration from the local cadre to centres abroad. As meagre salaries are one of the underlying reasons, offering better incentives may help
- a team-oriented focus allows all members of the project to have emotional and intellectual ownership in the developing program, thus exploiting the full advantage of each individual team member and it´s professional discipline (16).
- the teaching team has to be composed of specialized and experienced experts in their individual discipline. The teaching and training has to strive for creating a cadre of specially trained professionals.
- as the successful management of children after cardiac surgery is depending on unique requirements, the development of a robust paediatric cardiac intensive care (PCICU) unit is critical to the success of paediatric cardiac programs including heart surgery (16). A well-defined autonomous PCICU with a dedicated multidisciplinary team is to be favoured as with progress of developing there is an increasing demand for experienced personnel. But to keep realistic, often and at least in the starting or upgrading of an institution, a limited resources environment will not allow a specialized facility but an intensive care being part of adult cardiac surgery or even general surgery.
- for intensive care use, a manual as used in most specialized centres worldwide is of highest value in order to streamline the repetitive procedures, although the content should be translated into the local language and adapted to realistic local circumstances.
- out of ignorance of the abilities of the counterparts, the respect they deserve is too often underestimated (13): a humanitarian project will only be successful if the supporting team and the local team view themselves as equal partners.
- a humanitarian project will only be successful if the local partner is active and willing to take over responsibility for the selection of personnel needed and to be trained.
- in medicine, including humanitarian missions, we do not treat numbers but are aiming for best possible results for every individual patient. So for ethical reasons, body count mentality is to be dismissed.
- as to be expected, in a limited resources environment the obviousness of unrestricted equipment and devices as used in the own home institution is not available or possible. This is a fact and has to be changed to the better over time. Most activities are possible with less financial coverage and fewer and less sophisticated tools. Nevertheless, the issue of effective resource utilization and cost containment assumes an overwhelming importance (16). Part of this concept and a question to be answered is the re-use of disposables after appropriate sterilization as experienced in our centres decades ago. Under the light of limited resources, even the choice

of expensive drugs, blood products, or gases such as nitric oxide is to be evaluated according to strict individual indication.

- it seems ideal for a senior member of each of the local sub-specialities to visit a well-established centre and observe the day-to-day functioning of a specialized unit (16). Additional training possibilities offered abroad contribute to improved motivation for engagement and active participation in a program.
- maintaining of accurate records is the fundament for quality control and may help analysing continuously ongoing improvement
- for training reasons, all staff available should be invited to join the daily ward-rounds and should be encouraged to actively contribute to discussions.
- the PICU should be located close to the operating rooms and – if any possible – to the cardiac catheter laboratory. For emergency situations, life support equipment and the access to the operating room (including elevators etc.) have to be guaranteed at any time.
- intra-operatively, accurate closure of the chest with focus on bleeding is mandatory to minimize the necessity for reoperation consuming time, personnel, and even resources due to prolonged postoperative care
- the optimized strategy according to the well known KISS approach (Keep It Simple and Safe) is in principle most favourable: although we did strive for early primary surgical repair even during early infancy or within the newborn period, young age at operation proved an incremental risk factor.
- postoperatively – and suited to the patients profile – the policy of early extubation and fast tracking helps reducing costs, reduces the need for intensive care treatment, offers more capacities for following patients and may decrease the risk of prolonged intubation and catheter-induced infections. As expected, the patients requiring prolonged ventilation after surgery were younger, smaller, and more critically ill than those who met the criterions for early extubation (3)
- with the cooperation between our team and the local one, language barrier was rarely relevant. However, this was a major issue in contact with patients. Many were of very poor and low social origin and, with exceptions, direct communication between our team and parents was on a very low level and we had to rely on translating. Sometimes we got the impression that parents or patients had not fully understood the perioperative risks. Usually this mostly neglected topic was without consequences due to parents frighten but fatalistic attitude.
- a major impairment for developing projects is losing members of the local team after years of training. Although the striving for better financial and social living conditions abroad may be understandable, the waste in resources is aggravated when these persons never return to their home country.
- in limited resources environment some triage is mandatory in order to offer as many children as possible the options of cardiac surgery and at the same time to concentrate on teaching and training
- one should never perform operations abroad that one would not do on one´s own private patients at home (13)

– with the visiting team once in action, there is no time limit of working hours ensured
– opportunities to learn are bilateral

Patients with congenital heart disease are a public health problem in underdeveloped or less privileged countries. Factors such as rate of population growth, inefficient welfare policies, higher hospital costs for high complexity diagnostic and therapeutic procedures, specialist medical training improper for the current and local demands, increasing need for reoperations due to the improvement of surgical outcomes and prolonged survival are limiting the resources even more (17). According to this situation with increasing requirements and last but not least financial demands, several instances have to be involved in a developing process: beside the professionals of the local team and the team from abroad, persons heading the institutions (board of the clinic, head of the hospital), politicians responsible, insurance companies and others not only have to support the project full-heartedly in theories, but must even offer back-up over time and in difficult periods. There has to be a clear consent about the goal to strive for. In our experience, the continuous support of a cardiac programme by public media is most valuable to overcome dissent and problems with officials.

Success in establishing a paediatric cardiac care in a less privileged country by a humanitarian mission is depending on a dedicated team of experienced experts in all sub-disciplines required including teaching ability, good and realistic planning of the project, sustained efforts and perseverance, the competence to accept working in more limited and difficult circumstances without time limit as well as to deal with problems of all kinds. But all of this will not be enough to reach the goal without a collective motivation of local counterparts in all professions and accepting a huge workload even if remuneration is not adequate. In our experience the most important step is taken as soon as members of the local team – who were unenthusiastic at the beginning of the programme – recognize that every single person is important and absolutely necessary for the project and that the program brings advantages not only for the patients but even for themselves: knowledge, sense, and purpose. The cooperation creates a synergy with positive motivation to proceed towards increasing autonomy with good quality in performance and improving therapeutic results.

Unfortunately, there are no humanitarian solutions for humanitarian problems and – due to the complexity that exists in providing paediatric surgical services – a humanitarian solution will only provide palliation at best (3). The development of institutions such as a paediatric cardiac care unit in a region less privileged will only be successful if this process is supported by the national health care systems, local politicians, and governments as well as hospitals and if there is a genuine interest – for whatever reason. It is well known that, unfortunately, not all sites aiming for a paediatric cardiac surgical programme realize the complexity of this wish and the commitment necessary for succeeding (9). Humanitarian missions may demonstrate and underline the demand for cardiac surgery as well as confirming principle

feasibility. In addition, these "pro bono" campaigns can contribute to a developing process and assist and stimulate further progress.

But there is no doubt that in humanitarian medicine there is much room for co-operation rather than competition (3). For that reason we were happy to see the German Heart Centre Berlin organizing an adult cardiac surgery in "our" place in the University Clinics of Sarajevo. And as expected, the more intense surgical program with daily operations has proved to be substantially beneficial for the general skills of the local team. A similar development took place in the field of paediatric cardiac surgery with additional activities of a Swedish team on regular basis. With all this support and substantial contribution, we may expect the local paediatric cardiac care programme to become more and more autonomous with the initiating programmes from abroad assuming a consultant role.

But this is not enough: other areas in the Balkans are without proper solution for the surgical care of children with congenital heart disease. The numerous European centres with humanitarian projects and programmes are asked to contribute in solving this humanitarian demand. And a solution will be even easier with better cooperation and coordination of the humanitarian missions existing. In addition, the areas in question (mostly smaller countries with low population numbers) are well advised to avoid suboptimal and expensive nationalistic solutions but to strengthen cooperation and by this solving similar and comparable problems by establishing supra-regional centres of competence – backed with strong and concerted effort from more privileged European countries.

Individuals and groups supporting counterparts in less privileged regions are not just philanthropists or simply the "good ones". The important work of assisting development is an ethical duty as well. Analysis of European realities over the last decades made it very clear that the now flourishing cardiac surgery in Western Europe was substantially supported by American unselfish help after the World War II. Before this, medical fundamentals were severely damaged. Within a short period of time, help from abroad made possible a rise from ruins till highest standards. Until today many European countries, mainly in the former communist eastern part of our continent suffer poor economic conditions, some even severe socioeconomic consequences after the war in the Balkans, as Bosnia and Herzegovina. Even here the medical fundaments still are very good and help is needed to overcome economic problems and focussed educational and developmental deficits. Similar to the history of nowadays privileged Western Europe, these neighbouring countries today need help to help themselves in recovering ground, lost to fateful circumstances. All of us are part of one Europe: their future is our future (18).

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SODOBNA INTERVENCIJSKA PEDIATRIČNA KARDIOLOGIJA

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Izvleček

Intervencijski posegi se vse bolj uveljavljajo pri zdravljenju prirojenih srčnih napak. Pri novorojencih balonska atrioseptostomija omogoči mešanje krvi na nivoju preddvorov. Balonska dilatacija je uveljavljena metoda zdravljenja zožitve zaklopke pljučne arterije in aortne zaklopke, ter rekoarktacije aorte. Zdravljenje odprtega Botallovega voda je praviloma kateterско, razen pri nedonošenih otrocih. Večino defektov v pretinu preddvorov tipa sekundum je mogoče zapreti katetersko. Možno je katetersko zapiranje različnih defektov v pretinu prekatov. Zapiranju odvečnih krvnih žil so namenjena različna zapirala. Žilne opornice se uporabljajo za zdravljenje koarktacije in rekoarktacije aorte pri večjih otrocih in odraslih, ter za zdravljenje zožitev pljučnih arterij.

Uvod

Kirurgija je klasična metoda zdravljenja prirojenih srčnih napak. Ob tem se je v zadnjih desetletjih razvila vrsta kateterskih tehnik, ki so nadomestile ali dopolnile kirurško zdravljenje.

Kateterske intervencije v otroški kardiologiji imajo nekaj skupnih značilnosti. Izvajajo se v splošni anesteziji. Razen diaskopije se intervencije pogosto spremlja tudi s transezofagealno ehokardiografijo. Dostop se praviloma zagotovi preko stegenske vene in/ali arterije. Najprej se opravijo hemodinamske meritve, s katerimi se ovrednoti pomembnost napake. Nato se izvedejo angiokardiografije za natančen prikaz napake. Preko tarčne strukture se uvede kateter in preko katetra vodilna žica. Vodilna žica omogoči, da se terapevtski sredstvo namesti na želeno mesto. Balonski katetri se uvedejo preko vodilne žice nezaščiteni, medtem ko se žilne opornice in zapirala uvedejo skozi dolga uvajala.

Balonska atrioseptostomija

Balonsko atrioseptostomijo sta leta 1966 prva opravila Rashkind in Miller (1). Poseg se izvaja pri novorojencih pri katerih je potrebno zagotoviti mešanje krvi na nivoju preddvorov. To so praviloma novorojenci s transpozicijo velikih arterij. Z infuzijo prostaglandinov, ki ohrani prehodnost Botallovega voda in z balonsko atrioseptostomijo, se takšnega novorojenca stabilizira. V prvih tednih življenja se nato programsko izvede anatomska poprava napake.

Venski pristop se zagotovi preko stegenske ali popkovne vene. Preko vstopne vene, vene kave inferior in desnega preddvora se konico Rashkindovega katetra preko odprtega ovalnega okna uvede v levi preddvor. V levem preddvoru se balon na konici Rashkindovega katetra napolni s fiziološko raztopino. S hitrim, kratkim potegom katetra se z balonom raztrga pretin v področju ovalnega okna. Klasično se je poseg izvajal v kateterizacijskem laboratoriju pod diaskopskim nadzorom, sedaj pa se običajno opravi v enoti intenzivne terapije pod nadzorom ultrazvoka (2).

Poseg je najučinkovitejši v prvem tednu po rojstvu, kasneje uspešnost posega upade.

Balonska dilatacija zožitve zaklopke pljučne arterije

Balonska dilatacija je uveljavljen način zdravljenja zožitve zaklopke pljučne arterije. Poseg je indiciran pri novorojencih s kritično zožitvijo zaklopke in pri bolnikih z invazivno izmerjenim gradientom preko zaklopke $\geq$ 50 mm Hg (3).

Poseg se praviloma opravi preko stegenske vene (4). Opravijo se meritve tlakov v desnem prekatu in pljučni arteriji. Desni prekat in položaj zaklopke se prikaže z desno ventrikulografijo. Preko katetra se globoko v vejo pljučne arterije uvede delovno žico. Za dilatacijo se izbere balonski kateter z zunanjim premerom balona, ki je 1.2 do 1.4-krat večji od premera obroča zaklopke. Balonski kateter se preko delovne žice namesti čez zaklopko. Balon se napolni z razredčenim kontrastom, s tlakom 3 do 5 atmosfer, za približno 5 sekund. Zažem na balonu ob uspešni dilataciji izgine. Rezultat posega se oceni s ponovnimi meritvami tlakov, z desno ventrikulografijo in ehokardiografsko.

Balonska dilatacija zožitve zaklopke pljučne arterije je običajno učinkovita (5). Pri bolnikih s pomembno zaostalo zožitvijo ali s ponovno zožitvijo se poseg lahko ponovi. Pri bolnikih po uspešnem posegu je dolgoročno potrebno spremljati puščanje zaklopke. Dilatacija je neučinkovita pri bolnikih z displastičnimi zaklopkami (6). Pri teh bolnikih je zato indicirano kirurško zdravljenje.

Balonska dilatacija zožitve aortne zaklopke

Balonska dilatacija je nadomestilo kirurški komisurotomiji zožitve aortne zaklopke (7). Oba posega sta začasna, saj bolnik v nadaljnjem poteku zdravljenja potrebuje zamenjavo aortne zaklopke. Poseg se izvaja pri novorojencih s kritično zožitvijo

zaklopke, ter pri dojencih in otrocih s pomembno zožitvijo zaklopke. Pri otrocih, ki so brez težav, je indikacija za poseg invazivno izmerjen gradient preko aortne zaklopke ≥ 80 mm Hg. Pri otrocih s težavami in pri otrocih s spremembami veznice ST in vala T je poseg indiciran pri invazivno izmerjenem gradientu ≥ 50 mm Hg.

Za poseg se praviloma uporabi pristop preko stegenske arterije (8). Pri novorojencih se lahko uporabita tudi pristopa preko stegenske vene ali popkovne arterije. Opravi se aortografija. Izmerita se tlaka v aorti in levem prekatu. Preko katetra se v levi prekat uvede delovna žica. Izbere se balonski kateter z zunanjim premerom balona, ki je približno enak premeru obroča aortne zaklopke. Balonski kateter se namesti čez aortno zaklopko. Pri večjih otrocih se položaj balonskega katetra med dilatacijo stabilizira s hitrim prekatnim vzpodbujanjem (9). Balon se napolni z razredčenim kontrastom, s tlakom 3 do 5 atmosfer, za približno 5 sekund. Dilatacija se lahko v nekajminutnih razmikih večkrat ponovi. Ob uspešni dilataciji zažem na balonu povsem izgine. Po opravljeni dilataciji se ponovijo meritve tlakov in aortografija. Rezultat posega se oceni tudi ehokardiografsko.

S posegom se zmanjša gradient preko zaklopke (10). Po posegu se pogosto pojavi puščanje zaklopke, ki je v nadaljnjem poteku zdravljenja razlog za zamenjavo zaklopke. V primeru ponovne zožitve zaklopke se balonska dilatacija lahko ponovi.

Katetersko zdravljenje koarktacije in rekoarktacije aorte

Pri novorojencih, dojencih in manjših otrocih je kirurgija standarden način zdravljenja koarktacije aorte. Balonska dilatacija je pri teh bolnikih namenjena zdravljenju rekoarktacije aorte po predhodnem kirurškem posegu (11). Poseg je indiciran pri bolnikih z invazivno izmerjenim gradientom ≥ 20 mm Hg in angiografsko vidno zožitvijo aorte.

Poseg se običajno opravi preko stegenske arterije. Opravijo se natančne meritve tlakov nad in pod mestom zožitve, ter aortografije v vsaj 2 projekcijah. Za dilatacijo se izbere balonski kateter z zunanjim premerom balona, ki ne presega premera descendentne aorte na prehodu preko prepone. Preko delovne žice se čez zožitev namesti balonski kateter. Balon se s tlakom, ki ga dopušča izbrani visokotlačni balonski kateter, napolni z razredčenim kontrastom. Dilatacija se lahko v nekajminutnih razmikih večkrat ponovi. Ob uspešni dilataciji zažem na razpetem balonu povsem izgine. Uspešnost dilatacije se preveri s ponovnimi meritvami tlakov in aortografijami. Pri večini bolnikov je dilatacija rekoarktacije aorte uspešna (12).

Za zdravljenje koarktacije in rekoarktacije aorte pri večjih otrocih, adolescentih in odraslih se vse bolj uveljavlja vstavitev žilne opornice (13). Z vstavitvijo žilne opornice se zagotovi razširitev lumna aorte, ne glede na morfološke značilnosti zožitve. Ob tem je tveganje nastanka disekcije in aneurizme aorte manjše kot pri balonski dilataciji. Žilna opornica zagotovi, da lumen aorte ostane široko odprt, navkljub

elastičnim lastnostim stene aorte. Z žilno opornico se zaščiti področje aneurizme aorte po predhodni operaciji ali balonski dilataciji.

Za katetersko zdravljenje koarktacije/rekoarktacije aorte so se uveljavile predvsem Cheatham-Platinum žilne opornice (NuMED Inc, Hopkinton, NY, USA). V nekaterih primerih se vstavijo omenjene žilne opornice, ki so obdane s slojem ePTFE materiala (14). Za vstavitev teh žilnih opornic se običajno uporabi poseben BIB balonski kateter (NuMED Inc, Hopkinton, NY, USA). V novejšem času se vse pogosteje vstavljajo žilne opornice Advanta V12 (Atrium Medical Corp., Hudson, NH, USA) (15). Vse žilne opornice Advanta V12 so obdane s slojem ePTFE. Razen tega so te opornice že tovarniško pritrjene na balonske katetre različnih dimenzij.

Vstavitev žilne opornice se izvede v splošni anesteziji. Zagotovi se pristop preko stegenske arterije in vene. Opravijo se meritve pritiskov nad in pod mestom zožitve. Morfologijo zožitve se prikaže z aortografijami v različnih projekcijah. V desni prekat se uvede elektrodni kateter, ki omogoča hitro ventrikularno vzpodbujanje. Izbereta se žilna opornica in balonski kateter ustreznih dimenzij. Preko zožitve se uvede dolgo uvajalo, ki omogoči vstavitev žilne opornice čez mesto zožitve. Žilno opornico se namesti natanko na mesto zožitve in odstrani dolgo uvajalo. Aktivira se hitro ventrikularno vzpodbujanje. Balonski kateter se z visokim tlakom napolni z razredčenim kontrastom. S tem se žilna opornica pričvrsti na steno aorte. Balonski kateter se izprazni. Prekine se hitro ventrikularno vzpodbujanje. Balonski kateter se odstrani preko dolgega uvajala. Ponovijo se meritve pritiskov in opravijo kontrolne aortografije. Zaradi rasti je pri manjših bolnikih, nekaj let po posegu, potrebno žilno opornico z balonsko dilatacijo dodatno razširiti.

Katetersko zapiranje odprtega Botallovega voda

Katetersko zapiranje je običajna metoda zdravljenja odprtega Botallovega voda, razen pri nedonošenih otrocih in pri dojencih s telesno težo < 6 kg. Indicirano je zaprtje vsakega odprtega Botallovega voda, razen t. i. "tihega" odprtega Botallovega voda, ki ni slišen ob avskultaciji in je viden le na barvni Dopplerski preiskavi pljučne arterije.

Za zapiranje majhnih odprtih Botallovih vodov so se v preteklosti največ uporabljale prilagojene žilne spirale (16). Posebej za zapiranje odprtega Botallovega voda je bilo razvito Amplatzovo duktusno zapiralo (AGA Medical Corporation, Golden Valley, MN, USA) (17,18). Zapiralo je primerno za zapiranje srednje velikih in velikih odprtih Botallovih vodov. V zadnjem času se največ uporabljajo Amplatzova duktusna zapirala tipa II (19). Zapiralo se lahko vstavi preko stegenske vene ali arterije. Tehnika vstavljanja je enostavna. Sprva se opravi aortografija s katero se prikaže velikost in oblika Botallovega voda. To omogoči izbor zapirala ustrezne velikosti. Zapirala so namreč različnih premerov in dolžin, kar omogoča zapiranje Botallovih vodov različnih velikosti in oblik. Zapiralo je med posegom pritrjeno na implantacijsko žico. Preko dolgega uvajala se zapiralo namesti preko Botallovega voda. Dolgo

uvajalo omogoča izvedbo kontrolne aortografije s katero se preveri lega zapirala. Ustrezno nameščeno zapiralo se nato sprosti. Aortografija se ponovi.

Katetersko zapiranje defekta v pretinu preddvorov tipa sekundum

Katetersko zapiranje se je uveljavilo kot metoda zdravljenja defektov v pretinu preddvorov tipa sekundum. Med razpoložljivimi zapirali se največ uporabljajo Amplatzova septalna zapirala (20, 21). Indikacija za zaprtje defekta je levo-desni spoj z znaki volumske obremenitve desnega srca.

Za varno in uspešno zaprtje je ključen izbor bolnikov. Izbor se opravi s transtorakalnim in transezofagealnim ehokardiografskim pregledom preddvornega pretina in pljučnih ven (22). Defekti s premerom > 30 mm so za katetersko zapiranje preveliki. Razen tega mora biti rob defekta > 5 mm oddaljen od pomembnih bližnjih struktur: obeh atrioventrikularnih zaklopk, ter ustij pljučnih ven in koronarnega sinusa.

Poseg se opravi v splošni anesteziji. Zapiralo se vstavi preko stegenske vene ob nadzoru s transezofagealno ehokardiografijo in diaskopijo. Preko katetra se čez defekt v levo zgornjo pljučno veno uvede delovno žico. Z merilnim balonskim katetrom se izmeri raztezni premer defekta, ki je osnova za izbiro velikosti zapirala. Zapiralo se vstavi preko dolgega uvajala. Ves čas vstavljanja je zapiralo pričvrščeno na implantacijsko žico. V primeru, da je položaj zapirala ustrezen, se zapiralo sprosti. Sicer se zapiralo brez posebnih težav odstrani iz telesa. Bolnik 6 mesecev po posegu prejema aspirin v antiagregacijski dozi.

Za katetersko zapiranje defektov v pretinu preddvorov tipa sekundum je primerno do 70% defektov. Ostali defekti tipa sekundum, ter defekti tipa sinus venosus in tipa primum se zapirajo kirurško.

Katetersko zapiranje defektov v pretinu prekatov

Klasično zdravljenje defektov v pretinu prekatov je kirurško. Predvsem številni defekti v mišičnem delu pretina prekatov so za kirurško zdravljenje zahtevni. Nekatere lege defektov v mišičnem delu pretina prekatov so kirurgom težko dostopne. Zato se za zapiranje mišičnih defektov vse bolj uveljavlja katetersko zapiranje z Amplatzovimi mišičnimi VSD zapirali (23).

Posebna pozornost se namenja kateterskemu zapiranju perimembranoznih defektov v pretinu prekatov (24). Zapiralo, ki je namenjeno zapiranju teh defektov, je posebej prilagojeno tankemu membranoznemu pretinu in bližini aortne zaklopke. Zaradi bližine aortne in trikuspidne zaklopke je poseg tehnično zahteven. Največji problem kateterskega zapiranja perimembranoznih defektov je redek pojav kompletnega atrioventrikularnega bloka, kasno po vstavitvi zapirala (25).

Za perkutano zapiranje defektov v pretinu prekatov se običajno zagotovi pristop preko stegenske arterije in stegenske ali jugularne vene. Vstavitev zapirala se spremlja

z diaskopijo in transezofagealno ehokardiografijo. Defekt se prečka iz levega v desni prekat. Vzpostavi se arteriovenska zanka med stegensko arterijo in veno. Preko vodilne žice se iz vene v levi prekat uvede konico dolgega uvajala. Nato se v defekt vstavi izbrano zapiralo. V primeru, da sta položaj in oblika zapirala ustrezna se zapiralo sprosti. Predvsem po zaprtju perimembranoznih defektov se posebno pozornost nameni spremljanju srčnega ritma.

Katetersko zdravljenje zožitev pljučnih arterij

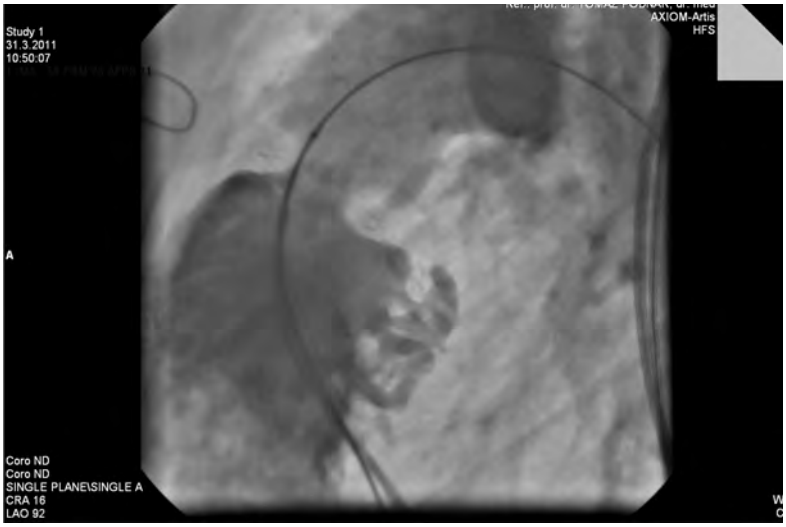
Zožitev pljučnih arterij je običajno sestavni del prirojene srčne napake, redkeje je izolirana. Pogoste so zožitve po predhodnem kirurškem zdravljenju. Pomembno je razlikovati proksimalne in distalne zožitve pljučnih arterij. Proksimalne zožitve so zožitve debla in obeh vej pljučne arterije.

Standardna kateterska tehnika zdravljenja zožitev pljučnih arterij je bila balonska dilatacija (26). V ta namen se uporabljajo visokotlačni balonski katetri. Rezultati balonske dilatacije so najboljši pri proksimalnih zožitvah, posebej po predhodnem kirurškem zdravljenju. V primeru, da je zožitev posledica zunanjega pritiska, nepravilnega poteka oz. zaradi elastičnih lastnosti žilne stene razrešitev po balonski dilataciji ni trajna, je potrebna vstavitev žilne opornice (27). V ta namen se pri nas največ uporabljajo Cordis Palmaz Genesis XD žilne opornice (Johnson & Johnson, Piscataway, NJ, USA). Vstavljene žilne opornice je potrebno zaradi otrokove rasti po nekaj letih razširiti z balonsko dilatacijo.

Pri distalnih zožitvah pljučnih arterij so rezultati balonske dilatacije slabši. V teh primerih se vse pogosteje uporablja balonska dilatacija s t. i. cutting baloni (Boston Scientific Inc., San Diego, CA, USA). Tudi pri distalnih zožitvah pride v poštev vstavitev žilnih opornic.

Kateterska vstavitev zaklopke pljučne arterije

Pri kirurškem zdravljenju prirojenih srčnih napak je pogosto potrebno všitje cevastega vsadka z zaklopko med iztočni trakt desnega prekata in pljučno arterijo. V ta namen se uporabljajo homografti in različni tipi bioloških zaklopk. Sčasoma se razvije zožitev in/ali puščanje zaklopke vsadka, kar zahteva kirurško zamenjavo vsadka (Slika 1). V zadnjih letih se namesto ponovne kirurgije vse bolj uveljavlja katetersko vstavljanja biološke zaklopke v že obstoječ vsadek (28). Največ izkušenj je bilo pridobljenih z vstavitvami Melody zaklopk. Melody zaklopka je biološka zaklopka Contegra (jugularna vena goveda) všita v žilno opornico. Za vstavitev Melody zaklopke so primerni vsadki s premerom med 16 in 22 mm.



Slika 1: Pomembno puščanje biološke zaklopke, ki je bila kirurško vstavljena v iztočni trakt desnega prekata po predhodni kirurški popravi tetralogije Fallot.

Poseg se opravi v splošni anesteziji, preko stegenske vene. Opravijo se meritve pritiskov v desnem prekatu in pljučni arteriji. Izvedejo se desne ventrikulografije in pulmonalne arteriografije. Izključi se možnost pritiska zaklopke na koronarno arterijo. V vsadek se najprej vstavi žilna opornica, ki vsadek učvrsti. Nato se v žilno opornico vstavi Melody zaklopka (Slika 2). Po vstavitvi se preverijo pritiski nad in pod zaklopko. Izvede se pulmonalna arteriografija.



Slika 2: V biološko pulmonalno zaklopko je vstavljena Melody zaklopka, tako da puščanja zaklopke ni več.

Srednjeročni rezultati po vstavitvi Melody zaklopke so obetavni (29). V že obstoječo zaklopko je mogoče vstaviti novo Melody zaklopko.

Katetersko zapiranje odvečnih žilnih struktur

Odvečne žilne strukture so pogosto pridružene prirojenim srčnim napakam ali pa gre za izolirane žilne anomalije. Najpogostejše odvečne žilne strukture so: aortopulmonalne kolateralne arterije, pljučne in sistemske arteriovenske malformacije, venske kolaterale in koronarne arterijske fistule. Za katetersko zapiranje teh žilnih struktur je na razpolago vrsta različnih tipov zapiral. Doslej so se v ta namen največ uporabljale žilne spirale, medtem ko so se v zadnjem času uveljavila Amplatzova žilna zapirala (30, 31).

Zaključek

Sodobna intervencijska pediatrična kardiologija omogoča zdravljenje vedno večjega dela enostavnih prirojenih srčnih napak. Kardiokirurgija je zato vedno bolj usmerjena v zdravljenje zapletenih napak. Pri zdravljenju prirojenih srčnih napak se kardiokirurgija in intervencijske tehnike vse bolj dopolnjujejo.

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ECHOCARDIOGRAPHY ASSESSMENT OF SYSTOLIC FUNCTION IN DIFFERENT LEFT VENTRICULAR GEOMETRIES

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Abstract

Congenital heart diseases (CHD) appear as a large variety of anomalies with different ventricular shapes, sizes and haemodynamics. Reliable assessment of ventricular function in children with complex CHD, such as univentricular heart or after a Fontan operation, is difficult, as the majority of echocardiographic (ECHO) parameters rely on geometric assumptions or haemodynamic factors.

A number of new echo methodologies, like Tissue Doppler Imaging (TDI), strain and strain rate have become available, allowing an assessment of different aspects of left ventricular (LV) contraction. In particular, evaluation of LV longitudinal systolic dynamics has progressively gained importance as a key aspect in the assessment of LV systolic function. Longitudinal measures of wall function are: annular displacement and velocity, the displacement index, myocardial performance index (MPI), as well as mean strain/strain rate.

Annular displacement, determined from M-mod, is a direct, early, sensitive, and easy-to-perform index of global LV systolic function, but is age-dependent. TDI is a quantitative non-geometric measure of systolic and diastolic ventricular function. The most commonly used indices are mitral annular systolic peak S-wave velocity (S') and MPI. The new parameter is displacement index (S'-wave velocity-time integral, divided by the end-diastolic distance from the mitral annulus to the LV apex), very sensitive, not affected by age, heart rate, or BSA.

Conclusions: Reliable assessment of systolic ventricular function in patients with complex CHD is possible through detailed study of LV long-axis dynamics. Most importantly, new, specific TDI indices provide evidence of subtle cardiac dysfunction long before clinical or traditional ECHO signs are appreciable.

Keywords: Congenital heart disease, Ventricular function, Echocardiography

Introduction

Reliable non-invasive assessment of left ventricular (LV) function is essential for the diagnosis and management of heart failure. Echocardiography is currently the technique most widely used for this purpose although cardiac magnetic resonance imaging (CMR) is becoming the reference method, but it is reserved only for a small number of selected patients [1–4]. The assessment of heart function is an indication for ECHO examination in about 60% of adult cardiac patients. In paediatric cardiology, the pathology is completely different, predominantly related to congenital heart diseases (CHD). The congenital malformations are a result of a huge number of genetic abnormalities and thus appear as a large variety of CHDs with different ventricular shapes, sizes and haemodynamic. Most of them involve an important component of volume and/or pressure load, which produces variable degrees of remodelling and adaptation for different loading conditions. Paediatric patients who require close surveillance of myocardial function can range from neonate after arterial switch or Norwood palliative reconstructive surgery, to children with different CHD (pre or post surgery), or an adolescent patient with dilated cardiomyopathy. Particular diagnostic problems appear for patients with systemic right ventricle (RV), single ventricle physiology or univentricular heart (UVH) corrected by Fontan procedure. Finding a common methodology for ECHO evaluation of ventricular function in hearts with completely different ventricular geometry, contraction, and regional wall motion abnormalities remains challenging, as the majority of techniques aimed at the assessment of heart function are developed for biventricular heart and for the LV. Furthermore, many of these patients have limited echocardiographic windows, and inadequate visualization of the endocardial border at end-systole and end-diastole [5]. Complementary diagnostic methods, like measurement of neurohormonal markers, such as brain-type natriuretic peptide (BNP) and N-terminal (NT)-pro BNP, have been increasingly used for children with cardiomyopathies, but also for various congenital anomalies [6, 7]. Unfortunately, several studies for single ventricle anomalies prove that levels of neurohumoral markers are variable and, therefore, this method is not recommended in this group of patients [8–10].

Background

The performance of the ventricle as a pump mostly depends on several components: primarily contraction of the myofibrils/sarcomers (contractility), then ventricular geometry, loading conditions, and heart rate. When we refer to ventricular systolic function, one should be aware of the difference between contractility (the intrinsic property of the myocardium) and ventricular pump function (ventricular performance). During the systole, the main event is force development which, at the myocardial level, results in the production of biventricular pressure as a result of fibre shortening, heart deformation and blood ejection. In clinical practice, ventricular systolic function usually denotes ventricular pump function, which is a global parameter (global function). In some diseases, the contribution of different myocardial

regions to the ventricular pump function can be altered and, in those cases, the analysis of individual wall segments is important – regional myocardial function.

The heart has a unique, three dimensional (3D) architecture, with specific complex fibre orientation [11]. Myofibers at epicardium have predominantly longitudinal (left-hand) orientation, then gradually change direction, to circumferential orientation, in the middle part of the wall before changing direction again in the endocardial (inner portion) of the wall to long-axis (right-hand) orientation. Because of such spiral fibres' orientation during systole, when myofibers shorten, they simultaneously thicken and twist, compressing each other in three directions, thus producing an effect of amplification of all those deformations through a squeezing effect on neighbouring fibres. As a result of this, we see an effect in a healthy heart that, during systole sarcomeres shortening of about 15%, results in 35–40% thickening, and the ejection of about 60–70% of blood volume [12]. In summary, during systole, ventricular walls move in longitudinal, circumferential and transmural (radial) directions, with the following deformations: longitudinal shortening, circumferential shortening and, as a consequence, transmural thickening.

This article is dedicated to the evaluation of global systolic function of the systemic ventricle.

Standard methods for evaluation of LV systolic function

Over the last 3 decades, a large number of ECHO parameters for the evaluation of LV systolic function were published. Most of them are too complex for everyday clinical practice, and only have scientific value, as they are time consuming. Traditional ECHO measures of LV systolic function include: M-mode, two dimensional (2D) examinations for dimensions and derived volume changes, and Doppler-derived ejection indices for ventricular performance. Most ECHO measures of LV systolic function represent ejection phase indices, such as: fractional shortening (FS) and ejection fraction (EF) (dimensional parameters from M-mode or 2D), or velocity of circumferential fibre shortening (Vcf), changes in peak and mean pressure over time ($\Delta p/\Delta t$) (Doppler parameters) and systolic time intervals.

Ejection fraction and fractional shortening

Ejection fraction and FS are still the most widely used measures of global systolic LV function today. Fractional shortening is more commonly used in children and its normal values range between 28 – 44%, with variations for age. EF is the most commonly used parameter in adults, mainly due to the large amount of prognostic information that is included in the cut-off points of EF values [13–15]. Normal values range from 56–78%. This is a single parameter with good perception of its value amongst cardiologists as well as surgeons; thus, it will remain in use in the foreseeable future.

Fractional shortening and EF calculation from LV linear measurements by early-used Teichholz or Quinones formulas, both based on geometrical assumptions, are no longer recommended; however, using 2D echocardiography with modified Simpson's rule with biplane planimetry of LV is currently recommended [16]. In everyday clinical practice the "eyeball" estimation of EF is often performed and experienced physicians get results comparable to those obtained using "trackball" methods [17]. Whichever method for measuring EF is applied to assess global LV systolic function carries important limitations due to its dependence on instantaneous loading conditions, picture quality, suboptimal test-retest reproducibility, and low sensitivity in detecting subtle LV systolic impairment [18]. The majority of new methods still compare their results with EF, as if it were the "gold standard" [19]. There is, however, one important limitation of EF, which is the reason why EF cannot be used in all patients! The EF was primarily introduced in order to characterize the reduced myocardial function in dilated LV, but becomes erroneous in the cases of reduced end diastolic volume (EDV), as well as severe myocardial hypertrophy [20]. A perfect example of this can be seen in those patients with clinical signs of heart failure and small, hypertrophic hearts, known widely as "heart failure with preserved EF (HFPEF)". Today, it is clear that the systolic and diastolic functions are closely related, since a significant part of the diastolic recoil is due to stored elastic energy from previous systolic contraction. It is important to stress that EF should not be used in smaller ventricles, as systematic errors are introduced [20].

Recently, more complex, slow, but accurate methods are becoming available to determine cardiac volumes and EF (e.g. CMR, 3D echocardiography), applicable especially to unusual ventricular geometries, but not in routine clinical practice [3, 21, 22]. There are few acquisition or analysis methods in 3D ECHO and none of them rely on geometric assumptions for volume/mass calculations, since the real geometry is captured by 3D imaging. As a result, none of the 3D methods have plane positioning errors, which can lead to chamber foreshortening [23, 24]. Studies comparing 3D ECHO LV volumes or mass measuring with the CMR, as the current gold standard, have confirmed 3D echocardiography to be accurate. Compared with CMR data, LV and RV volumes calculated from 3D echocardiography showed significantly better correlation and lower intra-observer and inter-observer variability than 2D echocardiography [16].

New methods for evaluation of LV systolic function

Newer ECHO techniques**,** such as TDI, 3D echocardiography, and deformation imaging allowed better understanding and evaluation of the complex mechanism of cardiac contraction and relaxation. Evaluation of LV longitudinal systolic dynamics has become crucial in the assessment of LV systolic function [18]. The idea of analyzing longitudinal motions of AV annulus as well as ventricular walls is based on the contribution of Leonardo da Vinci to cardiology. He anticipated that the heart functions as a double pump, with the atrioventricular plane as a piston, [25] and

later anatomical studies about myocardial fibre orientation in the heart [11]. Since 1990, functional importance of the long-axis dynamics of the left ventricle and the possibility of analyzing it by ECHO has been recognized, [26] and many published studies proved its superior value in comparison with traditional measures [27, 28].

The passive annular movements reflect the longitudinal systolic shortening of the ventricle, which, in a way, represents the global systolic longitudinal function. Annular displacement and velocity are good measurements of total ventricular shortening and shortening velocity (to assess global ventricular function) [20].

Currently, LV long-axis performance can be evaluated using the following techniques: 1. M-mode; 2. pulsed TDI; 3. colour TD-derived techniques (i.e. tissue velocity imaging, strain (S) and strain rate (SR) imaging, and 4. two-dimensional SR imaging.

M-mode indices

Mitral annular excursion

Determination of mitral annular apical systolic excursion (MAE) is possible using 2D-guided M-mode imaging of mitral annular motion from apical views. This is the easiest method of assessing LV global long-axis systolic performance. Variations in excursion across the annulus circumference require that, for precise MAE estimation, evaluation should be performed by averaging measurements obtained in multiple annular sites (usually 4 or 6) [29]. Measurements are usually performed from apical 4-chamber view at the septal and/or lateral annulus level, using zoom function at the level of the annulus (Figure 1) [30].

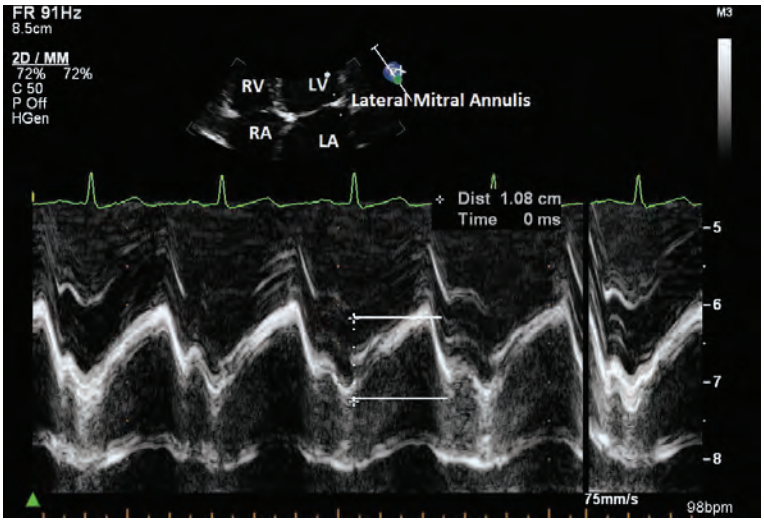

Figure 1. Recording of the motions of lateral mitral annulus by two dimensionally guided M mode, using zoom function. The vertical distance between the point of the annular most distant from the apex and the point closest to the apex is measured in M mode, as indicated.

A study of Emilson K et al. proved that MAE is dependent on the age and size of patient. The normal mean MAE in healthy adults ranges from 14 to 15 mm. These values are regularly higher in younger subjects, and have been reported to decline from 15 mm at 20–40 years, to approximately 10 mm at 61–80 years [31]. Practically, this means that the annular displacement should be normalized for heart size in children [19, 32].

Very good correlation was found between MAE and EF for adults. The value of 12 mm was selected as a cut-off point for MAE for detection of LVEF <50%, regardless of whether MAE was determined by M-mode, 3D echocardiography, or MRI [33, 34].

Additionally, MAE provides good prognostic information in heart failure patients. For example, in patients with myocardial infarction, with a threefold relative increase in the risk of mortality in patients with MAE<8 mm compared to those with MAE >8 mm over a two-year follow-up [35]. A similar study of Cline et al. [36] showed that mortality increased significantly if MAE was less than 6 mm (all patients died within one year).

A depression in MAE can evidence subtle systolic impairment in nearly one quarter of patients with: HFPEF, arterial hypertension and aortic stenosis with preserved EF [37-39].

For a majority of patients, echocardiographic determination of MAE is fast and easy and at the same time highly reproducible and sensitive index of global LV systolic function [18].

Pulsed tissue Doppler indices

Heart pump function significantly depends on the myocardial wall function, and changing the focus of diagnostics to the myocardium instead of cavity dimensions leads to a new quality in diagnostics. Doppler myocardial velocity measurement by TDI was introduced as a more objective, direct and quantitative method for assessing myocardial function, with the possibility to analyze regional contribution. From a practical point of view, measurements of longitudinal systolic and diastolic components give the best results, due to heart motion. The complexity of understanding TDI delays its implementation in clinical routine but, today, it should be considered a part of routine examination [40].

Peak annular velocity

Pulsed TDI is a technique that allows the recording of instantaneous maximal velocities within a predefined volume sampling region in real-time. By selecting a single sample volume in TDI, high temporal resolution is achieved. Among all the parameters that could be measured, peak annular velocity-Sm is the most commonly used for estimating the global LV long-axis systolic function. Recording should be

performed from apical views, by placing a sample volume at the junction between basal myocardium and mitral annulus. To improve the reliability of the systolic annular dynamics estimation, since inhomogeneity of velocities across annular circumference exists, values recorded in at least two different levels of the annulus (e.g., septal and lateral) should be averaged [18]. This parameter mostly depends on age and heart rate. Age-specific reference ranges for Sm were published [41]. Eidem et al. [42] analyzed the impact of growth on TD velocities during childhood. This study demonstrated that measures of cardiac growth, most notably LV end diastolic dimension and LV mass, had significant correlation with TD systolic and early diastolic velocities, particularly for neonates and infants. In the same paper [42] it was proven that HR has significant influence on tissue velocities. According to this study, normal values of mitral valve maximal systolic velocities (Sm) at the lateral mitral annulus (and basal septum) are presented at Table 1 [42]. Another large study from Roberson et al. [43] confirmed correlations of maximal TD annular velocity with age, body surface area (BSA) and heart rate (HR). Variations in Sm value between healthy children of different age and HR were much greater than in most prior studies. The principal contribution of this research is the development of *Z*-score tables from a large number of patients covering all ages, HR, and BSA. These tables serve as reference data for longitudinal-directed TD annular and septal Sm, as well as for diastolic parameter (E' and A') normal values in children [43].

Table 1. Normal values of mitral valve maximal systolic velocities (Sm) [42].

Age / Velocity (cm/s)	Less than 1 year	1 – 5 years	6 – 9 years	10 – 13 years	14 – 18 years
Lateral mitral annulus	5.7 ± 1.6	7.7 ± 2.1	9.5 ± 2.1	10.8 ± 2.9	12.3 ± 2.9
Basal septum	5.4 ± 1.2	7.1 ± 1.5	8.0 ± 1.3	8.2 ± 1.3	9.0 ± 1.5

Extensive debate regarding the influence of volume and pressure loading on tissue velocities has taken place. Initially, the prevailing opinion was that tissue velocities were relatively independent, an opinion that was later partially denied. Conflicting results still exist, but it seems that for the same preload, there is a difference in tissue velocities between acute and chronic types of disease [44]. Chronic volume overload [45] has a smaller effect on tissue velocities than the acute variety [46]. Pressure loading influences tissue velocities in the following way: increased ventricular pressure (acute or chronic, like in aortic stenosis), leads to decreased tissue velocities [47]. Kiraly et al. [48] showed that in children with aortic valve stenosis, longitudinal TD velocities were more reduced than TD radial velocities.

In patients suffering from CHD the RV is commonly affected by volume and/or pressure overload or by surgery. Tissue velocities have a great potential for assessment of RV function because the RV has predominantly longitudinal orientation

of myofibres. There are several studies of longitudinal RV function in tetralogy of Fallot (TOF), showing the usefulness of TDI in early recognition of RV, as well as LV dysfunction [59, 51].

The use of TD velocities in functionally univentricular hearts has also been studied. Vitarelli et al. [52] studied 24 patients who had undergone Fontan surgery and found a linear correlation between Sm and echocardiographic estimates of EF. In the large study undertaken by Rhodes et al., [53] performed on 416 Fontan patients, statistically significant correlations existed between Sm, Tei index, and echocardiography-based estimates of EF, but these correlations were weaker than the correlation between traditionally-calculated EF and new, more sophisticated parameters, as well as CMR-derived EF.

Mitral annular displacement index

Recently, a new and promising parameter of longitudinal ventricular systolic function was introduced by Roberson et al. [19], entitled Mitral Annular Displacement Index (MADI). This is a TD annular systolic (Sm) wave velocity time integral (VTI) divided by the end-diastolic distance from the mitral annulus to the LV apex. It is, in fact, the measure of relative change in longitudinal ventricular length during systole found through Doppler measurements (Figure 2). Doppler measurements are more precise than distance measurements and less observer-dependent if the beam direction is correct, wherein lies the reason as to why this method is promising.

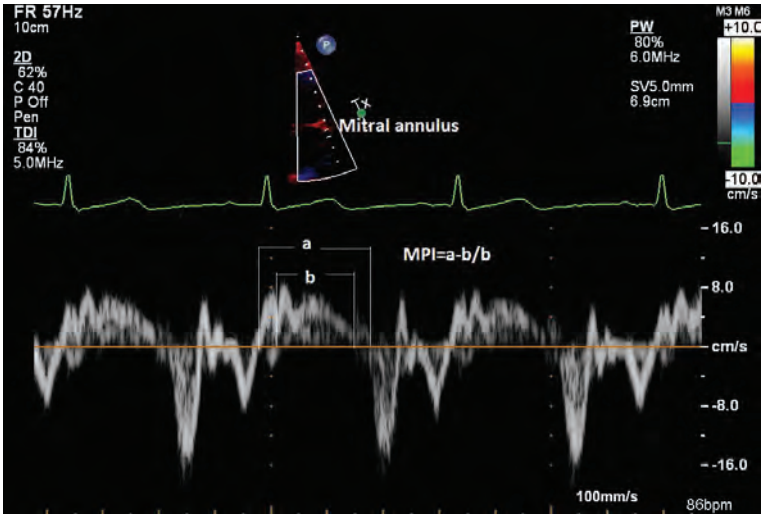

Figure 2. Left ventricular Myocardial Performance Index (MPI) calculation from mitral annulus tissue Doppler recording. The a component (isovolumic contraction time + ejection time + isovolumic relaxation time). The b component is ejection time. MPI=a-b/b

In the study of Roberson et al., [19] 80 children (age-range from 21 days to 18 years) were analyzed, with 46 of them displaying normal systolic function (EF>55%). The

normal values in this study population were displacement index 26 ±4%, with cut-off values of MADI less than 22% for myocardial dysfunction. Displacement index is not affected by age, HR, or BSA and, therefore, z-score tables or regression equation adjustments are not required. MADI also has low observer variability, is simple and rapid, and requires no complex computer analysis or special software. It can be obtained in the large majority of patients in our experience, and can be easily introduced in clinical practice [19]. MADI is similar to longitudinal LV mean Lagrangian strain and numeric values are similar as well.

Myocardial performance index

Myocardial performance index (MPI) is a measure of global myocardial performance, both systolic and diastolic. It was created by Tei et al. [53] with the idea of assessing overall cardiac function/dysfunction, bearing in mind that systolic and diastolic dysfunction frequently coexist and is widely known as a Tei Index. In fact, this is a parameter based on time intervals, used for a long time in the evaluation of myocardial function. MPI is the sum of the isovolumic relaxation time (IRT) and isovolumic contraction time (ICT) divided by ejection time (ET): MPI = (ICT+IRT)/ET. It can be determined by 3 different ECHO methods: M-mode, pulse wave Doppler (PWD) and TDI [45, 54-57]. For all 3 methods, one should measure two time intervals: the period from MV closure to the MV opening (*a* value), which equals the sum of isovolumic contraction time plus ejection time plus isovolumic relaxation time and ejection time interval (*b* value), and then calculate MPI as *a* -*b*/*b* (Figure 3).

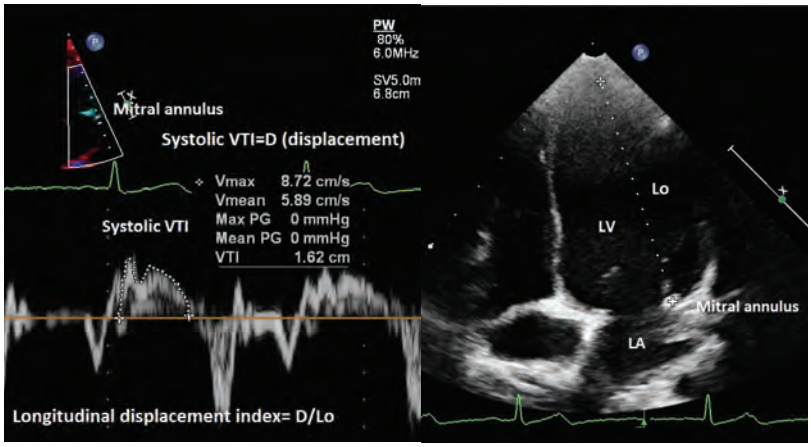

Figure 3. Method of measurement of longitudinal mitral annular systolic displacement index from mitral annulus TDI recording. LA-left atrium, LV-left ventricle, L0, distance from mitral valve annulus to LV apex at end-diastole; Systolic VTI-VTI of tissue Doppler systolic S wave.

Several studies were performed to determine the normal values of MPI in the paediatric population [42, 54–57]. Cui and Roberson [57] published normal values for

MPI in the paediatric population determined by all 3 methods and compared their result with other similar studies. There was no clinically significant dependence on age, heart rate, and BSA for paediatric patients. There were some differences between the LV MPI values for the 3 methods, as they in fact measure different time interval parameters for the *a* and *b* components of the MPI. The best method is the measuring of MPI by TDI, because it requires imaging in only one view; thus, *a* and *b* components are measured in the same cardiac cycle in all cases. Normal values of LVMPI determined by TDI ranged from 0.38±0.06 [57], to 0.42±0.09 [56]. Assuming the normal range for MPI is the mean ±2SD, the upper limit of normal for LV MPI should be considered as 0.50, determined by TDI or PWD, so the MPI value greater than 0.5 is a sign of global ventricular dysfunction [57].

MPI can be calculated for RV as well. The normal value of the RV MPI is 0.32 ±0.03 [58].

In patients with dilated cardiomyopathy, MPI is increased and has important prognostic value [59, 60].

For most patients with RV as a systemic ventricle, as with patients after Mustard repair for transposition of the great arteries, the RV is impaired. For many years these patients are asymptomatic or minimally symptomatic. MPI, NT-proBNP and VO2max are simple screening methods to assess patients with impaired cardiac dysfunction before they become symptomatic [61].

MPI has a particular value in the evaluation of heart function in patients with univentricular heart, pre or post surgery (Glenn or Fontan operation), and there appears to be a logical explanation for that fact. The majority of patients with this type of disease have a different degree and type of dysfunction – systolic and/or diastolic – and frequently have segmental wall motion abnormalities/dyskinesia. Over time their heart function usually deteriorates, but for a long time these patients are asymptomatic. There is a need for a sensitive and non-invasive method for assessment of their ventricular function. Additionally, many of these patients have a common technical limitation regarding the echocardiographic window, resulting in an inadequate visualization of the endocardial border. In routine clinical practice assessment of ventricular function is therefore subjective and semi-quantitative. In several studies related to ECHO evaluation of ventricular function of single ventricle it was found that MPI was increased. Williams et al. [62] found that MPI was significantly higher in patients with functionally single ventricle than in healthy children, but there was no difference in MP before or post bidirectional cavopulmonary anastamosis**.** Mahle et al. [63] evaluated systemic ventricular function in 35 asymptomatic patients with functionally single right ventricle, and found that MPI was significantly higher than in controls. In a large study by Rhodes et al. [5] on 416 Fontan patients, MPI was elevated, but there was no correlation between ECHO indices and CMR-derived EF. These studies all suggested that MPI is a sensitive and objective method of assessing of ventricular function in patients with single ventricles and has particular value for serial quantitative follow-up.

In conclusion, TDI is a very important tool in the assessment of longitudinal myocardial function. The suggested measurements are suitable for patients with CHD, as they are easily applicable, suitable for serial non-invasive analysis, do not rely on geometric assumptions, and are partially load-independent. This is especially important for analyzing patients with complex CHD with unusual ventricular geometry and especially the right ventricle in general. However, there are some significant intrinsic limitations of TDI velocity imaging: angle dependency, noise, and the unidimensional assessment of myocardial motion (longitudinal, circumferential, or radial). Global cardiac translation of the entire heart during the cardiac cycle also affects the measurement and tethering effects between myocardial segments. Originally it was expected that TDI would be a useful method for the assessment of regional myocardial function, but this is not the case. The main reason is that if a dysfunctional segment is moved by a healthy segment (tethering effect), regional dysfunction will be masked [64].

Deformation imaging – strain rate and strain

Previous TDI methods for analyzing myocardial function are based on motion images, where velocity and displacement are measured. In deformation imaging the basic concept is the same, but the strain rate (SR) and strain (S) are being measured. However, there are some advantages and some limitations in this new methodology in comparison with TDI.

In order to understand the concept of SR and S, one should be aware of the term of deformation. During the heart cycle ventricular walls are moving in different directions and with different velocities, meaning that the ventricular walls and the heart are deforming. Generally, during systole, the base of the heart moves toward the apex, which is stationary. There are the following main directions of wall motion and deformation: longitudinal, circumferential, and radial or transmural. Additionally, different segments of myocardium move with different velocities. For instance, the basal segment of ventricular walls moves faster than the middle or the distal segments. Upon analyzing radial (transmural) velocities of thickening and thinning, subendocardial myocardium is moving faster than subepicardial (there is transmural velocity gradient) [65]. The result of that entire phenomenon is a deformation of the myocardium, as well as the heart. Ventricular wall deformation can be shortening and lengthening, and thickening and thinning.

The essence of deformation imaging is the analysis of segmental movements. This analysis mainly provides information about regional myocardial function, but also global function as well (global and regional SR and S). It is possible to analyze deformation in all three directions, longitudinal, circumferential and radial.

Strain rate and strain are measures of deformation, not contractility. Strain rate is the velocity motion of one part of the wall, which is calculated from the difference between the velocities of surrounding parts of myocardium, thus eliminating the effect

of heart movement in the chest. Strain rate values are expressed as s^{-1}. The strain is deformation, or relative change to its original length, expressed as a percentage of change. Decrease of the dimension (shortening of the wall in longitudinal direction during systole, or decrease of the circumferential dimension during systole, as well as thinning of the wall during diastole) is marked with a negative number (has the negative sign –). Contrary increase of the dimension (lengthening of the wall in a longitudinal direction during diastole, or increase of the circumferential dimension during systole, as well as thickening of the wall during systole) is marked with positive number (has the positive sign *+)*.

There are two methods for SR and S imaging: colour TDI and speckle-tracking in 2D greyscale images. The first one is based on color TDI with the determination of velocities in predefined wall regions. This method is rather complex; the operator should be well-trained, with different software solutions and with significant inter-observer variability. There are also several intrinsic limitations of this method, such as noise, angle-dependence, etc. There are a limited number of publications in paediatric cardiology with experience in CHD [66–77]**.**

Another method, 2D speckle-tracking, is based on greyscale images. The basic principle is based on the normal presence of an irregular – random – speckled pattern in myocardium, with those speckles following the motion of myocardium. The machine recognizes speckles, then follows them and calculates new position, distance and velocity [78, 79]. This method is easier to perform, allows immediate quantification and is, therefore, more suitable for everyday clinical practice.

Normal values for SR have already been investigated in several studies. One of the largest studies was performed on 1266 healthy individuals (HUNT study), and normal values for SR and S were published. Differences in SR and S between walls are small: normal peak systolic LV SR values are around $–1±0.26$ s^{-1}, and for S –16.2–17.3±4.3% [80]. Weidemann et al. [81] published normal values of 33 healthy children for SR and S. LV longitudinal deformation was homogeneous for LV basal, mid and apical segments (peak systolic SR: $–1.9 ± 0.7$ s^{-1}, systolic S –25 ± 7%), which are higher than in the adult population.

Deformation imaging techniques (SR and S) have some important advantages over the standard ECHO techniques. The main benefit of regional S and SR lies in the rapid and objective detection of regions with delayed or decreased deformation, while for traditional ECHO methods, one has to rely on subjective assessment for this information. Another advantage of this technique is its independence of ventricular geometry; therefore, it is suitable for evaluating right ventricular function or function of hearts with single-ventricle physiology. In adult cardiology deformation imaging is extremely useful in myocardial infarction and other diseases with regional wall motion abnormalities. Unfortunately, those methods are loading-dependent and dependent of age and heart rate [66].

With regard to the assessment of global and regional myocardial deformation, deformation imaging techniques are becoming useful tools for children and adults suffering from different CHDs [*67*].

Assessment of right ventricular function in CHD is still a great challenge, and as a result, the majority of studies are performed in patients with TOF, hypoplastic left heart syndrome, or right ventricle on systemic position [68–70].

It is well known that RV function is impaired in TOF patients after surgery, but the new methodology allowed the analysis of regional wall motion abnormalities. Weidemann et al. [71] published the results of 30 asymptomatic patients after operation of TOF and found that abnormalities in RV deformation were more marked in patients with transannular patches versus infundibular patches and were associated with electrical depolarization abnormalities. From a practical point of view, in the long-term follow-up optimal timing for pulmonary valve replacement in TOF patient is still an important question. Knirsch W et al. [72] published their initial results regarding the SR and S in TOF patients following surgical replacement of the pulmonary valve. Surprisingly, 6 months after surgery, right ventricular SR and S were lower than before the operation.

Another very important group of patients are those with single-ventricle physiology, most commonly after Fontan operation. It is well known that their long-term outcome largely depends on ventricular morphology and ventricular function [73, 74]. Many studies have shown worse systolic and diastolic function in patients with the right ventricular morphology in comparison with the left one [75, 76]. Recently, Petko et al. [77] published a study about longitudinal myocardial deformation and dyssynchrony in children with left and right ventricular morphology after the Fontan operation by speckle-tracking. The global longitudinal S and SR were similar in left and right ventricular morphology patients in the early period after Fontan operation, reflecting similar adaptation of longitudinal function of both ventricular morphologies to the single-ventricle circulation. Clearly, more studies and experience are necessary in order to better understand the mechanisms of heart dysfunction and the usefulness of new diagnostic methods.

Conclusions

Echocardiography is currently the most widely used method in the assessment of ventricular function. There is no single ideal technique or parameter for this purpose, so the combination of several of them is necessary in order to have more comprehensive information about different aspects of heart function. Besides the traditional methods, with a long-lasting experience in clinical practice, new techniques should be introduced in clinical routine. Evaluation of longitudinal myocardial function is crucial, especially in patients with CHD, using methods like tissue velocities, strain, and strain rate. Their high temporal resolution, relative independence from volume-loading and ease of acquisition are significant benefits. It is important to stress that

serial evaluations are important. Each ECHO laboratory should introduce the set of parameters for assessment of ventricular function, so as to be able to select the right one for different clinical settings and to be able to achieve the right perception of their values. This article has attempted to suggest the group of parameters most suitable for patients suffering from CHD with different ventricular geometries.

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PAEDIATRIC ELECTROPHYSIOLOGY: WHERE DO WE GO TO?

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Abstract

Radiofrequency catheter ablation has become the first-line curative therapeutic modality of symptomatic patients in adults and children. The success rate of the ablation procedure is high and severe complications are uncommon. However, patients with CHD and SVT who undergo RF ablation have diverse anatomic and arrhythmia substrates. Compared to patients with anatomically normal hearts, this special population has a lower acute success rate. We will present our experience over the last decade and will specially focus on the most recent technical developments. In conclusion, radiofrequency catheter ablation recently is a reliable and safe tool. However, further advances in technology will open new indication fields, i.e. the epicardial approach for successful ablation in Brugada patients.

INTRODUCTION

Radiofrequency catheter ablation has become the first-line curative therapeutic modality of symptomatic patients in adults and children. The success rate of the ablation procedure is high and severe complications are uncommon. However, patients with CHD and SVT who undergo RF ablation have diverse anatomic and arrhythmia substrates. Compared to patients with anatomically normal hearts, this special population has a lower acute success rate. We will present our experience over the last decade and will specially focus on the most recent technical developments.

METHODS

The study design was a retrospective cohort study of consecutive children undergoing electrophysiology (EP) studies with or without radiofrequency ablation (RFA) at a tertiary care paediatric cardiology centre during the last decade. Medical records and EP studies data of all patients were reviewed, demographic and procedural variables

retrieved from this data and transferred into case report forms. The study protocol was approved by the local ethics committee (ethics committee of the Medical University of Vienna).

1. RESULTS

1.1 Patient demographic characteristics

A total of 317 children underwent EP study with or without RFA. One-hundred-fifty-nine patients (50.2%) were females, median age at time of EP study was 13.7 years (minimum 0.7; maximum 18.6) and median body weight was 49 kg (11; 105). Two patients were infants, seven patients (2.2%) were between 1 and 5 years, 73 patients between 6 and 10 years (23%), 118 patients (37.2%) between 11 and 14 years, and 117 patients (36.9%) between 15 and 18 years. Twenty-nine patients (9.1%) had congenital heart defects as underlying disease.

1.2 Procedural data

EP studies were performed under general anaesthesia in all patients. Vascular access was achieved via femoral vessels on both sides. Median fluoroscopy time was 12 minutes (1 – 104 min).

1.3 EP-studies results

As most frequent diagnosis, atrio-ventricular re-entry tachycardia (AVRT) was found in 49%, while in another 29%, atrio-ventricular nodal tachycardia (AVNRT) could be documented. Only 4% of EP studies (all of them performed in patients with syncope) were without pathological findings.

1.4 Radiofrequency ablation outcome

Of the 317 study patients undergoing EP studies, RFA was performed in 292 patients (295 diagnoses), while 27 patients (28 diagnosis) underwent EP study only. Radiofrequency ablation was successful in 279 patients (96.2%) for 283 EP diagnoses (95.9%), while in 11 patients (3.8%) with 12 EP diagnoses (4.1%), successful ablation of the arrhythmogenic substrate could not be achieved. Table 1 gives an overview of primary success of RFA.

1.5 Complications of EP studies and RFA

Overall mortality after EP study or RFA was 0%. There were five cases (2.9%) of complications associated with the procedure itself. In one infant of seven months, pericardial haemorrhage occurred during the EP study and surgical drainage of the pericardial effusion was needed. In four patients, vascular complications of the femoral vessels at puncture site occurred (one pseudoaneurysm, three arteriovenous fistulas).

Conclusion

Radiofrequency catheter ablation recently is a reliable and safe tool; however, further advances in technology will open new indication fields, i.e. the epicardial approach for successful ablation in Brugada patients.

Table 1. Primary successful ablation procedures in 292 paediatric patients.

	n	**successful**	**failed**
Total	292	289	3 (1%)
AVRT (Bypass tract)	160	159	1 (0.6%)
AVNRT	92	92	0
VT, VES, Outflowtract-ES/-VT	14	13	1 (7%)
Artial Flutter / - Fibrillation	9	9	0
EAT	7	7	0
PJRT	4	4	0
Mahaim-pathway	4	4	0
Inappropriate ST	2	1	1

COARCTATION OF THE AORTA

Bo Sahlgren

Abstract

This "simple" condition still raises many questions. Johan Meckel published 1768 "narrowing of the aortic conduit". 1944 was the first successful surgical repair performed by Clarence Crafoord and Robert Gross independently. In the 70-ties balloon angioplasty started and the development of transcatheter treatment is still in progress. The transcatheter treatments have become the treatment of choice for "simple" coarctation but surgical repair still has an important role.

Congenital coarctation (CoA) involves with very rare exceptions thickening of the media forming a ridge protruding from the posterior and lateral wall into the lumen. Further narrowing occurs with additional thickening of the intima. This narrowing occurs usually juxtaductal, opposite the position of ductus arteriosus. The constriction is almost always distal to the left subclavian artery but the origin of this vessel could be involved. Left ventricular afterload is increased by the mechanically induced resistance and the resistance associated with high blood pressure proximal to the constriction. The higher wall tension causes left ventricular hypertrophy. Proximal systolic hypertension and distal hypertension in varying degree is always present as well as change in the arterial waveforms above and below. The arterial pressures are not affected until reduction of lumen by 45–55%. Distally the systolic and diastolic blood pressure decreases gradually with less change in diastolic pressure producing narrow pulse pressure. Development of collateral vessels makes the alterations in blood pressures less pronounced. Primarily they arise from branches of the subclavian vessels, internal mammary arteries, intercostal and spinal arteries. Besides the mechanical obstruction with reduced aortic distensibility not fully compensated by proximal vessels, also resetting of baroreceptors and renal factors most likely contributes. The clinical picture is different in newborns and infants compared to older individuals.

Treatment: In the neonate prostaglandin dilates the arterial duct permitting flow via the ductus beyond the obstruction. Congestive heart failure is treated with furosemid, digoxin, vasoactive amines, phosphodiesterase inhibitors and calcium sensitizers. If blood pressure elevation is so severe that it requires treatment by pharmacological means, surgery is preferable.

Three methods are preferred 1) Resection and end-to-end anastomosis (standard method) 2) subclavian flap aortoplasty 3) synthetic patch aortoplasty. The surgical approach is usually from left posterolateral thoracotomy through the fourth left intercostal space. If additional

intracardiac repair is necessary the approach is through sternotomy. Balloon-angioplasty has been performed since approximately 1982. Percutaneous transluminal angioplasty was first demonstrated to be effective in restenosis after surgery. There may be protection against rupture of the aorta by post-operative scarring and in the aortic wall. A tear in the intima and partially in the media is required for a good result. The inflation diameter should be 2.5 times the narrowest diameter or 1–2 mm greater than the aorta diameter at the base of the subclavian artery but should not exceed the aortic diameter of the descending aorta at the level of the diaphragm. The dilation of the aorta is painful. Two balloons could be used to keep the femoral vascular trauma low.

Stenting of recoarctation as well as primary coarctation has become more and more popular. With the introduction of covered stents the risk of bleeding from wall rupture has been reduced and the stents also permit exclusions of aneurysms. Essentially the risks are stent-migration, damage to the femoral arteries and the same as with surgery. The stents need to be expandable to the normal size of the vessel in adulthood and the size of the equipment does not allow stenting of coarctation in children younger than approximately 10 years. Bare metal stents have also been used proximal to the isthmus across the subclavian and carotid artery. In rare cases, covered stents have been used also across the offspring of the subclavian artery when there has been proof of capacity of the circle of Willisi to provide collateral flow to the arm.

This "simple" condition still raises many questions. This spans from the aetiology and pathophysiology to the treatment.

HISTORY

Johan Meckel published 1768 "narrowing of the aortic conduit". 1944 was the first successful surgical repair performed by Clarence Crafoord and Robert Gross independently. In the 70-ties balloon angioplasty started and the development of transcatheter treatment is still in progress. The transcatheter treatments have become the treatment of choice for "simple" coarctation but surgical repair still has an important role.

Etiology and Anatomy

Congenital coarctation (CoA) involves with very rare exceptions thickening of the media forming a **ridge** protruding from the posterior and lateral wall into the lumen. Further narrowing occurs with additional thickening of the intima. This narrowing occurs usually juxtaductal, opposite the position of ductus arteriosus. The constriction is almost always distal to the left subclavian artery but the origin of this vessel could be involved.

Tubular hypoplasia is a combination of small diameter and abnormal length involving the transverse arch and/or the isthmus. Isolated tubular hypoplasia does not include the ridge in isthmus and the media in this region is normal. In infants The

length of the distal arch-segment (between left subclavian and left carotid artery) the proximal arch segment (between the left carotid and innominate artery) and isthmus should each not exceed 5 mm. Compared to the ascending aorta, the relative diameter of the segments should be: proximal arch 60%, distal arch 50% and isthmus 40%.

Associated Malformations

Bicuspid aortic valve: The most frequent lesion (13–85% in lit.) Mitral valve malformation of a wide spectrum to Shones syndrome with left heart obstruction in multiple sites.

Ventricular septal defect(s): The clinical manifestations when the VSD is moderate or large shift from high left ventricular afterload to more of left to right shunting and failure. This should be considered when examining newborns. The incidence of CoA is also increased with AVseptal defects and cyanotic VOC as Truncus arteriosus, TGA and DORV of Taussig-Bing type

Epidemiology and Genetics

CoA is present in 5–8% of VOC patients. Males dominate (2/3), less so in more complicated Coarctation syndrome, and abdominal CoA is more frequent in females. Seasonal peaks indicate some possible environmental influence. In full XO Turners syndrome an incidence of 15–20% is reported but mosaic forms have less incidence. Rare familial occurrence has been reported.

Embryology and Pathogenesis

Smooth muscle from the ductus extends into the aorta and ductus closure can unmask a CoA but is unlikely the sole cause of aortic constriction. The shelf in the aorta is a constant finding and is proposed to develop from pathological intrauterine conditions. Theoretically intrauterine shift in flow from the left to the right ventricle decreases the flow in isthmus which may become underdeveloped.

Physiology

Left ventricular afterload is increased by the mechanically induced resistance and the resistance associated with high blood pressure proximal to the constriction. The higher wall tension causes left ventricular hypertrophy. Proximal systolic hypertension and distal hypertension in varying degree is always present as well as change in the arterial waveforms above and below. The arterial pressures are not affected until reduction of lumen by 45–55%. Distally the systolic and diastolic blood pressure decreases gradually with less change in diastolic pressure producing narrow pulse pressure. Development of collateral vessels makes the alterations in blood pressures less pronounced. Primarily they arise from branches of the subclavian vessels, internal mammary arteries, intercostal and spinal arteries. Besides the mechanical obstruction

with reduced aortic distensibility not fully compensated by proximal vessels, also resetting of baroreceptors and renal factors most likely contributes. Experimental work in rats showed an increased blood pressure response to angiotensin II bolus, increase in renal vascular resistance and change in regulation of renal angiotensin II receptors. Constriction of the aorta distal to the takeoff of the renal arteries resulted only in decrease in the blood pressure in the femoral artery but the proximal pressure was normal. In dogs the blood pressure was normalized when the kidneys were transplanted to vessels proximal to the induced constriction of the aorta. Inconsistent data regarding the renin activity and actual angiotensin II levels in man indicate a more complex role of the Renin-Angiotensin system.

Clinical features

The clinical picture is different in newborns and infants compared to older individuals.

Coarctation past infancy

Symptoms: Most patients with isolated CoA have no cardiac symptoms. Minor complaints as cold feet and leg cramps seem more frequent. Par aesthetic pain and muscle weakness may occur in the lower extremities reflecting more likely compression of the spinal cord by a dilated anterior spinal artery or one of its branches impinging upon a nerve root exiting the vertebral canal rather than poor blood flow. Nose bleeds and headaches are seen. Claudicatio with sharp pain in the lower extremities limiting exercise makes abdominal coarctation more likely. Collaterals are more difficult to develop in the abdomen.

Physical examination

Reduced femoral pulses and hypertension are the most common findings that lead to further examination. In the lower extremities the blood pressure is low or hard to measure. Hypertension is almost always present. Turners' syndrome is recognized by short stature, webbed neck and shield chest and is associated with CoA. Difference in blood pressure between arms occur and depends on the relation of origin of the vessels in relation to the CoA and possible involvement of the left subclavian artery in the constriction – both left and right arm pressure as well as the pressure in the leg can in rare occasions be low and the pulses should then be compared with the carotid pulses. Murmur are best heard posterior on the left chest medial to the scapula, left infraclavicular area and axilla. Continuous murmurs due to collaterals can also be heard both anteriorly and posteriorly. Murmurs could be absent of atresia or low cardiac output and severe obstruction. Pulsating interscapular arteries with palpable or visible collaterals in the interscapular region are rare in childhood. Simultaneous palpation of brachial and femoral vessels may reveal delay of femoral pulses even if well developed collaterals or mild obstruction may permit palpable femoral pulses.

ECG

ECG is often normal in children even with significant CoA. Signs of left ventricular hypertrophy with increased voltage in left precordial leads may develop. Right bundle branch block is seen in approximately 50% of adults and older children and possibly reflects progression of neonatal ventricular hypertrophy.

Chest Roentgenography

The size of the heart is normal or mildly increased with left ventricular contour. In some patients the *3-sign* or double aortic curve as a result of pre- and poststenotic dilatation can occur. Rib notching is practically pathognomonic of thoracic CoA and its incidence increases with age.

Echocardiogram

Left ventricular wall thickness is increased reflecting the increased afterload. Suprasternal and high left views may show the CoA. It is important to examine the mitral valve, left ventricular thickness and shortening fraction, left ventricular outflow tract and the abdominal aorta. Magnetic Resonance Imaging and CT-scan:

This gives information of the degree of the coarctation, the localization and relation to the subclavian and carotid arteries and any collaterals. This is used to plan any catheter intervention or surgery. Any concomitant aneurysms, heart malformation and possible left ventricular hypertrophy could be detected. When considering more complex interventions, the course of vertebral arteries and the patency of circulus willisii are valuable information. The spinal blood supply is usually not seen but can hopefully be elucidated in a simple way in the future.

Cardiac catheterization and Angiography

Usually the indication for any treatment can be established by non-invasive studies and catheterization and angiography (in more modern labs - rotational angiography) is used for guiding and ascertaining the indication for intervention by estimation of the gradient. All factors with reduced cardiac output such as severe aortic valve obstruction, myocardial disease or anaesthesia per se, will reduce the gradient even if the obstruction is severe.

Coarctation in infancy

Often occurs in combination with other malformations e.g. VSD. In the majority of symptomatic cases there is varying degrees of pulmonary hypertension though seldom to super systemic levels. Different criteria are used to differentiate normal tapering of the aorta and coarctatio. Taussig suggest that the isthmus is not abnormal until it is narrowed to the width of one carotid artery. Moulaert concluded that the diameter of the isthmus should be less than 40% of the ascending aorta. The haemodynamics vary depending on site and severity of aortic obstruction, associated defects and any contribution of flow in the duct. In isolated CoA with a ledge

proximal to the duct a critical resistance to left ventricular emptying occurs only after birth when the ductus closes and runoff to the lower resistance pulmonary bed is abolished, resulting in severe left-sided congestive failure. This results in a clinical presentation of an infant in respiratory distress with severe cardiac failure. If the cardiac output is seriously impaired, a murmur may not be present until improvement of the cardiac output. With right to left shunt over the duct differential cyanosis occur with cyanosis more pronounced in the lower part of the body. With a coexisting VSD the symptoms are mainly those of large left to right shunting. The combination in an infant with CoA and heart failure imposes a high suspicion of associated defects. The anatomical and physiologic complexity of CoA is high in infancy. ECG: In isolated CoA there are signs of right ventricular hypertrophy or right bundle branch block. Left ventricular ECG-changes are uncommon in the neonate but left ventricular strain may reflect the increase in left ventricular afterload occurring with closure of the duct.

Echocardiogram: Increase in LV wall thickness may be seen. In failing children a dilated poorly contracting left ventricle is seen which also could be the case in cardiomyopathy or endocardial fibroelastosis. The changes are reversed after relief of the obstruction. Chest X-ray: The changes vary with associated defects from increased vascularisation as a sign of left to right shunting to venous congestion seen in severe coarctation or lesions with left heart obstruction. Rib notching is extremely rare.

Cardiac catheterizations are risky and should be avoided unless non-invasive examinations are not conclusive.

Unusual Coarctation

Atypical locations are ascending aorta, transverse arch and abdominal aorta. Multiple sites of obstruction are extremely rare. Abdominal CoA is more common in females. There are sometimes murmurs over the abdomen. Leg cramp and Claudicatio occurs. The obstruction is usually longer and is usually associated with *Takayasus syndrome* with marked intimal hypertrophy alternating with areas of aneurysm. When involving the upper extremity pulses and renal arteries, but sparing the femoral arteries, it can give reduced upper pulses but palpable femoral pulses and lower extremity hypertension – reversed coarctation. In *Pseudocoarctation or "kinked aorta"* the aorta is elongated and tortuous producing a kinking in the vessel. There is a medial ridge and probably a mild form of coarctation. Multiple sites of obstruction are rare as well as functional coarctatio produced by extrinsic compression.

Natural history

The lifespan is reduced with reported 90% mortality by age of 50 and the mean age of death being 35 years. Causes of death were intracranial haemorrhage (11%), aortic rupture or dissection (23%), endocarditic (22%) and congestive heart failure (18%). Berry aneurysms in the Circle of Willis are thought to occur in 10% of

patients with CoA. Cerebral haemorrhage in neonates with CoA is extremely rare. Dissection and rupture during pregnancy in patients with CoA is rare but is the main hazard in this situation.

Treatment

Medical

In the neonate, prostaglandin dilates the arterial duct permitting flow via the ductus beyond the obstruction. Congestive heart failure is treated with furosemid, digoxin, vasoactive amines, phosphodiesterase inhibitors and calcium sensitizers. In children, medication may be discontinued as collaterals develop. If blood pressure elevation is so severe that it requires treatment by pharmacological means, surgery is preferable.

Surgical Therapy

Earliest method of repair in an experimental animal was reported by Blalock and Park 1944. Surgical correction in humans was first performed by Crafoord and Nylin in1944 in Sweden and by Gross and Huffnagel in 1945. Surgical treatment of coarctatio in an infant was first reported by Kirklin et al. 1952. Surgery could be performed when collaterals were well developed. Three methods are preferred 1) resection and end-to-end anastomosis (standard method) 2) subclavian flap aortoplasty 3) synthetic patch aortoplasty. The surgical approach is usually from left posterolateral thoracotomy through the fourth left intercostal space. If additional intracardiac repair is necessary the approach is through sternotomy. When a Dacron patch was used, the late aneurysm was a late and serious complication.

Interventional catheterization

Balloon-angioplasty has been performed since approximately 1982. Percutaneously transluminal angioplasty was first demonstrated to be effective in restenosis after surgery. There may be protection against rupture of the aorta by post-operative scarring and in the aortic wall. A tear in the intima and partially in the media is required for a good result. The inflation diameter should be 2.5 times the narrowest diameter or 1–2 mm greater than the aorta diameter at the base of the subclavian artery, but should not exceed the aortic diameter of the descending aorta at the level of the diaphragm. The dilation of the aorta is painful. Two balloons could be used to keep the femoral vascular trauma low.

Stenting of recoarctation as well as primary coarctation has become more and more popular. With the introduction of covered stents the risk of bleeding from wall rupture has been reduced and the stents also permit exclusions of aneurysms. Essentially the risks are stent-migration, damage to the femoral arteries and the same as with surgery. The stents need to be expandable to the normal size of the vessel in adulthood and the size of the equipment does not allow stenting of coarctation in children younger than approximately 10 years. Bare metal stents have also been used

proximal to the isthmus across the subclavian and carotid artery. In rare cases covered stents have also been used across the offspring of the subclavian artery when there has been proof of capacity of the circle of Willisii to provide collateral flow to the arm.

Complications

Surgery: Recurrent laryngeal nerve injury, phrenic nerve injury, bleeding from collateral vessels and from the high pressure aortic suturline, chylothorax, postcoarctectomi syndrome (mesenteric arthritis), paradoxical post-operative hypertension and spinal cord ischemia with transient or permanent paralysis.

Interventions: Balloon-angioplasty is associated with immediate and late aneurysm formation. When late repair of this is done, the collaterals may have regressed and perfusion to the lower body may be needed. Paradoxical hypertension is rare.

THE ROLE OF DEFIBRILLATORS IN CHANNELOPATHIES

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The channelopathies, a group of disorders that can cause sudden death, may affect children and adults. Patients may be identified when investigated for loss of consciousness or by screening. These disorders cause ventricular tachycardia and ventricular fibrillation which in many cases can be aborted by shocking. Implantable defibrillators may be life-saving but may also be responsible for complications that can significantly impact on quality of life. Decisions are challenging as some patients are at higher risk than others. Defining who will benefit from a defibrillator is difficult and the stakes are high.

When considering whether to implant a defibrillator in a young patient it is important to weigh up the risks and benefits for that patient as an individual. Children and younger patients have a greater number of problems with defibrillators than their older counterparts due to lead fracture, inappropriate shocks and implant/device related complications. Inappropriate shocks can be extremely difficult for the patient.

The channelopathies have been called the "silent assassins" as they can present in an otherwise healthy person with a sudden and unexpected lethal arrhythmia, leaving no trace at subsequent autopsy. These disorders may be inherited or arise de novo in the patient and therefore screening of family members of affected patients plays an important part of management. The best known channelopathies are long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia.

Perhaps the best known channelopathy is long QT syndrome, estimated to affect 1:2000 people. Twelve different types have been described based on the genes identified to be causal. Most genes recognised code for proteins involved in the function or architectural make-up of ion channels responsible for ion movement within the myocardial cell. The different genetic types differ in their clinical course, morphology on ECG, trigger for arrhythmia and response to therapy.

Types 1, 2 and 3 account for 90% of genotyped Long QT syndrome and have been most studied. With the help of international registries established, we now have a greater understanding of many aspects of the condition. Risk stratification is important to enable us to identify patients who are not protected by beta blocker therapy alone and who might need an implantable defibrillator. Age and gender play a part in determining risk but perhaps the most important is QT length itself. High risk groups include: male children, adult women with Long QT 2 and patients with a QTc > 500. It would seem that Long QT 3 patients derive less protection from beta blockers. Recent research in Long QT 2 has shown that the position of the mistake in the protein, i.e. the individual mutation location, can give us further guidance in terms of risk and response to therapy. Those patients who have inherited or are born with two mutations are at risk, often present in infancy.

Peter Schwartz published the results of the European Long QT registry patients implanted with a defibrillator in 2010. 91% of recipients had been symptomatic with approximately half being survivors of cardiac arrest. However 9% were asymptomatic many of whom were long QT 3. 28% of patients received an appropriate shock, but in 11% they were inappropriate.

Brugada et al. described another channelopathy which is thought to account for the greatest number of sudden adult deaths. The only proven effective therapy is an implantable defibrillator and so those considered to be at high risk will benefit. Those at low risk may have a two and a half times greater risk of having an inappropriate than an appropriate shock in addition to other defibrillator complications. Risk stratification in Brugada syndrome is less clear than in long QT. Those survivors of a prior VF arrest would appear to be at high risk and should therefore have a defibrillator. Those who have had syncope or ventricular tachycardia also appear to be at high enough risk to make implantation of a defibrillator beneficial. Those asymptomatic patients either with a type 1 ECG at rest or revealed on administration of a drug are difficult to assess and the risk-benefit ratio of defibrillator implantation is controversial. Children may be affected by Brugada syndrome and although in general perceived to be at lower risk than adults can still be at risk. Decisions for this group are even more difficult.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is more likely to present in childhood than adult life with exercise related syncope or sudden death. Early recognition and intervention is very important to save lives. With a normal resting ECG the condition may be mistaken as epilepsy. Beta blockers are the treatment of first choice and many derive good protection, but not 100%. For those refractory to beta blocker therapy or those unable to tolerate beta blocker, left cardiac sympathectomy and/or a defibrillator needs to be considered. However, defibrillators are less than ideal therapy for this condition. The rhythms encountered are more diverse in CPVT and are difficult for current defibrillators to recognise correctly and accurately, leading to a high risk of inappropriate shocks. Arrhythmia may be self terminating so a defibrillator should be programmed to allow for this rather than

shocking early, this goes some way to limiting unnecessary shocks. Moreover arrhythmias seen in CPVT are often triggered as opposed to re-entry in mechanism so may not always respond to shocking.

Once the decision to implant is made, the type of defibrillator needs to be chosen. A conventional defibrillator with intracardiac lead can be employed from about 7 years upwards. In a small child an epicardial system needs to be considered. Because of the problems with intracardiac leads, the subcutaneous defibrillator has been developed and can be considered in children >30kg. With every device careful programming is an absolute requirement to attempt to limit inappropriate shocks.

In conclusion, the decision to implant a defibrillator needs to be made after careful definition of the individual patient's own risk. Choice of device is important. Strategies to reduce device related risks should be employed. Careful programming is imperative. Other therapies should be used alongside defibrillator therapy to limit the number of shocks required. With great care defibrillators can be used in affected children to save lives.

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ADULT PATIENTS WITH FALLOT'S TETRALOGY: NATURAL HISTORY, LATE OUTCOME AFTER OPERATION AND RV- LV INTERACTION

Jochen Weil

Abstract

Tetralogy of Fallot (TOF) is the most frequent cyanotic congenital heart disease. According to a recent prospective study on the prevalence of congenital heart diseases in Germany, 2.5% of all neonates suffer from TOF [1].

Without treatment this frequent occurring CHD has a high morbidity and mortality. Surgical treatment has improved this grim outlook dramatically.

In the following, the rate of survival and morbidity of the natural and unnatural history will be summarized.

Natural history

The degree of central cyanosis in patients with TOF depends on the severity of the RVOTO. In early infancy the cyanosis might be less significant, but with increasing age the RVOTO becomes more severe and the patient more cyanotic.

Before the era of palliative or corrective surgery the mortality and morbidity of unoperated patients was high.

In 1978 E.G. *Bertranou and coworkers* [2] analysed all published autopsy cases of patients with TOF who died without surgical treatment to determine the life expectancy of such patients. These data were compared with a study of patients living in Denmark in 1949 [3]. The rates of survival according to these two sources were remarkably similar. According to these data 75% of patients with TOF and pulmonary stenosis were alive at age 1 year, 60% at 3 years and 30% at age 10 years (Figure 1).

In the subset of patients with TOF and pulmonary atresia the survival rates were lower than in patients with pulmonary stenosis indicating that only 66% of patients were alive at age 6 months, 50% at 1 year, 33% at 2 years and 8% at age 18.

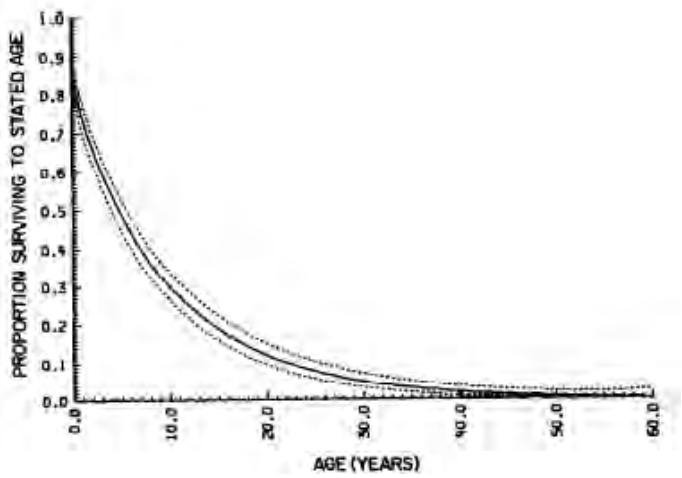

Figure 1: Life expectancy of persons with Tetralogy of Fallot without pulmonary atresia (After Bertranou et al. (1978) Life expectancy without surgery in Tetralogy of Fallot. Am J Cardiol 42(3):458-66, with permission)

These data were comparable to other publications. *M. Samanek* [4] studied the probability of survival in non operated children with CHD in Bohemia. For the patients with TOF, the actuarial survival rate at 1 year was 64%, at 5 years 49%, at 10 years 23% and only 4% at 15 years. *M. Campbell* [5] found the mean age at death in Fallot's Tetralogy of 8, 9 years.

There are several case reports on individuals with non treated TOF and unusual longevity such as the report on the American composer Mr. Henry Gilbert who died 8 days following left hemiplegia within a few months of his 60th birthday [6].

Morbidity in adult survivors of TOF without surgery is high. The chronic hypoxemia results in exercise of intolerance and excessive erythrocytosis with an increased risk of thrombosis. Cerebral abscesses are frequent since infectious agents can easily reach the brain via right to left shunting on ventricular level. The risk of thrombosis and brain abscess is increased in the presence of iron deficiency due to the impaired rheology.

Death occurs frequently secondary to RV failure due to long standing RV pressure load and secondary to endocarditis or to arrhythmia.

Patients with repaired TOF

The introduction of surgical repair of TOF has dramatically improved the survival and decreased the morbidity in these patients.

There are a number of issues which are important to consider for the long-term care of adult patients surviving surgical repair of TOF.

The following issues are dealt in this chapter:

– Survival
– Reoperations
– Changes of left heart

The issues of pulmonary valve regurgitations with requirement of pulmonary valve replacement, arrhythmia and sudden death are covered in the respective chapters.

Long-term survival after repair

It is obvious that the era in which a patient was operated would influence the outcome, as well the age in which the patient underwent the repair.

Kirklin and co-worker [7] reported a hospital mortality of 50% in 1955 and 15% in 1960. Nowadays the hospital mortality will be <5% in patients after repair in most centres [8].

There are several recent publications reporting an excellent survival over 3 decades after successful operation or primary repair.

Murphy and co-workers [9] reviewed the records of all patients who underwent complete surgical repair of TOF at the Mayo Clinic (USA) between 1955 and 1960 and survived the immediate (30 days) postoperative period. The overall 32 years actuarial survival rate among 163 patients was 86% as compared with an expected rate of 96% in a control population matched for age and sex (Figure 2).

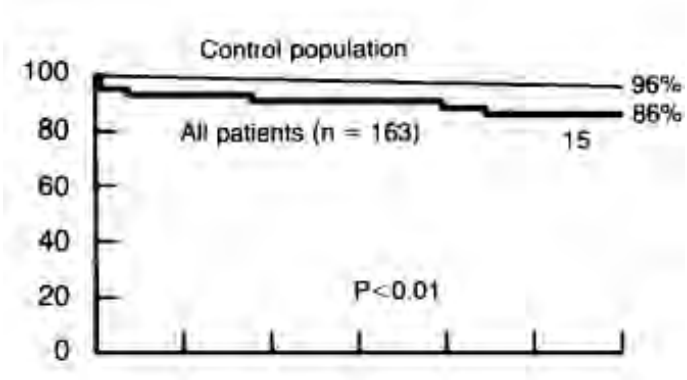

Figure 2: Long-term survival of patients with complete repair of Tetralogy of Fallot who survived the immediate postoperative period.

This panel shows the actuarial survival rate up to 32 years after surgery for all patient groups combined and the expected survival rate in an age- and sex-matched control population. (After Murphy et al. (1993) Long-term outcome in patients undergoing surgical repair of Tetralogy of Fallot. Engl J Med 329:593–599, with permission)

The survival rates among patients less than 12 years of age ranged between 90 and 93% which was slightly less than the expected rates. Among patients 12 years old or older at the time of surgery the survival rate was only 76% as compared with an expected rate of 93%. Primary palliation with a Blalock-Taussig shunt before repair was not associated with a reduced long-term survival nor was the need for a transannular patch at the time of surgery. A systolic RV-LV pressure ratio of 0.5 and more was predictive of a higher mortality during the first 20 years after surgery (92% versus 88% after 20 years).

Most patients had a good functional status with 77% in New York Heart Association (NYHA) functional class I, 17% in class II and 6% in class III at the late follow-up examination. Late sudden cardiac death occurred in 10 patients.

This study provides evidence that the rate of long-term survival – even in the earliest era of open heart surgery – is excellent, but remains lower than in the general population. The actuarial survival rate was 90% of the expected survival rate. The late functional status was also excellent. The occurrence of late sudden cardiac death accounted for approximately half of all late deaths.

Similar good long-term results were reported by *Nollert and co-workers* [10] in 490 patients who were operated from 1958 to 1977 and survived the first year after surgical repair. They found actuarial 10–, 20–, 30– and 36 years survival rates of 97%, 94%, 89% and 85% respectively. The most common cause of death was sudden cardiac death (n=13) followed by congestive heart failure (n=6).

It is important to realize that the mortality increased 25 years after surgery from 0.24% to 0.94% per year which emphasizes the need for close life-long follow-up examinations (Figure 3).

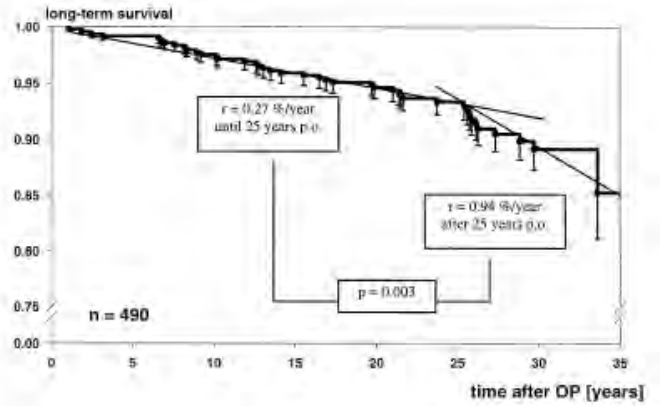

Figure 3: Long-term survival after correction of TOF. All patients who died within the first year after correction were excluded for calculation of long-term survival. The curve shows two different phases that are distinct. The early, low first phase lasts 25 years; thereafter, the risk increases significantly. Mortality risk (r) per year, as a linearized number, is calculated for each phase. Note the break in the y axis. OP = operation; p.o. =

postoperatively. (After Nollert et al. (1997) Long-Term Survival in Patients with Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year after Surgical Repair. JACC Vol. 30, No. 5:1374–83, with permission)

In the Single centre 50 years' experience with surgical management of Tetralogy of Fallot, *Lindberg and co-workers* [8] reported the long-term outcome in 570 patients showing that there was no difference in security from death or reoperation following primary repair versus primary palliation (Figure 4). This finding was in agreement with the previous publications by *Nollert and co-workers* [10].

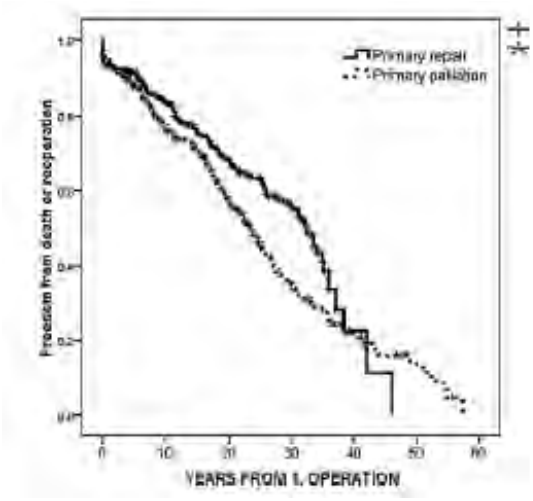

Figure 4: Long-time follow-up after different approaches in surgical treatment, primary repair or primary palliative surgery. (After Lindberg et al. (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

Furthermore it was shown that there was no difference in long-term survival between patient with and without transannular patch [8, 11,].

Reoperations

The long-term survival of patients after repair for TOF is excellent; these patients however continue to be at risk for long-term morbidity. With increasing length of follow-up from the time of primary surgery, problems will occur such as

– stenosis of the RVOT
– pulmonary valve regurgitation
– branch pulmonary arteries
– regurgitation of tricuspid valve

These problems may be well tolerated for the early years after operation, but with longer period of long-term follow-up there is an increased risk for ventricular and supraventricular arrhythmia, heart failure and sudden cardiac death.

Reoperations are required in about 10–30% of patients with TOF during long-term follow-up [9, 12, 13, 14].

The group from the Toronto Congenital Cardiac Centre for Adults reviewed its experience with reoperation in adults who got their primary repair at a mean age of 13.3 years [12]. Out of a total of 330 patients with repaired TOF over 18 years of age, 60 consecutive patients underwent reoperation between 1975 and 1997. Mean age at reoperation was 33.3 years and the mean follow-up after reoperation was 5 years.

The most common indication for reoperation was complications of the RVOT in 75% of patients. Severe pulmonary valve regurgitation (38%) and conduit failure (22%) were the most frequent problems of the RVOT. Less frequent indications were a significant leak after patch closure of the VSD and severe tricuspid valve regurgitation.

A bioprosthetic valve to reconstruct the RVOT was used in 42 out 60 patients. The number of reoperations increased in the recent years. Within the last 6 years (1990–1996) 72% of all reoperations were performed (Figure 5).

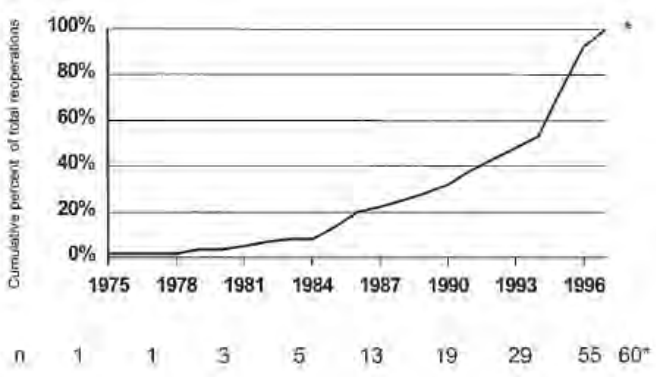

Figure 5: Cumulative percent of reoperations from 1975 until March 1997. There is a marked increase of reoperations in recent years. N indicates numbers of reoperations. Asterisk denotes March 31, 1997 (After Oechslin et al. (1999) Reoperation in adults with repair of Tetralogy of Fallot: indications and outcomes. J Thorac Cardiovasc Surg 118(2):245–51, with permission)

There was no perioperative mortality. The most recent follow-up examinations revealed excellent results after reoperation: 93% of the patients were in NYHA classification I or II. Actuarial 10-year survival reached 92% (Figure 6).

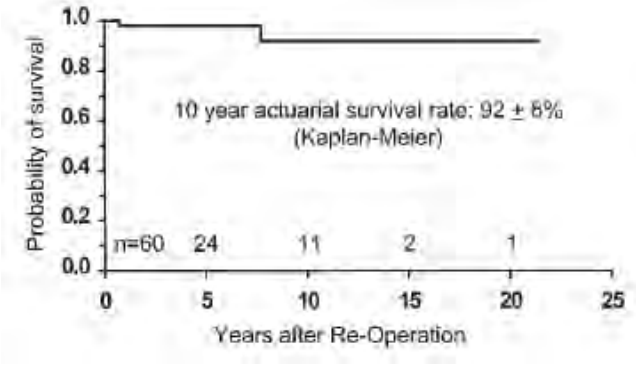

Figure 6: Kaplan-Meier actuarial survival analysis for patients after reoperation. N represents the number of patients entering each time interval. (After Oechslin et al. (1999) Reoperation in adults with repair of Tetralogy of Fallot: indications and outcomes. J Thorac Cardiovasc Surg 118(2):245–51, with permission)

In an earlier retrospective study from the Mayo Clinic (USA), a reoperation rate was found in 10% (16 patients) of 163 survivors who had their repair between 1955 and 1960 [9]. At that time the principal reasons for late reoperations were residual ventricular septal defects (10 patients) and false aneurysm of the pulmonary outflow tract (3 patients). Only 2 out of 16 patients requiring reoperations got a valve replacement for severe pulmonary valve insufficiency.

The use of a transannular patch does not influence the long-term survival, but increases the risk of reoperation due to severe pulmonary valve regurgitation.

Lindberg and co-workers [8] showed that the freedom from reoperation was significantly reduced in patients repaired with a transannular patch compared to patients without (Figure 7). These authors did not find an influence of previous palliation, transatrial or transventricular repair on the rate of survival or reoperations.

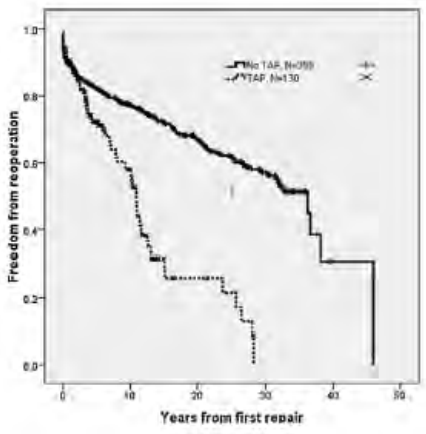

Figure 7: The influence of repair crossing the pulmonary annulus upon freedom from reoperation following surgery for Tetralogy of Fallot (After Lindberg et al. (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

Similar results were published by *Park and co-workers* [13]. They found a rate of reoperation or intervention in 31.7% (224 patients) out of 734 patients. The most common causes for reoperation or re-intervention were pulmonary valve regurgitation in 109 patients and branch pulmonary artery stenosis in 127 patients. It could be shown that preservation of the pulmonary annulus can reduce the reoperation rate.

Interestingly the rate of reoperations seems not to be changed over the last decades. The frequency of reoperations did not differ significantly during five decades from 1959–2009 according to the publications by *Lindberg and co-workers* [8] (Figure 8).

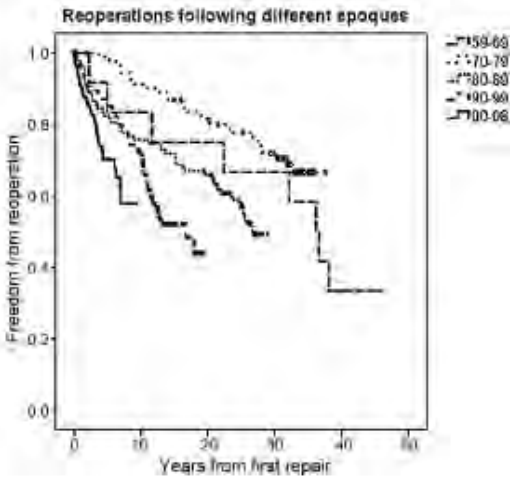

Figure 8: Survival and frequency of reoperations during the five different decennials following surgery for Tetralogy of Fallot (After Lindberg et al (2011) Single-centre 50 years' experience with surgical management of Tetralogy of Fallot. Eur J Cardiothorac Surg 40;538–542, with permission)

It is anticipated that the rate and the mode of reoperations will change in the present time or in the future.

Nowadays intraoperative echocardiography is performed in most centres. With the help of this intraoperative monitoring of the surgical results, a residual ventricular septal defect, significant tricuspid valve regurgitation or a severe RVOTO are detected and treated immediately. These lesions should require less frequent reoperation than decades ago.

Furthermore many reoperations can be replaced by non-surgical treatment in the catheterization laboratory. The most common morbidity in the long-term outlook is the problem with the RVOT and the pulmonary arteries.

Stenosis of branch pulmonary arteries can be now treated in most patients with balloon dilatation and/or implantation of stents. Re-stenosis or insufficiency of an

RV to pulmonary artery conduit are amenable to percutaneous pulmonary valve replacement.

Right-left ventricular interaction

Despite an excellent long-term survival after repair of TOF many patients will show a significant morbidity. This morbidity will increase with time after repair and is thought to be caused mainly by problems of the right heart such as stenosis and insufficiency of pulmonary valve with consecutive RV pressure and volume load. These changes lead to a reduced RV function with decreased exercise tolerances and functional status as well as atrial and ventricular arrhythmia and sudden death.

Over the last years it has become obvious that the changes of the right heart after repair for TOF will affect the morphology and performance of the left heart.

Broberg and co-workers studied the LV function with echocardiography in 511 adult patients with a mean age of 37.2 years. All patients had a successful repair of TOF performed at a median age of 6 years. In this large cross-sectional study LV systolic dysfunction was found in 20.9% of patients with TOF. LV dysfunction was defined as a LVEF < 55% showing increased LV diameter, decreased fractional LV shortening and a reduced myocardial performance index. A moderately (EF 35–44%) and severely (EF < 35%) reduced LV function was found in 5.2% and 1.1% respectively out of the 20.9% of patients with LV dysfunction (Figure 9).

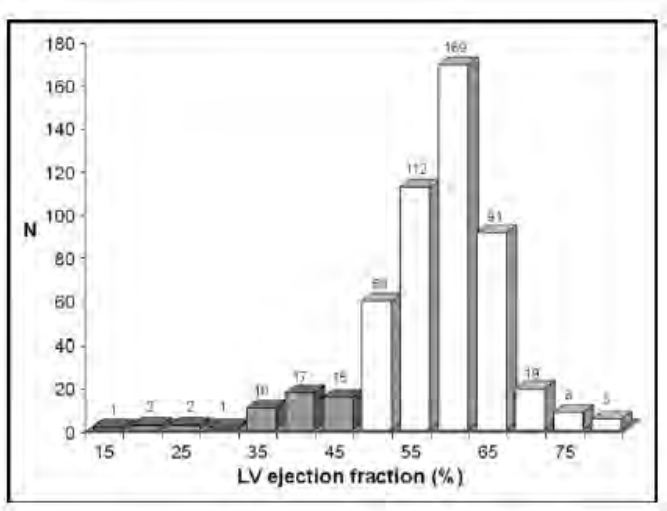

Figure 9: Histogram of estimated left ventricular ejection fraction displays the lower limit of each category (x-axis labels) and decreased ejection fraction (gray bars).
From Broberg.

There was a strong association between a reduced RV function and LV dysfunction. Most patients with normal LV function had normal RV function (67%) In patients

with moderate-severe LV-dysfunction only 28% had a normal right ventricle, whereas 44% had a moderate to severe RV dysfunction. (Figure 10).

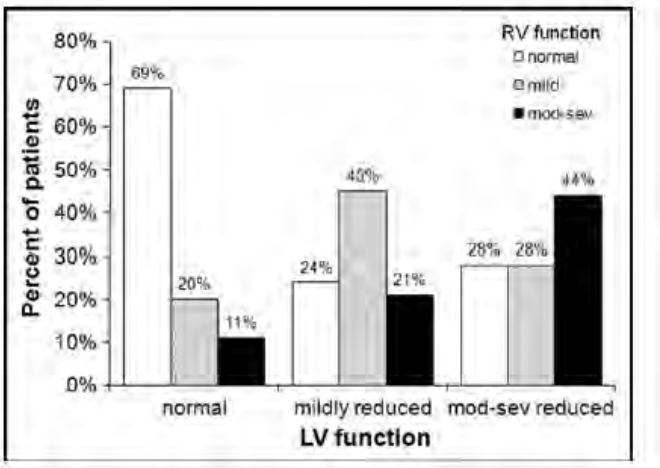

Figure 10: Histogram of estimated left ventricular function were more likely to have normal left ventricular function. In contrast, moderate-severe (mod-sev) right ventricular dysfunction was more prevalent in patients with moderately to severely decreased left ventricular dysfunction (p <0.001, chi-square test).

From Broberg

Interestingly there was no relation between the severity of pulmonary regurgitation and LV function. This is in accordance with a study by *Geva et al.* who did not find a correlation between the degree of pulmonary valve regurgitation and impaired clinical status.

A strong association, however, could be found between LV dysfunction and arrhythmia. Patients with LV dysfunction showed a wider QRS duration and had more often previous arrhythmia or implantation of a pacemaker and cardioverter-defibrillator, respectively.

The assumption that reduced LV function results in an increased risk of arrhythmia was supported by a retrospective survey of implanted cardioverter-defibrillator discharges in patients with TOF (*Khairy P, circulation Lit 15 and 16 bei Broberg).*In this study the strongest independent predictor for appropriate shock was an increased LV end-diastolic pressure, more than RV dysfunction, QRS duration or syncope.

There is further evidence that there is a close relationship between reduced RV and LV dysfunction suggesting an unfavourable ventricular-ventricular interaction in patients with repaired TOF. *Geva and co-workers* studied 100 consecutive patients with a median age of 21 years after repair. They correlated the clinical functional class of these patients with the ejection fraction of RV and LV determined by cardiac MRT. They found that a low LV ejection fraction – more than an RV dysfunction

– was to the strongest independent factor associated with impaired clinical status. The combination of lower LV EF (< 40%) and older age at TOF repair had a high sensitivity and specificity for being in NYHA functional class > III.

Furthermore a significant correlation was found between RV and LV ejection fraction in these patients (Figure 10). This finding confirmed the results of a previous publication in adults after TOF repair which showed an adverse right-to-left ventricular interaction in patients with RVOT aneurysm or akinesia (*Davlouros*)

All these data underline the necessity not only to focus on RV mechanics and its interaction with pulmonary valve regurgitation, but also on concomitant dysfunction of the LV. The mechanism that links RV dysfunction to a decrease in LV function is not clearly understood. Possible causes for LV dysfunction could be chronic hypoxemia, altered mechanics of IVS due to patch closure of VSD and volume loading of RV, damage of coronary arteries during repair or altered electro-mechanical interactions due to a long QRS duration.

Another cause for ventricular dysfunction could be ventricular fibrosis. *Babu-Narayan et al.* examined the extent of fibrosis in RV and LV detected by late gadolinium enhancement (LGE) using cardiovascular MRT in 92 adult patients with repaired TOF. Besides marked fibrosis in different parts of the RV, they found LGE in the LV (53%) not only at the apex consistent with apical vent insertion (49%), but also in the inferior or lateral wall consistent with infarction (5%) or in other areas (8%).

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SUDDEN CARDIAC DEATH AND CONGENITAL HEART DISEASE (CHD)

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CHD remains an important cause of sudden cardiac death to be recognized at adult autopsy. Bicuspid aortic valve and anomalous coronary anomalies are the most common malformations, comprising 36.9% and 26.2% of cases, respectively [1]. However, a wide spectrum of simple to complex malformations can be seen, with or without prior surgery, and over a wide age spectrum. CHD is now "grown-up" and will likely be diagnosed by forensic pathologists with increased frequency in the future [2].

The risk of sudden cardiac death (SCD) rises with the complexity of the cardiac abnormality and the surgery undertaken. In infancy mortality used to be high but now there is prolonged survival to adulthood and less operative mortality. Obviously complex lesions have a higher mortality. In a recent review forty-six patients had 2 functional ventricles and 23 had received palliation for a single-functional ventricle. Patients with a single ventricle died at a younger age than patients in the biventricular group. Thrombosis was the most common cause (61%) of death in the single-ventricle group. Arrhythmia or presumed arrhythmia was the most common cause (46%) of death in the biventricular group. Fifty-one patients had undergone surgery. Six patients had primary electrophysiological disease, and 5 had cardiomyopathy. Eight deaths occurred in patients with pulmonary vascular disease. Sudden unexpected death occurred at a frequency of at least 10 patients per year over an 8-year period with 55,730 patient encounters. Arrhythmias (30%) and pulmonary vascular disease (13%) are important causes of sudden death. Infants and young children with surgical shunts comprise 23% of sudden unexpected deaths that occur within a month of the last evaluation [3].

Simple aortic valve disease and hypertrophic cardiomyopathy are rare (4%) causes of sudden death in childhood.

Many patients with ventriculoarterial discordance survive to adulthood. Those with complete transposition of the great arteries have often had an atrial switch procedure (Mustard or Senning operation) performed, which leaves the morphological right ventricle (RV) supporting the systemic circulation. RV failure and tricuspid regurgitation are common. Atrial arrhythmias are frequent, and atrial flutter may be a marker for sudden death. Patients with an arterial switch procedure also have long-term problems include coronary stenoses, distortion of the pulmonary arteries, dilatation of the neoaortic root, and aortic regurgitation.

Patients with congenitally corrected transposition have both atrioventricular and ventriculoarterial discordance and therefore also have a morphological RV and delicate tricuspid valve in the systemic circulation. Associated defects, such as abnormalities of the tricuspid valve, ventricular septal defect, and pulmonary stenosis, occur in the majority of patients. Heart block occurs with increasing age. Atrial arrhythmias occur frequently. Progressive tricuspid regurgitation occurs with age and is associated with deterioration of RV function and sudden death [4].

Tetralogy of Fallot is the most common cyanotic heart disease. Its operative mortality and long-term result are good. At the late phase after the correction, pulmonary valve regurgitation associated with right side heart failure, aortic valve regurgitation, arrhythmia and sudden death become major adverse outcomes. The electrophysiological and haemodynamic substrate of sudden death resembled that of sustained ventricular tachycardia, with pulmonary regurgitation being the predominant haemodynamic lesion [5]. Pulmonary regurgitation following repair of Tetralogy of Fallot is a common postoperative sequela associated with progressive right ventricular enlargement dysfunction. Although pulmonary regurgitation may be well tolerated for many years following surgery, it can be associated with progressive exercise intolerance, heart failure, tachyarrhythmia, and late sudden death. It also often necessitates re-intervention. Identifying the appropriate timing of such intervention could be very challenging given the risk of prosthetic valve degeneration and the increased risk of reoperation. Pulmonary valve replacement performed in an experienced tertiary referral centre is associated with low operative morbidity and mortality and very good long-term results [6]. Double-outlet right ventricle is a cyanotic heart disease with a wide spectrum of morphology and is divided according to the site of ventricular septal defect: subaortic, subpulmonary, doubly committed and remote type. Its operative methods are completely dependent on its morphology, and vary such as intracardiac tunnel repair, Rastelli type repair, arterial switch procedure and Fontan type repair. Left ventricular outflow tract obstruction is one of the most important problems after the correction. Recent operative strategy for the treatment of tricuspid atresia and single ventricle is the completion of right heart bypass operation using total cavo-pulmonary connection with staging strategy. Pleural effusion, ascites, protein loosing enteropathy and supraventricular arrhythmia are major adverse outcomes after Fontan type repair, while extracardiac total cavopulmonary connection is expected to reduce the incidence of supraventricular arrhythmia [7].

Adults with congenital heart disease

Adults with repaired congenital heart disease represent a complex and heterogeneous group of patients that are increasingly surviving beyond childhood. Patients have a variety of diagnoses that include specific structural anomalies, assorted physiologic derangements, and unique techniques for surgical repair. During long-term follow-up, even the most excellent surgical outcome may result in anatomic stenosis and insufficiency, cardiac rhythm disturbance, and myocardial dysfunction. Any of these abnormalities, alone or in combination, may result in significant morbidity and mortality. Sudden death is common and arrhythmias are frequently suspected to be the cause. Unfortunately, arrhythmias are difficult to predict and may be lethal at their initial presentation. In addition, a wide spectrum of arrhythmias, both supraventricular and ventricular, are possible, depending on the specific diagnosis and type of repair performed. Supraventricular arrhythmias may be as lethal as ventricular arrhythmias, arrhythmia substrates develop in a unique manner when compared with other adult cohorts [8]. Sudden death may also occur in Turners syndrome [9].

In our database of sudden cardiac death 77/2000 (3.9%) cases died of a sudden cardiac death with congenital cardiac lesions. Simple CHD cases were atrial/ventricular septal defect (ASD/VSD, n=23), aortic stenosis (AS, n=3), Noonan syndrome (n=3) and Williams syndrome (n=2). Complex CHD cases were double outlet right ventricle (n=10), Tetralogy of Fallot (n=6), transposition of the great vessels (TGV, n=4), congenitally corrected TGV (n=2), atrioventricular septal defect (AVSD, n=4), anomalous pulmonary venous drainage (n=2), Ebstein anomaly (n=1) and hypoplastic left heart syndrome (n=1). There were cases of morphologically normal hearts with a functional bicuspid aortic valve (BAV) and no complications (n=3), healed VSD (n=2) and small ASD (n=1). Aortic CHD cases included coarctation of the aorta (n=4), sinus of Valsalva aneurysm (n=1) and aortic dissection with BAV (n=1). Complications of bacterial endocarditis occurred with AS (n=1) and AVSD (n=1). Finally there were cases of sudden death with pulmonary hypertension (n=2) secondary to CHD and ischaemic heart disease with CHD (n=2) [10].

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MOLECULAR GENETICS IN PAEDIATRIC CARDIOLOGY: APPLICATIONS AND CURRENT ADVANCES

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Abstract

This presentation is designed to provide the clinician with a summary of our current understanding of the contribution of genetics to the origin of congenital heart disease (CHD) and other heart defects that can occur in childhood. CHD can occur together with other congenital anomalies—there is a number of genetic tests that can help the clinician in diagnosing genetic alterations in the child with CHD like cytogenetic analysis, fluorescence in situ hybridization, microarrays, and DNA mutational analysis. We will discuss several syndromes that are diagnosed using those techniques like Williams-Beuren, Marfan, 22q11 deletion, and Noonan syndromes. Besides CHD, we will discuss the use of molecular genetic testing in diagnosing arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy (HCM), among others. Furthermore, we will look at the newest molecular approaches like whole genome sequencing in diagnosing children with heart defects.

Introduction

Cardiovascular disease affects both children and adults. It includes a wide range of conditions extending from diseases of the vascular system, diseases of the myocardium, diseases of the heart's electrical circuit, and congenital heart disease [1]. In this review, focus will be on the heart diseases commonly found in children, starting with the short description of the various paediatric cardiac defects, then description of their genetic components and types of genetic testing that should be performed in specific cases. At the end, there will be summary of the current advances in genetic research and diagnosis of cardiac defects together with the recent advances in the understanding of human heart development.

Cardiac defects in children – basics

Cardiac defects in children range from congenital heart defects, which are diagnosed prenatally or within the first year of life, to paediatric cardiomyopathies, which can be diagnosed within the first year or in the teenage period. In this section, basic cardiology of congenital heart defects and paediatric cardiomyopathies will be reviewed with the special emphasis to the genetic basis of those diseases.

Congenital heart defects – definition

Congenital heart disease encompasses cardiac malformations present at birth. It is one of the leading causes of death in the first year of life with prevalence of 4 to 50 per 1000 live births [2, 3, 4]. Current estimates are closer to 50 per 1000 live births, especially if other malformations like bicuspid aortic valve, left ventricular outflow tract obstructive disorders, isolated aneurysm of the atrial septum and persistent left superior vena cava are included [5, 6]. About half of the CHD are diagnosed in the first 12 months of life [7].

The underlying causes of the CHD are primarily unknown – however, increasing role of genetics has been crucial in understanding some types of malformations [5]. The determination of the genetic component (deletions, inversions, duplications, or mutations) will help the patients and their family because it can uncover other important organ system involvement, improve the understanding of clinical prognosis, and help other family members with potential reproductive risks [5]. For the explanation of the appropriate clinical diagnostic tests, please refer to another section in this review.

Paediatric cardiomyopathies – definition

The current definition of cardiomyopathies takes into account the molecular genetic aspects of cardiovascular diseases. By definition given by the Council on Clinical Cardiology, cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are present due to a variety of causes that are frequently genetic in nature. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure related disability [8].

In general, cardiomyopathies are divided into two major groups based on predominant organ involvement: a) primary cardiomyopathies (genetic, non-genetic, acquired) are those solely or predominantly confined to heart muscle and are relatively few in number and b) secondary cardiomyopathies which show pathological myocardial involvement as part of systemic disorders [8]. Primary cardiomyopathies that are genetic in origin are: hypertrophic cardiomyopathy (HCM), Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D), LV Noncompaction,

Conduction System Disease, and Ion Channelopathies. The primary cardiomyopathies of mixed origin are: Dilated Cardiomyopathy (DCM) and Primary restrictive cardiomyopathy [8].

Here we will discuss cardiomyopathies that can be found in children. Briefly, paediatric cardiomyopathy, or disease of the heart muscle, is a chronic and occasionally progressive disease of the myocardium (heart muscle), resulting in abnormally stiff and enlarged heart that cannot contract and relax properly. The consequence of the abnormal heart function is inability to pump blood to different parts of the body. Cardiomyopathy is the leading cause for sudden deaths heart transplants in children [9]. According to the US Pediatric Cardiomyopathy Registry, 1 in 100.000 children is diagnosed with cardiomyopathy. There are different types of primary cardiomyopathies that can be found in children, which include: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Dilated or congestive cardiomyopathy (DCM) is diagnosed when the heart is dilated and the heart chambers contract poorly. DCM is the most common form of cardiomyopathy, accounting for about 60% of all paediatric cardiomyopathies [10]. Causes can be both genetic and infectious/environmental, where about 30% of children with DCM have a relative with the disease, although they may not have the symptoms. If no other cause is found like viral infection (idiopathic DCM), specialized genetic testing can be performed to look for mutations commonly found in patients with DCM.

Second most common paediatric cardiomyopathy is hypertrophic cardiomyopathy (HCM), comprising about 35% of paediatric cardiomyopathies. HCM also affects adults, where the children under age 12 account for 10% of all cases. According to the Pediatric Cardiomyopathy Registry, HCM occurs in five per million children. It is typically diagnosed in infancy or adolescence. HCM patients have abnormal growth of heart muscle fibres, making the muscle stiff, resulting in difficulty to relax and fill the heart chambers. HCM usually affects the left ventricle with thickening of the septum, posterior wall or both. Majority of patients with HCM have a family relative with the disease. Genetic testing is available for some, but not for all forms of HCM.

Restrictive cardiomyopathy (RCM) is a rare form of cardiomyopathy, characterized by restrictive ventricular filling – contractile function and wall thickness is mostly normal, but the relaxation (filling phase) is abnormal. The ineffective relaxation and filling with blood results in the backup of blood into the atria, lungs and body, causing the symptoms of heart failure. About one third of all RCM patients have family history.

Arrhythmogenic right ventricular dysplasia (ARVC/D) is a rare form of cardiomyopahy which is characterized by dilated right ventricles which function poorly and contain fatty deposits within the walls. Patients are at the risk of fast heart rhythms

(ventricular tachycardia). Prevalence is about 1:1000 [11], and is more often seen in Europe, specifically Italy, than in the USA [12, 13, 14]. About one third of AVRD patients are familial [15, 16]. Most familial AVRD are transmitted in the autosomal dominant fashion. However, autosomal recessive form exists and is called Naxos disease. Patients with this disease have hyperkeratosis of the palms and soles and woolly hair.

Overview of basic genetics

The cause of most paediatric cardiomyopathies is still not well understood, but in a portion of children the cause is an error in a gene. Genes are encoded in DNA, which is situated within each cell of the body. Genes have many functions; one of them is to give instructions that determine how the parts of our bodies will be formed and how they will function. Mistakes in the coded instructions (DNA) are called mutations and they can cause problems with the formation and function of different organs. Many genes code for proteins that carry out various functions within the body including building organs or metabolizing various substances. Therefore, mutations may fail to produce the right amount of the protein or may produce a protein that does not function properly. If we focus on cardiomyopathies, mistakes in DNA can lead to isolated cardiomyopathy without other problems. In other cases, a DNA mutation can lead to cardiomyopathy, which is associated with other medical problems such as learning disabilities, muscle weakness, or poor growth.

Families which have a child diagnosed with cardiomyopathy are at increased risk for having another child or family member with cardiomyopathy. For that reason, it is crucial that once a cardiomyopathy is diagnosed within the family, all of the family members (brothers, sisters, and parents) are screened with an echocardiogram. Depending on the type of cardiomyopathy diagnosed, it may be necessary to repeat the echocardiogram periodically for younger children (childhood to mid-adult life). This is important specifically if close relatives were diagnosed with cardiomyopathy at an older age.

Cardiomyopathy in children can be caused by many different DNA mutations. In children with isolated hypertrophic cardiomyopathy, the disease is typically due to DNA mutations in genes that code for proteins found in the heart cell (e.g. sarcomere proteins). The diagnosis in such children is made by the confirmation of the mutation by molecular genetic testing. For many of those children, either the mother or father also have the same DNA mutation which they have passed on to their child. Such type of inheritance, where one parent and one child are both affected with the same disease is called autosomal dominantly inherited disease.

Here is a brief explanation of how genes (DNA) are passed from parent to offspring.

Each individual carries two copies of both genes (humans are diploid organisms) – one copy of each gene was passed on from mother and one from father. For autosomal

dominant diseases, a parent has a DNA mutation in one copy of the gene, while the other copy is normal (wild type). Therefore, the offspring of that parent has a 50–50 chance to inherit the mutation. In other words, autosomal dominant inheritance is such that a mutation in one gene of the parent is sufficient to cause the disease. In a family with an autosomal dominant condition, offspring have a 50% chance of having the disease. The reverse is also true – if an individual in affected family does not carry the mutation, the offspring will not have the disease.

If we focus on infants, it is important to remember that cardiomyopathies in that age group can be caused by inborn errors of metabolism. Most of these inborn errors of metabolism are inherited in an autosomal recessive fashion (e.g. fatty acid oxidation disorders and glycogen storage disorders such as Pompe disease will be discussed below). In autosomal recessive disorders, only when child has a mutation in both copies of the gene, the disorder can be observed. If a child has a mutation in one copy of the gene, he is the carrier but does not express the disease, in other words, having one abnormal copy does not cause disease because the other copy of the gene is sufficient to allow the normal heart function. Therefore, children with autosomal recessive diseases have mutations in both copies of a specific gene which they have inherited from both of their parents (both of their parents have the mutation in one copy of the gene and are thus called carriers). A child with an autosomal recessive cardiomyopathy, some of which are associated with inborn errors of metabolism, inherits a defective gene from each of his carrier parents. If both parents are carriers (have the mutation in one copy of the gene) the risk that other children (or future children) will have the cardiomyopathy is one in four or 25%. Usually the only individuals in the extended family at risk are brothers and sisters of the child with the cardiomyopathy.

Besides inborn errors of metabolism, there are other rare conditions that cause cardiomyopathies that are found in males. They are Duchenne or Becker muscular dystrophy or Barth syndrome. The cardiomyopathies in these conditions can occur in two ways: a) they may occur sporadically, i.e. not inherited from the parents or b) they may be inherited from their mother (X-linked). Mothers are females and thus have two X chromosomes. Usually they do not have any problems with X-linked diseases because the mutation is carried on one gene on the X chromosome while the other gene on the other X chromosome is normal. Males (boys) have only one X chromosome, so they have a 50% chance to inherit a mutated gene on the X chromosome from their mother. Since they have no second copy of the X chromosome, they may develop the disease. The daughters, on the other hand, will not have the condition although they may be carriers and could pass it on to their sons in the future.

Congenital heart disease – genetic basis

Even though Mendelian inheritance of CHD has been reported, the current hypothesis is that CHD is of multi-factorial aetiology – the interaction between the

environment and the genetic predisposition [5, 17]. Even with the accumulating molecular data on CHD, only a minority of patients has an identifiable genetic defect [18]. The proposed approach to newly diagnosed CHD patient is the routine examination of relatives with potential genetic contribution in order to obtain the accurate medical history [5]. The reasoning behind this approach is that although autosomal dominant pattern is theoretically easy to recognize, the problem lies with incomplete penetrance, like in the case of familial bicuspid aortic valve, which has reduced penetrance.

When faced with congenital heart defect, the clinician should request chromosomal analysis and possibly FISH testing for specific deletion syndromes – if chromosomal abnormality is found, the family has a clear explanation of the cause of CHD, which allows for the appropriate assessment of the recurrence risk. Furthermore, specific assessment of physical features should be done together with the geneticist (e.g. dysmorphic facies, eye and ear abnormalities, limb reduction defects, polydactyly, other skeletal defects, urologic defects, and neurological status – specific care should be paid to skeletal defects, cardiac aortic arch, pulmonary, liver and stomach situs).

In the next section, some of the most common genetic syndromes with congenital heart disease are presented.

Examples of genetic syndromes with heart disease

22q11 Deletion Syndrome – DiGeorge Syndrome

Patients with DiGeorge syndrome present with CHD, hypocalcemia, immunodeficiency, and facial dysmorphism. More than 90% of patients with the DiGeorge phenotype have a microdeletion on chromosome 22 [19]. Diagnosis is made by FISH because the deletion is small and can be missed on the karyotype. DiGeorge syndrome is part of the 22q11 deletion syndrome; the clinical features can vary among affected individuals, but most common characteristics are cardiovascular anomalies and palate anomalies, facial dismorphism, learning disability, feeding difficulty, renal anomalies and behavioural difficulties. A 22q11 deletion can be inherited from a parent in approximately 6% to 28% of cases [20]. The deletion in the parent is identified after the child's diagnosis and that parent often have subtle syndromic features. Such information is important for parental reproductive planning, since the implication is that half of future pregnancies will carry the deletion [21].

The most common cardiovascular defects associated with a 22q11 deletion include tetralogy of Fallot (8–35%), interrupted aortic arch type B (50–89%), truncus arteriosus (34–41%), VSDs (with aortic arch anomaly 45%), and aortic arch anomalies (24%) [5]. However, pulmonary stenosis, atrial septal defects, and hypoplastic left heart syndrome have also been reported. The importance of proper diagnosis of CHD child with a 22q11 deletion is augmented by several reasons: a) timely evaluation of

non-cardiac phenotypes for proper care, b) higher mortality of children with 22q11 deletion due to abnormalities of calcium metabolism and immunodeficiency [22].

Down's syndrome

About one half of Down syndrome patients have atrial-ventricular canal defects, ventricular septal defects, patent ductus arteriosus, atrial septal defect, and tetralogy of Fallot [53]. Diagnosis is made by conventional karyotype, but FISH can also be ordered if a rapid diagnosis is required.

Turner Syndrome

Turner syndrome is characterized by coarctation of the aorta. The diagnosis is evident clinically in the majority of cases. About half of the cases have 45, X karyotype, and the rest is due to mosaics, deletions, translocations and other cytogenetic aberrations.

Marfan syndrome

Marfan syndrome is a connective tissue disorder resulting in skeletal, ocular, and cardiovascular defects. The diagnosis is based on clinical parameters [54, 55]. The syndrome is inherited as a dominant trait, carried by the gene FBN1, which encodes the connective protein fibrillin-1. Because it is dominant, people who have inherited one affected FBN1 gene from either parent will have Marfan syndrome. Mutations in the fibrillin-1 gene on chromosome 15 (15q15-21.3) are responsible for 50–60% of cases with autosomal dominant inheritance, high penetrance and clinical variability [56]. The most fatal cardiovascular consequence is aortic dissection resulting from progressive aortic root dilatation in classic Marfan syndrome [55], but different clinical variances such as the MASS phenotype also result in mitral valve prolapse [58]. A Cystine to Arginine amino acid substitution in the fibrillin-1 gene has been associated with a more severe phenotype and may have cardiovascular implications: aortic root dissection, mitral valve prolapse (MVP), and others [55].

Testing is most useful in familial cases and can be used to identify family members who may have the defective gene and be at risk of cardiovascular complications.

Williams-Beuren Syndrome

Williams-Beuren Syndrome (WBS) is a connective tissue and brain disorder characterized by elfin facies, mental retardation, gregarious personality and congenital heart defects such as supravalvular aortic stenosis, supravalvular pulmonic stenosis, VSD, PDA and systemic hypertension [57], as well as diffuse arterial wall thickening including the coronary arteries. The cardiac defects often escape detection until developmental abnormalities bring this disorder to attention at about 6 years of age. Supravalvular aortic stenosis, which can be present in about 2/3 of cases [57] is associated with disruption of the elastin gene either from a deletion at 7q11.23 in the

majority of cases or from an autosomal dominant 6;7 translocation on chromosome 7 [59].

Ehler's Danlos Syndrome Type IV

Ehler's Danlos Syndrome Type IV is an autosomal dominant connective tissue disorder. There is hyperextensibility of the skin and hypermobility of the joints, but the disorder can present initially as a fatal event from aortic (or other arterial) rupture, bowel rupture or uterine rupture during pregnancy. The defect is due to mutations in the COL3A1 gene at 2q31-q32 which encodes for type III collagen [60, 61]. Because there are different mutations (polymorphisms), siblings may not be equally affected.

Paediatric cardiomyopathies – genetic basis

The genetic basis of different functional types of cardiomyopathy is given in this section, with emphasis on the specific genetic mutations responsible for different forms of cardiomyopathy and clinical implication of those mutations. In a population-based study of paediatric cardiomyopathies, DCM was found in 51% of the cases, while HCM was found in 42% of cases [23]. Therefore, we will focus on those types of cardiomyopathy.

Genetics of hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy, HCM, can be caused by mutations in one of 14 known genes that encode different sarcomere components – if caused by those mutations, HCM is characterized by LVH, left ventricular hypertrophy without predisposing cardiovascular conditions like aortic stenosis or long-standing hypertension [24]. Commonly the LVH is recognized in adolescence, but it can be seen at any age [25]. Familial HCM can be diagnosed based on the family history as well as molecular testing of the known 14 genes encoding sarcomere components. About 80% of mutations are found in two genes, MYH7 and MYBPC3, beta-myosin heavy chain (the first identified) and myosin binding protein C. The other genes appear to account for far fewer cases of HCM and include genes troponin T and I, regulatory and essential myosin light chains, titin, alpha-tropomyosin, alpha-actin, alpha-myosin heavy chain, and muscle LIM protein. It is important to mention nonsarcomeric mutations in two genes involved in cardiac metabolism responsible for regulating cardiac glycogen storage, which are found in older children and adults, but are clinically indistinguishable from other HCM. One gene encodes the gamma-2-regulatory subunit of the AMP-activated protein kinase (PRKAG2), associated with variable degrees of LV hypertrophy and ventricular pre-excitation [25]. The second gene is lysosome-associated membrane protein 2 (LAMP-2), resulting in Danon-type storage disease [8]. Clinical manifestations are confined to the heart abnormalities, presenting with massive degrees of LV hypertrophy and ventricular pre-excitation. These disorders are now part of a subgroup of previously described infiltrative forms of LV hypertrophy such as Pompe disease (discussed below), and Fabry's disease, an X-linked

recessive disorder of glycosphingolipid metabolism caused by a deficiency of alpha-galactosidase A [8].

Several other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring in infants and children less than 4 years of age, may resemble HCM caused by sarcomere mutations. These cardiomyopathies include secondary forms such as Noonan syndrome (discussed below), an autosomal dominant cardiofacial condition associated with a variety of cardiac defects

If familial HCM is diagnosed, genetic counselling is strongly recommended because the mode of inheritance is autosomal dominant [26, 27]. Histopathological findings include enlarged, disorganized myocytes, which die prematurely, leading to cardiac fibrosis. Clinical symptoms are highly variable and may include dyspnea, chest pain, palpitations, arrhythmias, and syncope. HCM is the most common cause of sudden death in healthy young individuals [27].

If we focus primarily on children with HCM, findings from the Pediatric Cardiomyopathy Registry [28] identified one disease in each of the following categories that accounted for most affected children: a) inborn error of metabolism (e.g. Pompe disease or glycogen storage disease type II), b) malformation syndrome (Noonan syndrome) and c) neuromuscular disorder (Friedrich's ataxia, FRDA).

Pompe disease (three forms: infantile, juvenile and adult-onset) is an autosomal recessive disorder that results from the deficiency in an enzyme acid alpha-glucosidase (GAA), causing the abnormal glycogen accumulation in all tissues [29, 30]. Carriers have no clinical manifestations. Different types of mutations in GAA have been described which lead to loss of protein product, reduced protein activity, reduced amount of protein, etc. The c.-32-13T → G mutation is the most common among adult form of the disease [29] and has not been reported in infants.

Noonan syndrome is defined by short stature, webbed neck, chest shape, and variable degree of developmental delay. Most patients with Noonan syndrome have congenital heart disease (pulmonary valve stenosis, atrial and ventricular septal defects, branch pulmonary artery stenosis and tetralogy of Fallot), and 20%–30% have HCM.

Cytogenetics is normal for Noonan patients, but four genes are known to be associated with this syndrome: PTPN11 (~50% of affected individuals), RAF1 (3%–17%), SOS1 (~10%), and KRAS (<5%). It is an autosomal dominant pattern of inheritance.

Friedreich ataxia (FRDA) is characterized by progressive ataxia that is diagnosed in teenage period. HCM is present in two thirds of patients. FRDA diagnosis is done by molecular testing of frataxin gene (OMIM 229300) and almost all patients have a mutation that reduces the amount of frataxin protein – the mutation is an intronic GAA repeat, which silences the gene transcription [31]. It is inherited in autosomal recessive fashion.

HCM genotype-phenotype correlations have been attempted, but care must be taken when intending to do genetic testing. In some cases the age of onset of HCM is associated with specific gene mutations, caution should be applied. About half of children with LVH have a mutation in one of the genes encoding components of sarcomere (out of which 49% a single occurrence in a family and 64% of familial cases).

Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

ARVC/D is inherited as an autosomal dominant disorder with incomplete penetrance, but autosomal form can also be found (Naxos disease). Clinical genetic studies suggest that about 30 percent of ARVC are familial [15, 16]. Multiple genes have been identified in 8 chromosomal locations, including ryanodine receptor 2 (RyR2), desmoplakin, plakophillin-2 and mutations in regulatory sequences of the transforming growth factor-beta, TGFB gene. Here is the more comprehensive list of the chromosomal locations associated with ARVD: 14q23-q24 (ARVC1), 1q42-q43 (ARVC2), 14q12-q22 (ARVC3), 2q32 (ARVC4), 3p25 (ARVC5), 10p12-p14 (ARVC6), 10q22, 6p24 (ARVC8), and 12p11 (ARVC9) [32-40].

Desmoplakin was the first gene to be identified and associated with ARVD, mapped to 6q24 (ARVC8). The protein product is the key component of desmosomes and adherens junctions that is important for maintaining the tight adhesion of many cell types. Once the junctions are disrupted, cell death and fibrofatty replacement take place. Mutations in desmoplakin have also been associated with left-sided ARVC and with autosomal recessive disease.

ARVD/C can also be associated with Naxos syndrome, an autosomal recessive disorder caused by mutations in the plakoglobin protein and characterized by severe problems with the skin, teeth, hair and nails in addition to the heart [41, 42]. Like desmoplakin, plakoglobin is a key component of desmosomes and participates in maintaining tight cell-cell adhesion.

A similar autosomal recessive disorder is Carvajal syndrome and is caused by mutations in the protein desmoplakin and is manifested by woolly hair, epidermolytic palmoplantar keratoderma, and cardiomyopathy [43].

Plakophilin-2, PKP2, (ARVC9) gene mutations can be found in more than one third of AVRC patients [40, 44]. Other genes associated with AVRC are desmoglein-2 gene, DSG2; desmocollin-2 gene; TMEM43 gene; cardiac ryanodine receptor RyR2; and TGF-beta-3 gene.

Genetics of Left Ventricular Noncompaction (LVNC)

Noncompaction of ventricular myocardium (LVNC) is a recently recognized congenital cardiomyopathy [8]. It is characterized by a distinctive morphological appearance of the LV myocardium. The inheritance pattern in LVNC can be autosomal dominant, X-linked or maternally transmitted due to mitochondrial mutations.

LVNC can be caused by mutations in the X-linked gene tafazzin (G4.5) that causes Barth syndrome and mitochondrial disorders, or it can be autosomal dominantly inherited if mutations occur in the alpha-dystrobrevin and ZASP genes (NKX2.5).

Genetics of Ion Channelopathies

Recently there has been a better understanding of the rare congenital arrhythmia disorders which include LQTS, short-QT syndrome (SQTS), Brugada syndrome, and CPVT that are caused by the mutations in ion channel proteins, responsible for membrane transport of sodium and potassium ions [8].

Long-QT Syndrome, the most common of the ion channelopathies, is characterized by two patterns of inheritance: a) a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen syndrome), caused by mutation in genes KCNQ1 and KCNE1, and b) autosomal dominant disease unassociated with deafness (Romano-Ward syndrome), which is caused by mutations in 8 genes – SCN5A (Na1.5, LQT3), KCNQ1 (KvLQT1, LQT1), KCNH2 (HERG, LQT2), ANKB (LQT4), KCNE1 (minK, LQT5), KCNE2 (MiRP1, LQT6), KCNJ2 (Kir2.1, LQT7, Andersen's syndrome), and CACNA1C (Ca1.2, LQT8, Timothy syndrome).

Besides Long QT syndrome, a new disorder was described in 1992, called Brugada syndrome (OMIM 601144), characterized by distinct ECG pattern and an increased risk of sudden cardiac death [45-47]. The syndrome is mostly diagnosed during adulthood, but occurs in infants and children (Antzelevitch, 2005). It is the major cause of sudden unexplained death syndrome (SUDS) and is the most common cause of sudden death in young men in Thailand and Laos [45]. Brugada syndrome is familial autosomal dominant disorder – 20% of patients have been linked to mutations in SCN5A gene (OMIM 600163, the same gene responsible for LQT3), also called Brugada syndrome type 1. However, there is a wide range of genetic heterogeneity in Brugada syndrome patients. There are several types: Brugada syndrome-2 (OMIM 611777) is caused by mutation in the GPD1L gene (OMIM 611778). Brugada syndrome-3 (OMIM 611875) and Brugada syndrome-4 (OMIM 611876) are caused by mutation in the CACNA1C (OMIM 114205) and CACNB2 (OMIM 600003) genes, respectively. Brugada syndrome-5 (OMIM 612838) is caused by mutation in the SCN1B gene (OMIM 600235). Brugada syndrome-6 (OMIM 613119) is caused by mutation in the KCNE3 gene (OMIM 604433). Brugada syndrome-7 (OMIM 613120) is caused by mutation in the SCN3B gene (OMIM 608214). Brugada syndrome-8 (OMIM 613123) is caused by mutation in the HCN4 gene (605206).

Genetics of dilated cardiomyopathy (DCM)

About 20%–35% of DCM patients have the familial form, although with incomplete penetrance [8]. Although genetically heterogeneous, the predominant inheritance is autosomal dominant. However, some cases are X-linked autosomal recessive and mitochondrially inherited (from the mother). Non-genetic cases like inflammation of myocarditis due to viral infection are also common.

Numerous genes have been correlated with DCM. Mutations in genes that code for cytoskeleton (delta-sarcoglycan, metavinculin, desmin, lamin A/C), Z-disk (ZASP, alpha-actinin-2, MLP, titin) and sarcomere (beta-myosin, alpha-tropomyosin, myosin binding protein-C, troponin-T) have been linked to DCM. Furthermore, X-linked genes, e.g. dystrophin, which causes Duchenne and Becker muscular dystrophies, have also been linked to DCM. Barth syndrome is another X-linked cardiomyopathy, caused by mutations in the G4.5/tafazzin gene. Like HCM, mutations in many of the sarcomeric genes (beta-myosin, alpha-tropomyosin, myosin binding protein-C, troponin T) can also cause DCM and are autosomal dominantly transmitted.

Other causes of DCM have been characterized. Abnormalities of mitochondrial function due to mutations in the mitochondrial DNA and inborn errors of metabolism related to the acyldehydrogenase genes can be causes of DCM in infants. Severe infantile cardiomyopathy is the most common clinical phenotype of VLCAD, very long chain acyldehydrogenase deficiency, and is found in about 67% of cases, often resulting in sudden death [23]. Majority of inborn errors of metabolism are inherited in autosomal recessive fashion and the diagnosis is commonly made by a blood test followed by an enzymatic test performed from a skin biopsy. The diagnoses of fatty acid oxidation disorders are important because the heart function can be improved by dietary manipulation with carnitine [23].

Methods in genetic testing

There are several genetic tests that can help the clinician in diagnosing genetic changes in the child with heart defects. Most commonly used tests are cytogenetic analysis (karyogram or karyotype), fluorescence in situ hybridization (FISH), SNP array (or oligo array), and DNA mutation analysis (DNA sequencing or PCR).

Karyotype—chromosome analysis

Karyogram is the typical complement of chromosomes [48]. Cytogenetics deals with karyotype analysis. The human karyotype has 46 chromosomes – 22 pairs of homologous chromosomes and one pair of sex chromosomes. Karyogram can be done in various cells and tissues, such as blood, bone marrow, amniotic cells, and tumour tissue. The sample is set up in a liquid nutrient medium under sterile conditions which allows cells to multiply, from 1 to 10 days, depending on the sample type [48, 49]. The culture is harvested when cells are in metaphase of cell division, placed on glass slides and stained. The chromosomes of one cell are analyzed in a karyogram to detect changes such as deletions, insertions, duplications and translocations. About 20 cells are analyzed for one sample (Figure 1) [50].

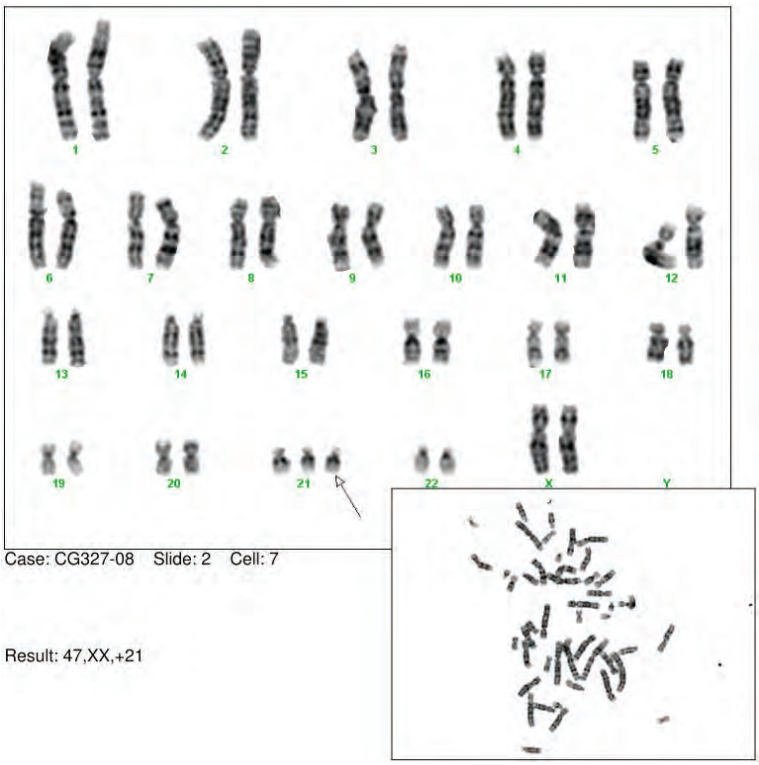

Figure 1. Female karyotype with 47 chromosomes – trisomy of chromosome 21 which indicates Down syndrome.

A standard chromosome analysis has a low pick-up rate – about 8% to 13% of neonates with congenital heart defect have detectable karyotypic aberrations [51].

However, with the use of other techniques like FISH and SNP array, the percentage is likely to be much higher. In contrast, of all children with chromosomal abnormalities, about one third have cardiac defects [52]. The standard metaphase karyotype (450 to 550 bands) is diagnostic for many chromosomal disorders, especially those of chromosome number such as trisomy (trisomy 21) or monosomy (45,X or Turner syndrome).

FISH

FISH, fluorescent in situ hybridization, is a molecular cytogenetics technique which can be used together with, or instead of the karyotype, depending on the disease and the extent of the chromosomal changes [48]. FISH utilizes fluorescently labeled DNA molecules as probes for a specific DNA sequence of interest (Figure 2). The advantage of FISH as compared to the conventional karyotype is that small changes cannot be seen on the conventional karyotype, but FISH can detect them. However, FISH can only detect specific changes that the physician is looking for, i.e.

if DiGeorge syndrome specific deletion is found in the sample or not (it cannot detect other changes in the sample). There are several disorders like DiGeorge; Williams-Beuren, Alagille, and Chi-du-chat have been associated with a microdeletion that frequently can be detected only by FISH.

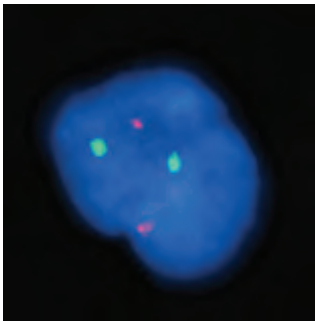

Figure 2. Example of FISH. The nucleus contains two red and two green signals. The red signal is specific for the microdeletion region characteristic for Williams syndrome – 7q11.23. The green signal is a control region, 7q31. This sample does not show deletion specific for Williams-Beuren syndrome.

If there is no obvious syndrome, a standard karyotype and FISH 22q11 should be obtained. If the FISH 22q11 is positive, a diagnosis can be established and the pending karyotype is unnecessary. If the FISH result is negative, the karyotype should be checked. If the karyotype is normal, SNP array should be performed. Further testing can be directed by the type of heart defects present or suspected.

SNP arrays

SNP (single nucleotide polymorphism) array is a useful technique for studying slight variations between whole genomes. Another analogous technique called Comparative genomic hybridization (CGH) or Chromosomal Microarray Analysis (CMA) is a molecular-cytogenetic method for the analysis of copy number changes (gains/losses) in the DNA content of a given subject's DNA. CGH detects only unbalanced chromosomal changes. Structural chromosome aberrations such as balanced reciprocal translocations or inversions cannot be detected, because they do not change the copy number. SNP arrays, however, have an additional advantage of being able to detect copy-neutral LOH (loss of heterozygosity, also called uniparental disomy or gene conversion), which is important in syndromes like Prader-Willi/Angelman.

DNA sequencing

The cytogenetic methods described above identify large changes in chromosome number or structure – SNP arrays do detect nucleotide changes, but their genome coverage might not account for the specific changes that are important in patients

with heart defects. However, there are microarrays that are designed to target only the genes specific to heart defects, but they can only be found in several institutions in the world and are not accessible to most physicians. Therefore, in certain disorders, changes occur at the level of a single gene and must be detected by alternative techniques that are more readily available. One of them is gene sequencing.

Genes are complex structures that include not only regions coding for the protein itself, but also other sequences involved in regulation of gene activity. Mutation analysis most often identifies changes in the coding sequence of the gene, including small nucleotide deletions, insertions, or nucleotide substitutions that alter the amino acids and affect the protein structure and function. Most commonly used method for sequencing is Sanger dideoxy method. However, in the last couple of years, another technology called next-generation sequencing, which is the sequencing of whole genomes or exomes, has become readily available.

It is important to emphasize the interpretation of sequencing results, which is not always straight forward. Currently, many mutations have been identified that cause heart defects. In future, the wealth of the sequencing data will have to be correlated with the pathogenesis of the specific aberrations, which would be the leading clues for new drug development.

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NUCLEAR MEDICINE IN PAEDIATRIC CARDIOLOGY

Elma Kučukalić-Selimović

Abstract

Nuclear medicine offers several methods applicable to the diagnosis and assessment of paediatric cardiovascular disorders which include: single photon emission computed tomography (SPECT), positron emission tomography (PET), first-pass radionuclide angiocardiography, radionuclide ventriculography (gated blood pool scan) and venography.

Myocardial perfusion SPECT is the most frequently utilized technique in myocardial imaging in paediatric patients, useful in the assessment of disorders of coronary perfusion such as: Kawasaki disease, transposition of the great arteries following arterial switch operation, cardiac transplantation, cardiomyopathy and anomalous left coronary artery. Radiopharmaceuticals for myocardial perfusion SPECT, PET perfusion and metabolic tracers are addressed in the paper.

Several nuclear medicine methods for the assessment of ventricular function in children are available. These include electrocardiogram (ECG)-gated myocardial-perfusion SPECT, gated metabolic PET (18F-FDG), gated blood-pool scintigraphy, and first-pass radionuclide angiography. Radionuclide assessments of ventricular function include right and left ejection fractions, detection of wall-motion abnormalities, ventricular volume, cardiac output, and regurgitant fraction. Clinical applications of radionuclide studies to assess ventricular function have been applied to several diseases including cardiomyopathies, atrial and ventricular septal defects and certain congenital heart diseases, before and after catheter intervention or corrective surgery. First-pass radionuclide angiocardiography is a rapid and non-invasive method that is useful in the diagnosis and measurement of left-to-right shunts and for assessing the magnitude of the shunt in patients before and after repair.

Dramatic improvements in nuclear medicine techniques provided an important role in the diagnostic and functional armamentarium of the paediatric cardiologist.

Keywords: paediatric cardiology, nuclear medicine, myocardial perfusion, SPECT, left-to-right shunt

Introduction

The application of radionuclides to study the cardiovascular system was first investigated by Blumgart and Yens and Blumgart and Weiss in 1927 [1]. These investigators used radium C and a primitive radiation detector to study blood flow velocity.

In 1948 and 1949, Prinzmetal et al. [2] described radiocardiograms of three patients with congenital heart disease using iodine-131 (131I), sodium iodine, and a Geiger-Mueller counter.

Congenital heart disease affects 0.8 per 100 live births. Nuclear medicine techniques play an important role in the diagnostic and functional armamentarium of the paediatric cardiologist. In the past three decades, tremendous advances in imaging techniques such as echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), and angiography have helped in the evaluation of anatomy and the understanding of physiology in children with heart disease in ways not possible before.

Furthermore, with dramatic improvements in technology (radio-pharmaceuticals and imaging instrumentation), nuclear medicine offers several methods applicable to the diagnosis and assessment of paediatric cardiovascular disorders. These include:

– single photon emission computed tomography (SPECT),
– positron emission tomography (PET),
– first-pass radionuclide angiocardiography,
– radionuclide ventriculography (gated blood pool scan), and
– venography.

1. Myocardial Imaging

Radionuclide imaging of the myocardium can be carried out with SPECT or PET, which can image myocardial perfusion, metabolism, neuronal innervation, and inflammation/infection. Myocardial perfusion using SPECT is the most frequently utilized technique in paediatric practice.

Myocardial perfusion SPECT is useful in the assessment of disorders of coronary perfusion such as:

– Kawasaki disease,
– transposition of the great arteries following arterial switch operation,
– cardiac transplantation,
– cardiomyopathy,
– chest pain and trauma,
– anomalous left coronary artery arising from the pulmonary artery.

Other less frequent indications include hyperlipidemia, supravalvular aortic stenosis, syncope, coarctation of the aorta, and pulmonary atresia with intact ventricular septum.

1.1. Kawasaki disease

Kawasaki disease is an acute, self-limited vasculitis of unknown aetiology that occurs predominantly in infants and young children of all races. The disease is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral

mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in 15% to 25% of untreated children with the disease and may lead to ischemic heart disease, myocardial infarction, or even sudden death [3, 4]. Myocardial perfusion SPECT has been widely used in the assessment of these patients. The presence of aneurysm may or may not be correlated with abnormalities in regional myocardial perfusion (Figure 1). Perfusion SPECT, with exercise or pharmacologic stress, may demonstrate regional myocardial perfusion impairment or improvement in perfusion after medical therapy [5] (Figure 2).

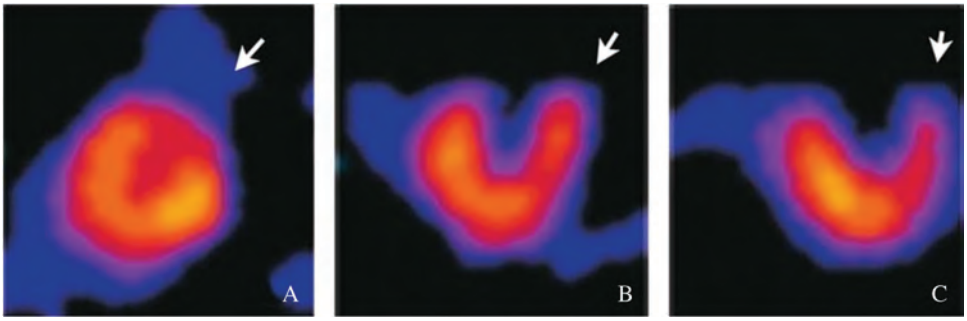

Figure 1. A 6-year-old boy with Kawasaki disease and severe aneurysms in the left anterior descending and the right coronary arteries. Short axis (A), horizontal long axis (B), and vertical long axis (C) slices reveal a perfusion defect in the anterior wall of the left ventricle (arrows) (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

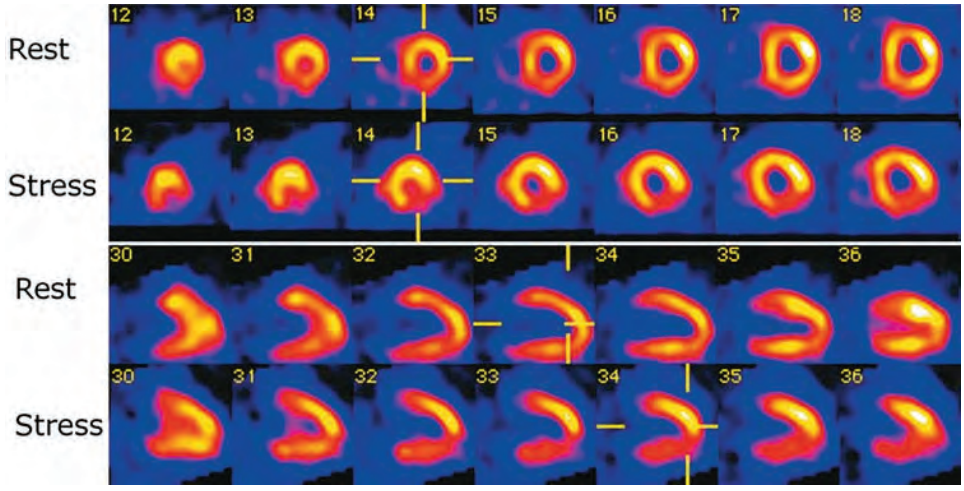

Figure 2. Patient with Kawasaki disease with severe ischemia of the inferior wall of the left ventricle, most pronounced during stress (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

1.2. Transposition of the Great Arteries: Arterial Switch Operation

In dextrotransposition of the great arteries (d-TGA), the aorta arises anterior from the anatomic right ventricle and the pulmonary artery arises from the anatomic left ventricle. This defect accounts for 5% to 7% of all congenital cardiac malformations [6]. Current medical and surgical treatment – arterial switch operation (ASO) – provides greater than 95% early and midterm survival. The short- and long-term success of this operative approach depends principally on the continued patency and adequate functioning of the coronary arteries [7, 8]. Abnormalities of myocardial perfusion in children after the ASO at rest and with the physiologic stress of exercise have been documented in nearly all patients using technetium-99m hexakis (2-methoxyisobutylisonitrile) sestamibi (99mTc-MIBI) myocardial perfusion SPECT (Figure 3).

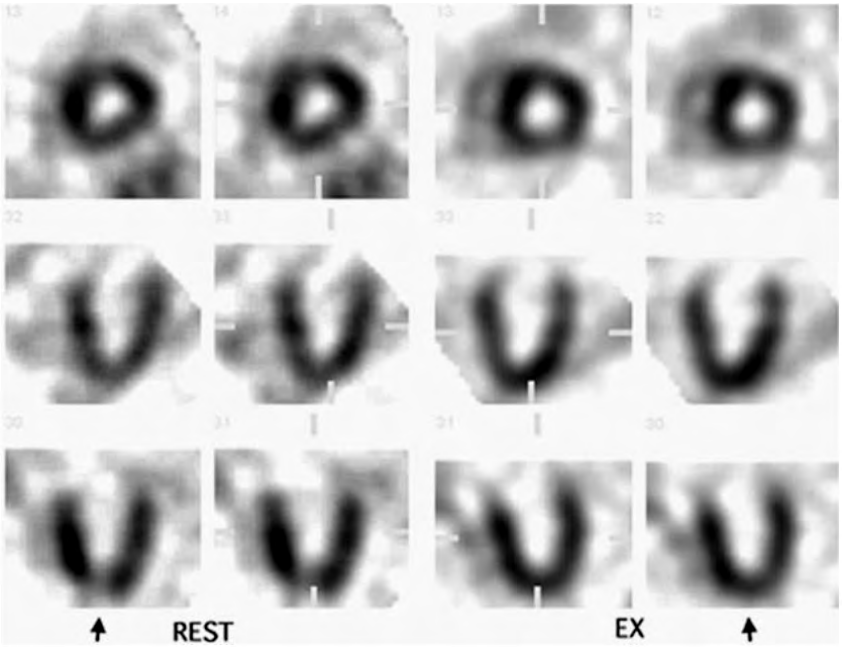

Figure 3. Arterial switch operation for transposition of the great arteries. At rest, there is an apparent apical defect that is not present at exercise (arrows) (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

1.3. Cardiac Transplantation

Paediatric cardiac transplantation is treatment option for neonates, infants, and children with end-stage cardiomyopathy or congenital heart disease not amenable to conventional surgical repair or palliation. Accelerated coronary vasculopathy which

involves some form of vascular immunologic injury has become the major cause of late morbidity and mortality following transplantation [9, 10].

Myocardial perfusion SPECT has been used to evaluate these patients on a regular basis and helps in the diagnosis of coronary artery disease and myocardial viability. In cases showing perfusion defects, fluorine-18 fluorodeoxyglucose (18F- FDG)-PET can determine myocardial viability [11]. Example of 99mTc-MIBI SPECT in patients following heart transplant is shown in Figure 4.

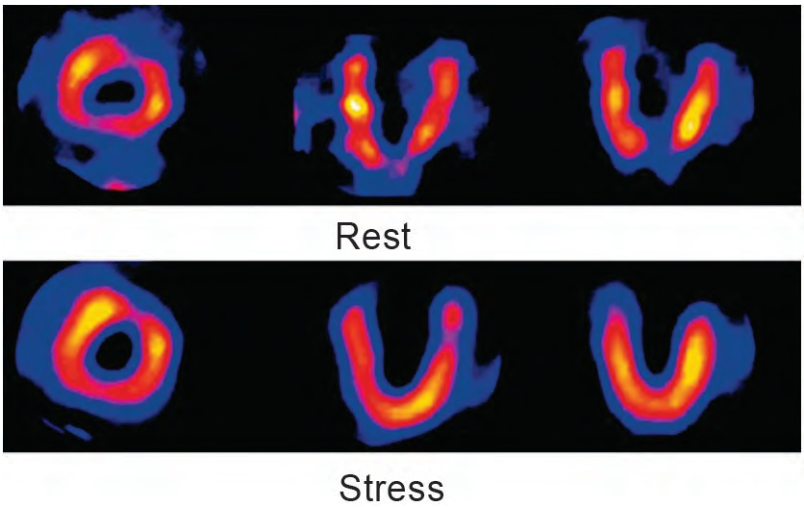

Figure 4. Cardiac transplant. Images at rest reveal irregular distribution of myocardial perfusion. This pattern changes during stress. The defect in the anterior wall remains, while the apical defect improves with stress (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

1.4. Anomalous Left Coronary Artery

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) results in severe myocardial dysfunction and ischemia during early infancy [12, 13]. Following birth, the left ventricle becomes perfused with desaturated blood at pressures that rapidly fall below systemic pressures. Classic findings include infarction of the anterolateral left ventricular free wall followed by mitral valve incompetence secondary to an infarcted anterior papillary muscle. This leads to symptomatic congestive heart failure in the first year of life. Myocardial perfusion scintigraphy may be helpful for assessing the severity of hypoperfusion and for the serial evaluation during recovery of function following repair [14] (Figure 5).

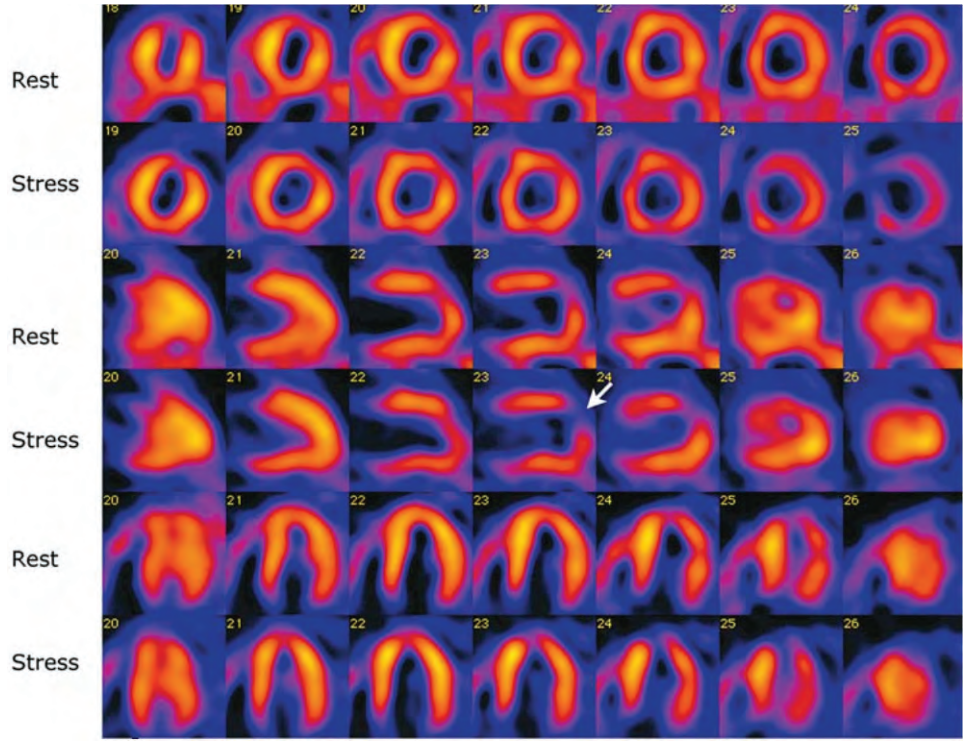

Figure 5. A 5-year-old boy with anomalous coronary artery departing from the pulmonary artery. A perfusion defect gets worse with stress (arrow) (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

1.5. Cardiomyopathy

Depending on the type and severity of the cardiomyopathy, myocardial perfusion SPECT can diagnose myocardial dilatation, myocardial thinning, focal ischemia, or infarction as well as myocardial contractility and wall motion abnormalities (Figure 6).

1.6. Chest pain

Chest pain is a common complaint in children. Cardiac causes of chest pain account for a small minority of potential etiologies including idiopathic (12% to 85%), musculoskeletal (15% to 31%), pulmonary (12% to 21%), psychiatric (5% to 17%), gastrointestinal (4% to 7%), other (4% to 21%), and cardiac (4% to 6%) [15].

Cardiac related causes of chest pain include anatomic lesions (such as aortic stenosis, anomalous coronary artery from the pulmonary artery, and coarctation), acquired lesions (cardiomyopathies, Kawasaki disease, dissecting aortic aneurysm) and tachyarrhythmias. Chest pain is not a frequent referral diagnosis for myocardial perfusion SPECT. However, it has been observed that this method is helpful to rule out cardiac ischemia as a cause of chest pain [11].

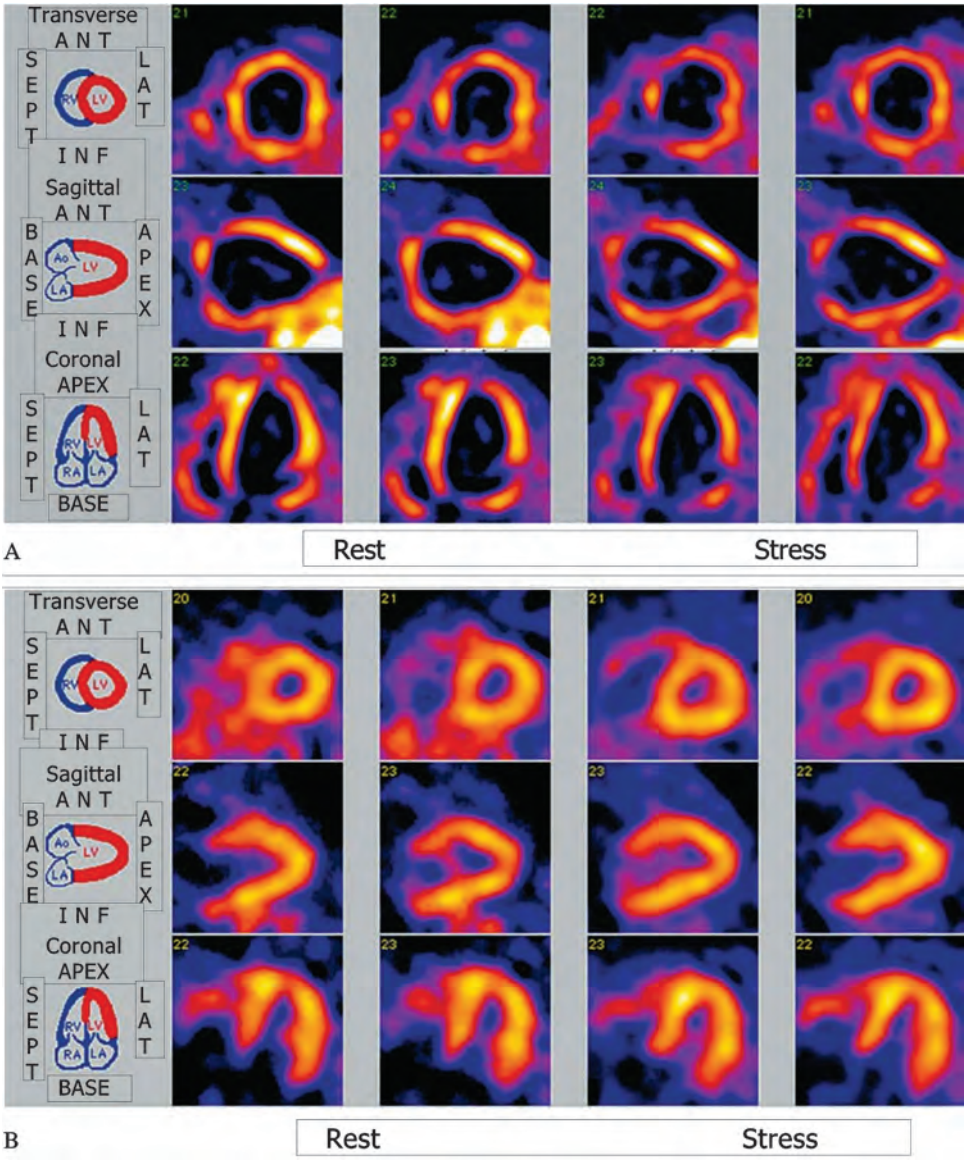

Figure 6. Patient with severe dilated cardiomyopathy. B: Same patient following successful cardiac transplantation (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

1.7. Right Ventricular Hypertrophy and Hypertension

In normal individuals, the right-ventricular myocardium has lower tracer uptake compared to the left ventricle, and therefore may not be clearly visible on myocardial perfusion SPECT. The right-ventricular wall can be seen in the normal individual

if the injection is made during or just after exercise. Increased 99mTc- MIBI and 201Tl uptake in the right ventricular myocardium at rest is seen in patients with right ventricular hypertrophy (Figure 7) [16, 17].

Visualization of the right ventricle on myocardial perfusion scintigraphy occurs in patients with congenital heart disease, such as tetralogy of Fallot (pre- and postoperatively), transposition of the great arteries (following Senning or Mustard's repair when the right ventricle is at systemic pressure), or after an ASO (with residual supravalvular pulmonary stenosis and secondary right ventricular hypertrophy) [11].

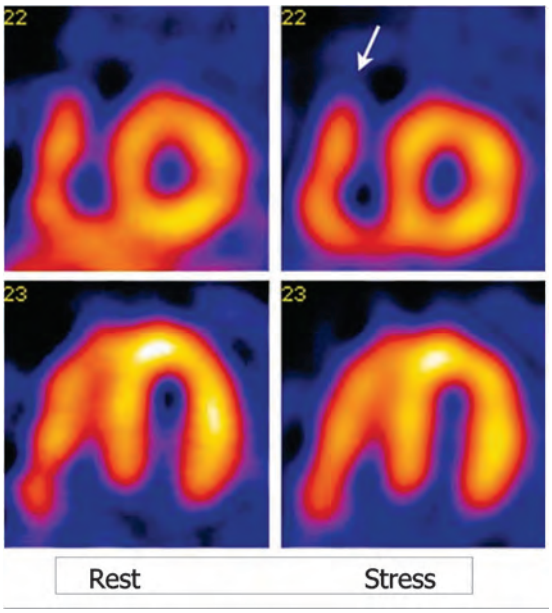

Figure 7. An 11-year-old girl with truncus arteriosus. The 99mTc-MIBI SPECT reveals increased right ventricular tracer uptake due to hypertrophy (arrow) (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

2. Radiopharmaceuticals for Myocardial Perfusion Single Photon Emission Computed Tomography

Myocardial SPECT in children can be carried out using one of the following agents:

– 99mTc-MIBI,
– 99mTc-tetrofosmin or
– thallium-201 (201TI)

Technetium-99m-MIBI is a cationic complex that accumulates in the myocardium according to regional myocardial perfusion. After intravenous administration, this agent is distributed throughout the body and concentrates in several organs including

the thyroid, myocardium, kidneys, and striated muscle. The agent clears rapidly from the blood with a fast initial component and with a half-time of 4.3 minutes. There is less, approximately 8%, of the administered tracer activity in blood by 5 minutes, and less than 1% of the tracer is protein-bound in the plasma. The major route of elimination of 99mTc-MIBI is the hepatobiliary system. The biologic half-lives of 99mTc-MIBI in myocardium and liver are 6 hours and 30 minutes, respectively. At rest, approximately 1.5% of the injected dose is taken up in the myocardium. Once 99mTc-MIBI is taken up by the myocardium, it remains fixed there and it shows no redistribution over time.

With 99mTc-MIBI, both resting and exercise stress evaluations can be performed; physiologic stress evaluations may be performed in patients old enough to cooperate with exercise testing (usually 7 years or older), and the pharmacologic stress can be used in all age groups [11].

Technetium-99m-Tetrofosmin is taken up in the myocardium to a maximum of 1.2% of the injected dose at 5 minutes and 1% at 2 hours, respectively. Activity in the blood, liver, and lungs is less than 5% of the administered activity at 10 minutes and less than 2% at 30 minutes. Tracer activity is eliminated in the urine (approximately 40%) and in the faeces (26%) within 48 hours [11].

Thallium-201 is considered a potassium analogue [18]. Clearance of potassium from the myocardium is faster than that of thallium, however after intravenous injection, the blood disappearance half-time of 201TI is less than 1 minute. The peak myocardial uptake, about 3% to 4% of the injected dose, occurs at approximately 10 minutes. At this time, the distribution of radiothallium in the heart appears to correlate with myocardial perfusion [19]. Thallium-201 is not fixed to the myocardium; it redistributes with time, exercise, drugs, and ischemia.

3. Positron Emission Tomography Perfusion Tracers

Rubidium-82 (82Rb), nitrogen-13 (13N), ammonia, and oxygen-15 (15O) water can be used to assess myocardial perfusion with PET [11].

Rubidium-82 is a generator-produced radionuclide with a half-life of 75 seconds. The parent radioisotope is strontium-82 with a physical half-life of 25.5 days. The generator eluant is injected intravenously into the patient as a continuous infusion. It is extracted rapidly in the myocardium depending on the flow. The short half-life of 82Rb permits studies to be performed in rapid succession [11].

Positron Emission Tomography Metabolic Tracers

Fluorine-18-fluoro-2-deoxyglucose (18F-FDG) is a glucose analogue. Fluorine-18 has a physical half-life of 111 minutes. Fluoro-2-deoxyglucose PET images regional myocardial glucose metabolism. Blood disappearance of 18F-FDG is rapid. Most of the activity leaves within 1 minute after intravenous injection, most of the remainder

leaves within 10 minutes, and a small fraction of the tracer remains in the blood pool in 90 minutes. Imaging can begin within a few minutes following tracer injection [11].

4. Assessment of Ventricular Function

Several nuclear medicine methods for the assessment of ventricular function in children are available. These include:

– electrocardiogram (ECG)-gated myocardial-perfusion SPECT,
– gated metabolic PET (18F-FDG),
– gated blood-pool scintigraphy,
– first-pass radionuclide angiography.

Radionuclide assessments of ventricular function include right and left ejection fractions, detection of wall-motion abnormalities, ventricular volume, cardiac output, and regurgitant fraction. Clinical applications of radionuclide studies to assess ventricular function have been applied to Kawasaki disease, anomalous origin of the coronary artery, cardiomyopathies, cardiac transplants, atrial and ventricular septal defects, cystic fibrosis, cardiac tumours, and certain congenital heart diseases, before and after catheter intervention or corrective surgery. Gated cardiac studies permit an evaluation of both global and regional ventricular function. Generally, no patient preparation is needed for this study, but patients under 3 years of age may require sedation in order to keep them still for the 20 to 30 minutes required for the recording [11].

4.1. Left-to-Right Shunts with first-pass radionuclide angiocardiography

First-pass radionuclide angiocardiography is a rapid, accurate, and non-invasive method that is useful in the diagnosis and measurement of left-to-right shunts in certain congenital lesions, including the following:

– Atrial septal defect
– Ventricular septal defect
– Truncus arteriosus
– Patent ductus arteriosus
– Complete atrioventricular canal
– Aortopulmonary collaterals

This method is useful for assessing the magnitude of the shunt in patients before and after repair.

Technetium-99m as pertechnetate is the most commonly used radiopharmaceutical for first-pass radionuclide angiocardiography. For the evaluation of left-to-right shunts, the technique of injection is of utmost importance in order to obtain a good-quality angiogram with high temporal resolution. Qualitative and quantitative analyses of angiocardiography are best done when the radiotracer is delivered as a single, small, rapid intravenous bolus injection, a point that cannot be overemphasized.

The majority of patients do not need sedation for this short procedure. If sedation is needed, it should be prescribed for each patient individually. Prior to positioning the patient under the gamma camera for the angiocardiogram, an intravenous needle or a short IV catheter is inserted.

The patient is placed supine on the imaging table. The gamma camera, equipped with a parallel-hole high-sensitivity collimator, is positioned anteriorly over the patient's chest. The field of view should extend from the suprasternal notch to just below the xiphoid and should cover both pulmonary fields. Radionuclide angiocardiography for the assessment of left-to-right shunting is recorded at two or four frames per second for 25 seconds on a 128 × 128 matrix [11].

In a normal radionuclide angiocardiogram, tracer is seen as it circulates sequentially through the superior vena cava, right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle, and aorta. The left ventricle and the aorta are clearly visualized with only minimal pulmonary activity. The relative sizes of the heart chambers can be appreciated on the angiocardiogram (Figure 8) [11].

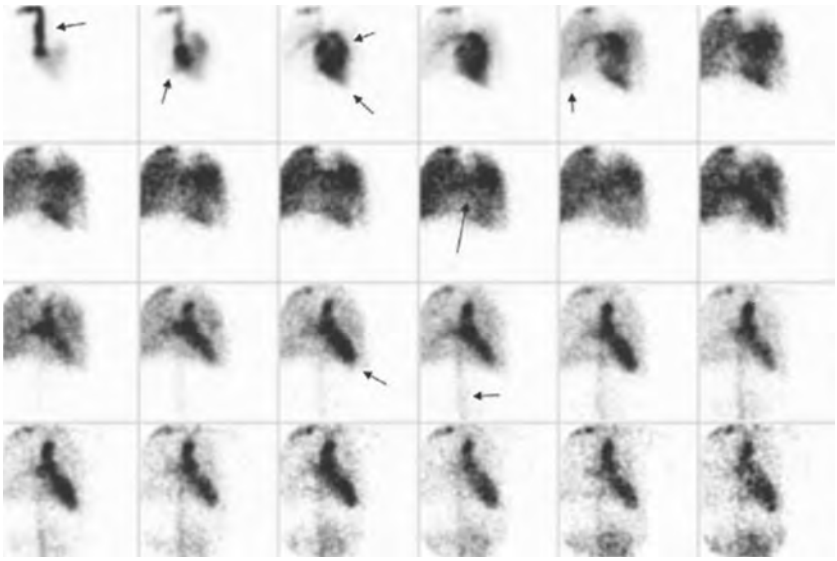

Figure 8. Normal radionuclide angiocardiogram. Tracer circulates in the superior vena cava (SVC), right atrium (RA), right ventricle (RV), pulmonary artery (PA), right lung (RL), left atrium (LA), left ventricle (LV), and aorta (Ao) (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

With left-to-right shunting, the radionuclide angiocardiogram reveals a persistence of tracer activity in the lungs caused by premature pulmonary recirculation of the tracer through the intracardiac shunt. The amount of persistent tracer activity in the lungs is directly related to the magnitude of shunt flow. In addition, in moderate to

severe left-to-right shunting, the left side of the heart and the aorta are not well visualized on the angiogram (Figure 9) [11].

These two radionuclide angiocardiographic features – persistent pulmonary tracer activity and poor visualization of the left side of the heart and aorta – are diagnostic for left-to-right shunting.

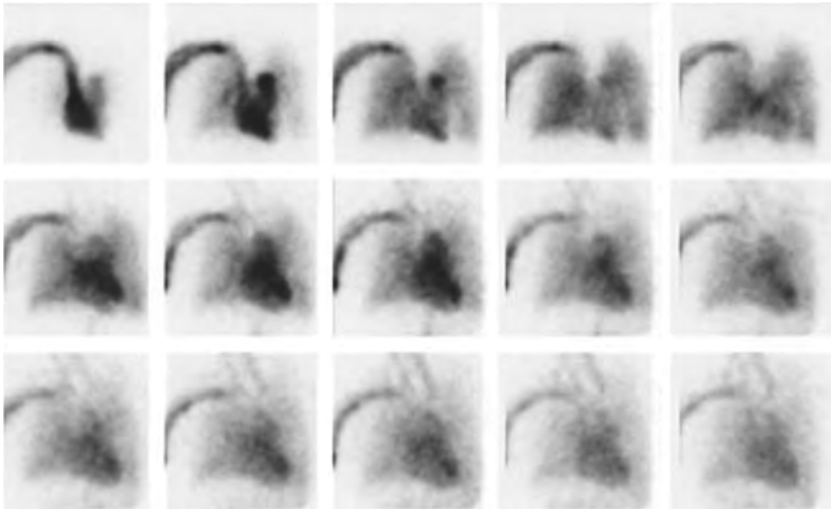

Figure 9. Left-to-right shunt. Radionuclide angiocardiogram from a patient with a moderate left-to-right shunt (S.T. Treves. Pediatric Nuclear Medicine/PET, 3ed ed. Secaucus, NJ: Springer Verlag, 2007).

4.2. Left-to-Right Shunts

With right-to-left shunting, the first-pass radionuclide angiogram reveals passage of the radiotracer within the superior (or inferior) vena cava, the right atrium, and the right ventricle. There is, depending on the level of the shunt, rapid appearance of the tracer within the left atrium or the left ventricle and the aorta (or both), which on the angiogram appears to occur at the same time or before the tracer reaches the lungs. For example, with tricuspid atresia, the tracer is seen to circulate from the right atrium into the left ventricle via the left atrium, presenting a rather unique angiographic pattern. Some examples of congenital lesions where radionuclide angiocardiography may be used to detect and quantify right-to-left shunts are as follows [11]:

– Tetralogy of Fallot
– Tricuspid atresia
– Pulmonary atresia/intact ventricular septum
– Tetralogy of Fallot with pulmonary atresia

Two approaches to the detection and quantitation of right-to-left shunts have been taken. The angiocardiographic technique is the same as that described for left-to-right shunting except that the patient (with levocardia) should be imaged in the left

anterior oblique projection to obtain maximum separation between the right and left ventricles.

Another technique uses large-molecularweight radioactive particles (99mTc-MAA). The major assumption in this method is that the particles are completely extracted from the circulation in one pass through either the pulmonary or the systemic capillary beds. This condition is largely met for particles larger than 10μm in diameter. It is also assumed that the particles are mixed uniformly in the blood, that the particles themselves do not affect the blood flow, and that the particles traverse the system in the same manner as the blood. After intravenous administration of radioactive particles to a patient with a right-to-left shunt, the ratio of particles that enter the pulmonary and systemic circulations equals the pulmonary blood flow/systemic blood flow ratio. The activity in the whole body is measured and compared with that in the lungs. Assessment of right-to-left shunting with 99mTc-MAA may be particularly useful in cyanotic patients with congenital heart disease to differentiate intrapulmonary versus intracardiac or extracardiac shunting.

Right-to-left shunting can also be detected by angiocardiography with an inert gas. An inert gas is almost completely removed from the blood in one transit through the lungs. The appearance of systemic activity after intravenous injection of an inert gas (dissolved in saline) indicates a right-to-left shunt. Prior to high-resolution echocardiography and cine-MRI, some investigators used both an inert gas and a nondiffusable indicator to define the nature of the cardiac defect, especially in complicated cases [11].

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