Perspectives in Paediatric Cardiology: Perspektive u pedjatrijskoj kardiologiji

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2012

Akademija nauka i umjetnosti Bosne i Hercegovine

https://bastina.anubih.ba/items/ff7d5ad2-af81-4f1b-8490-552285003fe6

UPDATE ON PAEDIATRIC CARDIOLOGY

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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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