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**Al III-lea Simpozion Naţional de Cardiologie Pediatrică**

# "Malformaţii cardiace congenitale - Noi abordări diagnostice şi terapeutice"

## Curs intensiv de Ecocardiografie Fetală

Tîrgu Mureş, România

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# Genetics And Congenital Heart Disease

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Congenital heart disease (CHD) is the malformations of the heart or the large blood vessels associated with the heart, affecting various parts or function. CHD is one of the most common major malformations in humans, contributing substantially to the financial and psychological burden of child healthcare.

The goal of this review is to provide more information for clinicians on the expanding knowledge of the involvement of genetic contributions to the origin of congenital heart disease. Techniques are discussed to evaluate children with heart disease for genetic alterations. Some of these techniques are now available on a clinical basis. The latest research are demonstrating that variations or alterations in genes contribute to the origin of CHD to a greater degree than previously suspected. The importance of genetics in the etiology of CHD is supported by the frequent association of CHD with genetic syndromes, the familial recurrence of certain defects These are grouped as multifactorial defects, however about 4 to 12% of the CHDs are found to be associated with various chromosomal anomalies. There are several reports of CHDs associated with chromosomal anomalies like trisomies, deletions, duplications and translocations (Smitha and Ramachandra 2005).

**Key Words:** congenital heart disease, genetics

## Introduction

Congenital heart diseases (CHD) are the most common of all birth defects and are the leading cause of mortality in the first year of life 16. It has been established that abnormal heart development is the major cause of the disease, which is mainly due to the combined effect of one or more genes interacting with various environmental risk factors. The most CHD occurs as isolated cases. On the basis of studies of recurrence and transmission risks, a hypothesis of multifactorial etiology was proposed 10. In this type of inheritance, the genetic predisposition of the individual interacts with the environment to cause the congenital heart defect. In recent years, separate environmental and genetic causes have been identified. Classic mendelian transmission of congenital heart defects in some families has been described in the literature.

## Prevalence of CHD

CHDs are the most common single group of congenital abnormalities accounting for about 30% of the total abnormalities. In most patients, CHDs occur as an isolated malformation, but also about 33% have associated anomalies 4. Cardiac malformations present at birth are an important component of pediatric cardiovascular disease and constitute a major percentage of clinically significant birth defects, with an estimated prevalence of 4 to 50 per 1000 live births. For example, it is estimated that 4 to 10 live-born infants per 1000 have a cardiac malformation, 40% of which are diagnosed in the first year of life7.

## Etiology

There is strong evidence supporting a genetic etiology for most congenital heart defects in human beings. The major genetic cause for congenital heart defects includes the following: chromosomal disorders and single gene disorders, environmental teratogens and multifactorial disorders. A multifactorial means both genetic and environmental factors interact, to interfere with the development of the heart. Increased incidence of CHDs has been noted with intrauterine viral infections, maternal drug and alcohol consumption during first trimester of pregnancy and pregnancy-induced systemic maternal disease 14. Although most CHDs occur as a sporadic event, many diseases are part of a well-defined genetic basis 1. In addition to Mendelian disorders, certain types of CHDs are associated to single gene or single locus defects.

- Chromosomal anomalies: the association of CHDs with chromosomal anomalies varies between 4-12%.
- Gene mutations: at present, very few candidate genes have been identified which

cause CHDs in human beings Many of the heart defects caused by gene mutations are part of a constellation of problems comprising a dysmorphic syndrome. (Fig 1.)

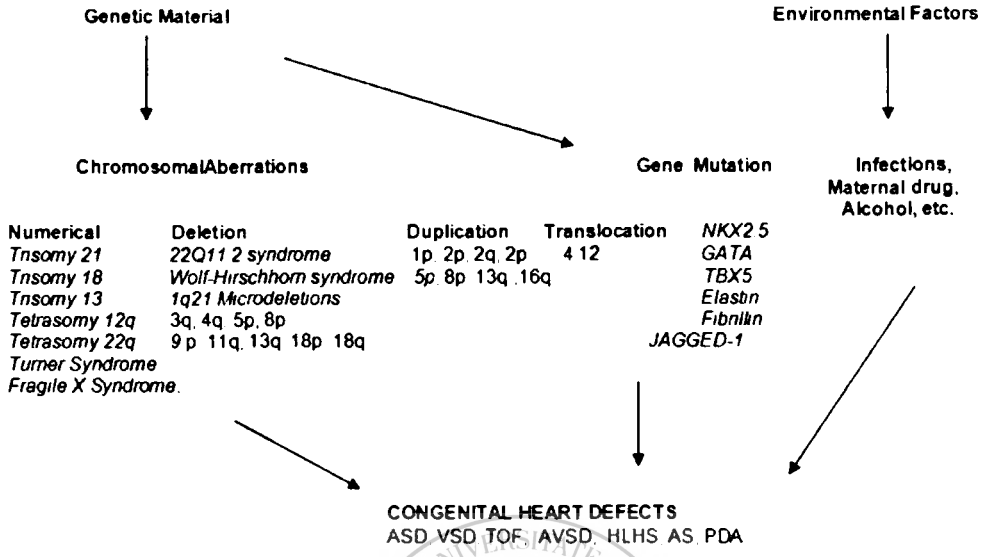


Figure 1. Etiology of CHD [Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Tetralogy of Fallot (TOF), Atrioventricular Septal Defect (AVSD), Hypoplastic left heart syndrome (HLHS) Aortic Stenosis (AS), Patent Ductus Arteriosus (PDA)]

## Importance of identifying the genetic basis of CHD

For the clinician caring for a child with CHD, it is very important to determine whether there is an underlying genetic pattern (eg, deletions, duplications, or mutations), for the following reasons (10):

(1) there may be other important organ system involvement;

(2) there may be prognostic information for clinical outcomes;

(3) there may be important genetic reproductive risks the family should know about; and

(4) there may be other family members for whom genetic testing is appropriate.

## Current genetic techniques for evaluation of congenital heart defects

Congenital heart defects often occur in the setting of multiple congenital anomalies, including abnormal facial features, or in association with limb anomalies, other organ malformations, developmental abnormalities, or growth abnormalities[10]. There are some genetic tests that can assist the clinician in diagnosing genetic alterations in the child with CHD. These include cytogenetic techniques, fluorescence in situ hybridization (FISH), and DNA mutation analysis.

### Chromosome Analysis

Standard chromosome analysis reveales chromosomal aberration in 8% to 12% of neonates with CHD. With improved resolution in cytogenetic analysis the prevalence of chromosomal abnormalities in selected congenital heart defects is estimated to be much higher (8). In contrast, of all children with chromosomal abnormalities, at least 30% have a congenital heart defect, with the incidence varying from that of the general population to nearly 100%, as in trisomy (18). Chromosomal analyses in children with various types of CHD, especially if they have other organ system anomalies, is currently an important part of their medical evaluation. 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 (Turner syndrome). A more sensitive test, high-resolution banding, evaluates chromosomes in prometaphase, which allows for the visualization of a greater number of bands (550 to 850 bands) than the standard karyotype. This technique better defines chromosomal structural abnormalities such as duplications, translocations between chromosomes, and interstitial or terminal deletions. In most centers, 7 to 14 days are required for standard karyotyping and up to 3 weeks for high-resolution banding. Chromosomes can be analyzed from a number of sources, including peripheral blood lymphocytes, cord blood, amniotic fluid, chorionic villi, and bone marrow.

Amniotic fluid cells are the primary means of prenatal chromosomal diagnosis. Amniocentesis is performed at 15 to 16 weeks' gestation. Chorionic villus sampling involves the biopsy of tissue from the villous area of the chorion transcervically or transabdominally, between 10 and 12 weeks' gestation.



### FISH technique

Fluorescence in situ hybridization (FISH) is an advanced cytogenetic techniques, used to identify microdeletions, microduplications, and/or subtle translocations. This technique uses a fluorescent probe linked to a specific DNA sequence. FISH is a method by which biotinylated test and control DNA probes are hybridized with metaphase chromosomes to determine whether 1 (deletion), 2 (normal), or 3 (duplication) copies of the test region are present.29 Specific DNA probes can be located by fluorescence microscopy and will identify well-known deletion syndromes such as del 5p (cri-du-chat), Williams-Beuren, Alagille, and the 22q11 deletion syndromes.

### Telomere analysis by subtelomere FISH

Micro deletions, duplications, or subtle translocations involving the most distal ends of each chromosome (telomeres) may be quite difficult to detect by cytogenetic techniques.

Fluorescent DNA probes for many interstitial chromosomal regions are able to detect abnormalities that involve the subtelomere-telomere regions (subtelomere FISH). Chromosome-specific unique sequences are present in these terminal regions, and fluorescent DNA probes can be specifically targeted to these areas. The subtelomere regions are thought to contain a very high concentration of genes; thus, rearrangements in these regions may have a significant impact on the phenotype of the individual. If the karyotype is normal in a patient with dysmorphic facial features, congenital anomalies, developmental delay, and mental retardation, then the clinician should consider ordering subtelomere FISH studies for further genetic evaluation.

Cardiac malformations reported to date in children with subtelomere chromosomal rearrangements include aortic arch anomalies, VSD, atrial septal defect, mitral valve insufficiency, and concomitant pulmonary stenosis with VSD. [2,16] Most of the published studies of subtelomere abnormalities indicate that a 4% to 9% prevalence of subtle chromosome rearrangements can be detected in children or adults with microcephaly, hydrocephaly, tracheoesophageal fistula, skeletal anomalies, multiple congenital anomalies, polycystic kidney, duodenal atresia, syndactyly, epilepsy, mental retardation, developmental delay, and/or dysmorphic facial features[2]. The use of subtelomeric FISH analysis has significant utility in individuals with normal karyotypes, especially if there are multiple congenital anomalies that include mental retardation or CHD.[15]

### DNA MUTATION ANALYSIS

The cytogenetic methods described above identify large changes in chromosome number or structure. However, in certain disorders, changes occur at the level of a single gene and must be detected by alternative techniques. 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 identifies changes in the coding sequence of the gene, including small deletions, insertions, or substitutions of nucleotides that alter the encoded amino acid and consequently protein structure. Most methods employ polymerase chain reaction– based assays.

**DNA sequence analysis** is performed by analyzing polymerase chain reaction **(PCR)** products derived from the individual exons, along with flanking splice-site sequences and regulatory regions, for a particular gene. PCR uses sequence-specific primers to amplify a sequence of interest for performing DNA sequencing. This requires only a small amount of blood, from which total genomic DNA is extracted from peripheral blood lymphocytes. Although this is currently only performed in research laboratories, the development of high-throughput DNA sequencing techniques makes it likely that mutation screening will eventually become widely available in clinical laboratories for patient diagnosis.[5]
At present, very few candidate genes have been identified which cause CHDs in human beings.

| Gene | Chromosome locus | Type of defects |
|---|---|---|
| CSX/ NKX2.5 | 5q34 | ASD, VSD, AV block, TOF, Ebstein malformations and Tricuspid valve abnormalities |
| GATA4 | 8p22-23 | ASD,VSD, AVSD, Pulmonary valve thickenings |
| TBX5 | 12q24.1 | ASD, VSD, AVSD,TOF, HLHS, AS |
| IRX4 | 5p15.3 | SV |
| JAGGED-1 | 20p12 | TOF |
| Elastin | 7q11 | AS |
| Fibrillin | 15q21 | AA |

**Table I.** – Genes causing different types of CHDs with there chromosomal region in humans

SYNDROMES ASSOCIATED WITH CONGENITAL HEART DEFECTS

| Chromosomal Disorder | Main Features | Percent With CHD | Heart Anomaly |
|---|---|---|---|
| Deletion 4p (Wolf-Hirschhorn syndrome) | Pronounced microcephaly, widely spaced eyes, broad nasal bridge (Greek helmet appearance), downturned mouth, micrognathia, cleft lip, palate, preauricular skin tags, elongated trunk and fingers, severe mental retardation and seizures; 1/3 die ininfancy | 50–65% | ASD, VSD, PDA, LSVC, aortic atresia, dextrocardia, TOF, tricuspid atresia |
| Deletion 5p (cri-du-chat) | Catlike cry, prenatal and postnatal growth retardation, round face, widely spaced eyes, epicanthal fold, simian crease, severe mentalretardation, long survival | 30–60% | VSD, ASD, PDA |
| Deletion 7q11.23 (Williams-Beuren syndrome) | Infantile hypercalcemia, skeletal and renal anomalies, cognitive deficits, "social" personality, elfin facies | 50–85% | Supravalvar AS and PS, PPS |
| Trisomy 8 mosaicism | Skeletal/vertebral anomalies, widely spaced eyes, broad nasal bridge, small jaw, high arched palate, cryptorchidism, renal anomalies(50%), long survival | 25% | VSD, PDA, CoA, PS, truncus arteriosus |
| Deletion 8p syndrome | Microcephaly, growth retardation, mental retardation, deep-set eyes, malformed ears, small chin, genital anomalies in males, long survival | 50–75% | AVSD, PS, VSD, TOF |
| Trisomy 9 | Severe prenatal and postnatal growth retardation, marked microcephaly, deep-set eyes, low-set ears, severe mental retardation; 2/3 die in infancy | 65–80% | PDA, LSVC, VSD, TOF/ PA, DORV |
| Deletion 10p | Frontal bossing, short down-slanting palpebral fissures, small low-set ears, micrognathia, cleft palate, short neck, urinary/genital, upper-limb anomalies | 50% | BAV, ASD, VSD, PDA, PS, CoA, truncus arteriosus |
| Deletion 11q (Jacobsen syndrome) | Growth retardation, developmental delay, mental retardation, thrombocytopenia, platelet dysfunction, widely spaced eyes, strabismus, broad nasal bridge, thin upper lip, prominent forehead | 60% | HLHS, valvar AS, VSD, CoA, Shone's complex |

| | | | |
|---|---|---|---|
| Trisomy 13 (Patau syndrome) | Polydactyly, cleft lip and palate, scalp defects, hypotelorism, microphthalmia or anophthalmia, colobomata of irides, holoprosencephaly, microcephaly, deafness, profound mental retardation, rib abnormalities, omphalocele, renal abnormalities, hypospadias, cryptorchidism, uterine abnormalities; 80% die in first year | 80% | ASD, VSD, PDA, HLHS, cardiac malpositions especially Dextrocardia (6%) |
| Trisomy 18 (Edwards syndrome) | IUGR, polyhydramnios, micrognathia, dolicocephaly, short sternum, hypertonia, rocker-bottom feet, overlapping fingers and toes, TEF, CDH, omphalocele, renal anomalies, biliary atresia, profound mental retardation; 90% die in first year | 90–100% | AVSD, VSD, PDA, TOF, DORV, D-TGA, CoA, BAV, BPV, polyvalvular nodular dysplasia |
| Deletion 20p12 (Alagille syndrome) | Bile duct paucity, cholestasis, skeletal or ocular anomalies, broad forehead, widely spaced eyes, underdeveloped mandible | 90% | Peripheral PA, hypoplasia, TOF, PS |
| Trisomy 21 (Down syndrome) | Hypotonia, hyperextensibility, epicanthal fold, simian crease, clinodactyly of fifth finger, brachydactyly, variable mental retardation, This chromosomal defect has the highest association with major heart abnormalities. | 40–50% | AVSD (50%), VSD, ASD, (TOF, D-TGA less common) |
| Tetrasomy 22q (cat eye syndrome) | iris colobomata, ear tags and imperforate anus | 30% | total anomalous pulmonary venous drainage, AVSD |
| Tetrasomy 12q (pallister killian syndrome): | is associated with mosaicism of chromosome | 25% | VSD, COA, PDA, ASD, |
| Deletion 22q11 DiGeorge, velocardiofacial, and conotruncal anomaly face syndrome) | Hypertelorism, micrognathia, low-set posteriorly rotated ears, "fish mouth," thymic and parathyroid hypoplasia, hypocalcemia, feeding/speech/learning/behavioral. disorders,ımmunodeficiency, palate/ skeletal/renal anomalies,heart disease-particularly conotruncal malformations, a characteristic facial appearance, Standard karyotypic analysis, even with high-resolution banding techniques will only detect 10-20% of 22q11 deletions | 75-80% | IAA-B, truncus arteriosus, isolated aortic arch anomalies, TOF, conoventricular VSD |
| Monosomy X (Turner syndrome, 45,X) | Lymphedema of hands and feet, widely spaced hypoplastic nipples, webbed neck, primary amenorrhea, short stature, normal ıntelligence | 30% | VSD, CoA, BAV, HLHS, aortic dissection, MVP |
| Klinefelter syndrome (47,XXY) | Usually normal appearing, tall stature, small testes, delayed puberty, emotional and behavioral problems common, variable mental retardation | 50% | MVP, venous thromboembolic disease, PDA, ASD |

**Table II.** – Representative chromosomal disorders associated with congenital heart defects

### Other syndromes

*Noonan syndrome:* Children with this syndrome have specific features such as valvular pulmonary stenosis, short stature, mild learning difficulties, and dysmorphic appearance. The cardiac disease seen in this syndrome includes PS,[33] ASD, PDA, VSD and asymmetric septal hypertrophy[14].

*Kabuki syndrome:* It is characterized by distinct facial anomalies, variable degrees of mental retardation, CHDs and skeletal malformation. The CHDs include ASD, VSD, TOF, PDA, TGA, aortic Coarctation, single ventricle with common atrium and right bundle branch block[3].

*Ellis- van Creveld:* It shows skeletal dysphasia characterized by short limbs, short ribs, postaxial polydactyly, dysplastic nails and teeth.36 CHDs occur in 60% of affected individuals that are disease in primary atrial septation; single atrium and Hypoplastic left heart syndrome[14].

*Fragile –X Syndrome:* It is caused by a trinucleotide repeat expansion (CGG) in the fragile X mental retardation gene (FMR1) at Xq27.3 (6). Cardiac disease include mitral valve prolapse, which can be seen in up to 50% of adult patients with Fragile X syndrome. There are also incidences of mild dilation of aortic root in adults[13].

*Chromosome deletion and duplication Syndromes:* Congenital heart lesions are common in most of the macro deletion syndromes and the cardiac anomalies vary widely even in those with apparently identical deletion breakpoints. It includes 3q, 4q, 5p, 8p, 9p, 11q, 13q, 18p, and 18q deletion syndromes. There are an equal number of duplication syndromes that also can be present with multiple congenital malformation and cardiac lesions such as 1p, 2p, 2q, 2p, 5p, 8p, 13q and 16q duplication syndromes[13].

### Gene mutations

*Holt-Oram syndrome/atrial septal defects* is characterized by atrial and ventricular septal defects in association with limb anomalies. Recently, this syndrome was found to be due to mutations in the gene TBX-5,a member of the T-box family of transcription factors.[14]

Williams syndrome/supravalvar aortic stenosis and pulmonary stenosis is a rare dysmorphic syndrome characterized by heart defects, most commonly, supravalvar aortic stenosis, peripheral pulmonary stenosis wich are associated with an elfin-like face, mental retardation, neonatal hypercalcemia, and a so-called cocktail party personality. This disorder is caused by a microdeletion at 7q11. Studies of patients with isolated supravalvar aortic stenosis and/or pulmonic stenosis have demonstrated that mutations in the gene encoding the structural protein elastin, which is located within the region deleted at 7q11, are responsible for these cardiac defects. Mutations in elastin are inherited in an auto-

somal dominant mode. Microdeletions can be detected with FISH using probes within the 7q11 critical region, although screening for elastin point mutations is currently only performed in research laboratories[5].

*Alagille syndrome/right-sided obstructive lesions and tetralogy of fallot* is a rare disorder characterized most commonly by peripheral pulmonic stenosis and tetralogy of Fallot, in association with neonatal jaundice caused by a deficiency of intrahepatic bile ducts. Recently, mutations in the JAG1 gene, which encodes a ligand for the notch receptor involved in signaling pathways in cell fate determination in early cardiac development, were found to cause this disorder.[12] Inheritance is autosomal dominant, and to date, mutation screening is only performed in research laboratories.

### Genetic evaluation for children with CHD

a) Cytogenetic testing should be considered in the following situations[10]:

1. Any infant or child with the phenotype of a recognizable chromosomal syndrome (eg, trisomy 21 or 18)
2. Because not all chromosomal abnormalities result in a clinically recognizable syndrome, any infant or child with a congenital heart defect combined with (a) dysmorphicfeatures, (b) growth retardation that cannot be explained by the heart defect, (c) developmental delay or mental retardation, or (d) multiple congenital anomalies
3. Infants or children with a family history of multiple miscarriages and/or siblings with birth defects
4. If major cardiac and/or other visceral organ malformations are documented by prenatal ultrasound and/or fetal echocardiogram

b) Genetic consultation is recommended in the presence of mental retardation, multiple congenital anomalies, or facial dysmorphia or if the standard karyotype is normal despite the clinical suspicion of a genetic abnormality (ie, normal karyotype in the presence of dysmorphism, mental retardation, and/or multiple congenital anomalies that include cardiac defects). In this situation, high-resolution banding or more advanced cytogenetic techniques may be indicated (FISH). Consultation with a clinical geneticist is recommended when a chromosomal abnormality is discovered so that appropriate counseling and evaluation of family members may be undertaken[10].

### Impact on patients

For individuals with CHD and their families, identification of a genetic cause is very beneficial. This allows confidence in the diagnosis and allows the physician to explain the exact genetic mechanisms to the family. It also alerts the clinician to investigate other

organ systems that may be involved in the syndrome and broadens the context of evaluation from the individual to other family members[10].


## Summary

Patients with CHD require multidisciplinary care. Pediatricians require knowledge about these issues in caring for multiple organ systems in children with genetic syndromes that include CHD. Families of these children will need information about recurrence risk.


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# Persistent Pulmonary Hypertension Of The Neonate (Pphn)

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Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes inadequate pulmonary perfusion developing refractory hypoxemia, right-to-left extrapulmonary shunting of blood, respiratory distress and acidosis. PPHN is failure of the normal circulatory transition that occurs after birth. It was first described by Gersony in 1969 as a neonatal condition characterized by cyanosis and hypoxemia. This pathophysiologic syndrome has been described also as: persistent pulmonary vascular obstruction, persistent fetal circulation, pulmonary vasospasm. This syndrome causes substantial morbidity and mortality in otherwise healthy, nearterm newborns.[3,4,9]

**Keywords:** persistent pulmonary hypertension of the newborn (PPHN), NO, PDE5 inhibitors

## Fetal pulmonary vasculature

The fetal pulmonary circulation undergoes striking developmental changes in vascular growth, structure, and function. Despite increases in pulmonary vascular surface area, PVR increases with gestational age, so the vascular tone increases during late gestation and is high prior to birth. Several factors maintain high pulmonary vascular resistance in fetal life:

- hypoxia: PaO2<40-45 mmHg (fetal PaO2 average is 20-25 mmHg). Hypoxia has a vasoconstrictor effect.
- mechanical compression of the pulmonary vessels, because the lungs are not expanded in utero.
- hypocapnia: PaCO2 < 30 mmHg, but it has a a minor role in maintaining vasoconstriction.
- low basal production of vasodilator products: prostacyclin (PGI2) and nitric oxide (NO).
- increased production of vasoconstrictors: endothelin-1 (ET-1) and leukotrienes.
- altered smooth muscle cell reactivity (increased basal tone).[3,9,13]

## Changes in the pulmonary and systemic circulation at birth

The fetus uses placental circulation for gas exchanges. The placenta is a very low resistance outlet for fetal systemic blood flow. In fetal life pulmonary blood flow is low, with less than 10% of the cardiac output directed to the lungs, and pulmonary vascular resistance is very high compared to systemic vascular resistance, wich is low resistance. Because of the high pulmonary vascular resistance, about 87% of right ventricular output crosses the foramen ovale and the patent ductus arteriosus and enters into the low resistance systemic and placental circuit, bypassing the lungs.

WAfter birth, with clamping of the umbilical cord the low resistance placenta is removed from the systemic circuit and systemic blood pressure rises (systemic vascular resistance increases). This in turn, increases pressures in the left ventricle and left atrium.

WThe lungs assume the function of gas exchange. During lung expansion, the arteries straighten out and become less resistant to blood flow, PVR decreases, and pulmonary blood flow increases dramatically. During rhythmic ventilation of the lung the oxygen tension in the alveolus and in arterial blood (PaO2) increases, pulmonary vasoconstriction relaxes and pulmonary vascular resistance becomes less than systemic vascular resistance. Increased oxygenation (PaO2) also results in constriction of the ductus arteriosus. Because the neonate is better oxygenated than the fetus, the ductus becomes functionally closed in the full-term infant by 24-36 hours, but it remains anatomically patent for several weeks to months after birth.

WThe rise in systemic pressure, the decrease in PVR and in pulmonary artery pressure, decreases the right to left shunt through the ductus arteriosus. It increases the pulmonary artery blood flow, increasing pulmonary venous return to the left atrium (high pressure in left atrium). When the left atrial pressure exceed right atrial pressure, the foramen ovale closes. With the redirection of blood into the lungs and the complete transition of the lung into an air-filled structure, neonatal cardiopulmonary adaptation is complete[15,21].

## The role of NO and prostacyclins (PGI2) in pulmonary vasodilatation

**Endogenous NO** is believed to be one of the major factors responsible for the fall in pulmonary vascular resistance necessary for normal conversion from fetal to neonatal circulation. NO is found in many different tissues and has numerous functions within the body; one of its primary functions is peripheral arterial-venous dilation. NO plays a role in the immune system, modulates the antiaggregatory activity of platelets within the vascular system, acts as a neurotransmitter, and is a very potent endothelium relaxing factor.[8,9,13,16]

NO is short-lived (half-life of approximately 1-3 seconds), highly reactive molecule, cleaved from its precursor, L-arginine, by the enzyme nitric oxide synthase (NOS). L-Arginine is converted to citrulline and NO. Pulmonary endothelial cells are an active site of NOS activity. NO production increases dramatically at the time of birth. NO generated

in the endothelium enters the adjacent vascular smooth muscle where it directly activates soluble guanylate cyclase (sGC) resulting in increased levels of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells. Activation of a cascade of GMP-dependent is upregulated during late gestation.[9,11,12,13]

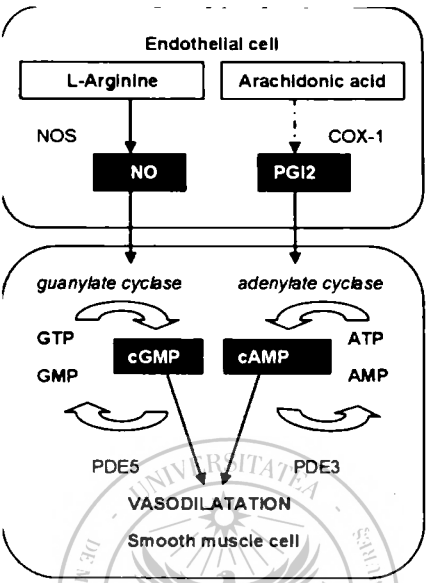


**Fig. 1** Vasodilatatory effects of NO and PGI2

The increase in estrogen concentrations in late gestation play a role in upregulating PGI synthesis. This leads to an increase in prostacyclin production in late gestation and early postnatal life. Prostacyclin interacts with adenylate cyclase (AC) to increase intracellular cyclic adenosine monophosphate (cAMP) levels, which leads to relaxation of pulmonary vessels.

Oxygen stimulates the activity of both eNOS and COX-1 immediately after birth, leading to increased levels of NO and prostacyclin. Oxygen also stimulates the release of adenosinetriphosphate (ATP) from oxygenated red blood cells, which increases the activity of both eNOS and COX-1. Advances in the understanding of the physiology of vasoactive mediators have revealed that there is a high concentration of phosphodiesterases (PDE) in pulmonary vasculature (Rabe 1994). PDE are a class of proteins whose most relevant biological activity concerns the modulation of intracellular levels of cyclic nucleotides: cGMP and cAMP. PDE isoenzyme 5 (PDE5) is specifically involved in cGMP inactivation in the smooth muscle cell, and PDE isoenzyme 3 (PDE3) exhibit a high affinity for inactivation cAMP and are specifically inhibited by cGMP.

The inhibition of the PDE involved in the degradation of cGMP to guanosine monophosphate (GMP), and cAMP to adenosine monophosphate (AMP) selectively reduce pulmonary vascular resistance.[15,19] (figure 1)

## Pathophysiology of PPHN

In some newborns, the pulmonary vascular resistance fails to decrease after birth, despite improved alveolar oxygenation and lung expansion, and the pulmonary vascular pressure remains abnormally high. The result is persistent pulmonary hypertension: the pulmonary vascular resistance remains equal to or greater than systemic vascular resistance, and the blood continuing to flow through the foramen ovale and ductus arteriosus. Persistent high pressure in pulmonary vessels leads to less blood flow to the lungs and therefore less oxygen reaching the blood, that causes severe hypoxemia. With high vascular resistance and the subsequent hypoxemia, myocardial performance (especially the right heart) may become extremely compromised resulting in right heart dilation, tricuspid insufficiency, and right heart failure.

Possible pathogenetic mechanisms include: *intrauterine closure of the ductus* with redirection of blood flow into the high-resistance fetal pulmonary vasculature (it may occur in mothers who take high dose aspirin near term-Perkin, 1980), *inability of the pulmonary vasculature to relax* after the stimulus for vasoconstriction is removed (birth asphyxia), *intrauterine hypoxia* (which stimulates the hypertrophy of medial smooth muscle which surrounds pulmonary arterioles, enabling vessels to constrict to an extreme degree for long periods of time (Haworth, 1976, Levin, 1978a, Murphy, 1981, Geggel, 1984), *undergrowth of the pulmonary vascular tree* (congenital diaphragmatic hernia or other causes of pulmonary hypoplasia) *alterations in vasoactive mediator levels*.[1,2,4]

PPHN appears in term or near-term infants and it can be *primary* (idiopathic) or *se-condary* to pulmonary parenchymal disease (meconium aspiration syndrome, surfactant deficiency), severe pulmonary hypoplasia (with or without congenital diaphragmatic hernia), polycythemia, hypoglycemia, neonatal sepsis or maternal ingestion of prostaglandin inhibitors (Adatia 2002, Gersony 1984). This condition is most often associated with perinatal asphyxia in 50-70% of reported cases.

The primary forms tend to occur in newborns born at term and near-term (>34 wks of gestation), in the absence of underlying parenchymal disease. In these cases, the syndrome is the result of an abnormally remodeled vasculature that develops in utero in response to prolonged fetal stress, hypoxia, and/or pulmonary hypertension. The result is an excessive and peripheral muscularization of pulmonary arterioles. Idiopathic PPHN is associated with a normal chest radiograph and no parenchymal lung disease and it presents like pure vascular disease. Some clinicians refer to this syndrome as black-lung PPHN or clear-lung PPHN (clear, hyperlucent lung fields on radiography).

PPHN often results when structurally normal pulmonary vessels constrict in response to alveolar hypoxia due to hypoventilation or parenchymal disorders, such as hyaline membrane disease, pneumonia or meconium aspiration syndrome (MAS).[5]

Incidence of PPHN syndrome: 2-6 cases per 1000 live births The incidence of PPHN was reported to be 0.37% among neonate delivered by elective cesarean section, almost five fold higher than in those who had normal vaginal delilvery. Mortality rate is up to 33% (Walsh-Sukyus 2000).

This syndrome is usually noted in term or post-term infants. Symptoms and signs include: progressing respiratory distress with *tachypnea, retractions* (but with minimal during the first day of life), *severe cyanosis* or desaturation unresponsive to supplemental O2, and *acidosis*. It can mimic the symptoms of cyanotic congenital heart disease. With a large right-to-left shunt through a patent ductus arteriosus, an oxygen tension gradient may be noted between the preductal arterial circulation (i.e. right upper extremity) and the postductal arterial circulation (i.e. lower extremities). O2 saturation in the lower extremities is 5% lower than in the right upper extremity. This is explained by the fact that the subclavian artery supplying the right upper extremity branches off from the aorta before the ductus arteriosus, thereby receiving relatively oxygenated blood. Most of the blood, which is deoxygenated, has been shunted away from the right side of the heart to the aorta through the ductus arteriosus, bypassing the lungs. However, this gradient may not be present if substantial shunting is present at the level of the foramen ovale. Supplemental oxygen is needed in an attempt to correct arterial hypoxemia. The infants chest radiograph may be normal (as noted in infants with primary PPHN) or demonstrate various abnormalities compatible with aspiration, pneumonia, diaphragmatic hernia, or hyaline membrane disease. Hypotension is a late finding usually resulting from both heart failure and persistent hypoxemia. Cardiac examination: *systolic murmur* secondary to tricuspid regurgitation. The patient may have evidence of *poor cardiac function and perfusion.* [3,7,14,15]

## DIAGNOSIS

Diagnosis is by history, examination, chest x-ray, and response to O2. It should be suspected in any near-term infant with lability of oxygenation, arterial hypoxemia and/or cyanosis, especially one with a suggestive history whose O2 saturation does not improve with 100% O2 (hyperoxic test). The clinical diagnosis of PPHN is considered when there is *hypoxemia* refractory to oxygen therapy: PaO2 < 55 mmHg despite FiO2 of 1.0 (Roberts 1997, Shah 2004) associated with a *preductal to postductal oxygen gradient* greater than 20 mm Hg.

The diagnosis is confirmed by *echocardiogram*, which can confirm: the presence of elevated pressures in the pulmonary artery using Doppler investigation, tricuspid regurgitation-allows indirect measurement of the PVR, ductual and foramen ovale shunting. Echocardiography is crucial to exclude cyanotic congenital heart disease (particularly transposition of the great arteries, and totally anomalous pulmonary venous return) but is not always available. It is also useful to assess myocardial function and the severity of PPHN and to assess responses to treatment.

## Prognosis

An oxygenation index ( OI ) > 40 predicts mortality of > 50%.

$$OI = \frac{MAP \times 100}{PaO_2(mmHg)} \times FiO_2$$

where MAP is Mean Airway Pressure,
PaO2 is the arterial oxygen tension in mmHg and
FiO2 is the fraction of inspired oxygen (100% = 1.0, air = 0.21)

However, many survivors exhibit developmental delay, hearing deficits, and/or functional disabilities.[16,17,18]

## Treatment

*Current management:*

- Correction of factors that may promote vasoconstriction (hypoxia, hypoglycemia, hypothermia, acidosis) Normal fluid, electrolyte, glucose, and Ca levels must be maintained. Infants should be kept in a neutral thermal environment and treated with antibiotics for possible sepsis until culture results are known.
- If surfactant deficiency is present, exogenous surfactant should be given. The use of exogenous surfactant in conditions characterised by surfactant inactivation (meconium aspiration syndrome and pneumonia) may be considered in individual cases.
- Parenteral nutrition to provide optimal nutritional support.
- Inotropic support with dopamine and/or dobutamine (continuous infusion: dose ranges from 5 - 20 mcg/g/min IV), alone or in combination, for maintaining adequate cardiac output and systemic blood pressure (above 50 mmHg) while avoiding excessive volume administration. Although dopamine is frequently used as a first-line agent, dobutamine is helpful when myocardial contractility is poor. Dobutamine produces selective positive inotropic effects and therefore produces a mild chronotropic effect. Dobutamine is characterized as a selective beta1-agonist as a result of its primary effect of increasing myocardial contractility by means of beta1 stimulation.
- minimal stimulation to minimize the need to handle the patient and to perform invasive procedures (suctioning).
- *Oxygen* and *mechanical ventilation* to maintain adequate oxygenation (recruiting areas of atelectasis but avoiding overdistension). Treatment with O2, which is a potent pulmonary vasodilator, is begun immediately to prevent disease progression. Ventilator settings have to maintain normal expansion of approximately 9 ribs on chest radiography, to avoid overdistension. Mechanical ventilation using inappro-

priate setting can produce acute paranchymal lung injury causing pulmonary edema, decreasing lung compliance and promoting lung inflammation. It is important to use low positive end expiratory pressure (PEEP) and prolonged expiration to prevent air trapping. FiO2 should initially be 1 but can be titrated downward to maintain PaO2 between 50 and 90 mm Hg to minimize lung injury. Once PaO2 is stabilized, weaning can be attempted by reducing FiO2 in decrements of 2 to 3%, then reducing ventilator pressures by only 1-2 cm H2O; changes should be gradual (slow weaning from ventilator) because a large drop in PaO2 can cause recurrent pulmonary artery vasoconstriction. It is recommended to use "mild hyperventilation" with avoidance of hypocarbia because it may cause cerebral vasoconstriction (maintaining PaCO2: 35–60 mmHg). In addition, prolonged hyperventilation reduces cerebral blood flow and oxygen delivery to the brain, potentially worsening neurodevelopment outcome. In newborns with severe airspace disease who require high peak inspiratory pressures (>30 cm H2O) or mean airway pressures (>15 cm H2O), consider *high-frequency oscilatory ventilation* (HFOV) to reduce barotrauma. When HFOV is used, the goal should still be to optimize lung expansion to avoid overdistension. Use of HFOV instead of traditional modes of mechanical ventilation such as intermittent mandatory ventilation (IMV) or synchronized IMV has produced remarkable improvements in oxygenation. HFOV maintains gas exchange at lower mean airway pressures and peak inspiratory pressures. Because increased alveolar pressure may increase the amount of gas exchange between the alveoli and the blood, HFOV may allow a higher concentration of inhaled nitric oxide than conventional IMV does. Combined therapy using HFOV and inhaled nitric oxide seems to be superior to either therapeutic modality alone in the treatment of hypoxemic respiratory failure. Because of their lability and ability to fight the ventilator, newborns with PPHN nearly always require sedation with Fentanyl, Midazolam. [6,10, 11]

- *avoidance of significant acidosis* by maintaining pH >7.30, alkalosis when it needed with sodium bicarbonate 8,4% (ventilation must be adequate). Forced alkalosis by using sodium bicarbonate and hyperventilation were popular therapies in the past because of their ability to produce acute pulmonary vasodilation and increase PaO2. However, hypocarbia is associated with constriction of the cerebral vasculature, reduction of cerebral blood flow, and systemic hypotension. Extreme alkalosis and hypocarbia are strongly associated with late neurodevelopmental deficits.
- *extracorporeal membrane oxygenation (ECMO)* may be used in patients with severe hypoxic respiratory failure defined by an oxygenation index > 35 to 40 despite maximum respiratory support, but this is an extremely invasive and expensive procedure that may predispose the infant to intraventricular hemorrhage. In addition, many infants with PPHN are excluded from possible ECMO treatments due to low birth weight, young gestational age, or problems with the central nervous or cardiovascular systems. The treatment may be associated with neurological complications. ECMO also requires the use of large amounts of blood products and is very

labor intensive. For these reasons, it is a treatment to be undertaken *only as a last resort.*

### Pulmonary vasodilators

- *Inhaled nitric oxide (iNO):* is considered the mainstay in the treatment of PPHN by virtue of its selective pulmonary vasodilator effects (Barrington 2001), but it is expensive and not available everywhere. The delivery system for the inhaled–nitric-oxide therapy adds the nitric-oxide gas into the inspiratory limb of the ventilator circuit in proportion to, and in synchrony with, the ventilator's gas flow. Treatment with iNO is indicated for newborns with an OI >25. iNO should be started at 20ppm (parts per million) and reduced to 5ppm as able, according to response and to stability. Methaemoglobin levels should be monitored. Most newborns require iNO for 5 days. In general, the dose can be weaned to 5 ppm after 6-24 hours of therapy. The dose is then weaned slowly and discontinued when the FiO2 is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided become it may cause abrupt rebound pulmonary hypertension. [11,12, 16, 20]
- *Magnesium sulphate* (MgSO4) may be used in refractory cases. The use of MgSO4 is controversial but may be indicated in selected instances. At high serum concentrations Mg is a potent vasodilator, muscle relaxant and sedative. It is the second most common intracellular cation. Magnesium the natural calcium blocker antagonizes calcium entry into smooth muscle cells, thus promoting vasodilation. It may also exert its favorable influence on nitric oxide synthetase, cyclicnucleotides, endothelins and prostaglandins. Some authors consider that MgSO4 is a nonaggressive and low cost treatment of short duration which is easy to apply. Doses: loading dose of 200 mg/kg given over 30 minutes, followed by a continuous infusion at the rate of 20–150 mg/kg/h.
- *Prostacyclin* may also be used in severe and refractory cases, although it is difficult to obtain and its use is controversial.
- *Phosphodiesterase 5 inhibitors (sildenafil)* lead to relaxation of pulmonary vascular smooth muscles (Humbert 2004). In the last years sildenafil has been used as a pulmonary vasodilator. Sildenafil is a potent, specific, orally available PDE5 inhibitor. Reductions in pulmonary vascular resistance have been shown with sildenafil in adults with pulmonary hypertension as monotherapy or in combination with inhaled prostacyclin. Dose: 1-2 mg/kg every 6 hours. Discontinuation of treatment with sildenafil will be decided when OI <20.[6,7,14,23]

### Outcome

If this syndrome is severe, it can result in death. Follow-up of survivors (without congenital diaphragmatic hernia) several months after birth has revealed few abnormalities

of pulmonary or circulatory systems. However, other significant problems have been reported. In those infants treated with hyperventilation, sensorineural hearing loss has been found in up to 53% of survivors (Walton,1991, Hendricks-Munoz, 1988).

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# The Role Of Noninvasive Multislice Angio Ct/Mri In Detecting And Defining Heart Malformations In Children

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Evaluation of congenital heart disease is an important application of multislice angio CT and MRI, because of an accurate description of the morphological anatomical heart defects and anomalous connections. Both technique are increasingly considered a useful non invasive examination in the diagnose and management of cardiovascular malformations, as a result in significant advances in technologies. Their utility is further increased especially during follow up patients after corrective surgery. This article want to present current multislice angio CT and MRI applications in common congenital heart malformations.

**Keywords:** multislice angio CT, MRI angiography, congenital heart defect, children.

## Introduction

Congenital heart disease occurs in 0.8 % of live newborns. A large number of patients undergo surgical procedure in newborn or childhood period. Nearly 50,000 adults with congenital heart disease have surgically treated, but despite this, at least 150,000 children and adults fall into a large subset of unrecognized, misdiagnosed and undiagnosed but untreated category.

From the historically point of view, catheter angiography has been the principle diagnostic tool in the assessment of congenital heart disease, but is usually associated with high dose radiation and prolonged sedation, affecting pediatric patients. Technological advances established echocardiography to be the gold method in detecting and diagnose of congenital heart disease, but despite of very clear imaging obtained from trans-esophageal echocardiography, this method still have his limits in the assessment of right ventricle, aorta, and the peripheral pulmonary arteries. An alternative for this exploration is non-invasive multislice angio CT or MRI angiography[4,9].

## CT angiography in pediatric patients with congenital heart disease

CT technology has changed the approach to non-invasive assessment of congenital heart disease, in both pediatric and adult patients. Rapid advances in spatial and temporal

resolution over the last 3-5 years, and in post-processing capability, allows much faster acquisition times and improved spatial resolution, because of more thinner slices 14. From 2000, every 2 years there had been doubling the detector rows, from 4 to 16, 32 and 64 rows. So, CT scan is becoming a leading modality for non-invasive imaging of cardiovascular pathology. In adults, multislice CT is considered to be superior to conventional invasive angiography, particular for coronary vessels.

In pediatric patients with complex congenital heart defects, sometimes ultrasound is not enough to visualize certain anatomic structures, despite the fact that cardiac ultrasound is the leading diagnostic modality for interrogation of intra-cardiac structures in children. For this situations, CT scan allows superior diagnostic capabilities, due to high precision three dimensional imaging. This indicates CT for precise diagnose in complex congenital heart disease, for preparation before cardiac surgery, sometime in place or before catheterization, and after surgery, to appreciate the results of surgical reconstruction, in high precision three dimensional imaging[3].

## Indications

If in adults the first indication of CT scan is noninvasive coronary angiography, followed by visualization of: pulmonary embolism, aortic dissection, aortic aneurism, arterio-venous malformations, in pediatric patients the indications are: complex congenital heart defects, visualization of aorta, pulmonary artery branches, coronary artery, systemic and pulmonary venous structures [9]. For this pediatric patients, CT allows superior diagnostic capabilities, because of high-precision three dimensional imaging provided. The speed of acquisitions, 6 – 8 seconds is so fast that sedation is most of the time not necessary, even for critical care of infants [12,14]. The information are comparable with catheter angiography.

## Technical data

Sedation is sometimes necessary in neonates, infants, small children, unable to achieve a 5 second breath – hold. The sedation can be done with intra-rectal Diazepam or Chloral hydrate oral, 30 minutes before investigation. For a good examination, it is necessary a heart frequency under 100 b/min and breath hold for 5 seconds, to prevent artifacts, which are more significant when the child is agitated and anxious. The aim of investigation is to acquire images as quickly as possible, when the child is lightly sedated or simply calm.

For a good angiography, the contrast solution is administrated by an automatic injector, to be sure that contrast solution passes at a uniform rate during the short acquisition period. Flow rate 0.5 ml/sec in neonates and 1-2 ml/sec in older children. Usually, contrast solution is gadolinium.

In older children sedation is avoided because breath-holding is possible, and also a good cooperation with the patient, which allow a good quality of acquisitions.

For the study of coronary arteries, a beta-blocker treatment is mandatory, to maintain a heart rate under 70 b/min. The treatment is done with Propranolol 1-2 mg/kg orally, 2 hours before the exam.

The contrast solution is gadolinium, 1.5 ml/kg, max. 70 ml, followed by 5 -10 ml saline solution, with a flow rate 2 – 3.5 ml/sec.

The acquisitions on standard slices are post–processed and analyzed in various planes, multi-planar and 3 D reconstruction [14]. For coronary CT angiography, analysis is more refined and requires reconstruction at different phases of cardiac cycle.

### Aortic angio CT application

A complementary method to echocardiography for evaluation of aortic morphology is angio CT. Supravalvular aortic stenosis, part of the Williams syndrome, can be well anatomically evaluated. Williams syndrome involve: elfin faces, hyper-calcemia, supravalvular aortic stenosis and sometimes peripheral pulmonary artery stenosis. Multislice angio CT can demonstrate the anatomically modifications of the vessels, especially the periferic pulmonary artery stenosis, often not visualized on transthoracic echocardiography [9].

Aortic coarctation and/or aortic hypoplasia, especially in newborn are extremely well evidenced. CT scan identifies the site of coarctation, defines the narrowing degree and precise the extent of hypoplasia. In older children relief the multiple dilatations of mamar arteries. It has major importance in relevance of seriated stenosis.

Angio CT of the vessels emerging from the aortic arch can reveal multiple malformations like: increased number of vessels (more than three), anomalous direction of the vessels, vascular ring, presence of lusoria artery, double aortic arch, etc. The location and direction of the aortic arch are well evaluated. The left aortic arch with aberrant right subclavian artery is the most common aortic arch anomaly, associated in 2-5 % with other cardiac malformations. The simplicity of the examination is due to the rapidity of image acquisitions, less than two seconds for newborns; the 3 D reconstruction offer a real anatomic aspect of the vessels for the cardiac surgeons. In vascular malformations, like vascular ring, multiplanar and 3D reconstruction demonstrates the origin and course of the vessels and also the relation with adjacent structures like airway tract [3,12].

In cyanotic children with pulmonary artery hypoplasia, MAPCA is well described, connecting aorta with pulmonary artery [10].

In patients with common arterial trunk, angio CT is the method of choice before surgery, précising exactly the type of the trunk and the branches going to the lungs.

In patients with untreatable value of blood pressure, where abdominal ultrasound is

irrelevant, multislice angio CT of abdominal aorta can reveal renal artery stenosis, location and aspect, determining the option of the treatment: stent dilatation or surgery.

### Coronary angio CT application

Despite the fact that in adults this method try to replace invasive angio-coronarography, and to select patients for stent implantation, in children it is used in some restricted malformations like: ALKAPA syndrome (anomalous origin of left coronary artery from pulmonary artery), or post surgery to evaluate the arterial switch operation for transposition of great arteries [13].

The 64 CT scan provide accurate imaging of the proximal coronary vessels, but this exploration remain in adults domain [18].

### Pulmonary artery angio CT application

The most common cyanotic congenital heart disease is Fallot Tetralogy. Pulmonary artery stenosis is one element of this disease.

Subvalvular stenosis and the right ventricle outflow tract can have a precise anatomic assessment.

Pulmonary atresia with VSD can not be well quantified by cardiac ultrasound, so that CT scanning by contrast can precise 3D mapping of the pulmonary arterial tree and reveal any aorto-pulmonary collaterals [14].

Systemic to pulmonary shunts can be evaluated and also the growth of the pulmonary arteries, after successive paleation. Also, measurements of pulmonary artery before stenting are very important, avoiding catheter exploration. Monitoring post stent implantation can reveal complications like aneurisms in the ejection tract.

Extremely rare can be seen coarctation of the pulmonary artery branch.

PDA visualization is useful when the echocardiographic window is of low quality.

### Venous return angio CT application

Complex congenital heart disease can associate partially or totally anomalous venous return, difficult for echocardiographic quantification[12,14]. Any patient with sinus venosus defect can be a candidate for totally or partially anomalous venous return. In partial anomalous pulmonary venous return, right sided anomalous drainage is more common than left. Scimitar syndrome, a rare anomalous drainage of right inferior pulmonary vein in inferior vena cava, associated with right diaphragmatic relaxation can be perfectly evaluated by angio CT.

Arterio-venous fistula can be localized with CT scan, describing the feeding artery and the receiving vein.

In cases of isomerism, for the planning of cardiopulmonary bypass, it is very important to have a real description of systemic venous return, where angio CT is absolutely relevant.

### ANGIO CT APPLICATION IN COMPLEX CONGENITAL HEART DEFECTS

Echocardiography remain the gold method of examination in congenital heart disease, but sometimes angio CT exploration is mandatory.

In patients with dextrocardia, L-TGA and cyanotic congenital heart defects, sometimes the echocardiographic window limits the exploration. For surgeons, angio CT and catheterism allow a good surgical repair. In case of complications, these can be accurately assessed with multislice CT[12,14].

In the heterotaxy syndromes, the organs from thorax and abdomen have abnormal symmetry. The description of these organ modifications from asplenia or polysplenia syndromes, associated with cardiac defects are best visualized by angio CT application.

### ANGIO CT VERSUS MRI IN COMPLEX CONGENITAL HEART DISEASE

There are a lot of complex malformations, that are well revealed by echocardiography, but need more clear confirmation, especially by MRI. Angio CT is perfect for anatomic reconstruction, but MRI describe the functional blood flow [17]. The ability to quantify ventricular function and the advancements in flow quantification, determine MRI to become a powerful technique in congenital heart disease exploration [11,21].

### MRI IN PEDIATRIC PATIENTS WITH CONGENITAL HEART DISEASE

Cardiac MR imaging generate high-resolution images in any orientation, create cine images of the heart and angiographic images of aorta, pulmonary arteries, systemic and pulmonary veins [4,6,8]. The MRI protocol for pediatric patients with congenital heart disease comprises of anatomic and physiologic components. ECG-gated spin-echo imaging and Contrast enhanced MR angiography is used for anatomic information [5,16]. Functional informations are obtained from Cine Trufi (steady-state free precession), Cine Flash (gradient-echo) and Cine phase-contrast sequences [15]. These protocols for cardiology provide complementary data of the morphology of cardiac anatomy as well as the functional information across valves, ventricles, defects, shunts, and connections.

## MRI INDICATIONS

The major indications for MRI in the evaluation of patients with congenital heart disease have been now determined and includes [19,20]:

– segmental description of cardiac anomalies,
– evaluation of thoracic aortic anomalies,
– noninvasive detection and quantification of shunts, stenosis, and regurgitations,
– evaluation of cono-truncal malformations and complex anomalies,
– identification of pulmonary and systemic venous anomalies,
– post-operative studies in detecting complications and follow up operated patients.

## MRI LIMITS

There are some big limits in MRI investigation [19,20]:

– long time exploration, needing long time sedation in uncooperative small age children, infants or newborns,
– serious ill patients,
– breath hold sequences which may be difficult to perform in a setting of infants with cyanosis and respiratory distress, adversely affecting the use cine sequences,
– cardiac arrhythmias, which can interfere in MR acquisition resulting in sub optimal and non conclusive studies,
– pacemaker carriers.

However, cardiac MRI has emerged as an accurate method for the evaluation of structure and function of the heart [22].

## CONCLUSIONS

Despite the fact that in the largest number of cardiac malformations, trans-thoracic echocardiography remain the gold method in establishing a diagnose, there is a number of selected cardiac complex malformations in which this method is not enough.

CT and MRI are techniques of revolutionary alternative in morphology evaluation of congenital heart defects.

The major advance in the imaging acquisitions of congenital heart defects is multislice angio CT with 3D reconstruction.

CT is preferable to MRI, because of a very short time of examination, that sometimes do not need sedation in very ill newborns. The time of image acquisition is less than 2 seconds in neonates, but this technique is irradiating. In CT exploration, the ALARA (As Low As Reasonably Achievable) principles have to be followed [1]. If in adults, the quantity of radiations from CT is lower versus catheter radiation, in children has to be followed [21]!

MRI is not irradiating, but takes a long time for exploration, needing sedation in small children, sometimes anesthesia and collaboration with the technician.

Invasive angiography tends more and more to be substituted by images obtained with the latest generations of multislice angio CT and MRI [7].

Continuing advancements in gradient and fast scanning technologies will further push the frontiers of cardiac CT and MRI applications in exploration of congenital heart defects and in follow up patients undergoing surgical repair.

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# Genetic Variants In The Methylenetetrahydrofolate Reductase Gene And The Risk For Congenital Heart Defects

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The origin of isolated congenital heart defects (CHD) is considered to be multifactorial, resulting from interaction beetwen genetic and environmental factors. Folat is necessary for the synthesis of purine and thymidine nucleotides and for the synthesis of methionine from homocysteine. The impact of folic acid intake on pregnancy outcome and the role of both maternal and fetal genes that code for critical enzymes in the folate and homocysteine pathways on CHD risk is discussed. A common polymorphism in the human Methylenetetrahydrofolate reductase *(MTHFR)* gene, 677C→T, reduced *MTHFR* enzyme activity and is present in about 10-12% of Caucasians of Northern European descents. The *MTHFR 677T* allele is associated with decreased concentrations of folate in serum, plasma and red blood cells. The studies published in the literature do not provide strong evidence for an association between CHD risk and the *MTHFR 677C→T* polymorphism, either in mothers or in their offspring. Further, large studies performed in countries where food fortification with folic acid is not yet introduced are requested to enable definite conclusions on one of the most frequent polymorphism in *MTHFR* gene and CHD.

## Introduction

Congenital heart defects (CHD) are the most common structural birth defects, affecting approximately 8 to 10 of every 1000 live births. They account for approximately one third of all congenital anomalies, and are the single largest contributor to infant mortality atributable to birth defects. By definition, isolated structural cardiac malformations are not associated with other anomalies and do not occur as part of a genetic syndrome. The aetiology of this nonsyndromic CHD is complex, involving both genetic, epigenetic and environmental risk factors so their origin is considered to be multifactorial, resulting from an interaction between genetic predisposition and environmental factors.

A periconceptional multivitamin intake, including folic acid, reduces the risk of congenital malformations, above all neural tube defects, but also urinary tract defects and cardiac defects [1]. Although the underlying mechanism by which folic acid, in isolation or in concert with other multivitamins, exerts its protective effect is unclear, the teratogenic process resulting from folate insufficiency may be related to hyperhomocysteinemia. It is widely accepted that the impact of folic acid intake on pregnancy outcome is modified by

variants in both maternal and fetal genes that code for critical enzymes in the folate and homocysteine pathways.

Additional support for the importance of folate in CHD risk reduction was provided by Hernandez-Diaz et al. [4] Their study showed that periconceptional intake of medications acting as folic acid antagonists, including anti-epileptic agents and the group of drugs consisting of dihydrofolate reductase inhibitors, doubled the risk of cardiovascular defects such as conotruncal defects, ventricular septal, and other cardiovascular defects: OR 2.2, 95%CI 1.4–3.5.

## The role of methylenetetrahydroflate reductase gene (MTHFR) in folic acid metabolism

Folate is a water-soluble B-vitamin and enzymatic cofactor that is necessary for the synthesis of purine and thymidine nucleotides and for the synthesis of methionine from homocysteine. The term folate-mediated one-carbon metabolism refers to a metabolic system comprising several interdependent metabolic pathways that use the cofactor tetrahydrofolate to chemically activate single carbons (referred to as one-carbon units) for cellular biosynthetic reactions [13].

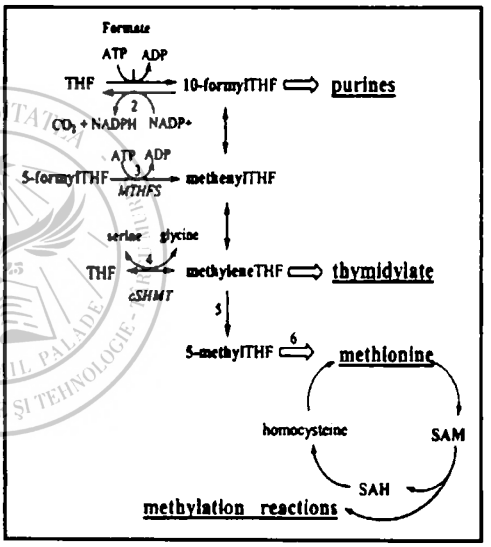


**Figure 1.** Folate metabolism. Methionine is converted to SAM (S-adenosylmethionine) which donates methyl groups for other one-carbon transfer reactions. (1) 10-formylTHF synthetase, (2) 10-formylTHF dehydrogenase (FDH), (3) methenylTHF synthetase (MTHFS), (4) serine hydroxymethyltransferase (cSHMT), (5) methyleneTHF dehydrogenase (MTHFR), (6) methionine synthase (MS).

Impairment of folate-mediated one-carbon metabolic pathways can result from B-vitamin deficiencies and/or single nucleotide polymorphisms, and increases risk for pathologies, including cancer and cardiovascular disease, and developmental anomalies [12]. Although several well validated metabolic and genomic biomarkers for folate deficiency exist, our understanding of the biochemical and genetic mechanisms whereby impaired folate metabolism increases risk for developmental anomalies and disease is limited, as are the mechanisms whereby elevated folate intake protects against these pathologies.

Methylenetetrahydrofolate reductase (MTHFR) catalyses the reduction of 5, 10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, which is the circulating form of folate. 5-Methyltetrahydrofolate donates its methyl group to homocysteine, forming methionine and tetrahydrofolate [13].

## Genetic polymorphisms in MTHFR gene

Single nucleotide polymorphisms (SNP) in genes that encode folate-dependent enzyme including *MTHFR*, methionine synthase and methionine synthase reductase can result in apparent folate deficiencies that can become symptomatic in the absence of frank folate deficiency or exacerbate the metabolic phenotypes that result from folate deficiency.

A common polymorphism in the human *MTHFR* gene, C677T resulting in a substitution of alanine to valine, reduced *MTHFR* enzyme activity. This leads to reduced capacity to remethylate homocysteine and generate SAM, and hypomethylation of lymphocyte DNA[3,10,14]. About 10-12% of Caucasians of Northern European descents carry the C→T substitution at position 677, in the *MTHFR* gene, referred to as 677TT genotype and they have approximately 25% higher homocysteine levels than 677CC genotype. The *MTHFR* 677T allele is also associated with decreased concentrations of folate in serum, plasma and red blood cells. The effect of the *MTHFR* 677CC genotype on homocysteine levels is more pronounced at low folate status[7].

Another polymorphism in *MTHFR* gene, 1298 A→C mutation, results in an amino acid change of glutamate to alanine in the regulatory C-terminal domain of the enzyme. In vitro, 1298C carriers showed a decreased enzyme activity, suggesting a functional importance of the A1298C polymorphism although through an unknown molecular mechanism. Nevertheless, it appears that the A1298C polymorphism alone does not significantly affect plasma homocysteinemia but may be determinant when combined with the 677T variant[16].

## Animal Models and folate deficency

In murine models dietary folate deficiency in mother has been shown to produce heart defects in embryos and an increased rate of early embryonic resorbtion. Folate deficient diets in rats showed that even transitory folate deficiency produced and increased the rate of cardiovascular and other systemic malformations in the embryos.

There has been reported that *Mthfr* +/– female mice, with a single null allele of Mthfr, give rise to offspring with CHD (mainly ventricular septal defects) and myocardial hypoplasia on gestational day 14.5 and there are evidence that maternal folate status and maternal *Mthfr* genotype, not embryonic genotype, are associated with the risk of CHD[9].

There are several possible mechanisms by which folate can affect proliferation. Folate derivatives are involved in a variety of critical cellular reactions, including nucleotide synthesis, amino acid synthesis, and methylation reactions. During embryonic development, myocardial cells undergo rapid mitosis or differentiation. Thus, it is not surprising that folate deficiency can affect proliferation. Another metabolic consequence of folate deficiency is an elevation of homocysteine, which was shown to inhibit proliferation in

vitro, and a decrease in methionine, which is required for the synthesis of S-adenosylmethionine for methylation reactions. Folate deficiency could therefore affect the expression of genes involved in cell proliferation, through an effect on DNA methylation [2]. The effect of folate deficiency on proliferation can account in part for the observed phenotypes (ventricular septal defects and myocardial hypoplasia) that has been reported.

### Fetal MTHFR genotypes

There are some studies focusing on fetal *MTHFR* genotypes. Junker et al. [6] were the first to suggest an association between the incidence of CHD and *MTHFR* 677C→T polymorphism. The authors observed a higher frequency of the 677TT genotype versus the combined group of CT and CC genotypes among children (n=114) with a CHD, compared with 228 controls. In particular, the frequency of the 677TT genotype in patients with pulmonary valve stenosis, hypoplastic left heart syndrome, coarctation of the aorta and aortic valve stenosis was significantly elevated, but the number of patients in these subgroups was rather small [6].

In another study[11] 32 allelic variants were determined including *MTHFR* 677C→T polymorphism, by genotyping 155 infants with conotruncal defects and 437 infants without malformations. They did not find an increased risk of conotruncal heart defects for the *MTHFR* 677CT or TT genotype. Analyses in that study, investigating a potential gene-nutrient interaction between maternal periconceptional vitamin use and *MTHFR* genotypes, did not indicate that the CT or TT genotype contributed to conotruncal heart defect risk in infants, even in the absence of maternal use of multivitamin supplements with folic acid.

### Maternal MTHFR genotypes

Hobbs et al [5] did not find an independent effect of the MTHFR 677C→T polymorphism in 275 women vs. 118 controls on the estimated risk of having a CHD affected pregnancy. This study was done after the introduction of food fortification with folic acid. Additional use of folic acid or folic-acid-containing multivitamins during the periconceptional period was not significantly different between cases and controls.

An association between maternal TT genotype, compared with CT and CC genotypes, with the occurrence of persistent ductus arteriosus in offsprings was fond by Zhu et al. [17]

The importance of the *MTHFR* 677C→T polymorphism and folate metabolism lies in the large number of reactions that may impact embryonic development in which the enzyme is involved. The presence of a gene-environment interaction, resulting in altered susceptibility, exists with respect to the *MTHFR* 677C→T polymorphism. Consequently, the *MTHFR* 677C→T homozygous genotypes (TT) and possibly the heterozygous mu-

tant genotypes (CT) are more likely to be related to CHD risk in the absence of periconceptional folic acid supplementation. Van Beynum et al. [15] found such an interaction for the maternal *MTHFR* 677C→T polymorphism in relation to CHD when the mother did not take folic acid periconceptionally. The maternal *MTHFR* 677CT and TT genotypes in combination with no use of periconceptional folic acid supplements were associated with, respectively, a three-fold (OR 3.3 95%CI 1.46–7.32) and six-fold (OR 6.3 95%CI 2.32–17.27) increased risk for conotruncal heart defects in offspring.

## Future goals and gaps

The goal of future research will be to better understand the relationship among folate, homocysteine, and *MTHFR* polymorphism in population. Families identified as high risk for CHD should be the focus of future studies to examine the possibility of multiple genetic mutations in this group. These studies are warranted to enable definite conclusions on the *MTHFR* 677C→T polymorphism and CHD. For such studies, sample sizes need to be large, to accurately estimate the causal relationship for finer phenotype categories of CHD. The results of such studies could have significant implications for the management of these patients. For example, we will then have identified a population of at-risk mothers who may become pregnant subsequently. The ability to modify their risk could have a significant impact on family planning for these patients.

As we increase our understanding of the underlying mechanism leading to CHD we move toward preventing these defects by tailoring pharmaceuticals and lifestyle-modifying strategies for woman of child-bearing age.

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# EISENMENGER SYNDROME

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Congenital heart disease is the most common inborn defect with a worldwide incidence of about 1%, and Eisenmenger syndrome represents the most advanced form of pulmonary arterial hypertension related to unrepaired congenital heart disease. Eisenmenger syndrome is a multisystem disorder associated with numerous life-threatening complications, including hemoptysis, erythrocytosis, cerebrovascular accidents, brain abscesses, arrhythmias and syncope.

Once Eisenmenger syndrome has developed, closure of the heart defect is no longer a therapeutic option and may precipitate death. Current practice is to avoid any intervention that may destabilize the delicately "balanced physiology" of these patients. In most cases treatment is symptomatic or directed at avoiding or ameliorating the complications associated with hypoxemia, hematological/ haemostatic abnormalities, infection and congestive heart failure.

For patients with irreversible pulmonary hypertension or Eisenmenger syndrome, lung transplantation with repair of the cardiac defects or combined heart-lung transplantation may improve quality of life and possibly survival in well selected patients; an option only for a small, selected group of patients and limited by the availability of donor organs.

Management options of patients with Eisenmenger physiology have until recently been limited: however, increased understanding of the pathophysiology of Ebstein physiology and the success of therapies in the treatment of other forms of pulmonary arterial hypertension offer new hope.

Such therapies include prostanoids, phosphodiesterase -5 inhibitors and endothelin receptor antagonists.

Although at present these is no cure for patients with Eisenmenger syndrome appropriate management of these patients reduces morbidity and mortality and may improve quality of life.

**Key words:** Eisenmenger syndrome, congenital heart disease, child.

Congenital heart disease (CHD) are among the most common major malformations at birth with an incidence of approximately 1%.

These defects are characterized by a heterogenous group of abnormal communication and connections between the cardiac chambers and vessels with different hemodynamic consequences and hence varying need for follow up an interventions. Patients with CHD develop pulmonary arterial hypertension (PAH) of variable seventy in 5-10%.[1,2]

Patients with PAH associated with CHD may initially exhibit a left-to-right (systemic-

to-pulmonary) shunt. Congenital systemic-to-pulmonary shunts are classified according to type of the defect, dimension, associated extracardiac abnormalities and correction status. Any of these factors may be relevant for the development of pulmonary vascular disease (PVD) and Eisenmenger physiology. The type and the size of the defect as well as the magnitude of the shunt are risk factors for development of PAH. Shear stress due to elevated pulmonary blood flow (PBF) and/or increased pulmonary arterial pressure play a major pathogenic role in the development of PVD. It is a difference between the pre-and post-tricuspid shunt lesions with regard to development of pulmonary vascular lesions. The exclusively laminar shear stress induced by the increase in PBF alone may not be similar to the laminar and circumferential (pressure) shear stress induced by posttricuspid shunt.

Surgical repair is an option for some patients and for these individuals the timing of surgery is of critical importance as it has to be done before the onset of high PVR. The status of the pulmonary vascular bed often is the principal determinant of the clinical manigestation, course, and feasibility of surgical treatment.

The complete cure and regression of the pulmonary vascular lesions are expected when surgical repair is performed early in life.

The treatment of choise for most patients with CHD is surgical correction, whereby the precise timing of the operation must be chosen carefully because the age at which operative repaire is carried out is a major factor determining the clinical outcome. In most children who undergo repair at 9 months of age, PVR is normal after one year; in children older that 2 years pulmonary vascular resistance may fall, but not to normal level[3].

As the disease progresses, vascular remodelling and disfunction lead to increases in pulmonary vascular resistance (PVR)4.5 and in extreme cases complete reversal to a right-to-left (pulmonary-to-systemic) shunt (Eisenmenger syndrome).

Eisenmenger syndrome is characterized by the development of PAH with consequent intracardiac right-to-left shunt and hypoxemia in patients with preexisting CHD. This condition is defined as a congenital heart defect that initially cause a major left-to-right shunt, induces severe pulmonary vascular disease and PAH, and finally results in reversal of the direction of shunting and development of cyanosis.[9]

The structural abnormalities of the lung circulation are histologically similar to those seen in other forms of PAH[13].

In these patients, the systemic circulation receives insufficient oxygenation causing cyanosis and reduced exercise capacity[8].

The risk of developing Eisenmenger's physiology (EP) and the prognosis of these patients depend on the type, location and dimensions of the underlying heart defects.

A genetic susceptibility is also suggested as patients with similar heart defects do not develop pulmonary vascular lesions similary[7].

Approximately half of all patients with large unrepaired ventricular septal defect (VSD) and around 10% of patients with large unrepaired atrial septal defect (ASD) are at risk of developing EP6. Onset tends to be much later for patients with ASDs, probably because of differing haemodynamics.

Eisenmenger syndrome is a multisystem disorder associated with numerous life threatening complication, including hemoptysis, cerebrovascular accidents, brain abscesses, arrhythmias, and syncope9. Dyspneea and exertional breathlessness is the most common symptom. Exercise capacity is severely impaird with dyspnea which may reduce quality of life in most patients with Eisenmenger syndrome; this is probably due to the inability of the right ventricle to raise cardiac output with exercise. Although exercise limitation and exertional dyspnea may remain stable for years, poor exercise capacity identifies the patient at risk for hospitalization or death6. More over, it carries a high risk of mortality in a relatively young patient population with limited treatment option.

Patients with Eisenmenger syndrome have a reduced life expectancy even if many can survive into their third or fourth decade.[7]

Therapeutic approach in CHD- PAH:

– left-to-right shunt with high blood flow and low PVR- Surgery

– bidirectional shunt with normal or slightly increased PBF and moderate increase in PVR – No surgery as high risk of no reversibility.

– right-to-left shunt with decreased PBF and high PVR- No surgery as lesions thought irreversible.

Once Eisenmenger syndrome has developed, closure of the heart defect is not longer a therapeutic option and may precipitate death. EP has been regarded as not amenable to conventional treatment of surgery. Theoretically some treatments may worsen the shunt and increase hypoxemia.

Current practice is to avoid any intervention that may destabilize the balanced physiology of the patients.

In most cases, treatment is symptomatic or directed at avoiding or ameliorating the complications associated with hypoxia, hematological/ haemostatic abnormalities/ infection and congestive heart failure.

Management of patients with Eisenmenger syndrome[14]:

– Regular follow- up in experienced center

– Avoid unnecessary non-cardiac surgery or in expert center with trained anesthetist and cardiac staff.

– Contraception and avoid pregnancy

– Avoid strenuous exercise

– Maintain fluid balance, avoid dehydration

– Annual immunization (influenza, pneumococcus)

Eisenmenger syndrome management algorithm:

Diagnosis: referral to PAH- CHD centre

History and examination, CxR, ECG

Non invasive tests-echocardiography, cardiac MRI, cardiac CT

Cardiac catheterization for selected patients.

Functional class/ other investigations, biochemistry iron studies

Education: Endocarditis prophylaxis, advice an exercise and other lifestyle contraception –risk of pregnancy very high.

General therapy: correct iron deficiency consider thromboprophylaxis, estimation of the role for reparative surgery/ catheter based intervention.

Advanced therapy: Bosentan therapy for class III patients or other advanced therapies. Even if survival has been considered better Eisenmenger patients deserve modern therapies.

Other therapy: lung or heart-lung transplantation for selected patients failing medical therapy.

It is important to keep the physiological balance and to prevent complication- endocardities prophylaxis.

Medical treatment:

– Cardiac Glycosides and Diuretics. The efficacy of cardiac glycosides in pulmonary arterial hypertension remain unknown; no study showing benefits of digoxin, maybe role in arrhythmias. The use of digitalis concomitant with calcium channel blockers may counteract the potentially negative inotropic effects of calcium channel blockers. Diuretics can be useful in reducing the increased intravascular volume and hepatic congestion. Meticulous monitoring of serum electrolytes is mandatory.

– Calcium channel blockers are considered as potentially dangerous (systemic vasodilatation) and empiric therapy should be avoid.

– Nitric oxide (NO) The use of newer vasodilator agents, particular NO, has been an important advance in determining vasoreactivity. INO therapy improves gas exchanges and selectively lowers pulmonary vascular resistance in several clinical disease, including IPAH and CHD.

– Prostacyclin is a potent short-acting vasodilator and inhibitor of platelet aggregation produced by the vascular endothelium. Prostacyclin decreases PVR and increases cardiac output and systemic oxygen delivery when acutely administered to patients with pulmonary hypertension, and these response has been used to determine whether long-term oral vasodilator therapy is warranted.

– Endothelins (ET). Another target for treatment of pulmonary hypertension is the vasoconstrictor peptide endothelin. The endothelinns are a family of isopeptides consisting of ET-1, ET-2, and ET-3. ET-1 is the potent vasoactive peptide produced primarily in the vascular endothelial cell, but also may be produced by smooth muscle cells. Two receptor subtypes, ETA and ETB, mediate the activity of ET-1. ET A receptors on vascular smooth muscle mediate vasoconstriction. ET B receptors on endothelial cells cause release of nitric oxide or prostacyclin and act as clearance receptors for circulating ET-1. ET-1 expression is increased in the pulmonary arteries of patients with pulmonary hypertension. Bosentan, a dual ET receptor antagonist, lowers pulmonary artery pressure and resistance and improves exercise tolerance in adults with pulmonary arterial hypertension. In children with PAH related to CHD or IPAH, bosentan lowered pulmonary pressure and resistance, and was well tolerated. In patients with PAH related to CHD

(Eisenmenger physiology) long term bosentan is safe, well tolerated, and effective. Selective ETA receptor blockade is also possible using Sitaxentan, an ET receptor antagonist with high oral bioavailability, a long duration of action, and high specificity for the ETA receptor. Ambrisentan is another oral ETA selective endothelin receptor antagonist that has been evaluated in 64 patients with exercise capacity and improved hemodynamics.

– Phosphodiesterase-5 inhibitors. Specific phosphodiesterase-5 inhibitors, such as sildenafil, also have a role in treatment of pulmonary hypertension; these drugs promote an increase in cGMP levels and thus cause pulmonary vasodilatation. In chronic PAH, phosphodiesterase type 5 gene expresion and activity are increased, rezulting in decreased cGMP levels. Sildenafil is as effective pulmonary vasodilator as iNO and may be preferred because it dose not increase pulmonary wedge pressure.

– Oxygen administration is controversial, there is no real report of efficacy in children with CHD- PVD or on natural history or physical capacity in Eisenmenger syndrome. Use indicated in specific cases, lung disease, desaturation.

– Anticoagulation. As a result of sedentary lifestyle, venous insufficiency, dilated right-sided cardiac chambers and sluggish pulmonary blood flow, patients with severe PAH are at risk for thromboembolic events. Although the usefulness of anticoagulation in patients with Eisenmenger syndrome has not been studied, it may be reasonable to use it in select cases when the risk for thromboembolism outweighs the likelihood of hemopthysis. Endothelial dysfunction may improve with therapy. Decrease fibrinolytic activity and release of procoagulant factors in PAH. Treatment correlation with pulmonary blood flow velocity, with antiplatelet, coumarin, other. The aim of warfarin anticoagulation is to maintain an international normalized ration (INR) of 1.5 – 2.

– Phlebotomy. Only in patients with symptoms of hyperviscosity- headaches, fatigues, vision problems, dyspnea, paresthesia, hemoptysis. Performed slowly with simultaneous volum replacement (250-500 ml in 45 minutes).

Microcytosis and iron deficiency should be treated immediately.

– Atrial septostomy. The general indications for atrial septostomy include pulmonary hypertension refractory to chronic vasodilator treatment and in symptomatic low cardiac output states. Children with recurrent syncope and signs of right heart failure who are refractory to medical treatment may benefit from atrial septostomy. Syncope and intractable right heart failure are indications for patients who are treated with vasodilators and remain refractory. This intervention can reduce right atrial pressure, increase cardiac output and systemic oxygen transport, improving exercise capacity and survival, risk associated with this procedure include worsening of hypoxemia with resultant right ventricular ischemia and worsening right ventricular failure, increased left atrial pressure, and pulmonary oedema. Atrial septostomy may serve as a palliative bridge to heart-lung or lung transplantation.

Target PAH treatment:

Management option of PAH-CHD patients with EP, have recently been limited: however increased understanding of the pathophysiology of EP and the success of therapies in the treatment of other forms of PAH offer new hope. Such therapies include prostanoids, phosphodiesterase -5-inhibitors and endothelin receptor antagonists[12].

Initial studies with prostacyclin analogues in patients with PAH-CHD demonstrated improvements in functional capacity, oxygen saturation and haemodinamics.[10.11]

Although the prosphodiesterase – 5 inhibitor sildenafil and endothelin receptor + antagonist sitaxentan have show beneficial effects in patients with PAH of various etiologies.

Two prospective studies of pediatric and adult patients with PAH-CHD demonstrated that the dual endothelin receptor antagonists (ERAs) bosentan significantly improved exercise capacity, WHO functional class and haemodynamics. 14.15 Also, significant improvements in WHO functional class, 6-minutes walk distance, oxygen saturation and haemodynamics (PVR and systemic vascular resistance) were seen in a 1 year open-label, prospective study of bosentan in patients with EP, compared with baseline. Bosentan was well-tolerated and no major or serious side effects were observed.[16]

BREATHE -5 is the first randomized double-blind, place to controlled study in patients with EP.9

Based on clinical evidence, bosentan is currently the only approved treatment in Europe for PAH associated with congenital systemic-to-pulmonary shunts and EP.[19]

Transplantation, preferable heart –lung transplantation, is an option only for a small, selected subgroup of patients, but is severely limited by the availability of donor organs.

For patients with irreversible pulmonary hypertension or Eisenmenger syndrome, lung transplantation with repair of the cardiac defect or combined heart-lung transplantation may improve quality of life and possibly survival in well selected patients.

Bilateral and single-lung transplantations maximize the use of a limited donor organ supply but heart-lung transplantation may be more beneficial for Eisenmenger patients, especially those with multiple congenital anomalies. Transplantation is associated with a high acute surgical risk (operation will take longer with longer ischemia time, more reperfusion injury and increased risk for infection) and with graft rejection. With a 10 year survival rate under 40%, heart-lung transplantation may only be an option for patients confronted with death or for those having an intolerable quality of life.

Transplantation has to be considered to improve prognosis and to improve quality of life. Timing of transplantation is extremely difficult1; predicted life expectancy < 2 years or less without transplantation;[14] risk stratification scores for end-stage congestive heart failure may not apply to Eisenmenger patients. Deteriorating quality of life, WHO functional class IV, need for additional hospital admissions, need for additional medication are listing for transplantation of Eisenmenger patients.

Bridging opportunities are: optimizing conservative treatment and initiating selective pulmonary vasodilatators, preventive implantation of automatic defibrillator in case of

# Diagnoses And Treatment Of Dilated Cardiomyopathy: Surprises

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Dilated cardiomyopathy is the most frequent form of cardiomyopathy. In most cases, unfortunately more than 60%, etiology remains unknown. The most frequent arrhythmia, which can produce dilated cardiomyopathy is the atrial ectopic tachycardia Atrial ectopic tachycardia is secondary to an ectopic focus with high automatism. In pediatric pathology it is, as frequency, the third supraventricular tachycardia.

The purpose of this study is the presentation of cases of two children with dilated cardiomyopathy, they have a favorable evolution with the normalization of ventricular function in spite of the diagnoses. Arrhythmia, especially tachycardia with continuous character represent a real cause of dilated cardiomyopathy in children.

**Methodology:** In both of cases a two-dimensional echocardiography with color Doppler was performed, with a Sonos 5500 echocardiograph. The left ventricular parameters were measured in M-mode echocardiography, parasternal long axis position. The ejection fraction was obtained with Simpson formula, with the transducer in four chamber apical position. The segmental kinetics of the ventricles was followed on short axis views. The severity of mitral regurgitation was measured with 2D echo views obtained with the transducer at the four chamber apical position with color Doppler. With pulsed wave Doppler and sample volume at mitral valve was followed the diastolic function of left ventricle.

**Conclusions :** On both cases good results were obtained with amiodarone, but on the second case, amiodarone administered as unique antiarrhythmic had initially an ominous effect on the heart, increasing the appearance of atrial tachycardia incidents with fast atrioventricular heading. Association a betablocker even in the conditions of a secondary cardiomyopathy, was beneficial by influence over the atrioventricular conduction.

**Key words:** Atrial ectopic tachycardia, child, dilated cardiomiopathy, amiodarone

## Introduction

Dilated cardiomyopathy is a cardiac disease with a very poor prognosis, has only one treatment, the cardiac transplantation which is difficult to realize in children.

In dilated cardiomyopathy the transthoracal echocardiography is relevant for the diagnoses, but in many cases the moment of the echocardiography is only, when the ventricular parameters are damaged. Recent clinical studies from the literature certify the utility of application of tissue Doppler for diagnose of dilated cardiomyopathy [1].

The purpose of this study is the presentation of cases of two children with dilated cardiomyopathy, they have a favorable evolution with the normalization of ventricular function in spite of the diagnoses.

**Material and methodology:** In both of cases a two-dimensional echocardiography with color Doppler was performed, with a Sonos 5500 echocardiograph. The left ventricular parameters were measured in M-mode echocardiography, parasternal long axis position. The ejection fraction was obtained with Simpson formula, with the transducer in four chamber apical position. The segmental kinetics of the ventricles was followed on short axis views. The severity of mitral regurgitation was measured with 2D echo views obtained with the transducer at the four chamber apical position with color Doppler. With pulsed wave Doppler and sample volume at mitral valve was followed the diastolic function of left ventricle.[2,3]

Case 1: 14 years old boy, with two sincopes in the personal history, because of them, he was diagnosed with epilepsy and treated with anticonvulsivants. Short after that he accused fatigue and weakness, was diagnosed with dilated cardiomyopathy and was confined in our clinic.

The clinical evaluation showed a cranky boy with poor nutritional state, tachycardia, left parasternal III/6 systolic murmur, which transmits to axilla, with gallop rhythm and hepatomegaly.

The chest roentgenography : cardiomegaly, cardiothoracic ratio 0.56.

Electrocardiography : sinus tachycardia, left ventricular hypertrophy, abnormal ST-T.

Echocardiography: Very dilated left atrium, gr II/III mitral regurgitation, dilated left ventricle with reduced fractional shortening and ejection fraction.

| Parameters | At the moment diagnosis | After 6 months |
|---|---|---|
| LVs | 4,67 cm | 3,23 cm |
| LVd | 5,47 cm | 4,85cm |
| IVS | 0,67/0,68 | 0,67/0,99 |
| LVPW | 0,67/0,68 | 0,8/1 |
| LA | 2,65 cm | 2,3 |
| EF | 14,75% | 60% |
| E-SIV | 1,6 | 0,8cm |
| E/A, TIRV | 1,6 ; 150ms | 1,7 ; 120ms |

**Tabel I.** – Left ventricle parameters – case 1

Holter ECG : frequent ectopic atrial tachycardia episodes with heart rate 200 b/min.

After the examinations the diagnosis was: Severe dilated cardiomyopathy possibly secondary of ectopic atrial tachycardia.

The patient was treated with amiodarone starting dose followed by supportive dose, treatment of congestive heart failure with ACE inhibitors and diuretics.

The follow up after one and 6 month until 2 years, showed a favorable evolution: sinus

rhythm, milder simptomatology and finally without that, decrease of cardiothoracic ratio, in time normal echocardiographic parameters of left ventricle. The treatment with amiodarone was not followed by side effects. After two years of follow up, the patient was asymptomatic and the followed parameters were normal, so the treatment with amiodarone was interrupted.

CASE 2: 6 years old boy, with positive personal history since he was 3 years old. He has repeated vomiting, palpitation, fatigue on exercise. He was investigated in a teritorial hospital for the digestive problems and treated for that. When he was 6 years old, he was diagnosed with dilated cardiomyopathy and confined in our clinic. At confiment he presented : dizziness, fatigability and weakness.

The clinical evaluation showed a cranky boy, normal colored skin, without signes of pulmonary congestion, dull, arrhytmic heart sounds, 155 b/min heart rate, left inferior parasternal III/6 holosystolic murmur, which transmits to axilla, palpable periferal pulse, blood pressure 90/60 mmHg, moderate hepatomegaly.

| Parameters | At the moment diagnosis | After 6 months |
|---|---|---|
| LVs | 3,89 | 3,1 |
| LVd | 4,67 | 4,2 |
| IVS | 0,75/0,80 | 0,73/0,88 |
| LVPW | 0,8/0,83 | 0,79/0,84 |
| LA | 2,5 | 2,2 |
| EF | 15,23% | 62% |
| E-SIV | 1,5 | 0,6 |
| E/A, TIRV | 1,7 ; 145ms | 1,7 ; 100ms |

**Table II** – Left ventricle parameters – case 2

The chest roentgenography (CXR): cardiomegaly with left chambers enlargement.

Electrocardiography: relative regular rhythm, 140 b/min heart rate, normal P waves in frontal axis, negative P in V1, ST segment shift. The heart rate and the aspect of P wave in V1 raise the suspicion of ectopic atrial tachycardia. Echocardiography: Dilated left atrium, significant mitral regurgitation, dilated left ventricle, with trabecular hypertrophyc walls, with reduced fractional shortening and ejection fraction, 1.5/1 cm intraventricular thrombus fixed to interventricular septum. After the examinations the diagnosis was: Ectopic atrial tachycardia. Spongiform cardiomyopathy. Secondary dilated cardiomyopathy. Severe mitral regurgitation. Left ventricular thrombus. The patient was treated with intravenous amiodarone starting dose followed by supportive dose, dopamine, glucose infusion with electrolytes, ranitidine, methoclopramide and enoxaparine.

The immediate evolution: ectopic atrial tachycardia, heart rate 180-240 b/min, decrease of blood pressure, anuria. Electrocardiography: narrow QRS waves, heart rate 250 b/min, arrhythmia, difficult identification of P waves. Because of immediate evolution, the treatment was completed with betablockers.

The evolution: atrial tachycardia with 130 b/min heart rate, in three days: sinus rhythm with short episodes of atrial tachycardia with 120 b/min heart rate. The treatment was continued with amiodarone perorraly and Sintrom.

After two weeks the 24 hours Holter ECG confirmed the predominant sinus rhythm with short episodes of atrial tachycardia 120 b/min. The periodic echocardiography: improvement of left ventricle systolic function, gr. II/III mitral regurgitation, normal parameters of right ventricle. After 6 months of treatment, the 24 hours Holter ECG confirmed sinus rhythm, 2 episodes of nonsustained atrial tachycardia 120 b/min. Echocardiography: normal parameters of left ventricle, with dimension of wall and cavities at normal superior values, with persistence of trabecular aspect of left ventricle. After one year of treatment with amiodarone he presented hypothyroidia without clinical manifestations, secondary of this treatment.

## Discussion

Dilated cardiomyopathy is the most frequent form of cardiomyopathy. In most cases, unfortunately more than 60%, etiology remains unknown [1]. Arrhythmia, especially tachycardia with continous character represents a real cause of dilated cardiomyopathy in children. The most frequent arrhythmia, which can produce dilated cardiomyopathy is the atrial ectopic tachycardia [6,9,10]. Atrial ectopic tachycardia arise because there exists a focus with high automatism located on atrial level. Depending on the localization of the ectopic focus the morphology of the P wave is different [7,8]. On the first case presented, the tachyarrhythmia diagnosis was done by Holter ECG monitoring, reason for which the localization of the ectopic focus could not be determined. If the ectopic focus is near the sinus node, the atrial ectopic tachycardia is hard to be dissent from the sinus tachycardia. In the case of the second patient the ectopic P wave has in frontal plan the same orientation as the sinus P, but, the ectopic P appearance, in thoracal derivations is different. In V1 ectopic P is negative. P waves with normal axis in frontal plan, but with the depolarisation vector modified in horizontal plan (P waves in right thoracal negative derivations) suggest the existence of an ectopic focus at right appandage.

On both cases good results were obtained with amiodarone, but on the second case, amiodarone administered as unique antiarrhythmic had initially an ominous effect on the heart, increasing the appearance of atrial tachycardia incidents with fast atrioventricular heading. Association of a betablocker even in the conditions of a secondary cardiomyopathy, was beneficial by influence over the atrioventricular conduction.

Control of dissrhythmia leaded in both cases to an important improvement of parameters of the left ventricle. Although tissue Doppler echocardiography is the most accurate method of evaluation of ventricular function and prognosis in children with dilatative cardiomyopathy, classical determinations of the paramethers is still very usefull. Ecocardiography revealed an important modification of left ventricle and atrium sizes, significant

decrease of ejection fraction, as well as a significant increase of the isovolumic relaxation time. All these paramethers were tracked in dynamics and recorded a net improvement.
Non compaction of the left ventricle or the spongyophorme cardiomyopathy, is a congenital cardiomyopathy considered as a very rare form of cardiomyopathy, however recent studies report an 9-10% incidence from the total number of cardiomyopathies [1]. The echocardiographycal trace of this disorder is the point out of an excessive trabeculated myocardium especially at the level of the medium segments of the lateral and posterior heart walls. The trabecular spaces fill in with blood, which can be seen with a color Doppler or contrast echocardiography [4,5]. In the second case these echocardiographycal diagnosis elements were pointed out, but most probable the arise of atrial ectopic tachycardia determined the arise of the symptomatology and the worsening of the left ventricle function. The pathological association (atrial tachycardia and spongyophorme cardiomyopathy) was a factor of unfavorable evolution towards the dilatation of the left ventricle and ventricular thrombosis.
Conclusion

Atrial tachycardia is a real cause of dilatative cardiomyopathy, tachycardia controle with obtaining the sinusal rhythm or the control of the frequency of the ectopic focus, leads to a normalisation of the echocardiographycal paramethers obtained after a classic bidimensional ecocardiography.

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# Cytogenetic Analysis In Congenital Heart Disease In Tg Mureş

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**Objectives:** To evaluate the frequency of chromosomal abnormalities in patients with congenital heart defects (CHD) associated with other anomalies in Pediatric Cardiology Clinic Tg Mures and to compare our results with those reported elsewhere.

**Methods:** We performed chromosomal analysis on 39 children with CHD from Pediatric Cardiology Clinic Tg Mures between January 2008 and august 2008. Indication for referrals for chromosomal rearrangements was CHD associated with other congenital anomalies or dysmorphic features, unclassified mental retardation, developmental delay, growth, and endocrine disorders. We carried out the lymphocyte culture according to standard methods.

**Results:** We found various types of chromosomal anomalies in 24 children and showed abnormal karyotypes in the form of trisomy 21 (20; 51,3%), trisomy 18 (1; 2,6%), sex chromosome aberrations (2; 5,12%) and other types of abnormalities (1; 2,6%). There was a considerable phenotypic-cytogenetic heterogeneity. We found a high rate of chromosomal abnormalities in the present study.

**Conclusion:** The higher incidence of the chromosomal abnormalities demonstrates the importance of cytogenetic evaluation in patients with dysmorphic features and congenital anomalies (CHD associated with another congenital anomalies). Our findings suggest that chromosome analysis is a useful tool in the investigation of children with genetic disorders of unknown origin for confirmation of clinical diagnosis and proper medical care followed by genetic counseling and management.

## Introduction

Cardiac anomalies, defined as structural abnormalities of the heart or intrathoracic vessels, taking all the different anatomic forms together, are some of the most common congenital anomalies at birth. Congenital heart defects (CHDs) are the most common single group of congenital abnormalities accounting for about 30% of the total abnormalities. In most patients, CHDs occur as an isolated malformation, but also about 33% have associated anomalies. CHDs are an important cause of morbidity and mortality affecting 8-10 in every 1000 children. One third of those affected have critical cardiac malformations, defined as those that require immediate investigation and treatment, or those that will

lead to death during the first year of life. As medicine has advanced and early detection become possible, many of patientes with CHD will survive and contribute to increase the population of adults with congenital heart disease [2].

There is strong evidence supporting a genetic etiology for most congenital heart defects in human beings. The major genetic cause for congenital heart defects includes the following: chromosomal disorders and single gene disorders, environmental teratogens and multifactorial disorders. The association of CHDs with chromosomal anomalies varies between 4-12% [1].

Chromosome analysis is an important component in the diagnosis and evaluation of genetic disorders. To date, reports include approximately 1000 chromosome syndromes, and while on an individual basis most of these are rare, together they make a major contribution to human morbidity and mortality [4]. Numerical and structural chromosomal rearrangements, such as aneuploidies, deletions, duplications, and other aberrations have been associated with congenital abnormalities. Detection of these genetic changes is possible by cytogenetic analysis. The karyotype is determined by analysis of metaphase or prometaphase chromosomes of peripheral blood lymphocytes after banding procedures.

## Methods

39 cases with CHD associated with other anomalies, referred to the Pediatric Cardiology Clinic Tg Mures between January 2008 and august 2008 were investigated. The study included children with a diagnosis of congenital heart disease confirmed by postnatal echocardiography, carried out by the pediatric cardiolog, age range newborn to 18 years. Patients with CHD included in our study had phenotypic abnormalities such as genetically uncertain syndromes, multiple congenital anomalies, developmental delay, growth and endocrine disorders, dysmorphic features and known syndromes. Cytogenetic analysis was carried out on all the patients. The study included peripheral blood lymphocyte culture using the conventional Geimsa banding (GTG banding) technique. For routine cytogenetic analysis 0.5 ml-0.6 ml of peripheral blood was incubated in complete lymphocyte culture medium in 5% CO2 incubator at 37°C for 3 days. Metaphases were harvested by adding colchicin solution (final concentration of 0.10 ug/ ml) followed by hypotonic KCl (0.075 M) treatment and fixation using standard 3:1 methanol and glacial acetic acid fixator. At least 20 metaphases were analysed for each probe and three cells were karyotyped according to the International System for Human Cytogenetic Nomenclature (ISCN 1995). If mosaicism was suspected 30 or more cell counts were undertaken. Analysis was carried out using a BX51 Olympus microscope and images captured with an automated image analysis system (Cytovision, Applied Imaging).

## Results

Of the 39 cases studied, 24 (61,5%) patients revealed obvious chromosomal abnormalities; of these, 22 (91.6%) involved autosomes, while only 2 (8,4%) involved sex chromosomes. *Table 1* summarizes the category and frequency of the identified chromosome abnormalities, and *Table 2* indicates the genetic disorders in patients referred for cytogenetic studies. Twenty-one patients had autosomal trisomy: twenty cases with Down syndrome or trisomy 21 (figure 1) and one case with Edward syndrome or trisomy 18 (figure 2). Trisomy 21 was detected in 83,3% of the cytogenetically abnormal cases, forming the majority. Two patients (8,3% of cytogenetically abnormal cases) had sex chromosome aberrations.

| Category | No. of cases | (%) |
|---|---|---|
| Trisomy 21(Down syndrome) (including mosaic, Robertsonian translocation) | 20 | 51,3 |
| Trisomy 18 (Edwards syndrome) | 1 | 2,56 |
| Pericentric inversion of chromosome 9 [inv(9)(p-2-q13)] | 1 | 2,56 |
| Monosomy X (Turner's syndrome) (includes mosaic) | 1 | 2,56 |
| 49, XXXXY | 1 | 2,56 |
| CHD ± Dysmorphic features / mental retardation / congenital anomalies / developmental delay, and so forth (normal karyotype) | 12 | 30,77 |
| Failure | 3 | 7,7 |
| Total | 39 | 100 |

**Table I** – Categories and frequency of the chromosome abnormalities identified in patients with CHD under study

| Karyotype | Phenotype | No. of cases |
|---|---|---|
| 47, XY,+21<br>47, XX,+21 | Down syndrome | 18 |
| 46, XY/ 47,XY,+21 (mosaic) | Down syndrome | 1 |
| 46,XX, der(14;21)(q10;q10),+21 | Down syndrome | 1 |
| 47, XX, +18 | Edward syndrome | 1 |
| 45,X / 46,XY | Mosaic Turner syndrome | 1 |
| 49,XXXXY | Polysomy X | 1 |
| 46,XX,inv(9)(p12q13) | Plurimalformative syndrome | 1 |
| 46,XX | Cornelia de Lange syndrome | 1 |
| 46,XX | Saethre-Chotzen syndrome | 1 |
| 46,XX<br>46,XY | Williams syndrome | 3 |
| 46,XX<br>46,XY | Plurimalformative syndrome | 5 |

**Table II** – Genetic disorders in patients with CHD referred for cytogenetic studies

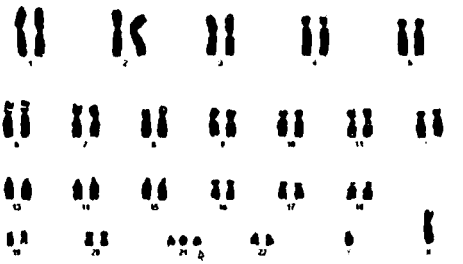

**Figure 1.** – Trisomy 21

**Figure 2.** – Trisomy 18

Turner syndrome was detected in one female patient. One male patient with atrial septal defect had polisomy X (49, XXXXY).

Twelve cases were referred because of CHD associated with dysmorphic features/ developmental delay or multiple congenital anomalies. The karyotypes in these cases were normal.

One of this patients had Saethre-Chotzen syndrome with ventricular septal defect and cranio-facial dysmorphism: craniosynostosis, a low frontal hairline, drooping of the upper eyelids, a slight down slant to the eyes, small and low-set ears, mild mental retardation, short fingers. It is an autosomal dominant disorder, but there are some patients with this syndrome with chromosome deletion of the short arm of chromosome 7.

Three of the patientes with normal kayotype had Williams syndrome. This is a rare dysmorphic syndrome characterized by heart defects, most commonly, supravalvar aortic stenosis associated with an elfin-like face, mental retardation, neonatal hypercalcemia. This disorder is caused by a microdeletion at 7q11, which can be detected with FISH using probes within the 7q11 critical region.

One patient with CHDs (double-outlet right ventricle; transposition of the great arteries; patent ductus arteriosus, right atrial isomerism) and plurimalformativ syndrome (facial dysmorphism, asplenie, right kidney agenesia) had an pericentric inversion of chromosome 9 (figure 3), karyotype: 46,XY,inv(9)(p12-q13).

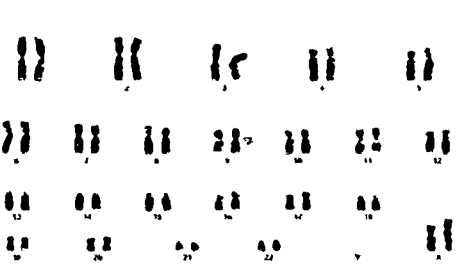

**Figure 3.** – Pericentric inversion of chromosome 9

Cytogenetic aberrations on chromosome 9 (aneuploidy, deletions, translocations, inversions) have been reported to be one of the most frequent abnormalities. The range of phenotypic consequences found to be associated with these abnormalities are mild growth retardation, malformations of the skull and facial (craniofacial) region, abnormalities of the hands and fingers, skeletal malformations, and/or cardiac defects (McAuliffe et al. 2005). Among these anomalies pericentric inversion of chromosome 9 is one of the most common balanced structural chromosomal aberrations found in 1 to 3% of the general population (Humphray et al. 2004). We found only one report of association of pericentric inversion of chromosome 9 [inv(9)(p11-q13)] with CHDs. That report predict that, the genes responsible for the normal heart development could be present on chromosome 9 around p11-q13 region, which might have been defective during the process of inversion and thereby resulted in CHD 5. In support of this, there are reports about abnormalities of chromosome 9 associated with several cardiac anomalies which includes truncus arteriosus, truncal valve stenosis, single carotid trunk, subclavian arteries arising from the distal part of the aortic arch, atrial and ventricular septal defects, atrioventricular septal defect, pulmonary artesia, right ventricular hypertrophy and hypoplastic left pulmonary artery (Robertst al. 1993; Nekarda et al. 1997; Sepulveda et al. 2003). In particularly, the chromosome 9p is found to be associated with series of CHDs, like ventricular septal defect with pulmonary valve stenosis and a marked hypoplasia of the pulmonary trunk (Schimmenti et al. 1995;Leichtman et al. 1996; Nakagawa et al. 1999).

Table 3 shows the types of congenital heart disease present in our patients, numerical and structural chromosomal abnormalities 3. Our study also reveals the phenotypic-cytogenetic heterogeneity.

## Discussion

Congenital heart anomalies constitute a major malformation leading to significant morbidity and mortality eventually affecting the clinical outcome of the affected individuals. There are several reports of CHDs associated with chromosomal variations like triso

| Type of CHD | Karyotype | Phenotype | No. of cases |
|---|---|---|---|
| ASD ± PDA | 46,XY<br>46,XX | Plurimalformative syndrome | 3 |
| | 45,X/46,XY | Turner syndrome | 1 |
| | 47,XY,+21 | Down syndrome | 4 |
| | 49,XXXXY | Polisomy X | 1 |
| PDA | 47,XX,+21<br>47,XY,+21 | Down syndrome | 2 |
| AS ± PS ,PDA | 46,XY | Williams syndrome | 3 |
| VSD | 46,XX | Saethre-Chotzen Syndrome | 1 |
| VSD ± PDA, | 47,XX,+21<br>47,XY,+21 | Down syndrome | 4 |
| VSD, ASD, PDA | 47,XX,+18 | Edwards Syndrome | 1 |
| AVSD ± DSA, PDA | 47,XY,+21<br>47,XX,+21 | Down syndrome | 6 |
| TOF | 46,XX | Facial dysmorfism | 1 |
| TOF, DSA,PDA | 46,XY/47,XY+21<br>47,XY+21 | Down syndrome | 2 |
| | 46,XX | Plurimalformative syndrome | 1 |
| Right medioventricular stenosis | 46,XX | Facial dysmorfism | 1 |
| Ebstein's anomaly | 46,XX | Facial dysmorfism | 1 |
| DORV, TGA, PDA, atrial isomerism | 46,XY,inv(9)(p12-q13) | Plurimalformative syndrome | 1 |
| BAV | 46,XX,der(14;21)(q10;q10),+21 | Down syndrome | 1 |
| DORV, Hypoplastic left heart syndrome (HLHS-ventricul stg hipoplazic, PDA, ASD | 47,XX,+21 | Down syndrome | 1 |
| VSD | 46,XX | Plurimalformative syndrome | 1 |

**Tabel III.** – Types of congenital heart disease present in patients with CHD and other anomalies

mies, deletions, duplications and translocations (see, Smitha and Ramachandra 2005). However, there is only one report of association of pericentric inversion of chromosome 9 [inv(9)(p11-q13)] with CHDs. This pericentric inversion is believed to be a frequent occurrence in the general population and inherited in a Mendelian fashion or might appear for the first time in a child without any apparent phenotypic consequences (Nielson and Silesen 1975; Ko et al. 1992; Luke et al. 1992; Teo et al. 1995; Humphray et al. 2004).

Among heart diseases that were feature of syndromes, the higher prevalence of chromosomal diseases was noticeable,

in particular forms of aneuploidy. The most common chromosome abnormality was trisomy 21 followed by sexual chromosom anomalies, as seen in other study. A high rate of chromosomal abnormalities (61,5%) found in our study demonstrates the importance of cytogenetic evaluation in children with CHD and multiple anomalies.

In cases of CHD complicated with chromosomal abnormalities, the pediatrician should choose the best way of management, taking into account not only the severity of heart disease but also other problems including the prognosis of motor and mental development. In conclusion, these findings suggest that chromosomal analysis is an important step in syndrome identification and is useful in the investigation of various genetic disorders of unknown origin for confirmation of clinical diagnosis, and has a significant contribution in the genesis of genetic diseases, and abnormal sexual development.

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# MINOR CYTOGENETIC ABNORMALITIES IN THE ETIOLOGY OF CONGENITAL HEART DEFECTS

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**Aim of the study:** To identify minor cytogenetic abnormalities, i.e. interstitial 22q11 microdeletion as a genetic factor responsible for some congenital heart diseases.

**Material and method:** The study included 188 patients admitted to/ examined at the Pediatric Clinic III Cluj-Napoca, diagnosed with congenital heart defects in the period 2000-2005. The criterion for inclusion in the study was the presence of conotruncal heart defects (aortopulmonary septal defects) with/without associated extracardiac malformations. Anamnestic, clinical and paraclinical data were collected and karyotyping and/or the FISH test was performed.

**Results:** There were 18 patients (29%) with aortopulmonary septal defects (APSD): tetralogy of Fallot (8 cases), transposition of great vessels (3), double outlet right ventricle (5), total anomalous venous return (2). Four patients also showed extracardiac anomalies. The patients were assigned to two groups: 1) those with at least one phenotypic feature, belonging to a certain syndrome (craniofacial dysmorphism, mental retardation or language retardation, etc.) and 2) those not belonging to a specific syndrome. In the second group, no patient showed the 22q11 microdeletion. Of the four patients with associated congenital extracardiac malformations, only one had the 22q11 microdeletion.

**Conclusions:**

1. APSD were present in 29% of the patients, of which the tetralogy of Fallot represented the highest percentage, followed by the transposition of great vessels and atrioventricular canal.

2. In patients with APSD without associated extracardiac anomalies, the 22q11 microdeletion was not evidenced.

3. The 22q11 microdeletion detected by the FISH test is the cause of some conotruncal heart defects (APSD) which also associate extracardiac malformations.

Key words: conotruncal heart defect, 22q11 microdeletion

## Introduction

Congenital heart defects (CHD) have a significant incidence during childhood, affecting 8 of 1000 live newborns, and involve high material expenses and a high mortality rate. In Romania, 800-1300 children with CHD are born every year, and mortality is higher than in other EU countries [4].

The major premise of efficient prevention and therapy is early and correct diagnosis, including etiological diagnosis. Over the past years, it has been discussed that 80% of congenital heart defects have a genetic etiology, which opens a wide field to research in this direction.

At European level, progress has been made regarding the etiological diagnosis of CHD, allowing the identification to a certain extent of the genetic component (numerical or structural chromosomal abnormalities, gene mutations, etc.). Microdeletion syndromes are genetic syndromes characterized by submicroscopic deletions which usually involve several genes [1,3].
In Romania, the genetic cause is suspected/speculated in many cases, but practical demonstration is more difficult.



## Aim

The aim of the research is the identification of minor cytogenetic abnormalities, i.e. interstitial 22q11 microdeletion as a genetic factor responsible for some congenital heart defects.

## Patients and method

The study included 188 patients, admitted to the Pediatric Clinic III Cluj-Napoca or examined in the ambulatory of the same clinic, diagnosed with congenital heart defects. The study extended over a period of 5 years: 2000-2005.
The only criterion for inclusion in the study was the presence of a conotruncal heart defect (aortopulmonary septal defect) with or without associated extracardiac malformations.

Anamnestic, clinical and paraclinical data were collected. Based on these, the patients with conotruncal heart defects were selected.

For the selected patients, a genetic analysis was performed:

– *karyotyping* was performed for patients in whom a numerical or structural, autosomal or gonosomal chromosomal aberration was suspected.

– *the FISH* test performed in the laboratory of cytogenetics diagnosed the chromosomes during the metaphase. We used Vysis tests (marketed by the Abbot company). These tests involve the impregnation of the control sample with various fluorophore substances in order to detect the chromosome of interest.

The cytogenetic analyses were performed at Genetic Lab Bucharest. For this purpose, we acquired two kits of 20 samples each: N25 (D22S75) and TUPLE1 (orange spectrum) 22q11.2, both being accompanied by a control sample LSI ASRA 22q13.3 (green spectrum).

## Results and discussion

The diagnosis of congenital heart defect was made in all the studied cases by objective examination, electrocardiogram, chest radiography and especially Doppler echocardiography. Some cases also required invasive diagnostic methods, catheterism and angiography, especially in palliative or radical preoperative preparation.

- ventricular septal defect 29%
- aortopulmonary septal defects 29%
- atrial septal defect 20%
- mitral valve prolapse 14%
- aortic coarctation 3%
- mitral stenosis/mitral insufficiency 3%
- tricuspid atresia 1%
- aortic stenosis 1%

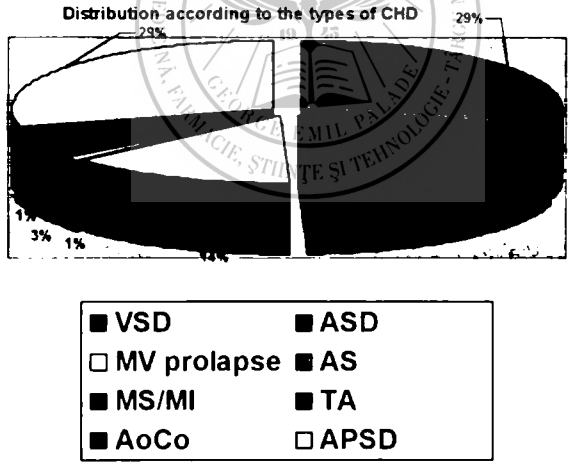


**Figure 1** – Distribution according to the types of CHD (VSD = ventricular septal defect, ASD = atrial septal defect, MV prolapse = mitral valve prolapse, AS = aortic stenosis, MS/MI= mitral stenosis/mitral insufficiency, TA = tricuspid atresia, AoCo = aortic coarctation, APSD = aortopulmonary septal defects

As the figure shows, ventricular septal defects and conotruncal (aortopulmonary septal) defects were found in equal proportions.

There were 18 patients with conotruncal heart (aortopulmonary septal) defects who were distributed depending on the CHD type as follows: tetralogy of Fallot 8 cases, transposition of great vessels 3, double outlet right ventricle 5, total anomalous pulmonary venous return 2. Four patients also had extracardiac anomalies.

In order to detect microdeletion syndromes, we performed the FISH test (fluorescent in situ hybridization).

The patients were divided into two groups: those with at least one phenotypic feature, belonging to a certain syndrome (craniofacial dysmorphism, mental retardation or language retardation, etc.) were assigned to group 1 and those not belonging to a specific syndrome, to group 2.

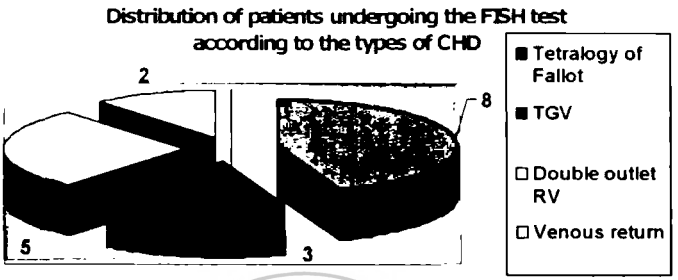


**Figure 2** – Distribution of patients undergoing the FISH test according to the types of CHD (TGV = transposition of great vessels, double outlet RV = double outlet right ventricle, venous return = total anomalous pulmonary venous return).

| No | Name | Age years | Sex | Type of CHD | Associated malformations | FISH test |
|---|---|---|---|---|---|---|
| 1 | M.S. | 4 | M | Tetralogy of Fallot<br>Bicuspid AV | Epicanthus<br>Hypertelorism<br>Enlarged base of nose<br>Thin upper lip<br>Low-set ears<br>Simian fold | Negative |
| 2 | G.L. | 2 | M | Tetralogy of Fallot | Amblyopia<br>Hearing loss<br>Nystagmus<br>Mental retardation | Negative |
| 3 | M.M. | 11 | M | Double outlet RV<br>Hypoplastic LV<br>VSD PS<br>Hypoplastic PA | Iris coloboma<br>Palatal insufficiency<br>Hernia<br>Mental and growth retardation | Positive |
| 4 | M.S. | 3 years 6 months | M | Tetralogy of Fallot<br>Bicuspid AV | Craniofacial dysmorphism<br>Cryptorchidism | Negative |

**Table I** – Distribution of the studied patients from group 1, according to age, sex, type of CHD, associated malformations and the result of the FISH technique

Group 2 included patients with conotruncal defects without associated anomalies.

The literature data show that in the phenotype of 22q11 microdeletion syndromes, immune and endocrinological disorders, palatal-velopharyngeal anomalies, psychomotor retardation, etc. have also been found along with congenital heart defects [2,6,9,11,20,23].

| *No.* | *No. of patients* | *Type of CHD* | *FISH* |
|---|---|---|---|
| 1 | 1 | Tetralogy of Fallot<br>PAS<br>PCA | Negative |
| 2 | 2 | Tetralogy of Fallot | Negative |
| 3 | 2 | Tetralogy of Fallot<br>PAS | Negative |
| 4 | 1 | TGV<br>Situs inversus<br>Mesocardia | Negative |
| 5 | 2 | TGV | Negative |
| 6 | 2 | DVPTA<br>Isomerism<br>Single atrium | Negative |
| 7 | 2 | Double outlet RV Transposition of great vessels<br>Valvular and subvalvular PS<br>Hypoplastic LV<br>Hypoplastic PAT<br>PCA | Negative |
| 8 | 3 | Double outlet RV | Negative |

**Table II** – Distribution of the studied patients from group 2, according to type of CHD and the result of the FISH technique.

In the second group, the 22q11 microdeletion was found in no patient. These data are in accordance with the literature data and emphasize the fact that aortopulmonary septal defects without other accompanying malformations are not normally associated with the 22q11 microdeletion [16,17,18].(Table III), (Table IV)

In the case of the following syndromes, isolated 22q11 microdeletion cases were described, without this mutation being characteristic [12,15,24]: (Table V)

At the same time, multiple cases were described whose phenotype suggested this mutation without this being detected .

This could be explained by the fact that the methods available cannot detect a mild cytogenetic defect. On the other hand, mosaicism might be involved and the microdeletion might not be present in all the cells. Or, a third hypothesis would be the presence of a point mutation, in gene regions that are still unknown.

| No. | Study | No. of patients Spor/fam | Type of CHD | Method | No. of patients with the 22q11 microdeletion |
|---|---|---|---|---|---|
| 1 | Amati 1995 | 102/5 | Tetralogy of Fallot | Southern FISH | 0 |
| 2 | Takahashi 1995 | 60/ | Conotruncal defects | FISH | 0 |
| 3 | Debrus 1996 | /36 | Conotruncal defects | FISH Genotyping | 0 |
| 4 | Trainer 1996 | /27 | Tetralogy of Fallot | FISH | 3 |
| 5 | Webber 1996 | 20/2 | Conotruncal defects | FISH | 0 |
| 6 | Rieβ 2000 | 10/1 | PV aplasia | FISH | 0 |
| 7 | Bachner 2007 | 5/ | Conotruncal defects | FISH | 0 |

**Table III** – he 22q11 microdeletion in patients with conotruncal defects without other associated anomalies

| Affected system | Type of defect | % of VCFS |
|---|---|---|
| Mental disorders | Psychoses<br>Chronic paranoid schizophrenia | 10 |
| Skeleton | Syndactyly<br>Polydactyly<br>Talipes equinovarus<br>Other formation defects<br>Scoliosis<br>Abnormal VC | 1<br>1<br>4<br>4<br>3<br>1 |
| Urogenital system | Renal aplasia and dysplasia Poly-cystic kidney<br>Double kidney<br>Renal ectopia<br>Hydronephrosis<br>Hydroureter<br>Vesicoureteral reflux<br>Ureterostenosis<br>Nephrocalcinosis<br>Testicular migration defects | 36 |
| Gastrointestinal system | Renal atresia<br>Hirschprung disease | 8 |
| CNS | Structural cerebral and cerebellar<br>Meningomyelocele<br>Congenital facial paresis<br>(Cayler syndrome) | 3 |
| Eye | Iris coloboma<br>Retinal defects<br>Glaucoma | 8 |
| Ear | Transmission defects | 18 |
| Diaphragm | Diaphragmatic hernia | 3 |

**Tabel IV** – Defects associated with CHD in 22q11 microdeletion syndromes
*(VCFS= velocardiofacial syndromes)*

| Syndrome | Phenotype | Study |
|---|---|---|
| CHARGE | Mutism<br>Involvement of cranial nerves VII-X<br>Congenital heart defects<br>C-coloboma<br>H-heart disease<br>A-atresia or stenosis of the choanae<br>R-retarded growth /development<br>G-genital hypoplasia<br>E-ear anomalies | *GIANOTTI 1994*<br>*DEVRIENT 1998* |
| Noonan | Short stature<br>Short and thick neck<br>Facial dysmorphism<br>Sternal deformation<br>Facial dysmorphism | *WILSON 1993* |
| Opitz-GBBB | Facial dysmorphism<br>Cleft lip and nose<br>Cerebellar agenesis<br>Corpus callosum agenesis<br>Cardiac malformation<br>Umbilical and inguinal hernia<br>Cryptorchidism<br>Anal atresia | *McDONALD-McDINN 1995* |
| Bernard-Soulier | Prolonged bleeding time<br>Thrombocytopenia<br>Giant thrombocytes | *BUDARF 1995* |
| Hypoplastic left heart syndrome | Hypoplastic LV<br>Mitral and aortic atresia<br>Permeable foramen ovale<br>Persistent ductus arteriosus<br>Hypoplastic ascending aorta and aortic arch<br>Common coronary arteries | *CONSEVAGE1996* |
| Cayler cardiofacial syndrome | Unilateral facial paresis (hypoplasia of the depressor anguli oris muscle)<br>Congenital heart disease | *GIANOTTI1994* |

**Table V** – Non-characteristic 22q11 microdeletion syndromes

Not least, the mutation can be in another locus (4q, 10p13, 7p8 or others). In this sense, the 10p13 microdeletion is the second most frequent cause of DiGeorge syndrome. Schuffenhauer reported in 1995 a case with monosomy 10p and tetralogy of Fallot, hypoplastic thymus, T lymphocyte defect, hypocalcemia and hypoparathyroidism19.

Other causes than genetic defects such as: teratogenic causes (retinoids, alcohol and drugs), viruses or maternal diabetes can induce cardiac malformations, cleft lip and nose or craniofacial dysmorphism.

A patient from group 1 (heart defects associated with other congenital extracardiac malformations) had a positive FISH test.

The patient was 10 years old, without a family history of genetic disease.

The objective examination showed: hypertelorism, antimongoloid palpebral slant, bilateral iris coloboma, low-set ears, large auricular pavilions distant from the skull, protrusion of the upper incisors.

**Figure 3** – Craniofacial dysmorphism of the patient with the 22q11 microdeletion

In addition to craniofacial dysmorphism, the objective examination also showed: ogival palatal vault as an expression of velopalatal insufficiency, non-reducible giant inguinoscrotal hernia.

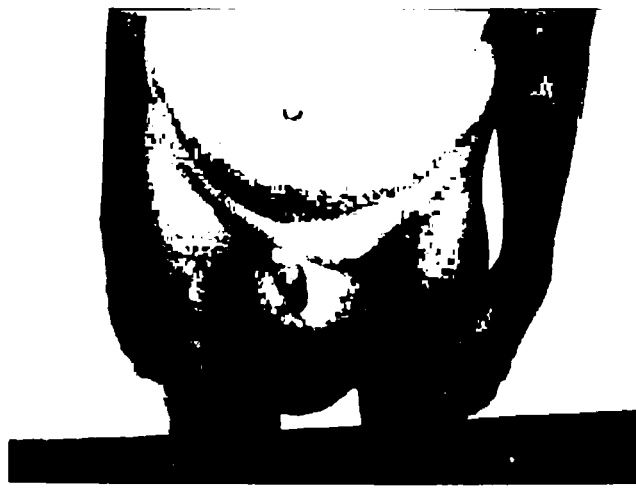

**Figure 4** – Non-reducible giant inguinoscrotal hernia

From the point of view of mental development, a psychoaffective retardation was seen, the patient being at the level of a 6-year-old. Language was also affected, the patient having dyslalia.

The examination of the heart indicated: rough systolic murmur grade IV/VI over the whole cardiac area, "vapor jet" systolic murmur grade III/IV in the PA focus. ECG-RS 75/minute, undetermined QRS axis, biventricular hypertrophy.

The echocardiography performed after surgery showed: normokinetic heart, small sized LV, IVS 7-8 mm, PPVS 8mm, double outlet RV, large sub-aortic VSD, valvular PS, hypoplastic PA; the Blallock-Taussig shunt was evidenced.

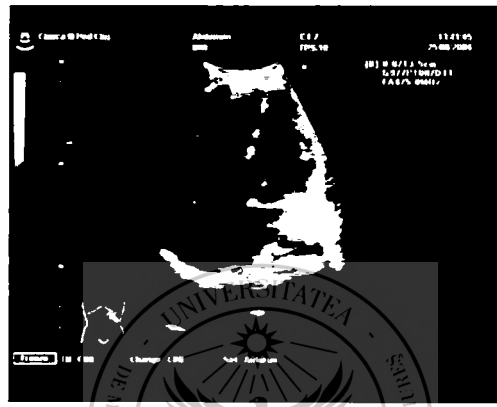

**Figure 5** – Echocardiographic image: double outlet RV, after palliative surgical correction



### CYTOGENETIC DIAGNOSIS

The FISH test demonstrates the microdeletion of the long q arm of the two chromosomes 22 in the 11.2 region. This diagnosis was possible using the specific probes for the DiGeorge N25 and TUPLE 1 regions. Approximately 50% of the cells have the mutation, so mosaicism might be involved, which is usually associated with familial inheritance.

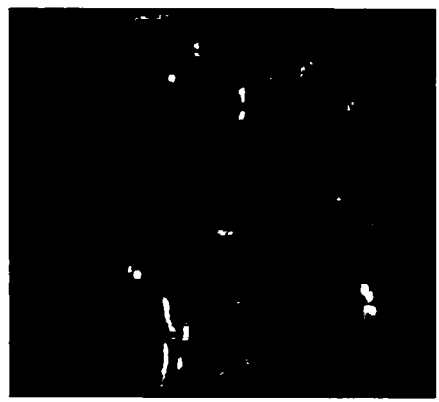

**Figure6** – Fluorescent in situ hybridization (FISH) in patient MM with a deletion at a chromosome 22q11 locus.

The 22q11 deletion extends over a length of 2000 kb in most cases, region which has been isolated and mapped using special probes. The so-called "critical DiGeorge region" covers a length of only 500 kb and is the smallest microdeletion region.

In December 1999, a group of researchers from Cambridge established the sequence and the type of the bases of chromosome 22: 545 genes and 134 pseudogenes, in total 34 million bases, which represents approximately 1.6-1.8% of the entire genetic material.

The advantages of the FISH technique are [5,10,13]: rapid sensitive and specific detection of congenital abnormalities, possibility to test the cell interphase and metaphase, direct labeling compared to indirect labeling (direct labeling means the absence of the background fluorescent signal, which simplifies the interpretation), dual staining for the majority of microdeletion detection tests (orange and green spectrum).

Finally, FISH testing (and when necessary counseling) should also be ensured for the parents of an affected child who consider a future pregnancy, because the incidence of deletions in the parents of children with a deletion syndrome is estimated at 25%. The counseling of a couple with a child affected by DiGeorge syndrome depends on their own deletion status. Recurrences have not been so far reported in the absence of a parental deletion, so there is a negligible risk in this case. For a couple in which the deletion is present, the risk of 22q11 deletions in future pregnancies is 50%. The early identification of the deletion may facilitate the investigation of associated anomalies, which can result in an improvement of results.

The study of congenital heart defects (CHD) increasingly benefits from the development of molecular diagnostic methods and the literature frequently reports the association of CHD and genetic defects, without the assignment to a specific syndrome being possible [7,8].

At the same time, for multiple syndromes associating heart defects, the causes, i.e. the genetic defect, have been established over the past years.

In 1996, the "Genetics of Congenital Heart Defect and Basic Sciences" working group was established as part of the European Association of Pediatric Cardiologists. This is the expression of the increasing importance of genetics in the etiology of congenital heart defects. This association is concerned among others with the planning and the performance of multicenter epidemiological and genetic studies. This collaboration at European level facilitates the examination of the patients and their families with a view to diagnosing rare congenital abnormalities.

Such an example is shown by the publication "Congenital heart defects associated with the 22q11 deletion", which concentrates data obtained from 558 patients with the 22q11 microdeletion, from 23 study centers. In more than half the patients, i.e. 68%, this genetic defect could be correlated with a conotruncal heart malformation:

- 23.2% tetralogy of Fallot
- 18.1 % interrupted aortic arch
- 13.4% ventricular septal defect with pulmonary valve atresia
- 12.5% common arterial trunk

– 1.4 % transposition of great vessels with pulmonary stenosis.

The notion of conotruncal malformation was used for the first time by Warkany, in 1971, with reference to aortopulmonary septal defects, common arterial trunk and ventricular septal defect with right aortic arch, double outlet right ventricle and transposition of great vessels 22.

In 1977, Van Mierop included in the category of conotruncal defects the semilunar valve defects, the aneurysms of the membranous ventricular septum, the stenosis of pulmonary valves, as well as the tetralogy of Fallot [21].

In 1965, DiGeorge described 4 cases in which thymus aplasia, congenital immune defect and congenital hypoparathyroidism were associated. One year later, TAITZ called this association DiGeorge syndrome.

Japanese researchers defined the so-called "face-heart syndrome", and Shprintzen described in 1978 the association of cleft lip and nose, craniofacial dysmorphism, cardiac malformation and mental retardation.

The phenotypic similarities and the similar pathogenetic mechanisms of these three syndromes have led over time to the search for a common genetic cause.

This supposition was validated in 1981 by the De La Chapelle's discovery of a chromosome 22 deletion that caused a DiGeorge syndrome.

Various studies followed, in particular Momma's study, which correlated cardiac malformations with the 22q11 microdeletion and established for the first time the risk of transmission [14].



## Conclusions

1. Conotruncal heart (aortopulmonary septal) defects were present in a proportion of approximately 29%. Of these, the highest percentage was represented by patients with the tetralogy of Fallot, followed by those with transposition of great vessels and atrioventricular canal.

2. One patient with a conotruncal defect associated with multiple extracardiac anomalies had a positive FISH test, consequently a 22q11 microdeletion.

3. In patients with congenital conotruncal heart defects without associated extracardiac anomalies, no 22q11 microdeletion was evidenced.

4. The 22q11 microdeletion detected by the FISH test represents the cause of some conotruncal heart defects.

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# The Diagnosis Of Congenital Heart Disease Arch Over Time

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**Goal of Study:** The evolution's comparative evaluation of the congenital heart disease diagnosis (CHD) according to the exploratory progresses of the last two decades.

Material and method: There were accepted in the study the patients hospitalized at Paediatric Clinic III Cluj-Napoca during the years 1992 (28 patients) and 2007 (83 patients), who were diagnosed with a form of CHD. The diagnosis aspects were evaluated.

**Results:** In 1992 the main diagnosed congenital heart diseases were with left-right bypass (ventricular septal defect and atrial septal defect), the distribution on ages being relatively homogeneous, the highest occurrence being in babies (28%), and the lowest in new-born babies (11%). Half of the patients were diagnosed with the help of echocardiography; the rest needed invasive techniques of diagnosis.

In 2007 most of the cases were complex congenital heart diseases, the highest occurrence being in the age groups of babies and of over 7 years old children. The positive diagnosis of the heart disease type was possible in all cases using only the echocardiography. A significantly high number of heart diseases with isolated obstacle (Valvular heart disease) was diagnosed due to the diagnosis progress of echocardiography and Doppler echocardiography.

**Conclusion:**

1. A higher number of CHD, mainly complex CHD, was diagnosed in 2007 comparatively to 1992.

2. In 2007, complex CHD was diagnosed mainly in babies as opposed to 1992 diagnosis with a homogeneous distribution on groups of age.

3. During the last years the main contribution to a CHD precocious and accurate diagnosis was brought by the echocardiography that gradually replaced the invasive diagnosis means.

**Key words:** Congenital heart disease, diagnosis, child.

## Introduction

Important progresses have been made during the last decade, regarding the diagnosis and therapeutic medical care of the child with congenital heart disease (CHD) in Cluj-Napoca academic center. The correct and precocious diagnosis represents the starting point of an efficient surgical therapy. From embryological point of view, most of the congenital heart diseases express moments of stopping in the development of certain heart and big vessel segments [1,2,3].

## Study's objectives

This paper's objective is the achievement of a comparative study of the congenital heart disease evolution, taking into account the diagnosis progress of the last two decades.

The comparison was made between the years 1992, respectively 2007, i.e. at a distance of 15 years, a period of time when serious changes were made in the pediatric cardiology of the patient with congenital heart disease.

## Material and method

The study material constituted of patients hospitalized in the Pediatric Clinic III Cluj-Napoca (medical unit with 80 beds) during 1992 (28 patients) and 2007 (83 patients), who were diagnosed with congenital heart disease.

Totally, there were 111 children with congenital heart diseases.

Both the diagnosis and evolution aspects were studied.

The patients of the study were grouped on age as follows:

- Babies (0-1 months)
- New-born babies (1 months -1 year)
- Children
  - 1-3 years
  - 3-7 years
  - >7 years

We compared the groups of the two reference periods according to the above-mentioned age groups.

## Results and discussions

In 1992 there were 28 patients with congenital heart diseases hospitalized in Pediatric Clinic III, while in 2007 the number of cardiac patients was 83.

The total number of admissions registered at the Pediatric Clinic III in the case of the patients with congenital heart diseases was 35 in 1992, respectively 119 in 2007, i.e. some of the patients were more times hospitalized during the same year. Following the number of the admission days for each patient, we emphasized the fact that the necessary time for diagnosis, paraclinical explorations, for the treatment of complications or associated pathologies was shorter in 2007 than in 1992:

- The average of admission days/patient is 6 days in 1992
- The average of admission days/patient is 4 days in 2007.

Though relative, this comparison can show that the patients' circulation is with 33 % quicker and the system of congenital heart diseases management is more efficient. The patients' life expectancy is higher nowadays due also to the shorter period of time between the diagnosis and surgical correction.

The occurrence of different types of congenital heart diseases among the pediatric general population was not significantly modified during the period of time of 15 years between the two reference periods of the study.

The differences resulted within the study represent mainly the consequence of the progresses achieved in the diagnosis of the children with heart diseases.

The patients' distribution according to the type of congenital heart disease was the following (table I).

| Type Of Congenital Heart Disease | Number Of Patients 1992 | Number Of Patients 2007 |
|---|---|---|
| Ventricular septal defect (VSD) | 13 | 11 |
| Atrial septal defect (ASD) | 6 | 13 |
| Valvular heart diseases (VHD) | 2 | 12 |
| Aortic coarctation (AoC) | 1 | 1 |
| Complex heart diseases (CHD) | 6 | 22 |
| Ventricular septal defect + pulmonic stenosis (VSD+PS) | 0 | 1 |
| Common atrioventricular canal (CAVC) | 0 | 6 |
| Persistency of arterial duct (PAD) | 0 | 15 |
| Dextrocardia | 0 | 2 |
| **Total Of Patients** | 28 | 83 |

**Table I** – Patients' distribution according to the type of congenital heart disease

In 1992 the main diagnosed heart diseases were registered as ventricular septal defect and atrial septal defect, these representing over 50% of the heart disease case-book record. All cardiopathies without diagnosis problems, especially of differential diagnosis problems were included into the group of complex cardiac heart diseases. The imagistic techniques, even the invasive ones did not succeed to accurately establish the type of congenital heart disease.

In 2007 though, most of the cases were complex heart diseases and the differential diagnosis of the heart disease type was possible in all cases.

The distribution of the two group patients on age groups was the following:

| AGE GROUP | 1992 | 2007 |
|---|---|---|
| New-born (under 1 month) | 3 | 1 |
| Baby (1 month – 1year) | 8 | 42 |
| 1-3 years | 7 | 14 |
| 3-7 years | 5 | 9 |
| Over 7 years | 5 | 17 |

**Table II** – Distribution on age groups of the patients of the two groups:

□ In 1992 it was relatively homogeneous, the highest occurrence being in the case of babies (28%), the lowest in the case of new-born ones (11%)

□ In 2007, 51% of the patients hospitalized with congenital cardiopathy were babies, 1% new-born ones.

□ The highest occurrence in 2007 are in babies and in the children over 7 years, fact that reflects a precocious diagnosis, respectively an improvement of the diagnosis and consequently, of life expectancy.

In our study:

a) In 1992:

□ Most of the cardiopathies were with left-right bypass (especially atrial septal defect and ventricular septal defect)

□ The percentage of heart diseases with isolated obstacle is reduced due to the small number of valvular diseases that could be diagnosed at the time.

□ There was no accurate diagnosis of complex heart disease, in this group being included all the severe heart diseases that could not be accurately differentiated.

b) In 2007:

□ The highest percentage of heart diseases is still represented by the ones with left-right bypass.

□ The number of heart diseases with isolated obstacle increased significantly due to the increase of the number of diagnosed valvular diseases (the progress of echocardiography and Dopller echocardiography)

□ An important percentage of complex heart diseases could be accurately diagnosed and with the help of echocardiography, the exact type of heart disease could be detected.

In the period of time of 15 years, the percentage of the invasive techniques in establishing the diagnosis decreased significantly, so that at present the cardiopathies can be detected only by an echocardiography performed by an experimented specialist.

In 1992 only half of the cardiopathy cases could be diagnosed with the ultrasound, the rest of the patients being subjected to certain invasive techniques of diagnosis, represented mainly by the cardiac catheterization and angiography. Part of the heart diseases couldn't be accurately diagnosed with the entire support of the invasive techniques (the case of the complex heart diseases).

Progresses achieved in the echocardiography diagnosis possibilities made that all cases of heart diseases to be accurately diagnosed in 2007, using only non-invasive means of diagnosis.

## Conclusion

1. A higher number of CHD, mainly complex CHD, was diagnosed in 2007 comparatively to 1992.

2. In 2007, complex CHD was diagnosed mainly in babies as opposed to 1992 diagnosis with a homogeneous distribution on groups of age.

3. During the last years the main contribution to a CHD precocious and accurate diagnosis was brought by the echocardiography that gradually replaced the invasive diagnosis means.



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# Atrial Septal Defect As An Uncommon Cardiovascular Malformation In Turner's Syndrome

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Turner syndrome is a condition usually associated with reduced final height, gonadal dysgenesis, and thus insufficient circulating levels of female sex steroids, and infertility. A number of other signs and symptoms are seen more frequently with the syndrome. Congenital malformations of the heart and the great vessels, hypertension and ischemic heart disease, and increased risk of aortic dissection are all conditions that the pediatrician or the physician caring for females with Turner syndrome should keep in mind. Cardiovascular malformations are frequently observed in Turner's syndrome. Bicuspid aortic valve and coarctation of aorta are commonly associated with Turner's syndrome while an atrial septal defect is unusual. Here we report a rare case of artrial septal defect with Turner's syndrome. Although cardiovascular malformations are well-recognized congenital anomalies in Turner syndrome (TS), other clinical features and a great variety of dysmorphic signs can also be observed.

**Keywords:** Congenital cardiovascular malformation; Turner's syndrome, karyotype

## Introduction

Turner syndrome is caused by the absence of one set of genes from the short arm of one X chromosome. In patients with 45,X karyotype, about two thirds are missing the paternal X chromosome. In addition to monosomy X, a similar clinical picture is found with a 46,Xi(Xq) karyotype and in some individuals with mosaic karyotypes.

Turner Syndrome, also known as Monosomy X (or Gonadal dysgenesis or 'Ullrich – Turner Syndrome), is a rare genetic disorder and occurs in 1 in 2500 female births. The karyotype can be either due to monosomy X (45,X), mosaicism (45,X/46,XX) or a structural abnormality of the X chromosome [2].

Few studies suggest that some Turner patients have Y chromosomal material in addition to the one X Chromosome [11].

The syndrome is characterised by short stature, ovarian failure and presence of other clinical features such as webbed neck, congenital cardiovascular malformations, renal

abnormalities, cubitas valgus [4]. The congenital cardiovascular malformations ranges 17 to 47% among Turner syndrome cases and have an increased risk of mortality [8].

Here we report an infant with Turner syndrome who has atrial septal defect as cardiovascular malformation.

Although short stature is the most proeminent characteristic of this disorder, a wide range of associated medical problems have been reported, which may lead to a three-fold increase in overall mortality and morbidity as well as reduced life expectancy by up to 13 years 12. Cardiovascular and renal anomalies, hearing difficulties and an increased incidence of autoimmune disorders are frequent comorbidities which increase life time risks. Disorders of glucose intolerance, type 2 diabetes, dyslipidemia, obesity and liver dysfunction often are delayed until adulthood and primary hypothyroidism occur both in childhood and adulthood. Individuals with TS clearly have increased risk for autoimmune thyroiditis and celiac disease [7].

All individuals with suspected TS should have a karyotype performed. A standard 30 cell karyotype is recommended by the American College of Medical Genetics (ACMG,2005) and identifies ≥10% mosaicism with 95% confidence, although additional metaphases may be counted or fluorescence in situ hybridization (FISH) studies performed if there is a strong suspicion of undetected mosaicism. The cytogeneticist should be consulted in this case. Although a peripheral blood karyotype is usually adequate, if there is a strong clinical suspicion of TS, despite a normal blood karyotype, a second tissue, such as skin, may be examined [5].

Testing for Y chromosome material should be performed in any TS patient with a marker chromosome (a sex chromosomal fragment of unknown origin, i.e. X vs. Y). This can be achieved by DNA studies or fluorescent in situ hybridization (FISH) using a Y centromeric probe, supplemented as necessary by short and long arm probes 1. The presence of virilization in a TS patient should prompt search for a gonadal, adrenal or midline tumor as well as investigation of the karyotype for Y-material 3. The prevalence and clinical significance of cryptic Y material detected only by FISH or DNA analysis in patients without virilization or a marker chromosome needs further investigation. False positives may be a problem with highly sensitive PCR-based Y detection methods. The presence of Y chromosome material is associated with an ~12% risk of a gonadoblastoma, which may transform into malignant germ cell neoplasms, hence, the current recommendation is for laparoscopic, prophylactic gonadectomy 9,10. It is often assumed that gonads in patients with TS and Y chromosome mosaicism have no reproductive potential, but spontaneous pregnancies in such women have been [6].

## Materials and methods

Informed consent was obtained from parents in accordance with the ethics committee. 2 ml of venous blood was collected in a sodium heparin precoated syringe. Peripheral blood was incubated in complete lymphocyte culture medium.

Giemsa (GTG) banding technique was performed to identify the chromosomes. Analysis was carried out using a BX51 Olympus microscope and images captured with an automated image analysis system (Cytovision, Applied Imaging).

Chromosomal anomalies were designated according to the standard nomenclature (ISCN 1995).

## Results

The female patient I.Z. is the first child born to 32 year old mother and 31 year old father. The parents are healthy and had no consanguineous marriage. There was no family history of congenital anomalies. She was born at full term of an uncomplicated pregnancy. The birth weight was 3000 g, she had a length of 49 cm and the head circumference was 35 cm.

The health problem was seen soon after the birth (bilateral feet lymphedema). At the age of 9 weeks she was sent to our clinic with the suspicion of renal peripheral edema. General examination of the proband revealed the following features: flat face, epicanthal folds, webbing of the neck, swelling of the feet, hyperconvex nails, broad chest and no cardiac murmur.

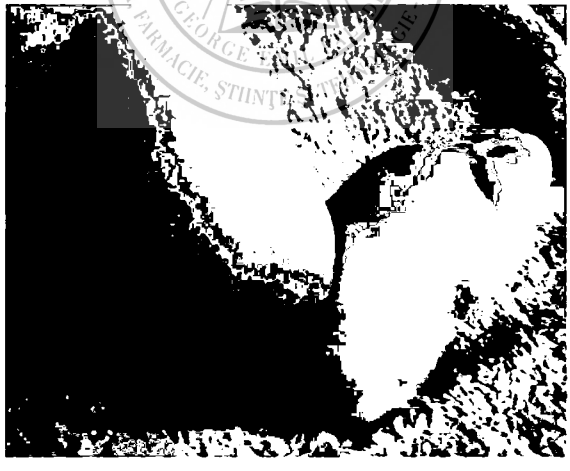

**Figure 1** – Foot lymphedema

Laboratory investigation and ultrasonography of kidneys and urinary tracts didn't revealed any abnormalities. Echocardiography revealed septal atrial defect ostium secundum and mild pulmonary hypertension.

Chromosomal analysis of the proband was performed on 35 well spread metaphase plates and monosomy of X chromosome was diagnosed in 34 methaphase, while one metaphase revealed 46,XY.

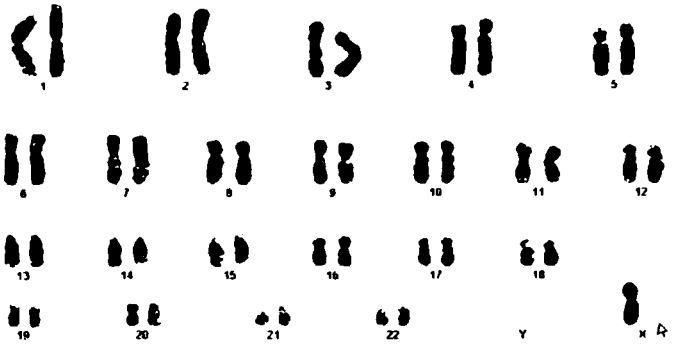

**Figure 2** – Karyotype: 45,X

**Figure 3** – Karyotype: 46,XY

Parents were informed about the result of the karyotype and the necessity of a prophylactic gonadectomy in the future.

## Discussion

1. The spectrum of congenital cardiovascular malformations in patients with Turner syndrome is variable.

2. Mazzanti and Cacciari (1998) studied a large series of 594 Turner patients from Italy. The prevalence of cardiovascular malformations was 23%. Bicuspid aortic valve and coarctation of aorta were the most prevalent defects [8].

3. Hirose et al. (1999) reported a rare case of atrial septal defect associated with Turner syndrome.

4. Our patient is one of the few cases of atrial septal defect associated with TS which exemplifies the varied spectrum and combination. The present case adds to the diversity of clinical abnormalities due to Turner syndrome [4].

5. There may be X-linked factors independently, synergistically or additively involved in the development of cardiovascular defects in these patients. Genetic counselling, family screening and fetal echocardiography should be available to these families.

6. Audiometry, echocardiography, ultrasonography of kidneys and urinary tracts, thyroid function tests, fasting blood sugar, lipid profile as well as anthropometric and blood pressure measurements should be assessed in all patients with TS.

7. This patient may has malignant gonadoblastoma or testicular tissue. Patients with 45,X/46,XY mosaicism may have mixed gonadal dysgenesis and are at a high risk for gonadoblastoma. These patients may require a prophylactic gonadectomy to prevent death from malignancy [1].

8. Turner syndrome is a lifelong condition. Most people live long and healthy lives, yet some are susceptible to numerous chronic conditions. Health supervision involves careful medical follow-up care, which includes screening for commonly associated chronic diseases.

9. Early preventive care and treatment are also essential. In childhood, growth hormone therapy is standard to prevent short stature as an adult. Estrogen replacement therapy is usually required, but starting too early can compromise adult height. Estrogen usually is started from age 12-15 years.

10. The medical care of children with Turner syndrome requires ongoing assessment and periodic review of specific problems at appropriate ages.



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# The Role Of Echocardiography In Diagnosis Of Double Outlet Right Ventricle In Children

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Double outlet right ventricle with a large variability in anatomy, represents a complex form of congenital heart disease , that includes ventricular septal defect (VSD) with significant override of the aorta, origin of both great arteries completly or predominantly from the right ventricle. The VSD is subaortic, subpulmonary, noncommitted or doubly committed. The definition is still controversial.

**Objective:** to evaluate the utility of echocardiography in diagnosing double outlet right ventricle (DORV) in children.

**Material and methods:** Thirty three patients with DORV were examined by two dimensional echocardiography, aged seven week to eleven years, median six months, between January and August 2008.

**Setting:** Department of Paediatric Cardiology Tg Mureş

**Results:** In this study echocardiography has shown that twelve patients were diagnosed with DORV type Tetralogy of Fallot, eleven with DORV with normally related great arteries and ten children were diagnosed DORV and transposition of the great arteries. Most VSD are nonrestrictive. Typical by two dimensional echocardiographic features were parallel orientation and origin of both great arteries from right ventricle, mitral- semilunar valve discontinuity demonstrated on parasternal long axis by the presence of muscular conus separate on.

**Conclusions:** Echocardiography was very useful to diagnose DORV in children as well as to identify its anatomic type. This technique also allows Double outlet right ventricle better recognition of spatial orientation of the great arteries and the position of the VSD relative to the great arteries.

**Key words:** Double outlet right ventricle, Echocardiography ,Children

Double outlet right ventricle comprises a number of complex clinical entities that require separate diagnostic and therapeutic approches. DORV is a rare cardiac defect in which, its freequency has been reported as approximately 0,09 case per 1000 births and represents 1% to 1,5% of patients with congenital heart disease [2].

Frequently is associated with -other congenital cardiac abnormalities. The definition is still controversial. Pathologyc DORV has been defined variously by different researches. Neufeld defined it as follows: both great arteries and trunks aries exclusively from the morphologic right ventricle, neither semilunar valve is in fibrous continuity with either atrioventricular (AV) valve, usually a VSD is present and represents the only outlet from the left ventricle(2). Pulmonary valvular or subpulmonary stenosis may be present or absent. The definition proposed by Lev et al. however requires less rigid criteria. They indicate that one complete arterial trunk and at least half of the other arterial trunk emerge from the right ventricle, and there may or may not be mitral- aortic or mitral-pulmonary continuity [4].

The pathologic classification focuses on the location of the VSD relative to the great arteries and the great artery relationships. Four types of great arteries relationships at level of the semilunar valves have been described in DORV:

1. Right posterior aorta (The aortic valve and trunk originate from the right ventricle at a location posterior and to the right of the pulmonary valve and its arterial trunk.

2. Right lateral aorta (side by side relationship). The aorta is to the right of the pulmonary artery and the semilunar valves lie approximately in the same transverse and coronal plane.

3. Right anterior aorta . The aorta is to the right and anterior to the pulmonary artery .

4.Left anterior aorta .The aorta is to the left and anterior to the pulmonary artery .

Position of the ventricular septal defect (VSD)

There are four types of VSD in DORV:

1. The subaortic type. The VSD is located closer to the aortic valve than to the pulmonary valve.

2. The subpulmonary type. The VSD is located above the septal limb of the crista supraventricularis. The type of DORV is considered synonimous with the Taussig- Bing complex.

3. The doubly committed or subaortic and subpulmonary type. The VSD is very large and is closely related to both semilunar valves.

4. The remote type.

*Objective:* to evaluate the utility of echocardiography in diagnosing double outlet right ventricle (DORV) in children.

Material and methods: Thirty three patients with DORV were examined by two dimensional echocardiography, aged seven week to eleven years, median six months, between January and August 2008. Cross sectional echocardiograms were recorded on either on Sonos 5500,transducer s4 MHz. The presence of atrioventricular concordance was established from subcostal or apical four chamber. The ventricles were identified according to the morphology of the atrioventricular valves, their attachments, and the overal appearances.

The great arteries were distinquished by their cours and branching pattern. The most reproductible view is probably the parasternal long axis . DORV was diagnosed if either

of the great arteries could be seen originating anterior to the ventricular septum or in this view the central closure line of the cusps of the posterior great artery lay anterior to the crest of the ventricular septum. DORV was diagnosed if more than half of both great arterial roots were connected to the right ventricle.

*Setting:* Department of Paediatric Cardiology Tg Mureş

*Results:* Of the 33 patients, 18 (57%) were male and 15 (43%) female. Their ages ranged from seven week to eleven years (median six months). In this study echocardiography has shown that eleven patients were diagnosed with DORV type Tetralogy of Fallot (Table II), eleven with DORV with normally related great arteries (Table I) and eleven children were diagnosed DORV and transposition of the great arteries. Most VSD are nonrestrictive.

Typical by two dimensional echocardiographic features were parallel orientation and origin of both great arteries from right ventricle, mitral- semilunar valve discontinuity demonstrated on parasternal long axis by the presence of muscular conus separate on.
The role of the outlet septum in determinig the relation between the interventricular comunication and the outflow tracts: the outlet septum was present in 29 of the 33 patients. It was the cours of this structures which outflow tract was more closely related to the interventricular comunication. This was best seen in subcostal in orientation between short axis and four chamber planes.DORV was associated with complete AV septal defect, isolated cleft of the anterior mitral leaflet, total anomolous venous return and straddling left or right AV valves.

Other associated anomalies such as ASDs, coarctation of the aorta patent ductus arteriosus was diagnosed primarily two- dimensional and Doppler echocardiography.



## Discussion

DORV is a difficult anomaly to treat surgical [7,8].A logical and step-by-step approch to the diagnosis and classification of DORV is essential. Atrial arrangement (and venous connections) must be ascertained, and the atrioventricular connections established with certainty. Identification of the way in which the two great arteries arises from the right ventricle is important. The size and morfology of the interventricular communication is also of great importance, particulary in reference to their relationship with the arterial outlet. Defects were categorised as subaortic, subpulmonary or uncommitted and doubly committed. Two dimensional echocardiographic findings for the diagnosis of double outlet right ventricle- three observations were noted:

1. Origin of both great arteries from the anterior right ventricle
2. Mitral- semilunar valve discontinuity
3. Absence of left ventricular outflow other than the SVD.

Parasternal long-axis scans demonstrate mitral- semilunar valve discontinuity with the presence of muscular conus separation. Mitral- semilunar valve discontinuity is dem-

onstrated by two dimensional echocardiographic as a dense echo fibromuscular or as a muscular conus separating the two valves [1] (Figure 1).

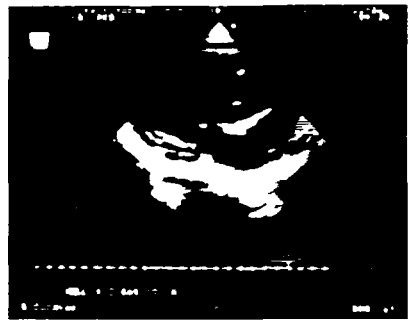

**Figure 1.** – Parasternal long axis scan in a patient with DORV and subaortic DSV.

Short-axis scans is helpful in demonstrating the commitment of both great arteries to the right ventricular cavity, as observed by their anterior position with reference to the plane of the ventricular septum[3] (Figure 3,4).

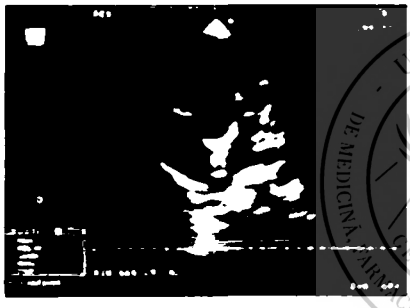

**Figure 3.** – Echocardiographic short axis scan in a same patient with DORV.

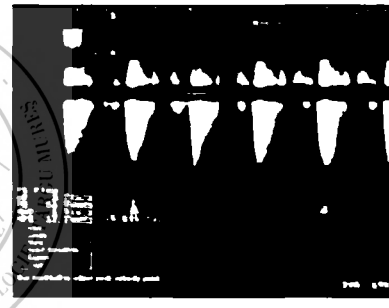

**Figure 4.** – Short axis scan parasternal. Doppler image of infundibular pulmonary stenosis (DORV type Fallot's Tetrallogy ).

Using both long and Short-axis scans allowes confirmation of the SVD- great artery relationships. Very large defects or doubly committed defects are recognized as appearing nearly equally commited to both great arteries. Remote defects or noncommitted defects are usually complete AV canal defects, but they may be isolated or multiple muscular VSDs (Figure 5). Complete Av septal defects are best recognized by apical or subcostal four chamber views (Figure 6).

The presence of pulmonary stenosis, the size of the RV outlow tract, the position of the orifices of the great arteries with respect to each other and particulary the size and location of the VSD in relation to the semilunar valves are important determinants for the surgical approch (Figure 3,4). In our experience subcostal examination provides the most information since it is invariably possible to show the interventricular comunication and at least one great artery (and usualy both) in the same cut (Figure 2).The disadvantage of

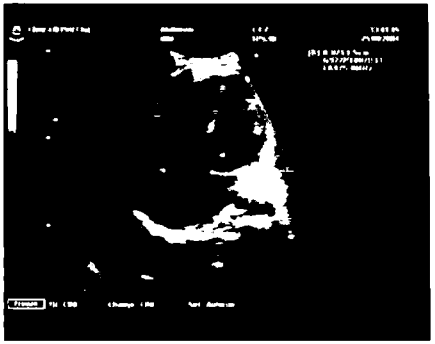

**Figure 5.** – Apical 4C scan in a patient with DORV and canal AV complet.

**Figure 6.** – Subcostal view- coronal scan,
visualising the outlet septum and great arteries „side by side".

**Figure 2.** – Subcostal view- coronal
scan, visualising the outlet septum.

the subcostal approach is firstly, that it is not always possible in older patients. Attention must also be paid to the anatomy and function of the atrioventricular valves and to the presence of other associated cardiac defects.

From the echocardiographic standpoint it seems preferable to concentrate on the following four point:

1 Is the outlet septum present ?

2 What forms of the interventricular communication is present?

3 Where are the atrioventricular valves inserted?

4 Which outflow tract is closest ton the interventricular communication?

*Conclusions:* Echocardiography was very useful to diagnose DORV in children as well as to identify its anatomic type. This technique also allows Double outlet right ventricle better recognition of spatial orientation of the great arteries and the position of the VSD relative to the great arteries.

| Sex | Age | VSD (type) | Associated defects (cardiac) |
|---|---|---|---|
| M | 9 months | subAo | ASD sec |
| F | 4 months | subAo | CAVC |
| F | 2 months | subAo | TAPVR, situs ambigus |
| F | 1 years | subAo | PDA.FOP |
| M | 2 months | subP | Co Ao |
| M | 8 months | subAo | |
| M | 1,7 years | subAo | PDA.FOP |
| M | 9 months | subAo | ASDs, PDA |
| M | 11 months | perimembranous | |
| F | 1,6 years | subAo | PDA, FOP |
| M | 2 months | subAo | Co A, PDA |

**Table I** – Double outlet right ventricle with normally related great arteries

| Sex | Age | VSD (type) | Associated defects (cardiac) |
|---|---|---|---|
| F | 5 months | subAo | PS, FOP |
| M | 8 months | subAo | PS |
| M | 3 years | subAo | PS |
| F | 5 years | subAo | MVPr |
| F | 1years | subAo | Infundibular St |
| M | 7 years | subAo | PS |
| F | 7 months | subAo | PS |
| M | 2 years | subAo | PS, PDA |
| M | 11 months | perimembranous | PS |
| F | 1,11 years | subAo | PS, FOP |
| M | 1, 2 months | subAo | PS, ASD s |

**Table II** – Double outlet right ventricle type F allot' s Tetrallogy with extreme dextroposition of the aorta

ASD- atrial septal defect; Co A- coarctation of the aorta; CAVC comon atrioventricular canal; PDA- patent ductus arteriosus; TAPVR- total anomolous venous return

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# Univentricular Heart – The Role Of Echocardiography

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The univentricular heart can be defined as one in which only one ventricle possesses an atrioventricular connection.
The aim of this study was to demonstrate the value of echocardiography in diagnosing of univentricular heart.

**Method:** 78 patients with univentricular heart were studied by echocardiography between Ianuary 2006 and June 2008. Classification into type of univentricular heart has been successfully achieved in 70 patients: 57 patients were with left type of univentricular heart, 12 patients were with right type of univentricular heart and only one patient had indeterminate univentricular heart. Also, the echocardiographic examination was carried out the type of atrioventrcular connection, the ventriculoarterial connections and the associated defects. In 61 patients with univentricular heart, after ecocardiogarphic investigation, the first terapeutic management has been started.

**Conclusion:** Two dimensional echocardiography is the most important method in diagnosing the morphological types of univentricular heart.

**Key words:** univentricular heart, echocardiography

Classification of univentricular heart remains a subject of heated debate. The majority of patiens submitted for functionally univentricular surgical repair does not possess anatomically univentricular hearts. An univentricular heart can be defined as one in which only one ventricular chamber possesses an atrioventricular connection 8. Such a definition does not exclude hearts which possess a second, rudimentary, ventricular chamber. On the basis of the morphology of the ventricles and rudimentary chambers three distinct morphological types of univentricular heart as thus defined can then be identified. Those of left ventricular type have an anterior rudimentary chamber with right ventricular trabecular pattern. Those of right ventricular type have a posterior rudimentary chamber of left ventricular pattern. Finally, those of indeterminate type do not possess a second chamber within the ventricular mass. This last type is the truely anatomically univentricular heart and it is found in a very rare circumstances [1,8,4].

In each of three morphological types the type of atrioventricular connection may be double inlet, absent right connection, or absent left. The mode of connection may be through two atrioventricular valves, one of which may be imperforate or straddling or overriding the trabecular septum, or through a common atrioventricularr valve which may also straddle or override the trabecular septum [1,6]. The purpose of this study was to investigate the value of two dimensional echocardiography in diagnosing the morphological types of univentricular hearts and in starting surgical treatment.

## Method

Seventyeight (78) pacients with univentricular heart were studied by echocardiography between Ianuary 2006 and June 2008. Two dimension echocardiograms were performed on each patient using a Sonos 5500 ecocardiograph. Each patient was examined from subcostal, parasternal and apical position, by long and short axis views. We used subcostal position to establish the abdominal and atrial situs, the position of the heart and the ventriculoarterial connection. In the most common type of univentricular heart all atrioventricular connections were committed to a chamber. Particular attention was directed to identify the rudimentary chamber. It was well-visualized in the parasternal long- and short-axis views. In univentricular heart of the left ventricular type the rudimentary chamber was located anterior to the main ventricle and it was separated from this chamber by an anterior trabecular septum. In univentricular heart of the right ventricular type the rudimentary chamber was located posterior. If a single chamber was present in the heart, with no evidence of a trabecular septum or rudimentary ventricle in any echocardiographic view, the diagnosis was the univentricular heart of indeterminate type.

Two-dimensional echocardiography showed the type of atrioventricular connection, either double inlet or absent right or left connection. Double inlet was characterised by both atria being in direct connection with the main ventricular chamber [3,8]. The characteristic of the hearts with absent right connection was the presence of a single, left sided atrioventricular valve and absence of any potential communication between the floor of the right atrium and the main or rudimentary ventricular chamber. Characteristically a wedge of sulcus tissue was interposed between the right atrium and the main chamber. Similarly in hearts with absent left connection, there was a single, right sided atrioventricular valve and no potential communication between the left atrium and the ventricular mass, sulcus tissue again has being interposed. In some occasions, only one valve was seen in any given echocardiographic plane. In these cases, without multiple views, the connection could be misconstrued as common inlet, imperforate right or left, or even absent connection [2,8].

Two-dimensional echocardiography showed the type of ventriculoarterial connections: concordant connections, discordant connections, double outlet from main chamber or double outlet from outlet chamber. It was also important to looked for associated defects.

Comprehensive hemodynamic assessment was included color-flow imaging and Doppler interogation. It was carried out: pulmonary stenosis or atresia, atrioventricular stenosis or regurgitation, restriction of the bulboventricular foramen.
In the majority of cases the echocardiograms were recorded on a video-display which allowed repeated examination.

## Results

The two dimensional echocardiography showed the precise ventricular morphology in 70 patient of 85.(Tabel I)

| Type of univentricular heart | Cases |
|---|---|
| Left | 57 |
| Right | 12 |
| Indeterminate | 1 |

Tabel I – Type of univentricular heart

*Univentricular heart of left ventricular type*
These were the most common examples of univentricular heart. The diagnostic feature of these hearts was that the atrioventricular connection or connections were identified posterior to the ventricular septum. (Tabel II and III)

| Type of left univentricular heart | Cases |
|---|---|
| Double inlet | 26 |
| Absent right | 30 |
| Absent left | 1 |

| Type of left univentricular heart | Cases |
|---|---|
| Double inlet-two AV valve | 18 |
| Double inlet-common AV valve | 8 |

**Tabel II, III** – Univentricular hearts of left ventricular morphology: type and mode of atrioventricular connection

In hearts with double inlet ventricle, the rudimentary chamber was found to be to the right in 32 patients and to the left in 25 patients.

*Univentricular heart of right ventricular type*

The pathognomonic feature of these hearts was the position of the septum posterior to the atrioventricular connection or connections.

*Univentricular heart of indeterminate type*

These were hearts in which no rudimentary chamber could be demonstrated by echocardiography in any of the planes. This type of univentricular heart was found in only one patient.

## ECHOCARDIOGRAPHIC EVALUATION OF THE VENTRICULOARTERIAL CONNECTIONS

With the univentricular heart, any ventriculoarterial connection were found including concordant connections, discordant connections, discordant connections, double outlet from the main or outlet chambers[7]. (Table IV)

| Ventriculoarterial connection | Left (tricuspid atresia) | Left (double outlet left ventricule) | Right |
|---|---|---|---|
| Concordant | 21 | | |
| Discordant | 3 | 26 | 3 |
| Double outlet to the main chamber | | 5 | 9 |

**Table IV** – Ventriculoarterial connections in univentricular heart

## ASSOCIATED DEFECTS

Two dimensional echocardography, Doppler color and Doppler pulsat exam showed the follow associated defects: situs inversus, atrial izomerism, left superior vena cava, pulmonary stenosis or atresia, stenosis of the atrioventricular valve, coarctation of the aorta[9]. (Tabel V)

| Type of UVH | PS | PA | AVS | AVR | LSVC | CoAo |
|---|---|---|---|---|---|---|
| Left | 22 | 2 | 3 | 5 | 5 | 2 |
| Right | 10 | 4 | | 7 | 2 | |
| Indeterminate | | 1 | | 1 | | |

**Tabel V.** – Associated defects

On the basis of the echocardioraphic investigation 61 patients of 70 had their first ever surgical procedure. (Tabel VI)

| Type of paleative intervention | SP shunt | B | G | B and G | Sep and SP shunt | Sep and G |
|---|---|---|---|---|---|---|
| Patients number | 24 | 9 | 17 | 6 | 2 | 3 |

**Tabel VI.** – Surgical interventions in patients with univentricular heart

## DISCUSSION

On the basis of classification of univentricular hearts used in this study we excluded those hearts in which was found the connections between one atrium and rudimentary chamber. In this way, the classification used here links together all those hearts in which the atria are connected to only one chamber in the ventricular mass [1,5,6].

The key in the echocardiographic diagnosis of the univentricular heart is the identification of the presence and position of a rudimentary chamber within the ventricular mass[1,2,5]. Posterior chambers in univentricular heart of right ventricular type are the most easily seen. Anterior chambers in hearts of left ventricular type are also readily identified in the majority of cases, though a search using multiple echocardiographic planes is sometimes required. When a second rudimentary ventricular chamber is seen on a short axis view at or just below the level of atrioventricular valves, its position relative to the main chamber is easily defined. In infants an anterior chamber is frequently not identified when this view is used to examine univentricular hearts of left ventricular morphology. When it is impossible by echocardiography to define a second chamber within the ventricular mass then it is most likely that the ventricular morphology is of indeterminate type.

Like in the other studies publicated in the speciality literature, the left type of univentricular heart was the most common type of univentricular type. Classical tricuspid atresia was the most frequently type of left univentricular heart with atrioventricular valvular atresia and double inlet left ventricule was the most often univentricular heart with two atrioventricular valves. Echocardiographic evaluation of the ventriculoarterial connections showed that in left univentricular heart the conncordant and discordant connectin were in aproximately equal frequencies. But, in left univentriculatr heart with right atrioventricular valve atresia ("classical" tricuspid atresia) the concordant connections were the most common, and in double inlet left ventricle were most frequently the discordant connections.

Pulmonary stenosis was the most common associated defect.

Routine preoperative catheterization before the initial operation was no longer a necessity. After a complete echocardiographic examinaton an important number of patients were operated.

## Conclusion

The echocardiography is the most important investigation in diagnosing the morphological types of univentricular hearts. Also, in many cases ecocardiographic examination provide sufficiency informations for started surgical management.

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# Mesoscopic Aspects Of Pulmonary Vascular Disease

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**The aim** of this study was to undeline the importance of using in parallel of several available methods for a correct diagnosis of pulmonary vascular lesions, and to briefly present some of the new methods, capable of aiding clinicians and morphopathologists in putting the real diagnosis.

**Materials and methods:** we examined histologically the state of the pulmonary arteries in order to apreciate the grade of the pulmonary vascular lesions (the necropsies provided the corrosion material, too). Along with the histological examination we examined the pulmonary vascular lesions by corrosion models with a stereomicroscope and with a high-tech digital camera (Sony DSC F717, 5x optical zoom, and 5Megapixel) too.

**Results:** Through qualitative histopathological analysis we identified six grade of pulmonary vascular lesions and by the steromicroscopic apperences of the corrosion models we saw some vascular lesions witch didn't appear using simple histopatologic evaluation (rarifying of density, lesion of vascular calibers and the dilatative lesions with modified arterial traiects.).

**Conclusions:** the methods described above, if used together, may be a real help in current medical practice in putting the correct diagnosis of pulmonary vascular disease, and deciding the adequate therapy.

**Key words:** Pulmonary vascular disease, histopathology

## Introduction

Pulmonary arterial hypertension associated with congenital heart disease (left/right shunt) is one of the most common cause of severe morbidity and premature mortality. Elevated pulmonary artery pressure in congenital heart disease is caused by pulmonary overcirculation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination [4]. Progressive histological changes occur in the small pulmonary blood vessels as an association of the chronic pulmonary hypertension complicating many congenital cardiac defects. The pathologic diagnosis of pulmonary vascular remodeling in hypertension pulmonar disease depends on the histological assessement of the cellular composition of pulmonary vascular walls, wich, if abnormal, is descriebed as pulmonary

vascular lesions [2,5]. The fuctional status of the hypertensive pulmonary circulation could be broadly correlated with a specific type of pulmonary vascular remodeling present at pathologic evaluation of the pulmonary arteries [5, 3, 6].

This progression is so stereotyped as to allow the recognition of six grades of change. Grading of pulmonary vascular lesions associated with congenital heart disease, introduced by Heath & Edwards (1958), has been widely used for assessment of the severity of hypertensive pulmonary vascular disease [5,1].

The aim of this study was to underline the importance of using in parallel of two methods for a correct diagnosis of pulmonary vascular lesions, capable of aiding clinicians and morphopathologists in putting the real diagnosis.

## Materials and methods

We examined histologically the state of the pulmonary arteries in order to apreciate the grade of the pulmonary vascular lesions. To determinate of diferent lesions we used some special and generate stains: Hematoxylin-Eozin, van Gieson stain and Szekely Trichrom methode.

Along with the histological examination we examined the pulmonary vascular lesions by corrosion models with a stereomicroscope and with a high-tech digital camera (Sony DSC F717, 5x optical zoom, and 5Megapixel) too.

## Results

Through qualitative histopathological analysis we identified the following lesion types: media thickening, intimal cell proliferation, fibrous luminal obstruction, the presence of dilateted segments, dilatative lesions (aneurismal, angiomatoid and plexiform lesions and vein like arterial branches), hemosiderosis and necrotic arterial inflamation.

We identified six grade of pulmonary vascular lesions.

Grade I. hypertrophy of the media of muscular pulmonary arteries. Extension of muscle into the wall of pulmonary arterioles. (Figure 1 a)

Grade II. muscle hypertrophy plus proliferation of intimal cells in arterioles and small muscular arteries. (Figure 1 b)

Grade III. muscle hypertrophy plus subendothelial fibrosis. Eventually, concentric mass of fibrous tissue and redublicated internal elastic lamina occlude the vascular lumen of arterioles and small musclular arteries. Large elastic arteries show atherosclerosis (Figure 1 c )

Grade IV. muscle hypertrophy is less apparent; progressive dilatation of small arteries, especially those near vessels with intimal fibrous occlusion. Plexiform lesions occur. (Figure 1.d )

Grad V. plexiform and angiomatoid lesions plus intraalveolar hemosiderin-filled macrophages. (Figure 1 e )

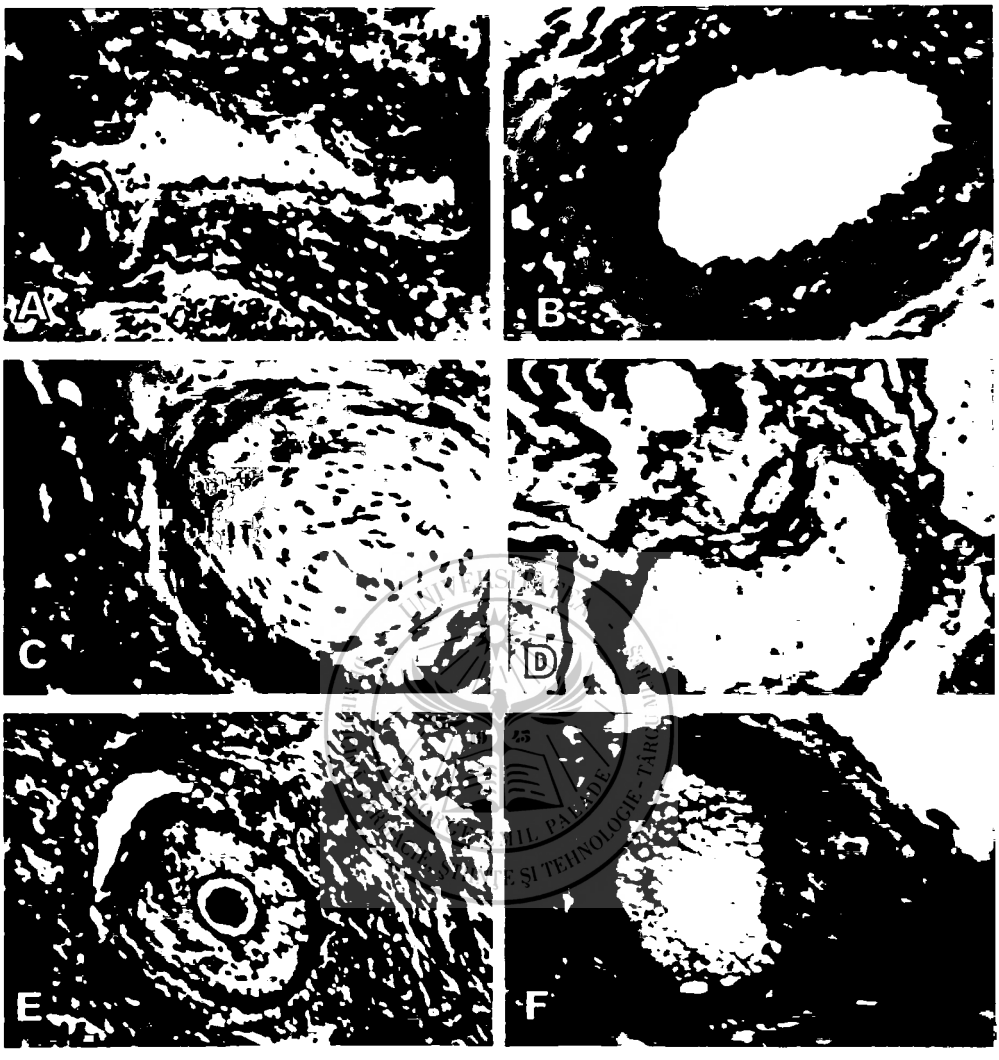


**Figure 1.** a- Pulmonary artery showing medial hypertrophy (10x, van Gieson stain); b- Pulmonary artery showing medial hypertrophy and lesions of external elastic lamina (10x, Orcein stain); c - Muscular pulmonary artery with concentric masses of intimal fibrous tissues formated by fibrocyte cells and smooth muscle cells, media is thin. (40x, van Gieson stain); d - Dilatation of small arteries (40x, HE); e - Plexogenic arteriopathy with intimal concentric fibrosis, muscle media, lumen of arterioles is obstruated. (10X, Tricrom-Szekely stains); f - Pulmonary artery with medial thicknening, eosinophil, with transmural infiltrate of polymorphonuclear leukocyte.

Grad VI. necrotizing arteritis with thrombosis. Fibrinoid necrosis of the arterial wall with transmural infiltrate of polymorphonuclear leukocytes and eosinophils. (Figure 1 f)

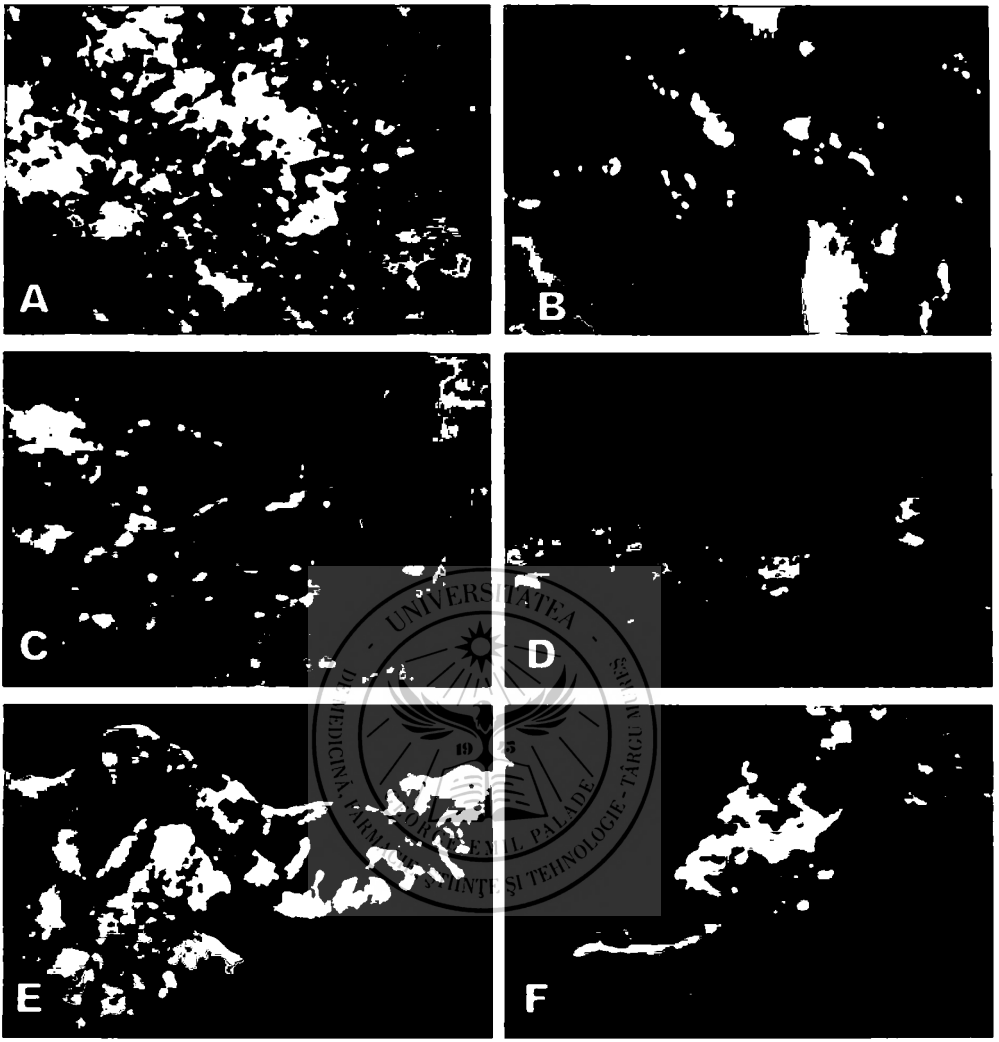


**Figure 2.** a - Rarifying of peripheral arterial branches by amputation of lobulare and preacinous arteriesin ventricular septal defect; b - Rarifying of peripheral arteries branches, with sinusoid aspects of the branches; c - Preacinoase artera with excentric stenosis; d - Excentric stenoses with lumen dilatate; e - Vascular calibers with stenose associated with dilation, plexiform lesions; f - Stenotic branch surrounded by a plexiform lesion

With high-tech digital camera (Sony DSC F717, 5x optical zoom and 5 Mega pixels), we concluded the following: 1. In case of pre-tricuspidian communications, the aspect of the corrosion model does not differ from the normal. 2. In ventricular septal defects, endocardial cushions or patent arterial duct, the presence of the lesions depends on the

dimension of the communication, the time of survival, and also on the association with other malformations. 3. The first mesoscopic lesions which appear at a relatively short period after birth affect the density of peripheral arterial branches; the rarifying which can be mild (ventricular septal defects), moderate (Figure 2 a) or severe, depending on the hypoplasia or amputation of intra-, and preacinous and lobular arterial branches (Figure 2 a) 4. Another category of lesions interest vascular calibers, like concentrical and excentrical stenoses (Figure 2 c), associated with lumen dilation (Figure 2 d, 2 e). 5. In case of non-corrected transposition of the great arteries, the pulmonary arteries may present a very bizarre look, characterized by reduced arterial density and caliber changes, also by severe dilatative lesions (aneurisms and plexiform lesions) (Figure 2 e, 2 f) And modified arterial traiects, with the presence of sinuous branches (Figure 2 b) 6. generally the lesions are situated distally.

## Discussions

Rubin M Tunder, John C. Marecki (2007) oppinion is that the fuctional status of the pulmonary circulation detremine the outcome and treatement of patinens who have pulmonary hypertension associeted with congenital heart disease. This status is depended by the histologically assassiment of the cellular composition of pulmonary walls.

Heath and Edwards (1958) described of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. First three grades contain the potenially reversible lesions, the last three grades include irreversible lesions.

Vascular corrosion casting has been used for about 40 years to produce replicas of normal and abnormal vasculature and microvasculature of various tissues and organs that could be viewed at the ultrastructural level. In combination with scanning electron microscopy (SEM), the primary application of corrosion casting has been to describe the morphology and anatomical distribution of intraluminal lesions of blood vessels in these tissues. However, such replicas should also contain quantitative information about that vasculature. We identified by corrosion model some vascular lesions witch didn't appear using simple histopatologic evaluation (exaple: the rarifying density of peripheral arterial branches wich can be mild, moderate or severe)

## Conclusions

The methods described above, wich complet each other, may be a real help in current medical practice in putting the correct diagnosis of pulmonary vascular disease, and deciding the adequate therapy.

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# The Role Of Perioperative Transesophageal Echocardiography In Congenital Heart Defects

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Transesophageal echocardiography is a monitoring and diagnostic tool for the care of children undergoing cardiac surgery. With the development of miniaturized probes nowaday intraoperative transesophageal echocardiography can be performed safely in the pediatric population. Pre- and postoperative transesophageal echocardiography is performed to confirm the anatomical arrangements, to assess cardiac function, to evaluate the surgical repair, to guarantee the absence of air in the cardiac chambers prior to the completion of intracardiac manipulation, all of which can assist surgeons in planning the most appropriate procedures. The operating room is a busy environment, so a comprehensive examination may not be practical or indicated in this environment especially during circumstances of hemodynamic instability. In such cases an abbreviated or focused examination is more appropriate. In this review are presented the transesophageal echocardographic features of the most important congenital heart defects.

**Key words:** echocardiography, transesophageal, intraoperative, congenital

Over the past 15 years transesophageal echocardiography (TEE) has become an important monitoring and diagnostic tool in the care of children undergoing surgery for congenital heart defects (CHD). According to the report from the Task Force of the Pediatric Council of the American Society of Echocardiography 1,12,15, there are strong evidence for the usefulness of TEE in surgery for congenital heart disease because it significantly improves the clinical outcome of these patients.

Until 1990, intraoperative evaluation of infants and children undergoing congenital heart surgery was not feasible with TEE because probe sizes were too large for most children. The subsequent development of miniaturized probes has generated a number of studies, which have demonstrated that TEE can be performed safely in the pediatric population and provide substantial benefit as well4,13.

It is suited to define complex anatomical structures, functional abnormalities, and flow disturbances that may not always be obtainable from transthoracic echocardiography (TTE) alone.

TEE has become a standard imaging technology for patients with CHD undergoing intervention in the operating room, or in the catheterization laboratory[7,14], as well as in the intensive care unit, or echocardiographic laboratory in some special cases.

Indications for intraoperative TEE in the patient with CHD[1]: the most common indication for TEE in patients with CHD is for assessment during cardiac surgery.

The task force recommends[1] that a preoperative TTE be performed in every patient undergoing TEE during congenital heart surgery and that the findings be reviewed by the echocardiographer before the intraoperative TEE is performed, that because there are limitations in imaging certain important structures with TEE alone, such as: transverse aortic arch, aortic isthmus, distal left pulmonary artery and collateral pulmonary vessels, as well as limitations in optimal Doppler alignment, limited time to perform a complex study.

TEE performed just before surgical intervention: may confirm or exclude preoperative TTE findings and assess the immediate preoperative hemodynamics and ventricular function of the patient.

Intraoperative TEE. [6,7,8,14] Performance of TEE in the patient with CHD immediately after surgery , but before chest closure, has been an important issue for the excellence outcome for congenital heart surgery achived in the past decade.

TEE provide the opportunity to detect significant and potentially treatable disease before disconnection of bypass cannulae, sterna closure and return to the intensive care unit. Also, TEE assess cardiac function, presence of intracardiac air, and may aid in the diagnosis of cardiac rhytm abnormalities. TEE has been also used to monitor ventricular function and loading conditions following cardiac transplantation.[16]

There are several studies that demonstrated the role of postoperative TEE, also in the need to return to cardiopulmonary bypass . Rosenfeld et al. 8 reported that TEE was a highly reliable predictor of potsoperative closure of ventricular septal defects, or the presence of aortic regurgitation, mitral stenosis and mitral regurgitation. Ungerleider suggested that postoperative TEE had the greatest impact on three types of surgical repairs, namely closure of ventricular and atrioventricular septal defects and relief of obstructed ventricular outflow tracts. Based on Xiao-Jing Ma , their surgeons needed to return to cardiopulmonary bypass to repair the residual problems or sequels in 3.7% of the patients.

In the intensive care unit, if TTE can not be performed because of limited transthoracic views, TEE permits assessment of ventricular function and ssissts in determining appropriate timing and hemodynamic effect of sterna closure or discontinuation of ventricular assist device or extracorporeal membrane oxygenation.

Also, TEE may be used postoperative in monitoring hemodynamic changes as inotropic drugs or adjusting ventilator settings.

Intraoperative TEE in high risk CHD patients (include those with complex CHD and significant residual anatomic defects, patients with myocardial dysfunction, cardiomyopathies or pulmonary hypertension) undergoing noncardiac procedures enhances monitoring of myocardial function and intravascular volume status.

Some current indications for TEE in the patient with CHD are [1]:

a. Diagnostic indications:

– Patient with suspected CHD and nondiagnostic TEE

– Presence of foramen ovale patent and direction of shunting as possible etiology for stroke

– Foramen ovale patent evaluation with agitated saline contrast to determine possible right-to-left shunt, prior to transvenous pacemaker insertion

– Evaluation of intra- or extracardiac baffles following the Fontan, Senning or Mustard procedure [3]

– Aortic dissection (Marfan syndrome)

– Intracardiac evaluation for vegetation or suspected abscess

– Pericardial effusion or cardiac function evaluation and monitoring postoperative patient with open sternum or poor acoustic windows.

– Evaluation for intracardiac thrombus prior to cardioversion for atrial flutter/fibrillation

– Evaluating status of prosthetic valves

b. perioperative indications

– immediate preoperative definition of cardiac anatomy and function

– postoperative surgical results and function

c. TEE guided interventions

– guidance for replacement of ASD or VSD occlusion

– guidance for blade or balloon atrial septostomy

– catheter tip placement for valve perforation and dilation in catheterization laboratory

– guidance during radiofrequency ablation procedure

– results of minimally invasive surgical incision or video assisted cardiac procedure.

*Contraindications for TEE* [1]

Absolute contraindications: unrepaired tracheoesophageal fistula, esophageal obstruction or stricture, perforated hollow viscus, poor airway control, severe respiratory depression, uncooperative, unsedated patient relative contraindications: history prior esophageal surgery, esophageal varices or diverticulum, gastric or esophageal bleeding, vascular ring, aortic arch anomaly with or without airway compromise, oropharingeal pathology, severe coagulopathy [1], cervical spine injury or anomaly – distort the normal orientation of the esophagus. Patients with Down syndrome have intrinsic narrowing of the hypopharyngeal region in addition to having increased incidence of cervical spine anomalies.

*Complications:* serious complications during pediatric TEE are very rare, but hemodynamics and respiration must be closely monitored. Blood pressure generally remains stable but can decrease precipitously if anteflexion or retroflexion compresses the aorta. Respiratory compromise can occur, peak inspiratory pressures can increase, and desaturation can be observed. There may be movement of the endotracheal tube during the TEE examination, resulting in extubation of the trachea. [11]

For TEE evaluation of different forms of CHD, whether comprehensive or abbreviated, the echocardiographer should display all pertinent structures in the heart. The operating room is a busy environment, so a comprehensive examination may not be practical or indicated in this environment especially during circumstances of hemodynamic instability. In such cases an abbreviated or focused examination is more appropriate. An example sequence is found in table I. [5]

| | |
|---|---|
| 1 | Midesophageal aortic valve short-axis (ME AV SAX) |
| 2 | Midesophageal right ventricular inflow-outflow (ME RV I-O) |
| 3 | Midesophageal right ventricular inflow-outflow Doppler flow of pulmonary valve (ME RV I-O w/CFD of PV) |
| 4 | Midesophageal aortic valve long-axis (ME AV LAX) |
| 5 | Midesophageal aortic valve long axis Doppler of aortic valve (ME |
| 6 | AV LAX w/CFD of AV) |
| 7 | Midesophageal bicaval (ME bicaval) |
| 8 | Midesophageal four chamber (ME 4CH) |
| 9 | Midesophageal four-chamber Doppler of mitral valve (ME 4CH of MV) |
| 10 | Midesophageal four-chamber Doppler of tricuspid valve (ME 4CH w/CFD of TV) |
| 11 | Midesophageal two-chamber (ME 2 CH) |
| 12 | Transgastric mid short-axis (TG mid SAX) |
| 13 | Transgastric two-chamber (TG 2CH) |
| 14 | Descendent aorta short-axis (desc aorta SAX) upper esophagian aortic arch short-axis (UE aortic arch SAX) |
| 15 | Descendent aorta long-axis (desc aorta LAX) |

**Table I.**

The most important CHD evaluated perioperative with TEE are:

*Atrial septal defect (ASD):*

TEE planes and information provided: Midesophageal four-chamber view (ME 4-CH): secundum and primum defects, pulmonary venous return, mitral valve anatomy (prolapsed), and Midesophageal bicaval view (ME bicaval): sinus venosus defect and pulmonary veins

Goals of the two-dimensional examination are: definition of defect location and size, determination of right-sided chambers and vessel dimensions, examination of the mitral valve prolapse or cleft, evaluation of pulmonary veins, assessment of ventricular function, detection of an interatrial shunt by the intravenous injection of agitatd saline solution or other echocardiography contrast agent. Goals of the Doppler examination are: assessment of flow across defect (color Doppler), detection of ricuspid or mitral valve regurgitation (color Doppler), measurement of tricuspid regurgitant jet velocity to estimate PA systolic pressure (spectral Doppler), estimation of the magnitude of the shunt (pulmonary and systemic blood flows) in the absence of significant atrioventricular valve regurgitation (spectral Doppler). Goals of the examination after surgical repair are: detection of residual interatrial shunts, assessment of ventricular function, evalu-

ation of valve competence (mitral regurgitation) and obstruction of pulmonary veins (sinus venosus ASD). [2,9,10,11]

*Ventricular septal defect (VSD):*

TEE planes and information provided: ME 4-CH and midesophageal aortic valve long–axis view (ME AV LAX) for perimembranous, inlet and muscular VSDs, chamber sizes, presence of ventricular septal aneurysm, and ME AV LAX and deep transgastric long-axis view (deep TG LAX) for the evaluation of aortic valve for regurgitation and herniation.

Goals of the two-dimensional examination are: assessment of defect location, size and extension, determination of chamber sizes and PA dimensions, inspection for associated abnormalities, identification of ventricular septal aneurysm, if present, evaluation of AV for herniation and prolapse, inspection for findings suggestive of pulmonary hypertension. Goals of Doppler examination are: detection of tricuspid and/or aortic regurgitation (color Doppler), enhancement or confirmation of the presence of a defect or additional defects (color Doppler), determination of the magnitude and direction of shunt flow (color Doppler), estimation of PA systolic pressure, estimation of the magnitude of the shunt in the absence of significant atrioventricular valve regurgitation (spectral Doppler).

Postsurgical evaluation include: detection of residual shunts, atrioventricular (AV) valve and semilunar valve competence and ventricular function. [2,9,10,11]

*Patent ductus arteriosus (PDA):*

TEE planes and information provided: difficult to visualize by TEE, however ductal flow can be detected in the midesophageal ascending aortic long-axis view (ME AsAoSAX) by presence of abnormal continuous high velocity aliased flow.

Goals of two-dimensional examination are: identification of associated cardiac malformations, detection of left-atrial or ventricular dilation, assessment of LV function. Goals of Doppler examination are: color-flow mapping to detect ductal flow into the main PA, evaluation of tricuspid and mitral regurgitation, estimation of the PA systolic pressure, document retrograde flow in the ascending aorta during diastole.

Postsurgical evaluation include: detection of persistent shunt, evaluation of the ventricle function. [2,9,11]

*Coarctation of the aorta*

TEE planes and information provided: upper esophageal aortic arch long-axis and short-axis views of decending thoracic aorta and aortic arch (UE AoArch LAX and SAX): posterior shelf, aliased flow by color Doppler and CW Doppler gradient. Other planes: ME 4-CH, 2-CH, AV LAX and TG SAX: for evaluation of LV mass and function, mitral valve morphology and function, aortic valve, subvalvular and supravalvular obstruction.

Goals of two-dimensional examination (limited evaluation of the aortic arch): identi-

fication of associated lesions and monitoring of LV function during aortic-clamp application. Goals of Doppler examination are: detection of turbulent jets in the descending aorta (color flow Doppler), determination of flow velocities across the area of narrowing.

Postsurgical evaluation: detection of residual gradient, recoarctation, aortic aneurysm formation.[2]

*Aortic valve stenosis:*

Goals of two-dimensional and Doppler examination are: determination of aortic valve morphology and motion, measurement of annular size, identification of poststenotic dilation of the ascending aorta (ME AV SAX, ME AV LAX and depp TG LAX), detection of concentric LV hypertrophy or dilation, assessment of global and segmental LV function (ME 4-CH), identification of associated pathology, identification of turbulent flow across the aortic valve and/or aortic regurgitation, estimation of gradient across the aortic valve (deep TG LAX).

Postsurgical evaluation: detection of the residual/recurrent obstruction, aortic regurgitation, bioprosthetic/mechanical valve function, perivalvar leak, ventricular function. After Ross procedure: aortic obstruction and regurgitation, function of right ventricular homograft, ventricular function (global and segmental). [2,9,11]

*Pulmonary stenosis*

Goals of two-dimensional and Doppler examination: determination of pulmonary valve morphology and motion, measurement of annular size, evaluation of the main pulmonary artery and proximal pulmonary artery branches, identification of poststenotic dilation of the pulmonary artery (ME AsAoSAX), assessment of the right ventricle including systolic function, detection of right ventricular hypertrophy or dilation, identification of associated pathology, identification of turbulent flow across the pulmonary valve and/or regurgitation, tricuspid regurgitation, peak-gradient across the pulmonary valve (ME RV inflow-outflow and deep TG LAX).

Postsurgical evaluation: evaluate the residual outflow tract obstruction, pulmonary regurgitation, right ventricle size and function). [2,9,11]

*Tetralogy of Fallot*

Goals of the two-dimensional and Doppler examination are: confirmation of diagnosis, characterization of rigt ventricular outflow tract (RVOT) obstruction, definition of the size and location of the ventricular septal defect, exclusion of associated pathology, determination of presence of an atrial septal defect, definition of coronary artery anatomy, assessment of biventricular function, assessment of flow across the ventricular septal defect, definition of the severity of the RVOT obstruction, evaluation of the aortic valve for incompetence, detection of tricuspid regurgitation, and flow across the atrial septal defect.

Postsurgical evaluation include: detection of residual RVOT obstruction, pulmonic or conduit stenosis, residual shunts, ventricular function, aortic regurgitation. [2,9]

*Transposition of the great arteries*

Goals of the two-dimensional and Doppler examination: confirmation of diagnosis, assessment of atrioventricular and ventriculoarterial connections (deep TG LAX), evaluation of associated pathology (intracardiac communications, outflow tract obstructions), estimation of ventricular sizes and systolic function (TG mid SAX), assessment of flow across intracardiac communications, the peak-gradient across an outflow tract obstruction, tricuspid and mitral regurgitation (ME 4CH).

Goals of the examination after surgical repair: after arterial switch operation: supravalvular (aortic/pulmonary) stenosis or regurgitation, left ventricular function, residual shunts. [2,9]

*Congenitally corrected transposition of the great arteries (levo-transposition)*

Goals of the two-dimensional and Doppler examination: confirmation of diagnosis, assessment of atrioventricular and ventriculoarterial connections, evaluation of associated defects such as: intracardiac communications, pulmonary outflow tract obstruction (ME LAX), tricuspid valve morphology and competence, estimation of ventricular sizes and systolic function (ME 4CH, 2CH, TG mid SAX), characterization of flow across intracardiac communications, assessment of gradient of the pulmonary outflow tract obstruction (ME LAX), tricuspid or mitral regurgitation.

Postsurgical evaluation following double switch operation: for the atrial baffle portion – baffle leaks, obstruction of venous pathways, atrioventricular valve competence, function of systemic ventricle, for the arterial switch portion – evaluation of the outflow obstruction, also the residual intracardiac shunts.[2]

*Single ventricle*

Diagnostic assessment of the functional single ventricle requires a combination of multiple imaging planes. The ME 4 CH view for demonstration of the crux of teh heart and characterizing the atrioventricular connections. Additional views: ME 2CH, ME LAX, ME bicaval and right ventricular inflow-outflow.

Goals of the two-dimensional and Doppler examination: confirmation of the diagnosis, assessment of atrioventricular and ventriculoarterial connections, evaluation of associated defects as intracardiac communications and outflow tract obstruction, estimation of size of ventricles and ventricular function, assessment of atrioventricular and semilunar valves for obstruction/regurgitation, estimation of gradient across any outflow tract obstructions.

Postsurgical evaluation (post Fontan): estimation of the cavopulmonary connection, Fontan baffle, aortic regurgitation, systemic outflow tract obstruction, atrioventricular valve competence, ventricular function, adequacy of atrial septal defect. [2,11]

*Atrioventricular septal defect*

Goals of the two-dimensional and Doppler examination: to define bridging leaflets, extent of intrcardiac defects, and position and number of papillary muscles, and to define left ventricular outflow tract (transverse and transgastric planes), evaluation of atrioventricular valve regurgitation and size of septal defects, to show the attachment of the atrioventricular valves to the underlying septum (ME 4CH).

Postsurgical evaluation: residual left or right atrioventricular valve regurgitation. Mild regurgitation may be acceptable, residual atrial septal defect/ventricular septal defect and ventricular septal defects not previously identified, atrioventricular valve stenosis if annuloplasty or cleft closure performed, left ventricular outflow tract narrowing and obstruction, assess ventricular function. [9,11]

*Truncus arteriosus:*

Goals of two-dimensional and Doppler examination: define truncal stenosis, override, and insufficiency, define truncal-pulmonary relationship (transgastric planes), visualizes the ventricular septal defect. [9,11]

## Conclusion

TEE has a considerable impact in pediatric congenital heart surgery. In many medical centers, TEE is now the standard of care for the intraoperative assessment of most congenital heart repairs before removal of bypass cannulas and closure of the sternotomy. TEE has become a valuable adjunct to intraoperative anesthetic and surgical management.



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# VASCULAR RING – IN AN INFANT WITH INTRACARDIAC ANOMALOUS DEFECT

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Right aortic arch with a vascular ring is a rare disease. Mostly, right aortic arch is accompanied by congenital heart anomalies diagnosed during childhood, and cause symptoms from the compression of the trachea and/or esophagus. Vascular ring reportedly represents less than 1% of all congenital cardiovascular anomalies, but this may be an underestimate because some conditions are asymptomatic. We report a form of vascular ring, that of a right aortic arch with an aberrant left subclavian artery, with retroesophageal diverticulum found incidentally, which was clearly defined by angio CT. An 11-month-old girl, diagnosed at 3-wheeks of age with partial endocardial cushion defect and patent ductus arteriosus, was evaluated in Department of Pediatric Cardiology Tg-Mures for failure to thrive, repeated respiratory infections and signs of congestive heart failure. The chest X-ray showed a elevate size heart and increased pulmonary vascular circulation. The electrocardiogram showed signs of the right atrial and ventricular hypertrophy. Echocardiographyc diagnose was right sided aortic arch, muscular ventricular septal defect, ostium primum atrial septal defect, ostium secundum atrial septal defect, stenosis of left pulmonary artery with hypoplastic left pulmonary artery and aneurismal dilatation of right pulmonary artery. From the results of these examinations, she was suspected to have right aortic arc with anomalous brachiocephalic vessel pattern, anomalous left pulmonary artery, associated with cardiac anomalies. CT was performed and a combination of right aortic arch with aberrant left subclavian artery, ventricular septal defect, atrial septal defect, stenoses of left pulmonary artery, aneurimal dilatation of right pulmonary artery, and partial anomalous pulmonary venous return was diagnosed. The surgery approach for right aortic arch involves dividing the ligamentum arteriosum, with will break the constricting ring.

**Key words:** vascular ring, congenital heart defect, echocardiography, resonance magnetic imaging

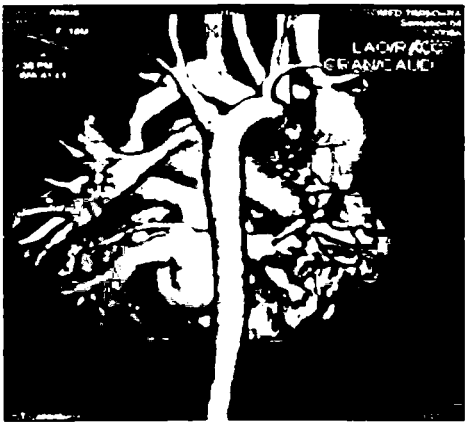
*Clinical history:* A 11-month- old girl, born at 36 weeks' gestation (1500 g birthweight), was diagnosed by echocardiography with partial endocardial cushion defect and patent ductus arteriosus. At the 11- month- old she was evaluated in Department of Pediatric Cardiology Tg-Mures for failure to thrive, repeated respiratory infections, and signs of congestive heart failure. A genetic syndrome was suspected, but the cariotip were negative.

*Electrocardiogram:* signs of right atrial and ventricular hypertrophy

*Chest X-ray:* elevate size heart, increased pulmonary vascular circulation

*Echocariography:* An IE-33 ultrasonic system with S8 transducer was used for echocardiographic examination. Echocardiographic assessment was performed at discharge using a standard method. The acoustic windows used included subcostal, apical, parasternal or supersternal views. The supersternal view was necessary for evaluation of the aortic arch. Echocardiographic diagnosis was: right sided aortic arch, with aberrant brachiocephalic vessel, muscular ventricular septal defect, atrial septal defect, stenosis of left pulmonary artery with hypoplastic left pulmonary artery and anevrismal dilatation of right pulmonary artery.

*CT:* Three-dimensional (3D) reconstruction was employed to obtain a clear visualization of the vascular anatomy. There is a right aortic arch that gives off the left common carotid, the right common carotid, the right subclavian and the left subclavian arteries. The left subclavian artery passes behind the esophagus. The vascular ring in this case is completed by the ligamentum arteriosum, passed between the left subclavian and the left pulmonary arteries. Pulmonary artery arises from right ventricle; there is a severe stenosis of left pulmonary artery, the maximum diameter of left pulmonary artery is 3,3mm. Right pulmonary veins and right superior pulmonary vein are connected with left atrium, but right inferior pulmonary vein is connected with left innominate vein.(Figure 1a, b)



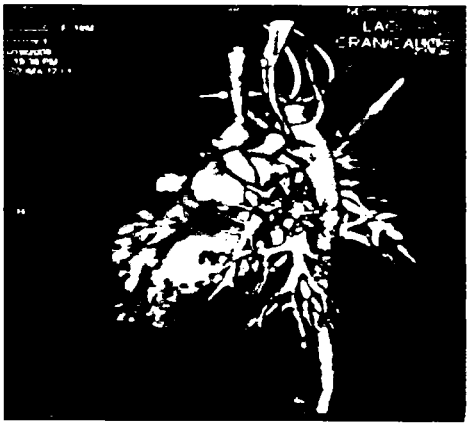


**Figure 1a and Figure 1b.** – CT images

The term "vascular ring" was first used by Robert Gross in his report describing the first successful dividing of a double aortic arch in 1945. Since that time, vascular rings have been used to refer to a group of congenital vascular anomalies that encircle and compress the esophagus and trachea [5, 7, 12].

Vascular rings are formed abnormally from improper regression of certain aspects of the branchial system. They have been classified into five groups: (1) double aortic arch, (2) right aortic arch with a left ligamentum arteriosum or persistent ductus arteriosus, (3) aberrant subclavian artery, (4) aberrant left pulmonary artery, (5) abnormally placed innominate artery. (Figure 2)

**Figure 2.**

| Anatomy | Ba-Esophagogram | Other X-Ray Findings | Symptoms | Treatment |
|---|---|---|---|---|
| Double Aortic Arch |   | Anterior compression of trachea | Respiratory difficulty (onset < 3 mos.) Swallowing dysfunction | Surgical division of a smaller arch |
| Right Aortic Arch with Left Lig. Arteriosum |  | | Mild respiratory difficulty (onset > 1 year) Swallowing dysfunction | Surgical division of the lig arteriosum |
| Anomalous Innominate Artery |  | Normal | Anterior compression of trachea | Stridor and/or cough in infancy | Conservative management, or Surgical suturing of the artery to the sternum |
| Aberrant Right Subclavian Artery |  | | Occasional swallowing dysfunction | Usually no treatment is necessary |
| "Vascular Sling" |  | Right-sided emphysema or atelectasis Posterior compression of trachea or Rt main-stem bronchus | Wheezing and cyanotic episodes since birth | Surgical division of the anomalous LPA (from the RPA) and anastomosis to the MPA |

*Figure 15–1. Summary and clinical features of vascular ring. Lat, lateral view. Lig, ligamentum; LPA, left pulmonary artery. MPA, main pulmonary artery; P-A, posteroanterior view; post, posterior; RPA, right pulmonary artery.*

Right aortic archs have in common a single aortic arch that crosses over the right mainstem bronchus, passing to the right of the trachea. There are four major types of the right aortic arch: (a) with mirror image branching, (b) with retroesophageal left subclavian artery, (c) with retroesophageal diverticulum, and (d) with left descending aorta. This case is an example of a right aortic arch with aberrant subclavian artery, with diverticulum of Kommerell [18].

Right arch with diverticulum of Kommerell is the second most common vascular ring after double aortic arch. It is far more common that its mirror image. It has as its first branch the left carotid artery, second the right carotid artery, third the right subclavian artery, and finally, a retroesophageal vessel from which the left subclavian artery arises and the left ductus arteriosus or ligamentum arteriosum connects. This combination of vessels produces a vascular ring [18].

Disappearance of the left fourth embryonic arch with persistence of the left sixth arch between the truncoaortic sac and left dorsal aorta accounts for the findings in this arch

anomaly. The left dorsal aorta is not merely the proximal left subclavian artery but is also the continuation of the left sixth aortic arch leading to the fused dorsal aortae.Since the normal fetus ductus carries nearly the entire output of the right ventricle, the left dorsal aorta would also carry that amount and would become significantly larger than the subclavian artery. This size discrepancy persists after ductal closure, giving the diverticulum its characteristic appearance [18].

One study noted that 63% of vascular ring cases were associated with cardiovascular anomalies. This may be due to an association with band 22q11 deletions or CATCH-22 syndrom [13]. Chromosome 22q11.2 microdeletions are seen in >80% of patients with DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes. Nearly one fourth of patients with arch anomalies but without intracardiac defects have 22q11 deletion [18].

The incidence of intracardiac defects is 5-12% which is higher than the normal population (<1%) but considerably less then patients with mirror image branching right aortic arch (98%). If congenital heart disease is present in patient with right aortic arch and aberrant left subclavian artery the lesions include tetralogy of Fallot (13%-34%), atrial septal defect or ventricle septal defect (21%) and coarctation of the aorta (7%). Many children with this arch anomaly are asymptomatic and therefore go unrecognized except for incidental discovery. Only 5% of these patiens develop compression symptoms due to a tight vascular ring.

Vascular rings are congenital anomalies of the aortic arch that result in either complete or partial encirclement of the trachea or esophagus, and often cause tracheal obstruction and respiratory distress. They are often the cause of unexplained respiratory symptoms in infants and young children [5,7,12]. Occasionally, in patients with associated intracardiac abnormalities, respiratory symptoms may mistakenly be attributed to the cardiac disease when, in fact, they are in part or completely due to the vascular ring 18. However, some patients are asymptomatic and discovered incidentally, and the diagnosis of and treatment for vascular rings are easily delayed.

Cardiac examination is usually normal, except in about 25% of patients in whom associated cardiac anomalies are present.

*Electrocardiography* is normal unless the vascular ring is associated with other congenital heart defects.

*Chest radiography* can be helpful in diagnosis of vascular ring if certain findings are present. With a right aortic arch, on antero-posterior view the aortic knob may be visualized on the right side and may cause deviation of the distal trachea to the left [13]. Hyperinflation or atelectasis may be seen in lobes of either lung. Chest X-ray has been shown to have lower detection rates of vascular rings then other diagnostic possibilities. However, a normal chest X-ray provides evidence against vascular ring in symptomatic children [2,9,16].

*Echocardiography* can be used to delineate the aortic arch sidedness and great vessel branching pattern. Practically, the sidedness of the aortic arch is usually determined indirectly with echocardiography by the branching pattern of the brachiocephalic vessels. As a rule, the first arch vessel contains the carotid artery opposite the side of the arch.

Whether in symptomatic or asymptomatic patients, when right aortic arch is shown by echocardiography, this important observation gives us a clue to examine the aortic arch more carefully, especially the branches of the arch. In cases in which echocardiographic visualization is difficult or the rings is of an unusual pattern, *contrast-enhanced thoracic CT with 3D reconstruction* may allow accurate diagnosis and clearly show compression of the tracheoesophageal tract. Ultrasonographic display of vascular ring anatomy has been limited to single-plane views. Vascular ring segments without lumens could not be displayed.

When all elements of the ring are patent, visualization, especially by CT or MRI imaging, is straightforward. In cases where the ring is completed by an atretic segment of aorta or ligamentum arteriosum, those segments cannot be visualized with current imaging technologies. Although the ligamentum arterisum is not visualized with any current imaging modalities, its presence is guaranteed by the chaeacteristic appearance of the tapered diverticulum. Echocardiography will show the left carotid artery arising alone as the first arch vessel, but definitive diagnosis requires that the diverticulum be followed out to the point at which the caliber changes to that of the smaller subclavian artery. This is usually not possible since the trachea itself and nearby lung may thwart attempts to see this area. However, these rings are recognizable by the presence of the one of three "d" s opposite the side of the aortic arch: diverticulum, dimple, or descending aorta. A diverticulum is a large vessel arising from the descending aorta that gives rise to a smaller-caliber vessel with a sudden taper. A dimper is a tapered, blindly ending outpouching from the aorta. Descending aorta opposite the side of the aortic arch refers to the location of the descending aorta in the upper torax. These three "d" s occur only when connected by a ligamentum arteriosum or an atretic segment of aortic arch 18. If the ductus arterisus is closed, it is not intuitive that one could distinguish the right aortic arch with retroesophageal diverticulum of Kommerell from the more benign right aortic arch with retroesophageal subcalvian artery (nonring). The difference is the diverticulum of Kommerell, which is a much larger vessel that the subclavian artery itself. Typically, the origin of the diverticulum is equal in diameter to the descending aorta and tapers to the subclavian artery caliber at the site of juncture with the left ligamentum 18. In our case CT image relieves the presence of a diverticulum and the descending aorta opposite the side of the aortic arch.

Echocardiography can be helpful in ruling out associated cardiac anomalies.

*MRI and CT* are probably the best imaging technics for diagnosis of vascular rings, because they well- delineate the abnormal anatomy and arterial branching patterns. However, these two tests cannot reveal ligamentum arteriosum [13].

*Barium esophagography* is frequently used in the diagnosis. With a right aortic arch, an indentation of the esophagus on the right side will be seen on the antero-posterior view and posterior indentation of the esophagus is almost always present [9,13].

*Angiography* was used in the past to better visualize vascular anatomy, but with MRI and CT it adds very little to the picture.

Prompt diagnosis of a vascular ring is important in a child with respiratory distress because the treatment is surgical. No medical therapy exists. Generally, all vascular rings that cause symptoms should be corrected. Respiratory distress and a history of recurrent pulmonary infections and apneic spells are indications for surgical intervention. Specific surgery depends on the type of vascular ring. The surgery approach for right aortic arch involves dividing the ligamentum arteriosum, with will break the constricting ring. After the ligamentum arteriosum is divided, connective tissue bands in the area will be divided as well. In general, surgical results are good, with most patients receiving symptomatic relief [2,11].

Towards to the form of richt aortic arch with retroesophageal diverticulum of Kommerell, most people with this arch anomaly are asymptomatic. Treatment is surgical division of the ductus or ligamentum in those patients who are symptomatic. In those patients undergoing surgery for another lesion such as an intracardiac abnormality, even an asymptomatic, ligamentum should be divided.

## Conclusion

Vascular rings are not difficult to diagnose. Patients, especially infants or young children with recurrent respiratory symptoms, such as chronic cough, stridor and wheeze, should be examined for the possible presence of congenital vascular rings. The sidedness of the aortic arch is usually determined indirectly with echocardiography, likewise the echocardiography can be particulary helpful in ruling out associated cardiac anomalies. Computed tomography (CT) or magnetic resonance imaging (MRI) show the relationship of the arch to the trachea and bronchi directly, thus eliminating ambiguity when atypical branching patterns are encountered. Both modalities have the advantages of the large fields of view and simultaneous visualization of vessel and airways, giving the surgeon a clear anatomic image, and both are minimally invasive. CT scans should be performed in all patients with echocardiographic evidence of vascular rings, such as abnormal branches of aortic arch or right aortic arch. Early surgical management of symptomatic patients is an effective way to treate congenital vascular rings. Most people with right aortic arch with retroesophageal diverticulum Kommerell are asymptomatic.

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# Pulmonary Arterial Hypertension Associated With Congenital Heart Disease In The Pediatric Cardiology Department Tg. Mures

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**Objective:** Congenital heart disease (CHD) are among the most common major defects at birth, a large part of them being associated with pulmonary arterial hypertension (PAH). This study wants to report the incidence of PAH associated to CHD in the Pediatric Cardiology Department from Targu Mures in the period of July 2007 - July 2008 and the Department's experience in evaluating and treating PAH associated with CHD.

**Material and method:** studying the cases of PAH associated to CHD presented to the Pediatric Cardiology Department from Tg Mures in a period of a year (July the 6th 2007 – July the 6th 2008). The Pediatric Cardiology Department from Targu Mures developed an evaluation and treatment strategy of children with PAH associated to CHD. It involves a clinical, laboratory, echocardiographical protocol and in case of pulmonary vasodilator treatment – a therapeutic protocol.

**Results:** 115 cases of PAH associated to CHD were registered in a period of a year; in most cases (51 cases - 44%) there was a moderate PAH. 20 patients with elevated PVR had indication for pulmonary vasodilator treatment. In 13 cases there was prohibitive PVR, nonresponsive to vasodilator test with nitric oxyde.There are 7 children with severe PAH associated to CHD and vasoresponsive pulmonary vascular bed who are under treatment with Sildenafil.

**Conclusions:** A large part of CHDs are associated with PAH. It is very important to treat CHD in time to prevent the development of obstructive pulmonary vascular disease. An appropriate management plan is necessary in order to treat and prevent the progression of PAH associated to CHD.

**Key words:** pulmonary arterial hypertension, echocardiography, treatment

Congenital heart diseases (CHD) are among the most common major defects at birth and account for about eight cases per 1000 births. Congenital heart defects are often associated with pulmonary arterial hypertension. The most important group of congeni-

tal heart disease associated with pulmonary arterial hypertension are left-to-right shunts. Still a growing number of patients present with malformations characterized by a so-called single ventricle physiology requiring a particular surgical approach (partial or total cavo-pulmonary anastomosis) 3.

PAH is defined as a mean pulmonary artery pressure > 25mmHg at rest or > 30mmHg with exercise. The severity of PAH can be further delineated on the basis of this pressure: mild: 25- 45mmHg, moderate: 46-65mmHg, severe: > 65mmHg.

PAH includes idiopathic PAH and PAH associated with various conditions such a congenital systemic-to-pulmonary shunts, connective tissue diseases, portal hypertension and HIV infection. All these conditions involve similar obstructive pathological changes of the pulmonary microcirculation suggesting shared pathological progresses among the disease spectrum of PAH.

During the Third World Symposium on PAH in Venice, in 2003, congenital cardiac shunts were classified in the same group as idiopathic pulmonary hypertension, underscoring their shared pathophysiology, pathology, and like hood of similar therapeutic responsiveness [1]. (Table I.)

1. Pulmonary arterial hypertension (PAH)
   - Idiopathic PAH
   - Familial PAH
   - Associated with:
     - Connective tissue diseases
     - Congenital heart disease
     - Portal hypertension
     - HIV infection
     - Drugs and toxins
     - Other
2. PH with left heart disease
   - Atrial or ventricular
   - Valvular
3. PH with lung diseases/hypoxemia COPD
   - Interstitial lung diseases
   - Sleep-disordered breathing
   - Developmental abnormalities
4. PH due to chronic thrombotic and/or embolic disease
   - TE obstruction of proximal PA
   - TE obstruction of distal PA
   - Non-thrombotic PE
5. Miscellaneous
   - Sarcoidosis, histiocytosis X, lymhangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing medistinitis)

**Table I.** – Clinical Classification of Pulmonary hypertension (Venice 2003) 2

The number of children with congenital heart disease admitted to Paediatric Cardiology Department from Tîrgu Mureş increases every year and a large part of this cases associate pulmonary arterial hypertension of various degrees. The paediatric cardiologist working in our Department developed an evaluation and treatment strategy of children

with PAH associated to CHD. It involves a clinical, laboratory, echocardiographical protocol and in case of pulmonary vasodilator treatment – a therapeutic protocol.

Echocardiography is the best noninvasive method of PAH evaluation. It evaluates the size and function of the right ventricle (RV), systolic and diastolic function of the left ventricle (LV), anatomy and function of the valves, the pericardial effusion, CHD. Assessment of PAP represents a part of the echocardiographic examination. 2D echo suggest the presence of PAH. Doppler echocardiography is the first noninvasive method of PAP evaluation.

The echocardiographic protocol of PAH evaluation has eight important steps:

1. Right atrial pressure assessment
2. Estimation of systolic PAP – tricuspidian regurgitation
3. Estimation of medium PAP – pulmonary regurgitation
4. Right ventricular outlet acceleration time
5. Pulmonary vascular resistance calculation
6. Assessment of the right ventricular function
7. Right ventricle inlet measurement
8. Pulmonary artery ring measurement

PVR is an important hemodynamic variable in the management of patients with pulmonary artery hypertension and traditionally is obtained by cardiac catheterization. Our department uses the Doppler method for estimating PVR – dividing tricuspid regurgitation velocity (TRV) by the RVOT time velocity integral (TVI).

$$\mathbf{PVR = 10 \times (TRV / RVOT\ TVI) + 0.16}$$

Myocardial performance index (Tei) is defined as the sum of the isovolumic contraction and the isovolumic relaxation time divided by ejection time:

$$\mathbf{Tei = ICT + IRT / ET}$$

Tei incorporates elements of the both systolic and diastolic phases and reflects the global RV function. It is easy to assess and can be estimated in the same session as the echocardiographic PAP.

The accuracy of echocardiography for the detection of PAH increases when the echocardiographic systolic PAP is combined with an elevated RV Tei- index. By applying the Tei-index the number of negative catheterizations can be minimized.

The electrocardiogram, cardiothoracic X-ray, cardiac catheterization and laboratory tests also play an important role in the diagnosis of pulmonary arterial hypertension. Among laboratory tests, the liver and kidney function assessment is very important, especially during treatment with vasodilators. We determine also the NT-pro-brain natriuretic peptide (NT-proBNP) as a marker of ventricular function. The 6 minute walking test is also very useful in the assessment of PAH associated to CHD, but because of the age group and the CHD it is hard to apply this test in the paediatric field.

Children with elevated PAH estimated by echocardiography undergo cardiac catheterization to establish the PVR and to evaluate the vasodilator response of the pulmonary vascular bed. Children with PAH associated to CHD with increased PVR, but with vaso-

dilator responsive vascular beds should undergo preoperator treatment with vasodilators such as Sildenafil. Our department developed a treatment protocol for Sildenafil. If the patient has responsive vascular beds he will begin the treatment with Sildenafil according to weight, using increasing doses for 3 months and monthly clinical, biological, echocardiographical and therapeutical reevaluation.

After 3 months of treatment a cardiac catheterization is performed to estimate the PVR and the possibility for surgical repair of the congenital heart disease. If the surgical intervention is possible, the patient will undergo surgery and he will continue the treatment with Sildenafil for 6 months, with monthly reevaluation. After six months of treatment with Sildenafil the patient will undergo cardiac catheterization to establish the indication of interruption or continuation of the vasodilator treatment.

Studying the cases of pulmonary arterial hypertension associated with congenital heart disease admitted to our department between July the 1st 2007 and July the 1st 2008, we discovered that there were 115 patients with pulmonary arterial hypertension, representing approximately 6.76% of the children admitted in this period of time to the Paediatric Cardiology Department. Among them 44% were boys and 56% were girls. (Figure 1)

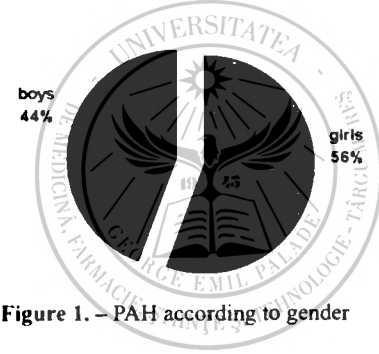


**Figure 1.** – PAH according to gender

Most frequently (51 cases – 44%) there was a moderate PAH. Severe PAH was encountered in approximately 39% of the cases and mild PAH in 17% of the cases. (Figure 2)

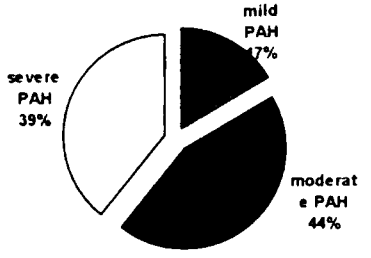


**Figure 2.** – Severity of PAH

In our department, from all the catheterized patients with severe PAH associated with CHD, 20 patients with elevated PVR had indication for pulmonary vasodilator treatment. In 13 cases there was prohibitive PVR, nonresponsive to vasodilator test with nitric oxyde.

These patients are candidates for pulmonary vasodilator treatment with Bosentan. There are 7 children with severe PAH associated to CHD and vasoresponsive pulmonary vascular bed who are under treatment with Sildenafil. After a preoperative treatment period of 3 months, 3 patients underwent surgical treatment and they are now on postoperative therapy with Sildenafil for residual PAH. The other 4 are still on the preoperative treatment period (Figure 3).

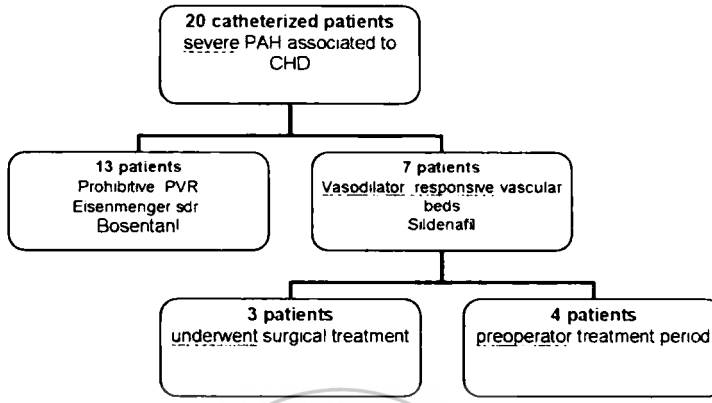


**Figure 3.** – Responsive versus nonresponsive patients with severe PAH asscociated to CHD

The median age of the patients with Sildenafil treatment in our department is 12 years. The most frequently involved CHD was the ventricular septal defect (4 cases), followed by complete endocardial cushion defect (2 cases) and persistent ductus arteriosus (1 case). (Figure 4)

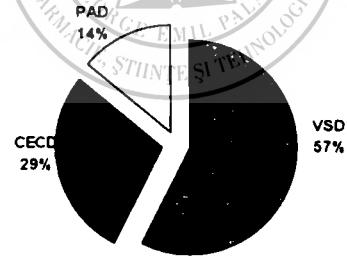


**Figure 4.** – Type of the CHD

In conlusion:

- This study showed the elevated medium age of the children with severe PAH associated to CHD diagnosed in our department
- The most frequently involved CHD was the ventricular septal defect
- Because of the late diagnosis of the CHD, the cardiac catheterization reported the predominance of patients with nonresponsive pulmonary vascular bed

□ Our objectives are the following: echocardiographic evaluation of PAH using the above-mentioned parameters, comparing of the echo parameters with the catheterization data, evaluation of the response of the pulmonary vascular bed to vasodilator medication.

□ A large part of CHDs are associated with PAH. It is very important to treat CHD in time to prevent the development of obstructive pulmonary vascular disease. An appropriate management plan is necessary in order to treat and prevent the progression of PAH associated to CHD.

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# Two Cases Of Familial, Isolated, Complete Right Bundle Branch Block

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**Introduction:** Right bundle branch block (RBBB) has typical ECG characteristics: wide QRS complexes with a terminal R wave in V1 and slurred S wave in V6. The most common cause of RBBB in children is surgically induced, after VSD repair. In rare cases it could be familial or associated with Brugada or Kearns-Sayre Syndrome.

**Case presentations:** We report here two cases of asymptomatic male patients – father and son, with the same typical RBBB patterns on ECG. The ultrasound examinations, laboratory investigations, Holter and effort ECG (of the father) as well as the follow up during a year didn't reveal any pathological modifications. We made ECGs for the other members of the family: the nephews of the father, 3 and 6 year-old boys, but their ECG were normal.

**Conclusion:** The familial RBBB has benign course and as the other authors said, may be authosomal, genetic anomaly which is inherited dominantly.

**Key words:** right bundle branch block.

## Severe Cardiac Malformations In Genetic Anomalies
Poster

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Congenital abnormalities, which include cardiac malformations, account for 20-25% of perinatal deaths. Cardiac malformations can be isolated or associated to a genetic syndrome.

**Objective:** The objective was to evaluate the association of severe cardiac malformations with genetic anomalies.

**Methods:** This retrospective study included 764 children diagnosed between 2003 and 2007 with cardiac malformation.

**Results:** We found a 1.68% cardiac malformations prevalence in the large group of admitted children, 45.334, in that period. In this group, 75 children from the 764 (9.8%), suffered palliative or definitive surgical interventions and 44 deceased (5.75%). In the first group 26.6% were DSV, 17.3 % DSA, 12% TGA, 9.3%, aortic coarctation, 8%, PDA, 8% tetralogy of Fallot, 8% CAVC, 6.6%, pulmonary stenosis, 4.2%, associated DSV, DSA, and PDA. In the deceased group there was an association with genetic syndromes in 34%, 15 cases, the most frequent being the Down syndrome (21 trisomy), in 12 cases, 27.2%, and with minor genetic abnormalities in 17 cases, 38.6%. 27.4%, 12 cases, from the deceased children presented isolated cardiac malformations.

**Conclusions:** There was an important association between genetic abnormalities and severe cardiac malformations in the deceased children. The most frequent genetic syndrome associated with cardiac malformation was Down syndrome

# The Eficiency Of Treatment With Iloprost And Sildenafil In Neonatal Primary Pulmonary Hypertension. Case Presentation

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**Introduction:** Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by elevated pulmonary vascular resistance that causes refractory hypoxemia and right-to-left extrapulmonary shunting of blood through patent ductus arteriosus and foramen ovale. The main causes of primary pulmonary hypertension in neonate are: excessive muscularization of pulmonary arterioles and alterations in vasoactive mediator levels.

**Goals:** to assess the efects of Iloprost and sildenafil administration in treatment of a newborn with primary PPHN.

**Material and method:** the authors present a case of PPHN in a term, LGA newborn, treated with Iloprost and sildenafil, in a situation where the standard of practice (inhaled nitric oxide, high-frequency ventilation, and extracorporeal membrane oxygenation) is not available (in our unit). The protocol was: Iloprost iv 1-2ng/kg/min, and Sildenafil po 1-2mg/kg/dose q 6 hours.

**Results:** Iloprost administration increases arterial oxigen concentration (PaO2) in the first hour of administration, augmented by sildenafil administrated orraly. Iloprost was withdrawn after 96 hours, sildenafil administration was continued 18 days with decreasing doses. Dopamine was associated in the first 6 days. Side efects: mild vasodilation. Follow-up evaluation showed normal neuromotor development.

**Conclusions:** association of Iloprost and sildenafil had high clinical efficacy in this case. Further data is needed to determin efects on larger groups of newborns with PPH.

**Keywords:** Iloprost, sildenafil, PPH

# The Diagnosis And Treatment Of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease In Children

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Described a half century ago as the final stage of patients with congenital heart disease with left-to-right shunt, pulmonary arterial hypertension is of a great interest even today, being the subject of numerous studies. PAH is defined as a mean pulmonary artery pressure >25mmHg at rest or >30mmHg with exercise. Pulmonary arterial hypertension can be caused by cardiac lesions with left-to-right shunt, by lesions associated with increased venous pressure or by anomalies of the pulmonary artery or pulmonary veins. The clinical findings depend on the type of the cardiac anomaly and the pulmonary vascular resistance. The electrocardiogram, cardiothoracic X-ray, echocardiography, cardiac catheterization, pulmonary functional tests and laboratory tests play an important role in the diagnosis of pulmonary arterial hypertension. The treatment of most cases of pulmonary arterial hypertension is difficult. The objectives of pulmonary arterial hypertension treatment are prevention and removal (when it's possible) of the cause and of the associated anomalies. The therapeutical options are the following: digoxin, anticoagulation, vasodilator therapy, atrial septostomy, heart-lung transplant. Pediatric cardiology departments and heart surgery departments have an important role in the diagnosis and treatment of congenital heart defects, but all these medical acts are inefficient if neonatologists and family doctors don't discover in time the patients with suspected congenital heart defects.

# Angio Ct Detecting The Etiology On Unmanageable High Blood Pressure In Children

**Gabriela Doros[1], Anca Popoiu[1], M. Gafencu[1], Bogdana Zoica[1], Oana Ciocarlie[1], Andrada Oprisoni[1], Adina Gologan[1], Mariana Marusteri[2], G. Miclaus[2], Dana Elekes[2]**

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**Aim:** To present two cases of children admitted for recurrent headache and vomiting. They were detected with high blood pressure, but with no treatment.

**Material and methods:** Both patients, one male, 12 y old, and one female, 18 y old, were explored for the etiology of hypertension. They perform clinical examination, ECG, echocardiography, cardiopulmonary X ray and laboratory tests. They were treated with diet, diuretics, and ACE inhibitors.

**Results:** The girl was referred by the HIV department. The values of the blood pressure were between 170/120 mmHg and 160/100 mmHg. All blood tests for detection the etiology of hypertension were negative. The ECG, echocardiography and cardiopulmonary X ray were normal and abdominal ultrasound apparently normal. The boy was overweight, with low grade of bradipsyhia, suspected of hypothyroidia. Ultrasound of the thyroid was modified, but with normal hormones. He is followed by endocrinologist. Both patients took antihypertensive drugs, in maximal dosage, without results. Angio CT of the abdomen was the last option in detecting renovascular changes. Severe left side renal artery stenosis was detected in boy. After stent dilatation the blood pressure normalized. No drug except Plavix has to take. The girl present abdominal aortic stenosis associated with renal artery stenosis. She is still on medication and has to perform vascular surgery.

**Conclusions:** Renal artery stenosis is a common cause of hypertension in children. Angio CT/MRI of the abdomen is the most performant exploration in detecting this malformation. Stent dilatation or vascular surgery has to be done to resolve the hypertension.

# Aortic Stenosis And Williams Syndrome

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**Aim:** Williams syndrome is caused by deletion of genetic material from the region q11.2 of chromosome 7, including more than 20 genes. We want to present two cases of supravalvular aortic stenosis, selected from the group of aortic stenosis children, admitted in our Pediatric Clinic between 2007-2008, considered to be Williams syndrome.

**Material and method:** The patients were one girl and one boy, with moderate mental retardation, extremely friendly, short stature, characteristic elfin face, joint laxity, systolic murmur and attraction to music. They performed clinical examination, ECG, echocardiography, cardiopulmonary X ray and angio CT. They were referred to the genetic, ENT and ophtalmologic department.

**Results:** Supravalvular aortic stenosis was confirmed in both cases, associated with hypoplasia of the aortic arch and large coarctation of the aorta in girl. She had from birth irreducible inguinal hernia, operated in newborn period, followed by cardiopulmonary arrest, resuscitated. The inghino-labial hernia reoccurs. She also still has feeding problems for semisolid food. Barium examination reveal large esofageal stenosis in the 1/3 inferior part. Both of them have prominent lips with an open mouth, defective tooth enamel and spaced teeth. The girl associated hypercalcemia.

**Conclusions:** Complete examinations of both patients allow us to consider them Williams syndrome. They need the genetic FISH test for confirmation of this syndrome. We intend to cooperate with the International Williams Syndrome Children Association, developing the Romanian registry of rare diseases. The patients are now in follow up program. More doctors need to be involved in detecting rare diseases.

# New Opportunities In The Diagnose Of Complex Congenital Heart Defects

**Gabriela Doros[1], Anca Popoiu[1], M. Gafencu[1], Bogdana Zoica[1], Oana Ciocarlie[1], Andrada Oprisoni[1], Adina Gologan[1], Mariana Marusteri[2], G. Miclaus[2], Dana Elekes[2]**

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**Aim:** to present 3 cases of CHD, two diagnosed in infancy and one de novo, admitted in our clinic for the first time for a cardiac exploration.

**Material and methods:** They had: CC- TGA and VSD-first case, Fallot Tetralogy-second case and one boy admitted for a routine check before performing competitive sport. All performed clinical exam, ECG, echocardiography, and cardiopulmonary X ray. The results changed diagnose, needing angio CT/MRI of the thorax.

**Results:** The first case with CC-TGA and VSD was 9 y old boy; the clinical exploration revealed signs of heart failure, and echocardiography showed an associated Ebstein disease, with severe tricuspid regurgitation strait to pulmonary artery via VSD from the left ventricle, producing pulmonary hypertension. The second case was also a 9 y old boy, diagnosed with Fallot disease; the echocardiography revealed a severe stenosis of the LPA branch, followed by dilatation, undetected before. The third case had systolic murmur, right atrial dilatation on ECG, but echocardiography showed a perforated membrane sharing the right atrium in two, without gradient, suspecting the diagnose of cor triatriatum right. Angio CT/MRI of the thorax confirmed the diagnoses, mentioning that the second patient had a pulmonary artery branch coarctation.

**Conclusions:** Angio CT/MRI of the thorax could reveal and confirm suspected diagnoses. CC-TGA with Ebstein disease and VSD produced pulmonary hypertension, in treatment now. Pulmonary artery branch coarctation is a rare condition, confirmed by angio CT. The third case was stopped in performing competitive sports, allowing him only in casual sport.

# The Role Of Angio Ct In Detection Of A Complex Vascular Malformation: Scimitar Syndrome, Persistance Of The Primitive Hepatic Venous Plexux And Inferior Vena Cava Interruption

**Gabriela Doros[1], Anca Popoiu[1], M. Gafencu[1], Bogdana Zoica1, Oana Ciocarlie[1], Andrada Oprisoni1, Adina Gologan[1], Mariana Marusteri[2], G. Miclaus[2], Dana Elekes[2]**

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**Aim:** to present a 15 years old boy, discovered at the age of 1 with: right diaphragmatic relaxation, right inferior pulmonary tumor (negative at surgery), hepatic hemangioma; he was followed for recurrent respiratory infections.

**Material and methods:** The patient performed complex cardiac exploration because of a bronchial asthma: clinical examination, ECG, echocardiography, cardiopulmonary X ray, and abdominal ultrasound. The results revealed a complex and rare congenital vascular malformation, confirmed by angio CT.

**Results:** A continuous abdominal murmur and hepatomegaly was clinically discovered. ECG was normal, but cardiopulmonary X ray revealed right diaphragmatic relaxation and a Scimitar shape shadow of the right inferior lung. Echocardiography showed a particular filling of the RA, directly from hepatic veins. Abdominal ultrasound demonstrated inferior vena cava interruption, right hepatic vein draining in the inferior vena cava, but also in connection with extremely dilated middle and left hepatic vein that join together, entering directly in the RA; multiple hepatic arterio-venous shunts were proved. Angio CT of the heart and abdomen complete the diagnose with: right lung hypoplasia, partial abnormal pulmonary venous drainage of the right inferior pulmonary vein in the inferior vena cava, arterial vessel directed from the celiac trunk posterior to the right inferior pulmonary vein.

**Conclusions:** Angio CT of the thorax and abdomen proved the Scimitar syndrome, persistence of the primitive hepatic venous plexus, multiple hepatic arterio-venous shunts, and inferior vena cava interruption. These associations had been rarely reported.

# The Value And Limits Of Echocardiography In The Hemodynamic Assessment Of Pulmonary Hypertension

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Echocardiography is the only noninvazive test that can reliably and rapidly screen for the presence of pulmonary artery hypertension (PAH). It provides an estimation of right ventricular and pulmonary artery systolic pressure, information regarding structural cardiac changes and assessment of possible cardiac causes of PAH. Echocardiography can only suggest the presence and severity of PAH. It cannot definitively diagnosis PAH because it cannot determine left-sided filling pressures. The reliability of the results are dependent on several factors, such as: the difficulty in adequately imaging the right heart, the presence of underlying parenchymal lung disease, the experience of the sonografer. Doppler flow velocities have been used to assess right ventricular systolic pressure and pulmonary artery pressure - PAP (systolic, diastolic and mean pressures). The echocardiographic method most widely used for assessing systolic PAP is to measure the peak systolic velocity of the tricuspid regurgitation jet. In the presence of pulmonic insufficiency the PA diastolic pressure can also be estimated by echo. The markers of prognosis in PAH are the presence of the pericardial effusion and direct echoassessment of right ventricular structure and function. The echo examination is essential to rule out left heart disease as a cause of PAH because the diagnosis implies the absence of left heart disease. Also, serial echo examination can be used to assess the evolution of patients receiving PAH specific therapies. Echocardiography remains the first step to properly select the patients who need to undergo catheterization for a definitive diagnosis.

# The Echocardiographic Follow Up Of The Patients After The Correction Of The Aortic Coarctation

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**Aim:** Although aortic coarctation is considered a curable disease by surgery or by angioplasty in the late years a large number of complications were diagnosed after the treatment of this disease. In this study we have investigated the cardiovascular morbidity after the correction of the aortic coarctation and we have identified risk factors for late cardiovascular pathology.

**Method:** A number of 33 pts with corrected aortic coarctation hospitalized in the Clinic of Cardiology between 2001-2007 were examined. Mean age was 29 years, mean age when the correction was made 18 years. The mean time between the correction time and the follow up was 11,6 years. Clinical exam, ECG, echocardiography(M mod, 2D, CW,Color Doppler,TDI at the level of the walls of the left ventricle and ascending aorta) vascular echography at the level of the carotid arteries (intima media thickness and E tracking at the level of the carotid arteries which allowed us to us to evaluate the indexes of aortic stfness, pulse wave velocity and augmentation index) and cardiovascular risk factors (cholesterol, HDL, LDL, tryglicerides, serum glucose and serum creatinine) were measured.

**Results:**24(71,7%) pts had arterial hypertension, restenosis 8 pts(26,4%), ascending aorta aneurysm 2 pts(3,8%), descending aorta aneurysm 2pts (3,8%), aortic valve pathology was present in 11 pts (32,7%). The age at the moment of the correction and the gradient remained at the level of the descending aorta were statistical significant for the persistence of the arterial hypertension after the correction. The gradient restant after the correction and the ankle – arm index were predictive factors for developing complications. The intima media thickness and the indexes of the aortic stiffness were increased and are considered as markers of early development of atherosclerosis lesions.

# Genetic Causes And Prenatal Detection Of Congenital Heart Anomalies

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The aim of study is to resume the knowledges of etiology in cardiac congenital anomalies (CCA). CCA have a great incidence (50/1.000 newborns) affect severely the patient, impose high costs, have a high mortality and can be prevented. The majority of CCA are isolated, having a multifactorial determinism. In many cases CCA are a component of a chromosomal or non-chromosomal genetic syndrome. The chromoosmal anomalies that generate CCA are: trisomies 21 (Down syndrome) 18 (Edwards syndrome) 13 (Patau syndrome) X monosomy (Turner syndrome) deletions 4p (Wolf-Hirschhorn syndrome) 5p (cri du chat syndrome) 7q11.23 (Williams syndrome) 11q (Jacobsen syndrome) 17p11.2 (Smith-Magenis syndrome) 20p12 (Alagille syndrome) 22q11 (DiGiorge syndrome) and 22q11duplication (cat-eyes syndrome). The most frequent CCA in chromosomal diseases are atrial septal defect (ASD) ventricular septal defect (VSD) patent ductus arteriosus (PDA) and coarctation of the aorta (CoA). Non-chromosomal CCA are represented by some plurimalformative syndromes. In some of these the mutant gene is known, like in: Noonan syndrome (valve stenosis (VS), ASD, VSD – mutation PTPN11, KRAS sau SOS1) Costello syndrome (VS, VSD - mutation HRAS) Leopard syndrome (VS – mutation PTPN11) Holt-Oram syndrome (ASD, VSD – mutation TBX5) Ellis van Creveld syndrome (ASD – mutations in 2 genes located 4p16) Rubinstein-Taybi syndrome (ASD, VSD – mutation CREBP) Goldenhar syndrome (ASD, VSD) Marfan syndrome (ASD– mutation in fibriline genei) Kabuki syndrome (ASD, VSD) Cornelia de Lange syndrome (VSD – mutation NIPBL) Apert (VSD – mutation FGFR3). Prenatal detection of CCA impose echocardiography, followed by amniocentesis and chromosomal analysis and/or molecular analysis.

# Echocardiographic Features Of Genetic Syndromes A Case Based Approach

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The goal of this presentation is to provide information for clinicians on the involvement of genetic factors to the origin of congenital heart disease (CHD). For a long time there has been considered that most CHD occurs as isolated cases. Based on studies of transmission risks and recurrence, the hypothesis of multifactorial etiology was proposed. The multifactorial etiology hypothesis refers to the individual's genetic predisposition interacting with the environmental factors that leads to a particular CHD. Recently, various environmental and genetic causes for CHD have been identified. Mendelian transmission of CHD among some families' members is already known in current practice for anomalies such as atrial septal defect, ventricular septal defect or patent ductus arteriosus. Molecular genetic studies have exploited these observations of families with multiple affected individuals and have provided insights into the genetic basis of several forms of CHD. These initial discoveries demonstrate that the genetic contribution to CHD has been significantly underestimated in the past. This review includes descriptions of some genetic syndromes, including Noonan syndrome (NS), DiGeorge syndrome, Williams's syndrome and Marfan syndrome, along with numeric and structural chromosomal abnormalities are highlighted for the purpose of illustrating their diagnostic particularities. Along with clinical picture and genetic studies, echocariographic features in each syndrome represent an essential element of the diagnostic algorithm.

Preconception genetic counseling is the first step in hereditary cardiac defects prevention. During pregnancy diagnosis is based on ultrasound screening, morphometry and fetal echocardiography and genetic analyses. Management of patients with genetic syndromes associating CHD imposes a wide team of medical personnel, including geneticist, pediatric cardiologist and pediatrician, adult cardiologist, internist, obstetrician, cardiac surgeon and nurses, in order to insure efficient prophylaxis and treatment for the patient with congenital heart disease. Taking into account the important number of diagnosed cases and the complexity of hereditary cardiac malformations a national CHD registry for Romania is mandatory.

**Key words:** congenital heart disease, echocardiography, genetic syndromes, diagnosis.

# TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION – CASE PRESENTATION

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In total anomalous connection of the pulmonary veins, the connection between the four pulmonary veins and the left atrium is absent. Three types of anomalous connection exist.

**Aim of the study:** presenting two cases of infants with total anomalous pulmonary venous connection diagnosed in Pediatric Cardiology Department from Tîrgu Mureş.

Material and method: the diagnosis of the cardiac anomalie was made by transthoracic echocardiography in one case and by transthoracic and transesophageal echocardiography in the other case. In both cases the aspect of the right-to-left shunt at the atrial level was the key of the echocardiographic diagnosis.

**Results:** both cases underwent surgical treatment with good post operatory rehabilitation.

**Conclusion:** trasthoracic and transesophageal echocardiography are the most important method for the diagnosis of total anomalous pulmonary venous connection.

# Transposition Of The Great Arteries In The Pediatric Pathology

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**Aim of study:** Transposition of the great arteries ( TGA ) is the second most common cause of cyanosis in infancy. Pulmonary and systemic circulations form two separate circuits, a mixing between these two circuits is absolutely necessary for life.

**Methods:** We studied the patients with TGA admitted and operated in the Institute of Cardiovascular Disease and Transplantation from Tg. Mures between ianuary 2004 and august 2008.

**Results:** We have been examined 41 patients with TGA, 36 patiens with simple TGA, 5 patients with associated RVOT obstruction, large VSD, coronary anomalies. The surgical procedure performed were: in 28 cases the arterial switch, in 1 case atrial switch ( Senning ), in 5 cases atrialseptectomy. 1 case with TGA+ PS benefited of the Blalock-Taussig shunt, in 1 case initially has been performed a pulmonary banding followed by a bilateral Glenn. 1 case with TGA+ large VSD+ PS was treated using the REV ( Lecompte ) procedure. 11 patients needed Rashkind balloon atrialseptostomy . 7 patients ( 25% ) died after arterial switch procedure, 1 patient after atrial switch and 5 patients died before the surgical treatment because of the severe hypoxia and acidosis.

**Conclusions:** TGA is a severe cyanotic congenital heart disease. Applied in the first 2-3 weeks of life, arterial switch is the only surgical treatment capable to cure this congenital anomaly. We consider our results encouraging even if the mortality in our cases is higher then those presented in the literature (5-15%) $p < 0,01$.

# Cardiomyopathies Associated To Muscular Dystrophy

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**Aim:** To asses patients with different kind of muscular dystrophy (MD) and their cardiac involvement, with the different fenotypic expressions.

**Material and method:** We assessed 11 patients (9 males, 2 females), aged 4 month – 17 years with different forms of muscular dystrophy in the last year. All cases were referred for a cardiologic examination by the neurologist. All patients were evaluated by echocardiography, ECG, 4 also by thoracic radiography.

**Results:** From 5 patients with Duchenne muscular dystrophy, 3 had left ventricular dysfunction, 3 limb-girdle muscular dystrophy patients -1 had hypertrophic cardiomyopathy and 1 bradycardia, 1 Becker MD with dilated cardiomyopathy, 1 congenital MD with hypertrophic cardiomyopathy, 1 Charcot Marie Tooth neuropathy with dilated cardiomyopathy. Clinical presentation was dominated by the muscular dystrophy in all cases, excepting the congenital MD where a pulmonary edema was the main feature, and the LGMD with hypertrophic cardiomyopathy where effort dyspneea was striking. There were no parallelism between the severity of muscular involvement and the cardiac one.

**Conclusion:** Muscular dystrophy is determined by the mutation of the dystrophin gene having an X-linked transmition. The limb-girdle form is a genetic disease where genes encoding muscular proteins are affected, usually having an autosomal recessive transmition. Cardiac involvement in muscular dystrophy is common. The same form of MD may have different cardiac expressions. As skeletal and cardiac involvement in muscular dystrophy can progress at different rates, the extent of cardiac impairment cannot be deduced from the assessment of skeletal muscular weakness. Their for cardiologic surveillance of these patients is important.

# Genetic Syndromes Associated With Heart Defects

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**Aim of the study:** To review the genetic syndromes associated with heart defects diagnosed in our clinic in the last two years, excepting the Down syndrome.

**Material and method:** In the last 2 years we diagnosed 9 different genetic diseases associated with heart defects in 12 patients, excepting the well known Down syndrome. In all patients we performed ECG, echocardiography, thoracic X-ray, and some of them also genetic testing.

**Results:** Following syndromes with corresponding heart disease were diagnosed: 2 cases of Williams syndrome (supravalvular aortic stenosis), 2 Noonan's (pulmonary stenosis/ Fallot), 1 Cornelia de Lange (cushion defect), 1 Seckel syndrome( ventricular septal defect, persistent ductus arteriosus), 2 Di George syndromes( pulmonary atresia, persistent ductus arteriosus), 1 Sprintzen syndrome (Fallot disease), 1 Goldenhaar syndrome (pulmonary sling), 1 Turner syndrome (hypertrophic cardiomyopathy), 1 Holt Oram syndrome (atrial septal defect). A genetic confirmation of the diagnosis was done in 3 cases – Turner and Di George syndromes.

**Conclusion:** Searching heart defects in genetic diseases belongs to the diagnosis of the disease, and often establish the prognosis of the syndromes. The literature describes specific associations in some genetic diseases, also variation of the heart malformation may occur – like the hypetrofic cardiomyopathy in Turner syndrome, cushion defect in Cornelia de Lange, ventricular septal defect in Seckel disease.

# Five Years Review Of Cases With Anomalous Pulmonary Venous Connections

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**Aim:** To review all the cases with anomalous venous pulmonary connections (AVPC) in the last 5 years, to asses their clinical presentation and their outcome.

**Material and method:** Between 2003 -2008 we diagnosed 8 cases of AVPC aged 2 days – 5 years (median age 3,6 ± 2,4 month). All cases were diagnosed by echocardiography, 3 cases were confirmed by MRI, other 2 during surgery. The male – female ratio was 6:2.

**Results:** Three cases had isolated AVPC with atrial septal defect. Although clinical signs occurred earlier, a correct diagnosis was made at a median age of 6 ± 2 month. Two cases were operated with good results, 1 had residual pulmonary hypertension. The third is waiting for surgery. Five cases had complex heart defects – complete cushion defect with imbalanced ventricles (1), tricuspid atresia (1), double outlet right ventricle with severe pulmonary stenosis (3), 3 of these associating heterotaxia. All these cases were symptomatic in the first month of life. None was operated due to the complex heart defects. Three died shortly after diagnosis, 2 are still alive. Concerning the anatomic subtype of the venous connections 6 had supracardiac drainage by a common venous collector, 1 mixed, 1 infracardiac.

**Conclusion:** Although a rare cardiac defect, AVPC is important to diagnose as early as possible. Echocardiography is a sure method for diagnosis, MRI offers better anatomical details. Late diagnosis and surgery is associated with residual pulmonary hypertension. Isolated AVPC has an excellent prognosis when operated soon, while in the complex one the prognosis is poor.

# Cardiac Abnormalities In Marfan Syndrome In Children

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Marfan syndrome is a genetic disorder defined by skeletal, cardiac, ocular and skin abnormalities produced by defective collagen structure. Inheritance is autosomal dominant, with variable expressivity. Heart defects commonly identified in affected persons are aortic dilatation and mitral valve prolapse.

**Aim:** to study heart defects identified in children diagnosed with Marfan syndrome in our hospital. Material and method: the study group is formed of 13 children (aged 1-17 years) recorded with the diagnosis of Marfan syndrome in the files of the Medical Genetics Center of "Sf Maria" Children's Hospital. The examination protocol included: physical examination, anthropometric measurements, ophthalmologic examination, ECG, cardio-thoracic radiography and echocardiography (2D, M, color Doppler and spectral).

**Results:** ECG was normal for all cases. Cardio-thoracic radiography identified globulous heart in 2 cases. Echocardiography revealed: anterior mitral valve prolapse in 5 cases, prolapse of both mitral valves with severe mitral insufficiency in 3 cases and dilatation of aortic root in 2 cases.

**Conclusions:** Echocardiography is the only noninvasive investigation the can appreciate precisely the type and severity of heart defects in children with Marfan syndrome. Early examination is important, as well as regular check-up in order to prevent complications.

# Common Genetic Disorders With Cardio-Vascular Defects In Pediatric Pathology

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Genetic disorders are an important component of pediatric pathology, approximately 10% of newborn infants carrying a disorder that is expressed immediately after birth or later in life. Cardio-vascular defects represent a major category of genetic disorders.

**The aim** of this presentation is to discuss the most important categories of genetic disorders with a cardiac component, to illustrate the features suggestive for the diagnosis with cases diagnosed in our service and to discuss the importance of genetic testing for the management of the patient and his family. Major categories of genetic disorders are represented by chromosomal abnormalities (numerical or structural), monogenic disorders (autosomal/ X-linked, dominant/recessive), multifactorial disorders, mitochondrial disorders and cancer. Cardio-vascular defects could be included in any category. For each class frequent entities and suggestive features for the diagnosis will be illustrated with cases. Finally, an investigation protocol will be provided.

**In conclusion**, we present our experience in the diagnosis of genetic disorders with a cardiac component in order to help the recognition of the most common genetic entities by practitioners, but also to discuss the sequence of evaluation of such patients, as well as the importance of genetic testing for patient/ family management.

# The Genetic Basis Of Cardiac Anomalies: From Contiguous Genes Syndromes To The Cardiac Genes

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**Objective:** Developmental abnormalities of the heart have been widely recognized as the underlying cause of many congenital heart malformations. Hence, the complex developmental mechanisms that orchestrate the heart formation and morphogenesis have received much attention among clinical and molecular geneticists. The familial clustering of congenital heart disease (CHD) has long suggested a role for genetic mutations, but the extent to which mutations contribute is poorly defined. The paper try to present the significant progress made in the field of candidate genes for human CHD coming from the contiguous syndromes studies.

**Material and methods:** A contiguous genes syndrome is caused by a microdeletion or a microduplication that spans genes tandemly positioned along a chromosome. The paper will present the contiguous genes syndromes that include heart defects among the characteristic signs and symptoms: Wolf-Hirschhorn syndrome (deletion 4p), Cri du Chat syndrome (deletion 5p), Williams Syndrome (deletion 7q11.2), Rubinstein Taybi (deletion 16p11.3), Smith Magenis syndrome (del 17q11.2), Miller Diecker syndrome (deletion 17p13.3), Alagille syndrome (deletion 20p12), DiGeorge syndrome (deletion 22q11.2), Cat Eye syndrome (duplication 22q11.2). The human heart expression of the genes from the critical regions have been checked using the genomic data bases (Ensembl, USCS).

**Conclusions:** The loss of some genes from the critical region involved into a specific contiguous syndrome has been clearly associated with the cardiac anomalies: ELN gene-7q11.2, JAG1 gene -20p1.2, TBX1 gene-22q11.2. In other cases, even there is no direct genotype-phenotype correlation, the cardiac anomalies can be explained by a positional gene effect or by new gene functions and interactions.

# The Importance Of Transesophageal Echocardiography In Surgical Treatment Of Common Atrioventricular Septal Defect

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The common atrioventricular canal is the extreme form of endocardial cushion defect. In this malformation there is a common atrioventricular valve, a defect of the lower portion of the interatrial septum (ostium primum) and a defect of the high, posterior portion of the interventricular septum (inlet).

**Aim of the study:** to demonstrate the value of transesophageal echocardiography in the success of the surgical treatment of common atrioventricular septal defect.

**Material and method:** in five cases of children with common atrioventricular septal defect Rastelli type A diagnosed with transthoracic echocardiography, a perioperative transesophageal echocardiography was performed. The first exam was performed before the surgical procedure and the other exam after the correction. The transesophageal echocardiography used the four chamber view from medium oesophagus and the transgastric transverse plan to evaluate the size of the atrial and ventricular septal defects, as well as the morphology of the atrioventricular valve. The second exam was made for the determination of the residual lesions.

**Results:** in one case there was a small residual ventricular septal defect and in the other two cases there was a small mitral and tricuspid regurgitation.

**Conclusion:** transesophageal echocardiography is a very important exam for the success of the surgical treatment of the common atrioventricular septal defect.

# Management Of Postoperative Pulmonary Hypertensive Crisis In Pediatric Patients

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**Objective:** The management of the pulmonary hypertensive crises in pediatric patients after cardiac surgery remains a challenge. Children with acute increases in pulmonary arterial pressure may develop a fatal right ventricular failure. The objective of this paper is to review the therapeutic measures for the neonatal and pediatric patient in this critical condition.

**Materials and methods:** We performed a comprehensive review of the literature published in the last 10 years. We searched MEDLINE articles with the following keywords in various combinations: pulmonary hypertension, treatment, postoperative, open heart surgery, cardiac surgery, crises, acute, right ventricular failure. We analyzed only those human studies limited on neonatal and pediatric population (0-18 years old) and concerning the therapeutic measures used in acute care settings.

**Results:** Although several studies have evaluated the postoperative treatment of the patients with pulmonary hypertension, there are few addressed to neonatal and pediatric population. We identified only 3 randomized studies and 1 systematic review related to prevention or treatment of the acute pulmonary vasoconstriction after cardiac surgery. Postoperative management includes pharmacologic and non-pharmacologic therapy of the right ventricular failure and of the increased pulmonary vascular resistance.

**Conclusions:** The management of the pulmonary hypertension after cardiac surgery in neonatal and pediatric patients is based on studies involving adult patients. An important issue of the postoperative management in such cases is to prevent the acute pulmonary vasoconstriction. The pulmonary hypertensive crises are requiring immediate medical intervention, focused on reducing afterload and on sustaining the contractility of the right ventricle.

# Aspects Of Congenital Heart Anomalies In Neonatal Period

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[3] Spitalul Orasenesc Marghita Bihor

**Aim of the study:** Congenital heart anomalies represent a unique pathology of the newborn that influences neonatal mortality and morbidity. The study aims to establish congenital heart diseases incidence for newborns managed by Neonatology Department Ginecology I Clinic Cluj-Napoca over a period of 5 years,diagnosis and treatment modalities, risk factors and factors that influence newborns survival.

**Material and method:** This is a retrospective study, over 5 years, including 65 newborns with heart anomalies ASD, VSD, TGV, PS, pulmonary atresia, AS, Fallot tetralogy, PDA only associated with heart malformations or causing major hemodynamic changes. Results: Gestational age average in the study group was 37.66±2.46 weeks and weight average 2886±717.09. Most of the heart anomalies were complex. Of all cases 37% were from Cluj. Percents attributed to each heart anomaly were: TGV 21.5%, VSD 28%, ASD 29%, PDA 43%. Of all heart anomalies 11% were associated with chromosomal malformation syndromes, genetic syndromes or other etiology. Cases of Down syndrome confirmed by karyotype were 3 and 1 case associated with Apert syndrome. Antenatal diagnosis was made only for 3 newborns, most of the cases being diagnosed postnatal. Duct dependent heart anomalies benefited of medical treatment with Prostaglandin E1. Surgical curative treatment was applied in 4 cases.

**Conclusion:** Prevalence of heart anomalies was 6.6% of all newborns managed by our department. Management of a newborn with congenital heart anomaly presumes an interdisciplinary equipe: obstetrician, neonatologist, genetician, cardiologist and cardiovascular surgeon.

# The First Initiative In Forming The National Register Of Congenital Heart Disease

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Congenital heart disease (CHD) are among the most frequent anomalies present at birth with the reported incidence of 8/1000 live birth.

Pulmonary arterial hypertension (PAH) is a frequent complication of CHD, and the most important group of CHD that associates PAH is CHD with left-to-right shunt. There is no National Register of CHD and no National Register of PAH associated to CHD.

The Pediatric Cardiology Department from Tîrgu Mureş had the first initiative for starting the first Register of children with CHD, in the first stage six counties were included, with a total number of patients with CHD of 1954. the most frequently CHD was atrial septal defect (44.3%), followed by ventricular septal defect (19,7%), patent ductus arteriosus (14.2%). Other CHD like tetralogy of Fallot, coarctation of the aorta, common atrioventricular septal defect, transposition of the great arteries, double outlet right ventricle, pulmonary atresia, tricuspid atresia and single ventricle had a smaller percentage. In the first stage we concluded also that the most frequently encountered CHD associated with PAH was ventricular septal defect, followed by atrial septal defect, persistent ductus arteriosus, common atrioventricular defect.

The pathology of our Department may reflect the pathology at national level, because the Pediatric Cardiology Department from Tg. Mureş is the only Center specialized in the evaluation and treatment of CHD.

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## Scientific Studies Realised In The Research Project Mami No.41-042/2007 Financed By The Roumanian Ministery Of Education, Research And Youth.

1. **Genetic Variants In The Methylenetetrahydrofolate Reductase Gene And The Risk For Congenital Heart Defects,**
   *Ionela Pascanu, Rodica Toganel, Claudia Banescu, Carmen Duicu*
2. **Pulmonary Arterial Hypertension Associated With Congenital Heart Disease In The Pediatric Cardiology Department Tg. Mures,**
   *Rodica Togănel, Cristina Blesneac, Carmen Şuteu, Reka Borka Balas, Amalia Făgărăşan, Sorina Paşc, Liliana Gozar, Iolanda Muntean*
3. **Atrial Septal Defect As An Uncommon Cardiovascular Malformation In Turner's Syndrome,**
   *Carmen Duicu, Claudia Banescu, Rodica Toganel, Iolanda Muntean, Eva Kiss*
4. **Cytogenetic Analysis In Congenital Heart Disease In Tg Mureş,**
   *Claudia Bănescu, Rodica Togănel, Ionela Paşcanu, Carmen Duicu*
5. **The First Initiative In Forming The National Register Of Congenital Heart Disease,**
   *Rodica Togănel, Koncság Előd, Cristina Blesneac, Carmen Şuteu, Reka Borka Balas, Amalia Făgărăşan, Sorina Paşc, Liliana Gozar, Iolanda Muntean*


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