

Demystifying the Pediatric Cardiomyopathies

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Introduction

Cardiomyopathy presenting in the pre-adolescent differs significantly in possible causes, clinical expression and prognosis from that occurring in the adolescent or adult[1, 2]. Even within the pre-adolescent age group cardiomyopathy has different clinical manifestations and management concerns at different developmental stages: fetal, neonatal, early childhood and late childhood[3-5]. The etiology of childhood myocardial disease more often remains undetermined than with adult cardiomyopathy, but when diagnosed much more likely will be a metabolic or inherited disorder[1]. This poses the conundrum of pediatric cardiomyopathy – a relatively uncommon condition, which has a large number of potential causes that are rare, have important genetic implications and require intensive and expensive investigations to resolve[6].

Incidence and Impact

Much of the North American epidemiologic data for childhood cardiomyopathy derives from the Pediatric Cardiomyopathy Registry (<http://www.pcmregistry.org/>), a multicenter cooperation for the study of pediatric cardiomyopathies[7]. Lipshultz et al reported an overall annual incidence of 1.13 per 100,000 children under 18 years of age[8]. Infants comprise the largest age group, with an incidence of 8.34 per 100,000 children below one year of age. Approximately 1000 to 5000 new childhood cases of cardiomyopathy are diagnosed annually in the United States[9]. For comparison, approximately 2500 new cases of cystic fibrosis occur annually in the United States[10]. A study by Nugent et al published simultaneously with that of Lipshultz et al identified an annual incidence in Australia of 1.24 cases per 100,000 children below 10 years of age[11]. Both studies recognized dilated cardiomyopathy as the most common type (51% in Lipshultz et al and approximately 59% in Nugent et al), followed by hypertrophic cardiomyopathy (42% in Lipshultz et al, 25.5% in Nugent et al).

Cardiomyopathy accounts for approximately 2% of new admissions to the cardiac ward at Toronto's Hospital for Sick Children and is responsible for just over 50% of the hospital's heart transplants[12, 13]. The outcome for cardiomyopathy clinically diagnosed in childhood remains poor[1]. A recent study by Towbin et al found only 46% of children with dilated cardiomyopathy survived and did not receive heart transplant 10 years after diagnosis[2]. Survival related to the specific cause of cardiomyopathy in that study, underscoring the importance of determining etiology. Unfortunately, for pediatric cardiomyopathy the underlying cause remains unknown in approximately two thirds of cases[14].

Definitions and Classifications

As with any disease, the definitions and classifications of cardiomyopathies aim to provide diagnostic criteria, potential or established etiologies and ultimately some guidance to clinical management for the condition. In 2006 an American Heart Association Scientific Statement presented a consensus for revised definitions and classification of cardiomyopathies (Appendix) to replace the 1995 WHO/ISFC classification that had been the standard for the last decade[15, 16]. The AHA statement derives from advances in molecular genetics of cardiomyopathies, incorporates newly described entities, de-emphasizes the traditional dilated-hypertrophic-restrictive clinical-morphologic designations and adds the channelopathies and other electrical disorders of myocardium to the classification of cardiomyopathy. It segregates those disorders that solely or predominantly affect the heart, called “primary”, from those that have myocardial involvement as a concomitant or uncommon manifestation, called “secondary”. Consequently, the new AHA classification aligns with and promotes the multidisciplinary approach required for the investigation, diagnosis and management of pediatric cardiomyopathies. It emphasizes the increasing importance of molecular genetic testing in the delineation of the cardiomyopathies.

Pathology Investigations

The pathologist generally confronts a pediatric cardiomyopathy case well after clinical, diagnostic imaging and metabolic-genetic evaluations have been initiated. This pre-pathology processing aims to identify a secondary cardiomyopathy, or if excluded, then reveal a primary cardiomyopathy etiology. Clinical strategies for such investigations have been presented for both childhood and adult cardiomyopathies[17-19]. However, since the cause in two thirds remains undetermined or the clinical differential diagnosis requires histologic confirmation, the pathologist often receives tissue during the work-up of pediatric cardiomyopathies. This usually consists of endomyocardial biopsy tissue, but may be an explanted heart, heart tissue from septal myomectomy or other cardiac surgical procedure, or, unfortunately, an autopsy specimen. In some cases non-cardiac tissues may be obtained, such as skin or conjunctival biopsy for evaluation of metabolic storage disease, or muscle biopsy for clinically suspected mitochondriopathy or neuromuscular disorder. Regardless of the specimen type, the pathologist remains responsible for not only documenting and interpreting the gross and histologic features, but also for appropriately allocating tissue for the potential histochemical, ultrastructural, microbiologic, biochemical and molecular genetic studies. Especially for the limited sample amounts obtained by endomyocardial biopsy, optimal tissue dispensation requires consultation with the cardiologist and metabolic geneticist colleagues.

A. Endomyocardial Biopsy

Although frequently performed during the investigation of cardiomyopathy, the value of endomyocardial biopsy remains debated[20, 21]. Firmer indications for biopsy include dilated cardiomyopathy and suspected diagnoses of viral myocarditis, primary metabolic,

mitochondrial or arrhythmogenic right ventricular cardiomyopathies[22-24]. In addition to those reasons, the clinical protocol at the Toronto Hospital for Sick Children includes biopsy for acute fulminant heart failure, resulting in about 20 non transplant-related endomyocardial biopsies performed annually.

Toronto Sick Kids Division of Pathology non-transplant endomyocardial biopsy protocol:

- minimum of 5 biopsy pieces
- 3 pieces for light microscopy
 - H&E stain x 3 slides (ribbon)
 - elastic-trichrome stain x 1 slide
- 1 piece for electron microscopy
- 1 piece snap frozen
 - histochemistry: ORO, PAS+/-diastase, succinic dehydrogenase, NADH reductase, cytochrome c oxidase
 - immunohistochemistry: dystrophins (for males)
 - remainder for potential PCR (additional piece snap-frozen for viral PCR if myocarditis suspected or for metabolic chemistry if mitochondriopathy suspected)

B. Explanted Heart

As of January 2007, close to 200 heart transplants have been performed at the Hospital for Sick Children, just over half for pediatric cardiomyopathy. The etiologic diagnoses for these cases may be established, suspected or unknown. The principle of tissue allocation for potential multidisciplinary studies applies to explanted native heart specimens as it does to endomyocardial biopsies.

Toronto Sick Kids Division of Pathology cardiomyopathy explanted native heart protocol:

- apical left ventricle myocardial sample snap frozen in the operating room
- apical left ventricle myocardial sample placed in universal fixative for electron microscopy
- explant examined in sequential-segmental manner with measurements and photographs
- explant sampled for histology (H&E and elastic-trichrome stains), at least one full thickness section from the inflow and outflow of each ventricle and complete transverse section of mid interventricular septum
- histochemical, immunohistochemical, ultrastructural, biochemical and PCR examinations undertaken as suggested by the clinical and specimen gross and microscopic findings

C. Autopsy Heart

Cardiomyopathy encountered at autopsy may be in a child known to have the condition or be an unexpected finding. In the Australian study, the first presentation of pediatric

cardiomyopathy was sudden death in 3.5% of cases[11]. A review of Toronto Sick Kids autopsy records for sudden death in children due to previously undiagnosed cardiac causes found 21 cases of cardiomyopathy[25]. This represents approximately 0.5% of all autopsies performed in the 20 years review period. Dilated cardiomyopathy accounted for two thirds of the cases. The autopsy heart should be handled like the explant heart, acknowledging that the post mortem interval may impede histochemical, ultrastructural and biochemical tests. Where termination of life support for a child known to have a cardiomyopathy of unknown etiology becomes a consideration, consent for a “metabolic” or urgent autopsy may be raised with the parents. At Toronto Sick Kids this sensitive discussion involves a multidisciplinary team that includes a bereavement nurse, chaplain, the attending cardiologist, the consultant metabolic geneticist and the medical intensivist. In our experience with this process, tissue can usually be obtained between one and two hours after the child’s death. This has proven satisfactory for many histochemical, ultrastructural and biochemical tests on myocardium and skeletal muscle, for instance in cases of suspected mitochondrial cardiomyopathy[26]. The longer post mortem interval associated with unsuspected cardiomyopathy deaths generally precludes the use of such tests. However, DNA genetic testing can be made on tissues several hours or even days post mortem. Our protocol includes making a blood-spot card, submitting skin for fibroblast harvesting and snap freezing samples of heart, liver and kidney.

Post Pathology

The pathologist’s job doesn’t end with making a diagnosis of pediatric cardiomyopathy. The information must be passed on to those who can ensure that the immediate relatives of the deceased child are appropriately evaluated for familial cardiomyopathy. This is usually not an issue with endomyocardial biopsy results or explant heart surgical pathology reports, but may be one with the autopsy discovery of a cardiomyopathy. Particularly with deaths investigated under coroner or medical examiner jurisdiction, which are often removed from exposure at hospital mortality and morbidity reviews, mechanisms for consultation with cardiologists and geneticists need to be established.

Conclusions

Pediatric cardiomyopathies are “mystifying” because they are uncommon, have many rare potential causes often with significant genetic implications, have a broad morphologic spectrum and are cloaked with controversies in definition and classification. Demystifying the pediatric cardiomyopathies requires a multidisciplinary approach, much of which is done well before the pathologist enters the picture. However, for the two thirds of cases that remain etiologically undetermined, the pathologist becomes a pivotal element, contributing not only potentially diagnostic morphologic evaluations but also judiciously dispensing tissues to the other disciplines to optimize the information locked in the diseased myocardium.

Appendix: 2006 AHA Scientific Statement[15]

Definition: “Cardiomyopathies are a heterogenous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic orders, often leading to cardiovascular death or progressive heart failure-related disability.”

Classification:

Primary Cardiomyopathies

Genetic

Hypertrophic cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy

Left ventricular noncompaction cardiomyopathy

Glycogen storage disease

PRKAG2 defect

LAMP2 defect (Danon disease)

Conduction defects

Progressive cardiac conduction defect (Lenegre disease)

Mitochondrial myopathies

Ion channel disorders

Mixed (genetic and nongenetic)

Dilated cardiomyopathy

Restrictive (nonhypertrophied) cardiomyopathy

Acquired

Inflammatory (myocarditis) cardiomyopathy

Stress-provoked (Tako-Tsubo) cardiomyopathy

Peripartum cardiomyopathy

Cardiomyopathy of infants of insulin-dependent diabetic mothers

Secondary Cardiomyopathies*

Infiltrative

Storage

Toxicity

Endomyocardial

Inflammatory (granulomatous)

Endocrine

Cardiofacial

Neuromuscular/neurological

Nutritional deficiencies

Autoimmune/collagen

Electrolyte imbalance

Consequences of cancer therapy

* see reference [15] for complete list

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NEW GENETIC INSIGHTS INTO THE NORMAL AND ABNORMAL DEVELOPING HEART

By Mona Nemer

The objectives of the presentation will be as follows:

- To provide a state-of-the-art overview of heart development
- To summarize the genetic pathways involved in heart morphogenesis
- To explain how basic knowledge of heart development can translate into prevention and/or improved care of human congenital heart disease

HAND OUT:

General Background:

Congenital heart defects (CHDs) affect 1-2% of newborn children and are the leading cause of death in infants under one year of age. CHDs represent the single largest class of birth defects and account for 25% of all human congenital abnormalities. Since heart development requires the execution of specific genetic programs, furthering our knowledge of gene transcription will translate into better prevention, diagnosis and treatment of congenital heart disease.

Numerous epidemiologic studies have established the heritable nature of CHDs. Despite this, very few CHD-causing genes have been identified. The presentation will illustrate how analysis of heart development has helped understand the genetic basis of some CHDs.

I. Heart development: from lineages to chambers

In higher vertebrates, heart formation is a complex process (*Fig. 1*) that starts at early stages of embryogenesis, prior to the end of gastrulation, with commitment of anterior lateral plate mesoderm cells to the cardiogenic lineage, their migration and organization into the cardiac crescent.

Commitment to a cardiac fate is the result of inductive signals from the underlying endoderm which include bone morphogenetic proteins (BMPs), basic fibroblast growth factors (bFGFs) and the Wnt proteins. The second stage involves formation of the beating linear heart tube, the first functional organ of the developing embryo, which results from migration and fusion along the ventral midline of the specified precursors from the cardiac crescent. Failure of the bilateral myocardial rudiments to fuse results in cardia bifida. The mechanisms underlying these early stages of cardiogenesis are not fully understood; nevertheless, transcription factor (TF) GATA-4, which we initially identified as one of the key TFs required for expression of the cardiac natriuretic peptide genes ANP and BNP 5, is emerging as the critical regulator of the earliest stages of cardiogenesis. First, GATA-4 is the competence factor required to allow cells to respond to cardioinductive substances, and its combined action with another TF, Nkx2.5, mediate BMP signalling. GATA-4 acts synergistically with the SMAD proteins, the intracellular effectors of the TGF/BMP signaling pathway to activate Nkx2.5 transcription. Ectopic GATA-4 expression is sufficient to induce cardiogenesis in ES cells 9

and in *Xenopus* embryonic ectoderm. GATA-4 cardiogenic activity reflects its activation of cardiogenic growth factors like BMP-4 as well as other TFs required for heart formation. Thus, GATA-4 is a central player of a self reinforcing feedback loop at the onset of cardiogenesis.

As development proceeds, the primitive heart tube undergoes a series of complex events which include chamber specification, septation and trabeculation, to form the definitive four-chambered heart. Defects in compartmentalization and proper communication between the four chambers account for the majority of human congenital heart defects (CHD). Although the molecular mechanisms underlying cardiac morphogenesis remain largely unknown, the production of mice in which specific genes were inactivated ("knock-outs") has allowed the identification of proteins involved in chamber maturation and heart morphogenesis [reviewed in].

Chamber specification is thought to be a very early event since the beating heart tube is organized with an antero-posterior polarity and specific segments are already fated to become, from anterior to posterior, the aortic sac, the conotruncus, the right ventricle, the left ventricle, the atria, and the sinus venosus of the mature heart. Thus, subtle alterations in early myocyte differentiation could lead to defects in cardiac looping, septation, and compartmentalization. The mechanisms controlling heart tube regionalization are poorly understood and the timing of atrial and ventricular specification is presently controversial; although fate mapping studies suggest that atrial and ventricular lineages are specified and separated during gastrulation, work in chicken and zebrafish suggest that the fate of cardiac progenitors can be altered – by retinoic acid treatment for example – within a specific window of time raising the possibility that lineage commitment occurs later on. Because tissue-specific TFs that control expression of differentiation genes participate in the earliest decisions of cell specifications, atrial and ventricular specific TFs represent ideal markers for tracing the origins of atrial and ventricular myocytes. The homeodomain protein Nkx2.5, one of the vertebrate homologues of tinman, a drosophila gene required for specification of cardiac and visceral mesoderm, may play a role in cardiac regionalization. Although Nkx2.5 is expressed uniformly throughout the heart, detailed analyses of a null mutation of Nkx2.5 in mice suggest that Nkx2.5 is required for ventricular myocyte differentiation.

In addition, two basic helix-loop-helix (bHLH) TFs, Hand1 and Hand2, which are expressed in the precardiac mesoderm as well as in non-cardiac precursor cells have been associated with right and left ventricular specification. Hand2 is expressed throughout the straight heart tube but becomes restricted to the future right ventricle during looping while Hand1 is restricted to the anterior and posterior regions of the heart tube, which are fated to become the conotruncus and left ventricle, respectively. Inactivation of the Hand2 gene in mice results in embryonic lethality at the looping stage and the segment of the heart tube destined to form the right ventricle is absent. Loss of Hand1 results in even earlier embryonic lethality due to placentation defects but chimeric analysis (that rescues the placentation defect) suggests that Hand1 is required to ensure proper cardiac looping. Finally, one member of the growing family of T-box factors, Tbx5, is essential for atrial formation. Interestingly, Tbx5 is the gene mutated in Holt-Oram syndrome (detailed later on).

In addition to heart tube derived myocytes, the mature heart contains myocytes derived from a distinct heart field, located in the pharyngeal mesoderm and referred to as the secondary or anterior heart field (AHF). Cells from the AHF are incorporated in the growing heart tube during the looping stage at the venous and arterial poles. Recently, it was shown that the myocardium of the right ventricle is derived from the AHF, further underlining the differences between the two ventricular compartments. Thus, myocardial cells appear to derive from two embryologically distinct mesodermal lineages. This knowledge is important in understanding the molecular basis of disease.

II. Cardiac transcription: a multi-partner affair

The complex morphologic events and tissue remodeling that take place during heart formation are accompanied by equally complex changes of gene expression that produce dynamically regulated chamber as well as left-right specific patterns. Despite important efforts devoted to the study of chamber-specific gene expression and the identification of several cardiac TFs involved in heart formation, the molecular mechanisms underlying spatio-temporal regulation of transcription within the heart remain unclear. A few promoters have been shown to target transgenes to the heart (Table 1), but the regulatory elements therein, hence the pathways responsible for cardiac and often temporal and regional specificity, have yet to be defined.

The GATA family. Three GATA factors are expressed within the heart, GATA-4, -5 and -6, where they show cellular and/or regional specificity and are differentially regulated throughout development with GATA-4 being the predominant transcript in cardiomyocytes at all stages. GATA-6 is also found in myocardial as well as vascular smooth muscle cells. GATA-5 transcripts are largely restricted to endocardial cells while GATA-4 is detected in all cardiac progenitors. By far, the most extensively studied member of the family is GATA-4, initially isolated as an upstream regulator of BNP. The number of cardiac promoters regulated directly by GATA-4 is over 30. The importance of GATA-4 in heart development is evidenced by the presence of CHD in mice and human with GATA-4 haploinsufficiency. At the molecular level, GATA-4 interacts with several other TFs to control diverse genetic programs and cardiac cell fates. At present, GATA-4 is the most studied cardiac transcription factor and the one that comes closest to the definition of a “Master” regulator.

The NK family. As stated earlier, Nkx2.5 was isolated in a screen for mammalian homologs of Tinman, a NK-class homeodomain-containing protein required for mesoderm segmentation and heart formation in drosophila 33. In mice, loss of Nkx2.5 did not result in the absence of heart formation but rather revealed essential roles for Nkx2.5 in establishment of a ventricular gene expression program and in septal morphogenesis. While the less severe phenotype observed in mice may reflect redundancy with other NK factors, studies so far have failed to identify the conserved presence and involvement of other NK members in vertebrate hearts. In human, mutations of Nkx2.5 are associated with septal defects and conduction abnormalities.

The Mef2 family. Mef2 proteins were originally isolated by virtue of their binding to A/T rich regulatory sequences present on several skeletal muscle promoters. They are derived from 4 genes which produce several isoforms through alternative splicing. Gene targeting in drosophila and mice suggest a role for Mef2 in later stages of cardiomyocyte and vascular cell differentiation. In humans, mutation of Mef2A are linked to genetic predisposition to sudden death.

The T-box family. Tbx proteins form a newly identified family of important developmental regulators that share a conserved 180 AA region (the T-domain or T-box) responsible for DNA binding. Over 20 members have been identified so far in mammals. The first evidence for a role of Tbx proteins in the heart came from the finding that Tbx5 is the gene mutated in Holt-Oram

syndrome, which is characterized by heart and limb malformations and the demonstration that a dominant negative Tbx protein interferes with *Xenopus* heart development.

Combinatorial interactions. The spatio-temporal complexity of gene expression during heart development would necessitate a very large number of regulators which need to be finely regulated themselves. Even then, since few cardiac genes are coordinately regulated at any given developmental time, it would be virtually impossible to achieve this complex regulation except through different combinations of TFs. In 1998, based on our own analysis of ANP transcription, we proposed that combinatorial interactions govern heart development; in particular, we demonstrated that GATA-4 and Nkx2.5 act cooperatively and, on the basis of this, we predicted that the *Drosophila* GATA factor *pannier* will collaborate with *Tinman* (*Drosophila* Nkx2.5) in cardiogenesis, which indeed turned out to be the case 50. Since then, we and others have shown that GATA-4 interacts with several other cardiac-specific and stimuli inducible TFs. Combinatorial interactions are not restricted to GATA factors. Nkx2.5 was shown to collaborate with SRF and Tbx5 (App. 1). We also documented physical and functional interactions between MEF2 and GATA proteins as well as with the cardiac bHLH factors, Hand1/2. The importance of protein-protein interactions in heart development are evidenced by 1) their evolutionary conservation from *Drosophila* to mammals and 2) the finding that point mutations that disrupt these interactions produce developmental heart defects in mice and human. Our findings of cooperative interaction between Nkx2.5 and Tbx5 have, among other, provided a molecular framework for understanding how mutations in different genes can lead to similar cardiac abnormalities. *Figure 3* illustrates how defects in the same gene can lead to different malformations and how the same malformations can be caused by different genes.

Conclusion and Prospective

The past decade has witnessed spectacular progress in identifying the molecular mechanisms of heart development. In particular, several genes essential for heart development have been identified. Genetic analysis using classical human genetic approaches, as well as the direct sequencing of candidate genes – which are essential for normal heart formation in families with affected members have started to unravel the genetic basis of CHDs. Moreover, the finding that complex regulatory circuits control heart development and the identification of the various regulators of cardiac morphogenesis has provided molecular explanation for the linkages of the same malformation (e.g. ASD or VSD) to more than one gene. The identification of the genes whose mutation causes CHD opens the way for understanding gene-environment interactions and offers further avenues for understanding the genetic basis of disease.

The presentation will provide an overview of recent advances and show how present and future basic knowledge can translate into patient care.

Reference:

18 Olson EN. A decade of discoveries in cardiac biology. *Nature in Medicine* 2004; **10**: 467-474.

Table 1. Promoters conferring cardiac-specific expression in transgenic mice

Gene	Promoter length (Kb)	Developmental Expression
α MHC	5.5	atria
β MHC	2.5	atria + ventricle
α -cardiac actin	3	atria + ventricle
Tropoinin I	4.2	inflow tract + ventricle
MLC2c	0.28	outflow tract + right ventricle
MLC3f	2	right atrium +left ventricle
Desmin	1	outflow tract + right ventricle
SM22 α	2	outflow tract + right ventricle
α B-crystallin	4	outflow tract + right ventricle
Dystrophin	0.9	outflow tract + right ventricle
Nkx2-5	14	outflow tract + right ventricle + left ventricle
ANP	0.695	atria + ventricle

Fig. 1 Transcription factors involved in cardiac development

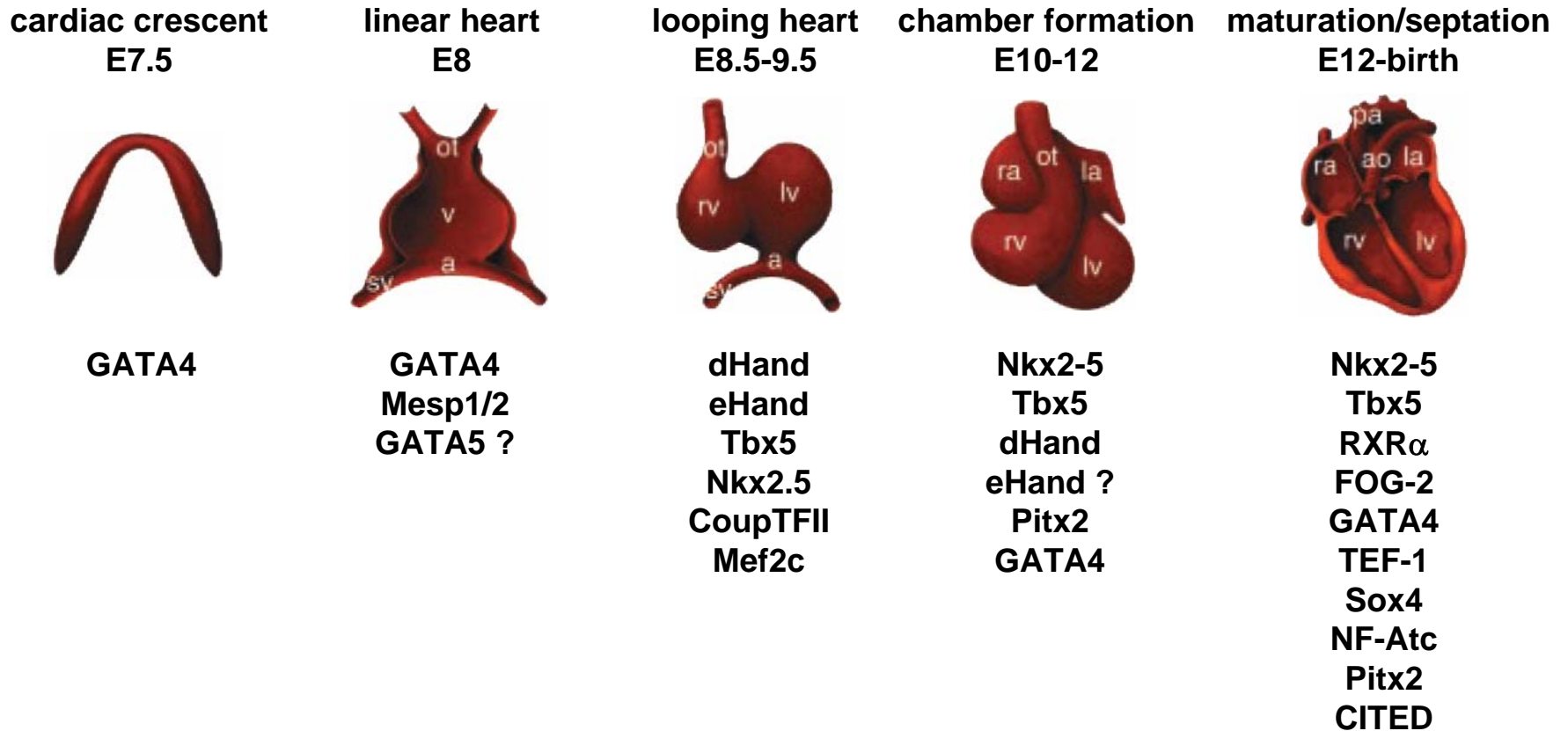
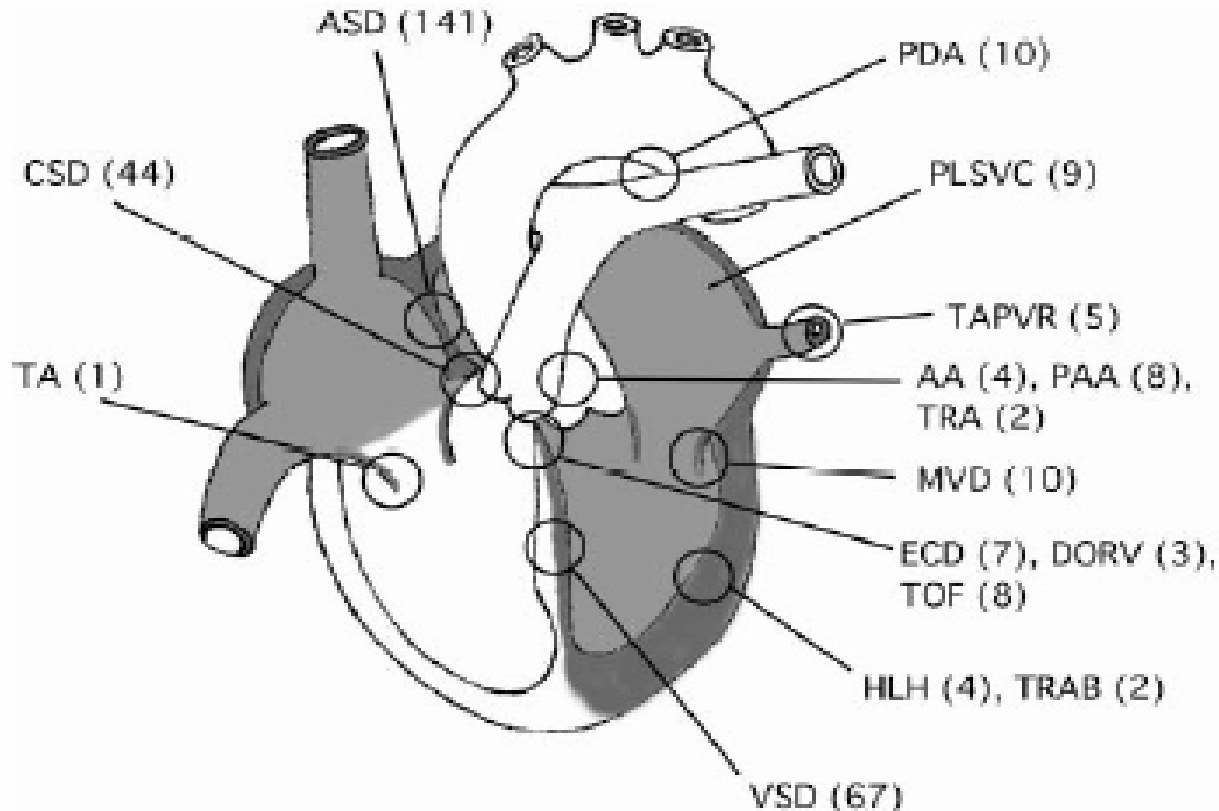


Fig. 2 Cardiac malformations in Holt Oram syndrome



ASD: atrial septal defect

CSD: conduction system defect

VSD: ventricular septal defect

MVD: mitral valve defect

PDA: patent ductus arteriosus

PLSVC: persistent Left Superior Vena Cava

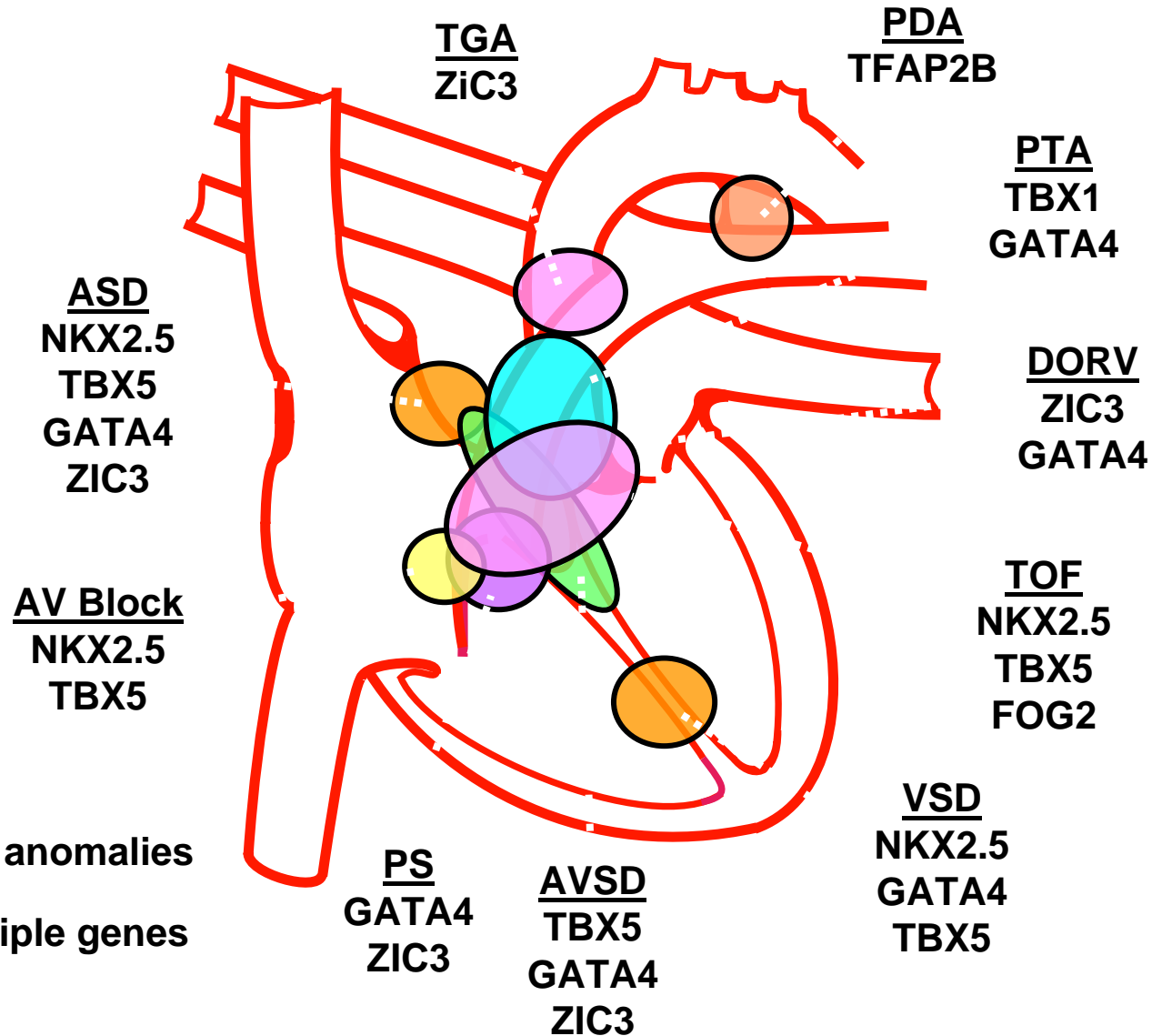
TOF: Tetralogy of Fallow

ECD: endocardium cushion defect

Note: Variable phenotypes and different expressivity of the same mutation

How can we establish genotype-phenotype correlations?

Fig. 3. Sites of structural anomalies associated with transcription factor mutations



Note: 1 gene = multiple anomalies
1 anomaly = multiple genes

Pathophysiology of Adult Congenital Heart

I. Shunt lesions

A. *Ostium secundum atrial septal defect*

1. Size and direction of shunt determined by defect size and relative ventricular compliances
 - a) Large defects typically have large left-to-right shunts in childhood and are usually repaired by catheter-placed devices
 - b) Small left-to-right shunt in childhood and young adulthood can progress to large left-to-right shunt in adulthood due to worsening left ventricular compliance from coronary artery disease
2. Rare to have signs of heart failure (other than growth failure) in childhood
3. May develop pulmonary vascular disease in third decade
4. May develop atrial arrhythmias particularly during pregnancy; even after surgical repair
5. May develop congestive heart failure in fifth decade or later

B. *Partial anomalous pulmonary venous connection*

1. If isolated, usually asymptomatic and incidental finding with small left-to-right shunt
2. Frequently associated with sinus venosus type atrial septal defect with clinical findings and physiology similar to ostium secundum atrial septal defect above
3. However, unlike secundum ASD, sinus venosus ASD requires surgical repair in order to redirect anomalous pulmonary vein(s)

C. *Incomplete common atrioventricular canal*

1. Also known as “ostium primum atrial septal defect,” which itself has physiology similar to ostium secundum atrial septal defect. However ...
2. Always has associated atrioventricular valve abnormality – so-called “cleft mitral valve”
3. Many develop left-sided atrioventricular valve regurgitation, which exaggerates the left-to-right shunt through the atrial septal defect
4. Abnormal atrioventricular valve subdivides the left ventricle into inflow and outflow portions (not present in the normal left ventricle); hence, left ventricular outflow tract in common AV canal is inherently small

D. *Ventricular septal defect*

Pathophysiology of Adult Congenital Heart

1. Size and direction of shunt determined by defect size and relative pulmonary versus systemic vascular resistance
 - a) Large defects typically present with heart failure from large left-to-right shunt in infancy (1-3 mos)
 - b) If unrepaired may begin to develop pulmonary vascular disease as early as 2 years of age but may survive into early adulthood
2. Many are small to start with or become small over time and present little risk of heart failure or pulmonary vascular disease but are the most likely congenital heart defect to develop bacterial endocarditis
3. Spontaneous closure in early childhood is common but can probably occur throughout period of growth

E. Patent ductus arteriosus

1. Size and direction of shunt determined by defect size and relative pulmonary versus systemic vascular resistance
 - a) Large defects typically present with heart failure from large left-to-right shunt in infancy (1-2 mos)
 - b) Small ductus while hemodynamically insignificant can calcify, form aneurysms, be a nidus for endocarditis in adulthood
2. Most are repaired in infancy or early childhood
3. Repair in infancy and childhood is typically by catheter-placed device or simple ligation via minithoracotomy or thoracoscopy; whereas repair of a calcified ductus often requires cardiopulmonary bypass for repair

II. Cyanotic lesions

A. Tetralogy of Fallot

1. Most common cyanotic congenital heart defect
2. Consists of a large (malalignment type) ventricular septal defect plus small subpulmonary infundibulum
3. Typically the subpulmonary stenosis is sufficient to force some of the right ventricular blood right-to-left through the VSD, contributing desaturated blood to the systemic output
4. Systemic output is usually maintained at normal levels (by systemic baroreceptors). Pulmonary blood flow is reduced according to the degree of outflow tract obstruction (but, unlike the systemic circulation, has no other regulatory mechanism). The degree of cyanosis is inversely proportional to pulmonary blood flow.

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- a) Cyanosis is improved (but not eliminated) by increasing pulmonary blood flow (e.g., systemic-pulmonary surgical shunt), increased systemic vascular resistance (e.g., supplemental oxygen, phenylephrine, squatting)
- b) Cyanosis is worsened by decreased pulmonary blood flow due to a) worsening subpulmonary stenosis, b) decreased systemic vascular resistance (e.g., with exercise, after eating, fever, general anesthesia)

5. Repair includes patch closure of VSD so that aorta is baffled entirely to left ventricle, and right ventricular outflow tract is enlarged – muscle resection and/or patch enlargement

6. In some cases patch enlargement of pulmonary valve annulus is necessary, resulting in pulmonary regurgitation and potentially in right ventricular dilatation and failure in adulthood

B. D-Transposition of the great arteries

1. Morphologic right atrium connected to morphologic right ventricle connected to aorta; left atrium to left ventricle to pulmonary artery. All patients have at least a patent foramen ovale at birth
2. Separate systemic and pulmonary circulations; cyanosis is related to degree of mixing rather than amount of pulmonary blood flow (as in tetralogy)
3. When isolated virtually always repaired in infancy (arterial switch operation – since 1980s) or early childhood (atrial inversion – prior to 1980s)
4. About ½ have more complex disease: VSD with or without aortic or pulmonary outflow obstruction – may survive childhood without repair but usually have pulmonary vascular disease

III. Functional single ventricles

A. Only one substantial ventricle – must become the systemic ventricle

1. Generally morphologic left ventricles make better systemic ventricles than morphologic right ventricles
2. Typically patients with single ventricle physiology can live into the 4th decade as long as they do not have excessive or inadequate pulmonary blood flow
3. If aortic outflow obstruction, must convert pulmonary valve to be systemic semilunar valve – Norwood and Damus-Kaye-Stansel operations
4. Fontan operation uses principle that with one good ventricle and unobstructed pulmonary circulation (arteries, arterioles, veins), blood will flow directly from venae cavae (surgically anastomosed) to pulmonary arteries without an intervening ventricle

B. Functional single left ventricle

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1. Tricuspid atresia
2. Double inlet (single) left ventricle with outlet chamber (remnant of right ventricle)

C. Functional single right ventricle

1. Hypoplastic left heart syndrome
2. Heterotaxy syndrome with functional single ventricle – typically unbalance common atrioventricular canal with hypoplasia or absence of one ventricle (usually the left)

IV. Systemic right ventricles (in a two-ventricle system)

A. L-Transposition of the great arteries

1. Morphologic right atrium connected to morphologic left ventricle connected to pulmonary artery; left atrium to right ventricle, to aorta
2. Frequently accompanied by other anomalies: septal defects, Ebstein anomaly of left-sided (systemic) tricuspid valve (i.e., systemic AV valve regurgitation), congenital or acquired heart block
3. While physiologically “corrected” most patients die in childhood or early adulthood from associated abnormalities or in early to mid adulthood from failure of the morphologic right ventricle (the systemic ventricle)
4. Recently some centers have begun performing so-called “double switch” operation: atrial inversion operation plus arterial switch to make the morphologic LV the systemic ventricle

B. Atrial inversion repair of D-transposition

1. Patients born prior to the mid 1980s had atrial inversion operations (baffling systemic venous return to mitral valve, to left ventricle; pulmonary venous return to tricuspid valve, to right ventricle) for physiological repair of D-transposition of the great arteries
2. Morphologic right ventricle remains the systemic ventricle similar to L-transposition
3. Many patients develop atrial arrhythmias because of the surgery, but systemic right ventricular failure remains an additional problem

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Take Home Points

- Physiologic changes related to maturation and then development of vascular disease of the pulmonary vascular bed affect physiology of shunt lesions in different ways
- There are two main physiologic types of cyanotic heart disease: those dependent on the amount of pulmonary blood flow and those dependent on the amount of mixing of systemic and pulmonary circulations
- Morphologic right and left ventricles behave differently as systemic ventricles
- Some patients with one functioning ventricle can survive with a unique physiology when surgically reconstructed

New surgical strategies for the pediatric heart

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Over the past decade, continuing evolution in the surgical treatment of congenital and acquired heart disease in the pediatric population has resulted in significant improvement in overall morbidity and mortality for virtually all lesions. Refinements in management are evident in all aspects of clinical management including the preoperative, intraoperative and postoperative phases. Although it is often difficult to determine the true beneficial effect of changes in management on clinical results, three relatively recent developments in pediatric cardiac care have clearly had an important impact on improved patient outcome.

1. ABO-incompatible infant heart transplantation

Orthotopic heart transplantation has become an acceptable therapeutic option for infants and children with lethal forms of congenital heart disease or intractable life-threatening heart failure and recent experience has demonstrated improving results. The expected overall one-year survival after pediatric heart transplantation is approximately 85%, and, after the first year following transplantation, the mortality remains relatively constant at 2% per year. The availability of donor organs remains a significant limiting factor in adults, with the challenges facing organ donation being even more apparent in the pediatric population. Infants with lethal cardiac disease often die before transplantation because of this donor shortage which is compounded by problems with finding organs of compatible blood types and an appropriate size. Blood-group antigens are a major immunologic barrier to solid organ transplantation and the risk of hyper-acute rejection is a contraindication to transplantation between donors and recipients of incompatible blood groups. While the scarcity of donor organs has prompted the use of ABO-incompatible organs in liver and kidney transplantation with some degree of success, ABO-incompatible transplantation of the heart has, in the past, been performed only rarely as an inadvertent occurrence and with little success. The immunological response to heart transplantation is much different in newborn infants as compared to older children since they do not produce isohemagglutinins, and serum anti-A / anti-B titers usually remain quite low until 12 months of age. Accordingly, ABO-incompatible heart transplantation during early infancy has been demonstrated to be safe and effective and is now employed successfully by numerous institutions.

2. Pediatric mechanical assist devices

Mechanical circulatory support as a bridge to either recovery or transplantation has become standard therapy in pediatric cardiac surgery and is currently used routinely in most centers in the form of extracorporeal membrane oxygenation or ECMO. However, the numerous complications associated with ECMO poses limitations on the duration patients can be successfully supported that often exceeds the time required to find a suitable organ donor. Although ventricular assist devices (VADs) have been used very successfully as a long-term bridge to transplantation in adults, current VADs employed in North America are designed primarily for adult sized patients. Pediatric sized ventricular assist devices were introduced to clinical application in the early 1990's in Europe and have only recently been adopted for use in North America. These devices are applicable to patients with severe heart failure of different etiologies including cardiomyopathy, myocarditis and congenital heart disease and are available in sizes to accommodate patients ranging from newborn to adult age. Several improvements in device design along with management of anticoagulation and clinical decision making have resulted in a significant increase in survival especially in children less than one year of age. Pediatric patients are typically supported for periods of 7 - 8 weeks with early extubation and mobilization within the hospital setting. However, some children have been supported for over one year and can be discharged from hospital while waiting for a suitable donor organ or for native myocardial recovery to allow explantation of the device. Overall, current survival approaches 80% in a patient group that would otherwise likely face mortality rates in excess of 90%.

3. Atrioventricular valve assessment by 3D echocardiography

Normal atrioventricular valve function is complex and dependent on leaflet morphology, supporting apparatus, as well as annular dynamics which are directly influenced by ventricular function. Disturbances to any of these, either in isolation or in combination, can result in valve dysfunction. Although two-dimensional echocardiography provides useful information about atrioventricular valve morphology and function, it is not adequate to understand the more subtle anatomical alterations that result in valvular regurgitation. Three-dimensional echocardiography provides a more detailed understanding of valve structure and function and provides information that is particularly useful in the preoperative planning of atrioventricular repair in pediatric cardiac surgery. It is well established in the adult that successful atrioventricular valve reconstruction confers numerous advantages to valve replacement in terms of morbidity, lifestyle changes and, most importantly, early and late patient survival. These benefits are even more important in an active, growing pediatric patient in whom valve replacement may require lifelong attention to anticoagulation issues with mechanical valves or numerous re-operations with bioprosthetic valves. The ability to accurately assess the precise cause of valve regurgitation preoperatively and carefully plan the surgical repair outside the tense environment of the operating room likely increases the probability of achieving a successful valvular reconstruction.

Pediatric heart tumors

Introduction

Pediatric heart tumors are comprised primarily of non-neoplastic hamartomatous lesions. These include two lesions of cardiomyocyte derivation, namely rhabdomyoma and histiocytoid cardiomyopathy (sometimes designated Purkinje cell hamartoma). Cardiac fibroma is the most commonly excised pediatric tumor, is sometimes also found in adults, and like rhabdomyoma is likely not a true neoplasm. Germ cell tumors may involve the pericardium or, less commonly the myocardium, and are generally of the non-seminomatous type, most typically immature teratoma or yolk sac tumor. Mesenchymal proliferations of the myocardium, other than fibroma, are extremely rare in the pediatric age range. Embryonal rhabdomyosarcomas primary in the heart is a tumor of children and young adults; alveolar rhabdomyosarcoma may occur in the heart as a metastatic lesion. Recently, inflammatory myofibroblastic tumors have been described as originating from the endocardium. The precise nature (reactive / neoplastic) of cardiac IMFT remains undetermined.

Rhabdomyoma

Cardiac rhabdomyoma is highly associated with tuberous sclerosis complex (TSC). Two disease genes have been identified: TSC-1 at chromosome 9q34, and TSC-2 at chromosome 16p13. Over 50% of patients have sporadic mutations. The familial form of TSC exhibits autosomal dominant inheritance. The TSC-1 gene encodes hamartin, and TSC-2 tuberin, proteins involved in tumor suppression. Loss of heterozygosity is often found at the TSC-1 and TSC-2 loci in tumors from patients with tuberous sclerosis. The precise roles of TSC-1 and TSC-2 in the development of cardiac tumors and regulation of embryonic and neonatal cardiomyocyte growth remain to be elucidated. More than 50% of patients with tuberous sclerosis have cardiac hamartomas. Multiplicity of tumors is especially associated with TSC.

Rhabdomyomas are most commonly diagnosed tumor of the prenatal period by fetal echocardiography. Intrauterine as well as sudden death after birth has been attributed to them. Clinical and hemodynamic findings are related to the number, position, and size of tumors. Symptoms include those related to valve obstruction or occlusion of chamber cavities, arrhythmias, and fetal hydrops. The tumors may cause infant respiratory distress, congestive heart failure, or low cardiac output. Right-sided tumors that cause obstruction may cause cyanosis, or features suggestive of tetralogy of Fallot or pulmonary stenosis. Left-sided tumors may present as subaortic obstruction or hypoplastic left heart syndrome. They can be associated with structural cardiac defects.

Echocardiography is a sensitive modality for the diagnosis of rhabdomyomas and shows relatively homogeneous well-circumscribed echo-bright intramural or intracavitary masses that can be found virtually anywhere in the heart, but most commonly in the

ventricles. Cardiac MRI is reserved for selected patients in whom tumor type is questionable after echocardiography or when additional anatomical or functional information is required. Rhabdomyomas appear as well-circumscribed masses, usually in the ventricles but they can be found anywhere in the heart, with hyperintense signal on T1- and T2-weighted spin echo images. Compared with the signal from uninvolved myocardium, the masses are hypointense on post-gadolinium imaging. MRI is often used in patients with rhabdomyomas to evaluate the brain, liver, and kidneys for evidence of tuberous sclerosis.

Cardiac rhabdomyomas are well-demarcated nodules of enlarged cardiac myocytes with cleared cytoplasm. In some cells, strands of eosinophilic cytoplasm stretch from a central nucleus to the cell membrane giving rise to cells that resemble a spider (“spider cells”). The majority of cells show vacuolization with sparse myofilaments. There is a strong reaction with periodic acid-Schiff reagent, reflecting the glycogen content of rhabdomyoma cells.

Immunohistochemical studies document the striated muscle characteristics of rhabdomyoma cells, which express myoglobin, desmin, actin, and vimentin. Tumor cells do not express cell proliferation markers, indicating that the lesions are more likely hamartomas as opposed to neoplasms.

By electron microscopy, the cells resemble altered myocytes. They possess abundant glycogen, small and sparse mitochondria, and cellular junctions resembling intercalated disks surround the cell periphery. In contrast, the intercalated disks of differentiated myocytes are located exclusively at the poles of the cell. Intercalated discs and myofibrils or collections of Z band material are present.

Rhabdomyomas have a natural history of spontaneous regression, and many patients are followed with surgery. However, serious symptoms may precipitate the need for surgical resection. When arrhythmias are the presenting symptom, treatment with anti-arrhythmic drugs is commenced. If drugs fail to control arrhythmias, surgical resection is indicated.

Fibroma

Most cardiac fibromas are discovered in children and often before 1 year of age, but the upper range of age at presentation extends into late adulthood. Approximately 3% of patients with Gorlin syndrome have cardiac fibromas. Gorlin syndrome results from germline mutations in the PTC gene, which maps to chromosome 9q22.3 and is homologous to the *Drosophila* patched (*ptc*) gene.

Fibromas are generally single lesions and often cause symptoms necessitating surgical resection. The most common site of cardiac fibroma is the ventricular septum, but the free walls of the left and right ventricle are other common locations. Atrial fibromas are quite rare. Cardiac fibromas cause obstruction of blood flow, interference with valvular function, cause significant arrhythmias, syncope or sudden death. Magnetic resonance imaging shows the location, size, boundaries, and relations with adjacent structures, including the epicardial coronary arteries. On T1- and T2-weight standard or fast spin echo sequences cardiac fibroma appears as a well-defined, usually large, solitary intramyocardial mass with inhomogeneous signal intensity. Compared with the signal intensity of adjacent uninvolved myocardium, fibroma is slightly hypointense.

Gadolinium-enhanced MRA and first pass perfusion imaging demonstrate a hyperperfused tumor core that is readily distinguishable from the surrounding perfused myocardium.

Histologically, they resemble fibromatoses, with infiltrating margins. There are usually abundant elastic fibers. Cellularity may be quite marked in young infants, but usually decreases with age. Calcification is not uncommon.

Histiocytoid cardiomyopathy

Histiocytoid cardiomyopathy is a rare, arrhythmogenic disorder caused multifocal hamartomatous proliferation of cardiac cells with oncocytic features. The female:male ratio is 3:1. Approximately 5% of reported cases have occurred in families. Arrhythmias associated with histiocytoid cardiomyopathy include paroxysmal atrial tachycardia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, premature atrial contractions, premature ventricular contractions, Wolff-Parkinson-White syndrome, and right or left bundle branch block. Extracardiac anomalies occur in 17% of patients. The cause of death may be presumed SIDS until histologic evaluation of myocardial tissue is performed. Pathologically, there are typically subendocardial yellow-tan nodules or plaques. They can also be seen in the inner myocardium and subepicardial areas. The lesions may be grossly difficult to identify, but there is generally a subtle color difference separating the lesion from normal myocardium. The histologic findings are pathognomonic, with nests of foamy-appearing myocytes resembling macrophages.

For patients that are diagnosed pre-mortem, electrophysiological mapping is indicated if anti-arrhythmics are ineffective in ablating arrhythmias and allowing regression of the lesions. Treatment includes surgical excision or direct-vision cryo-ablation of the multiple small nodular tumors. Surgical intervention, electrophysiological mapping, and ablation of the arrhythmogenic foci result in a survival rate of approximately 80%. Rare patients have been treated with heart transplantation.

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumors (IMFTs) are proliferations of uncertain histogenesis, which vary in appearance from inflammatory, reactive-appearing proliferations to low-grade sarcomas. There is probably organ-specific variation in the histologic characteristics of IMFT. In the heart, they invariably arise from the endocardium, are variably cellular, but usually have abundant myxoid matrix and surface fibrin. Most lesions designated IMFT in the heart are likely non-neoplastic. However, embolic symptoms and sudden death from coronary occlusion may occur.

We have recently reported a series of cardiac IMFT-like lesions seen in consultation (see table).

Cardiac IMFT

#	Age, years	Sex	Race	Symptom	Previous medical history	Endocardial location	Other cardiac findings	Tumor maximal dimension, cm	Follow-up
1	5 weeks	M	Caucasian	Shortness of breath	None provided	Right atrium	None	6	Not available
2	2	F	Caucasian	Recurrent seizures	Seizures, recurrent cerebral infarcts (embolic)	MV anterior leaflet extending to the LV wall	None	4	Died 2 years
3	5	F	Caucasian	Right sided hemiplegia, seizure	None	MV, extending to LV wall	None	3	Not available
4	6	F	Caucasian	Syncope	Recent myocardial infarction of LV wall and IVS	MV at junction of posterior and medial leaflets extending down chordae tendineae of anterior papillary muscle	None	3	Explant
5	8	M	Caucasian	Chest pain/dyspnea=> Sudden death	None provided	Left coronary sinus with occlusion of LAD and LCA, and obstruction of R coronary ostium	Anomalous LCA arising from proximal RCA	2.5	Death
6	10	M	Hispanic	Heart murmur	None provided	Right ventricular outflow tract	None	1.5	Not available
7	12	M	None provided	Transient ischemic attack	None provided	Right ventricle	None	6.0	Not available
8	17	F	Hispanic	Incidental murmur, sports physical	None	Right ventricle, involving tricuspid valve	None	5.0	Not available
9	19	F	Not provided	Fever, myalgias (6 months)	None provided	Thin pedicle from the LV free wall	None	3.2	NED, 6 years, 9 months
10	21	F	Not provided	Fatigue, dyspnea (1 1/2 months)	Pulmonary hypertension	Interventricular septum in the right outflow tract extending to the pulmonic valve	Enlarged right atrium, moderate tricuspid regurgitation, moderate pericardial effusion	4.0	NED, 11 years

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