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Pulmonary Atresia or Persistent Truncus Arteriosus: Is It Important to Make the Distinction and How Do We Do It?

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The congenital cardiac anomaly known as tetralogy of Fallot (TOF) is characterized by right ventricular outflow tract obstruction caused by subpulmonary stenosis, dextroposition (overriding) of the aorta, a ventricular septal defect, and right ventricular hypertrophy. The right ventricular hypertrophy is secondary to the presence of right ventricular outflow obstruction (pulmonic valvar or subvalvar stenosis or in the most severe case, atresia). Cyanosis in these patients is due to the passage of systemic venous blood into the aorta, bypassing the lungs, with the degree of cyanosis dependent on the severity of the outflow tract obstruction. The malformations that are classified as persistent truncus arteriosus (PTA) are characterized by a single multicuspid semilunar valve with a single vessel, the truncus, arising from the ventricles and giving rise to systemic, pulmonary and coronary circulations. Thus both PTA and TOF with pulmonary atresia are characterized by a single vessel emanating from the heart. In PTA the septation that would divide the common arterial trunk into an aorta and pulmonary trunk is missing, while in TOF with pulmonary atresia, it is unclear whether this septation is missing or misplaced. Diagnosis of TOF with pulmonary atresia relies on the presence of a pulmonary valve remnant by clinical imaging. This criterion permits differentiation of TOF with pulmonary atresia and PTA. However, if the pulmonary atresia develops embryonically before a valve is formed, then this criterion would not distinguish PTA from TOF with pulmonary atresia. New findings in experimental mouse models by Théveniau-Ruissy et al. reported recently in Circulation Research shed unexpected light on the embryogenesis of these defects and may allow differentiation of the two defects in ways that have not been used previously.[1]

The myocardium and smooth muscle at the arterial pole, that is the subaortic and subpulmonary myocardium and the smooth muscle at the base of the aortic and pulmonary arterial trunks is added from a specific region of the ventral pharyngeal mesoderm caudal to the attachment point of the outflow tract with the pharynx that has been called secondary heart field [2,3]. The secondary heart field contains the progenitors of both the myocardium and smooth muscle of the arterial pole and ablation of this region has been shown to result in pulmonary stenosis/atresia with overriding aorta [4]. This implicates secondary heart field as the defining cell population associated with pulmonary stenosis/atresia. Other experimental causes of

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pulmonary stenosis/atresia are associated with decreased proliferation in this field of progenitors. Decreased proliferation is experimentally associated with decreased FGF signaling.[5] Tbx1- null mice also have decreased proliferation in the secondary heart field and this is associated with TOF [5,6].

Papers from Margaret Buckingham's group in the last 3 years have shown that myocardium originating from this region has unique aortic and pulmonary identity well before septation of the outflow tract. This group has identified two separate loci that specifically express a lacZ reporter in outflow myocardium in what will become the subaortic and subpulmonary myocardium. The first report used the y96-Myf5-nlacZ-16 (96-16) transgene that marks the pulmonary aspect of the outflow myocardium. The paper confirmed rotation of the outflow tract using DiI injection. They were also able to show that the outflow failed to rotate in Splotch, Pitx2δc mutants with persistent truncus or double outlet right ventricle or transposition of the great arteries [7]. A second paper from this group showed another transgene A17-Myf5-nlacZ-T55 (T55) which is expressed in the outflow myocardium in a pattern complementary to 96-16 and continues development as the subaortic myocardium. The two myocardial populations represented by the 96-16 (subpulmonary) and T55 (subaortic) appear from a clonal analysis to arise from distinct precursor populations [8].

The article by Théveniau-Ruissy et al. identifies the gene that is represented by the 96-16 transgenic as Semaphorin3c (Sema3C).[1] Sema3c, a secreted growth factor associated with axonal pathfinding and angiogenesis and has been reported previously to be expressed in the outflow myocardium, although not specifically identified as subpulmonary myocardium. Sema3C mutant mice have cardiovascular defects that include conotruncal malformations although these are, sadly, not well described.[9] Plexins are the receptors for semaphorins and PlexinA2 is expressed by neural crest cells. In Sema3C null embryos distribution of the plexinA2 expressing neural crest cells in the outflow tract is altered but the cells are present in the outflow tract [9]. Further, cardiac neural crest form the outflow septation complex abnormally although this is also not well described. Data from the two published papers suggest that semaphorin or the semaphorin-expressing myocardium in the outflow tract are important for neural crest to set up a normal outflow septation complex.[10] The mutant embryos for the most part have double outlet right ventricle. While some had a single outflow that was described as PTA, the hearts were not analyzed thoroughly enough to distinguish PTA from pulmonary atresia [10].

Microdeletion of chromosome 22q11.2 is associated with DiGeorge and Velocardiofacial syndromes which include conotruncal malformations. The most commonly associated conotruncal phenotype is TOF. TBX1, a T-box transcription factor is located in this interval and is thought be a primary cause of the phenotype. However, to date, only five different point mutations in TBX1 have been reported in association with the DiGeorge/Velocardiofacial features. In the three original patients described 2/3 had TOF while 1/3 had VSD and interrupted arch [11]. The mutations described in the five patients produce either loss- or gain-of-function suggesting that the same or similar phenotype is produced by either condition (Zweier et al., 2007). This is supported by the fact that there is little phenotypic variability in a knockout mouse model of *tbx1*, while reducing mRNA level to 20% of normal recapitulates the human phenotype more accurately [12]. Even so, it appears that *tbx1* is an excellent gene to study in pathogenesis of the DiGeorge/Velocardiofacial phenotype.

To this end, using the T55 transgene (subaortic myocardial identity) Theveniau-Ruissy et al. showed that the ventricular outlet in the *tbx1*-null mouse has a predominantly subaortic identity suggesting a severe reduction of the 96-16 (subpulmonary myocardium) or a conversion of this myocardium to a subaortic identity.[1] While the authors describe the phenotype as PTA, this may be debatable. Because *tbx1*-null mice have dramatically reduced proliferation of the

myocardial outflow progenitors in the secondary heart field, this suggests that there is a reduction in subpulmonary myocardium rather than conversion of subaortic to subpulmonary myocardium [6]. Two other features support this conclusion. The first is the presence of a single outflow valve with three leaflets and the second is that the outflow channel is closer to the size of a normal aorta than an undivided arterial trunk.

As mentioned in the introduction, PTA is characterized by a single vessel that leaves the base of the heart. In 69% of patients diagnosed with PTA the truncal valve is tricuspid while it is described as quadricuspid in only 22% [13, 14]). This is interesting because embryologically it would be difficult to get a tricuspid valve without division of the outflow cushions that are normally four in number. The diagnosis of PTA is made because no second atretic semilunar valve is present [15]. In the article by Théveniau-Ruissy et al., however, no atretic valve is present, but because of the missing subpulmonary myocardium, this situation may represent pulmonary atresia rather than PTA. Furthermore, the single arterial trunk in PTA has biventricular origin in 68-83% of patients while in 11-29% of patients the common trunk arises entirely from the right ventricle[14]. The correlation of tricuspid truncal valves with biventricular origin of the arterial trunk is intriguing. In virtually all the animal models of PTA, the arterial trunk arises from the right ventricle.

To summarize these comments, the diagnosis of PTA and pulmonary atresia in patients has used criteria that may not have recognized variants of pulmonary atresia beyond an atretic pulmonary valve. If the subpulmonary myocardium never grows into the heart as in the case shown by Theveniau-Ruissy et al., the outflow tract and right ventricle would lack this tissue from very early and not have a chance to form a pulmonary outlet. Because septation of the arterial pole requires an entirely different developmental process involving neural crest cells which appear to be guided by the junction of the subpulmonary and subaortic myocardium, it is possible that septation is present, albeit in the wrong place because of the reduction in the subpulmonary myocardium. This implies an altogether different embryogenesis of PTA (a septation problem) and pulmonary atresia (a problem with development of the subpulmonary myocardium). Even though the clinical treatment of the two types of patients is the same, in order to ultimately understand the genetic and epigenetic causes of the two defects requires that the criteria for diagnosis be reevaluated.

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