

Topic 10 – Pediatric and congenital heart disease

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Congenital heart defects in twin pregnancies: a series of 226 cases

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Background: The relative risk for congenital heart defects (CHD) is increased in monozygotic twins. The respective contribution of genetics of cardiac development and environmental risk factors such as twinning per se are scarcely known.

Aim: To analyze CHDs in twin pregnancies in which one or two foetuses were diagnosed to have a CHD and to identify the role of chorionicity and amnionity on CHD type and concordance between twins.

Methods: Over a period of 16 years, 226 twin pregnancies with one or two foetuses having a CHD were reviewed. Chorionicity, amnionity, presence of twin-twin transfusion syndrome (TTTS), cardiac phenotypes, anatomical/CHD type (7 groups of CHD), concordance between twins and outcomes were analyzed.

Results: Pregnancies were bichorionic-biamniotic (BCBA) in 103 cases and monozygotic in 112 (biamniotic 92-MCBA, monoamniotic 20-MCMA) and the remaining 11 were unknown. Overall the 2 foetuses were affected in 35 cases (15.4%) with the two CHDs belonging to the same group in 23 (65.7%). The two foetuses had a CHD in 35% of MCMA, 14.1% of MCBA and in 10.7% of BCBA. The most frequent defects were conotruncal defects (n=71) with concordance in 13/71 (8/20 MCBA, 3/5 MCMA). For other groups concordance in all pregnancies, in MCBA and in MCMA were respectively: right outflow tract obstructions 5/48, 0/33, 0/0; obstructive left heart diseases 7/42, 2/13, 1/1; laterality defects 2/36, 0/6, 2/12; ventricular septal defects 5/19, 1/9, 0/0; atrioventricular septal defects 3/9, 1/2, 0/0; functionally univentricular heart 1/15, 0/5, 0/1. MCBA pregnancies were more frequent in right outflow tract obstructions (33/48; 69% – $p<0.01$) and discordance between twins was constant (pulmonary stenosis in the recipient twin) and was associated with proven TTTS in 22/33. MCMA were more frequent in laterality defects (12/36; 33%– $p<0.01$) and discordance between twin of was observed in 10/12.

Conclusion: Concordance for CHD between twins is low even in monozygotic (certainly monozygotic) twins. Discordance in monozygotic twins might be related to twinning per se for laterality defects in MCMA and pulmonary stenosis in MCBA-TTTS.

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Anatomy and position of the coronary orifices on the aortic/truncal circumference in cardiac outflow tract defects: a marker of outflow tract rotation.

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Background: Coronary arterial anatomy is often abnormal in cardiac outflow tract defects (OTD), particularly in common arterial trunk (CAT). Our hypothesis is that the position of the coronary orifices on the aortic/truncal circumference in OTD could be related to the location of a coronary-repulsive subpulmonary myocardial domain (SPD) that influences the epicardial course of the main stems and their final connection to the aorta.

Material: We analyzed 101 heart specimens with OTD from the anatomic collection of the French Reference Center for complex congenital heart defects: 46 CAT, 15 tetralogy of Fallot (TOF), 29 TOF with pulmonary atresia (TOF-PA), 11 double-outlet right ventricle with subaortic ventricular septal defect (DORV), and 17 controls.

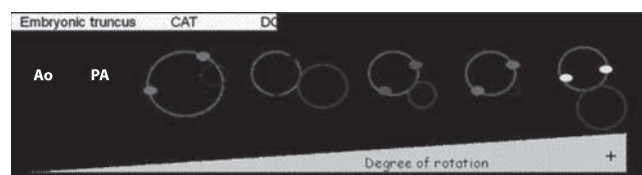
Methods: Hearts were analyzed in anatomic position with the extremities of the right and left atria on the intersecting line of a horizontal and vertical plane. The position of left and right coronary orifices (LCO, RCO) was measured in degrees on the aortic/truncal circumference. We calculated the anterior angle between LCO and RCO (α) that represents the area devoid of coronary orifices.

Results: The LCO was more posterior in OTD compared to control, mean position 0° in controls, 31° in TOF, 47° in TOF-PA, 44° in DORV, 63° in CAT ($p<0.005$). The LCO was more posterior in CAT than in other OTD ($p<0.05$).

The RCO was more anterior in TOF (242°), TOF-PA (245°) and DORV (271°) than in controls (213°, $p<0.05$), but not in CAT (195°).

The α angle was similar in TOF, TOF-PA, DORV and control (respectively 149°, 162°, 133° and 147°) but significantly larger in CAT (229°, $p<0.0001$).

Conclusion: In all OTD but CAT, the posterior displacement of LCO and anterior displacement of RCO, while the α angle remains constant, might be due to incomplete rotation of the myocardium at the base of the outflow tract, leading to abnormally positioned SPD. The larger α angle in CAT could reflect its dual identity, aortic and pulmonary.



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Clinical presentation and long-term clinical outcomes of non immune, isolated atrioventricular block diagnosed in utero or early childhood.

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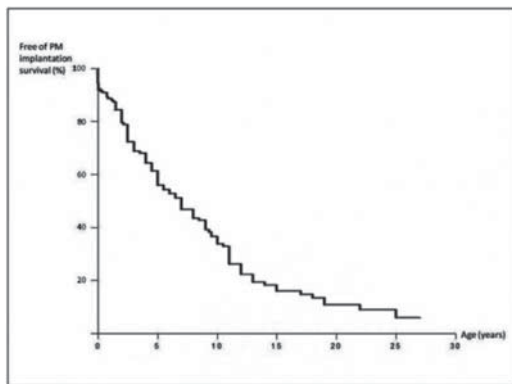
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Purpose: The natural history of congenital or childhood, isolated, non-immune atrioventricular (AV) block is poorly known.

Methods: We retrospectively studied 141 children with isolated, non-immune AV block diagnosed in utero, or up to 15 years of age, at 13 French medical centers, between 1980 and 2009. Patients with structural heart disease or maternal antibodies were excluded.

Results: AV block was asymptomatic in 119 (84.4%) and complete in 100 (70.9%) patients. Incomplete AV block progressed to complete in 29 (70.7%) patients with incomplete block over 2.8 ± 3.4 years (1-155 months). Narrow QRS complex was present in 18 of 26 patients (69.2%) with congenital, and 106 of 115 (92.2%) with childhood AV block. Pacemakers were implanted in 112 children (79.4%), during the first year of life in 18 (16.1%) and before 10 years of age in 90 (80.4%). The mean delay between diagnosis of AVB and pacemaker implants was 2.6 ± 3.9 years (0-300 months). The pacing indication was prophylactic in 70 children (62.5%). During a median follow-up of 11.6 ± 6.7 years (1-32 years), no patient died or developed dilated cardiomyopathy. The long-term follow-up was uncomplicated in 127 children (90.1%).

Conclusions: In this large multicenter study, the long-term outcome of congenital or childhood, isolated, non-immune AV block was favorable, regardless of the patient's age at the time of diagnosis. No patient died or developed dilated cardiomyopathy, and pacemaker-related complications were few. The progression of incomplete to complete AV block in nearly 70% of patients suggests a postnatal degeneration of the specialized conduction system.



Actuarial survival free from pacemaker implantation

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Cardiac progenitors issued from human embryonic stem cells: a novel therapeutic agent in right ventricular dysfunction secondary to congenital heart diseases?

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Right ventricular (RV) failure is a major long-term complication of congenital heart disease, leading to morbidity and mortality. Since conventional therapy gives poor results, cell therapy may be a therapeutic option for cardiac repair. The ability of embryonic stem cells (ESC) differentiation towards a cardiomyogenic phenotype makes them attractive candidates. Our aim was to evaluate, in a large animal model, the effects of cardiac-committed human ESC transplantation on the RV function.

A model of RV dysfunction was created in 8 piglets using a surgical procedure mimicking RV tract sequelae of repaired tetralogy of Fallot leading, after 4 months, to a chronic combined RV overload. Four pigs received vehicle and 4 others received HUES-24 derived human cardiac progenitor cells injected at multiple sites into the free wall of RV myocardium. All pigs were immunosuppressed using tacrolimus. Myocardial function was measured 3 months after cell transplantation by conductance catheter technique using maximal elastance (E_{max}) slope and ventricular energetics (stroke work, pressure-volume area). The risk of ventricular arrhythmia was evaluated by programmed ventricular stimulation at the end of the follow-up. Structural remodelling was assessed by histological examination.

All pigs survived and no complication occurred related to either myocardial injections or immunosuppression. No ventricular arrhythmia was induced. In all treated pigs, myocardial contractility was improved as assessed by an increasing E_{max} slope relative to controls at the follow-up end (0.58 ± 0.03 vs 0.40 ± 0.08 , $p < 0.05$) whereas stroke work was similar in both groups. Improvement of contractility in treated pigs occurred without increasing of pressure-volume area suggesting that the myocardium is more efficient. In treated pigs, myocardial fibrosis appeared peritrabecular whereas, in controls, it was found in peritrabecular and perimyocyte areas.

Cell therapy by multiple trans-epicardial injections of ESC derived human cardiac progenitor cells in failed RV is feasible, improves RV myocardial contractility and allows a better adaptation to chronic overload.

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Clinical outcome and therapeutic strategies in non proband children with genetically confirmed LQTS

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Introduction: Congenital long QT syndrome (LQTS) is a frequent cause of sudden cardiac death in children without structural heart disease. Given the recent progress in molecular diagnosis, a growing portion of LQTS patients is genetically affected but still asymptomatic. Their clinical outcome has not been clearly evaluated, and their optimal treatment is still discussed.

Methods: Our database was searched for all patients with genotyped LQTS, identified by familial screening and aged 16 or less at diagnosis. We retrospectively recorded demographic and electrocardiographic data, personal and family histories and genetic diagnoses.

Results: 90 non proband children with genetically confirmed LQTS were included. Mean age at diagnosis was 7.3 ± 5.2 years, and mean follow-up duration was 4.6 ± 4.3 years. 7 (7.8%) were symptomatic before diagnosis, and 4 (4.4%) experienced LQTS-related symptoms during follow-up. No sudden cardiac death was reported. One LQT1 patient presented aborted cardiac arrest while swimming. Beta-blocker therapy was initiated in 51 patients (56.7%). Device therapy was infrequently used (one pacemaker, no implantable cardioverter defibrillator). Corrected QT interval (QTc) was the only factor correlated to the risk of LQTS-related symptom ($p=0.02$). Initiation of betablocker therapy was associated with mutations in KCNQ1 or KCNH2 ($p < 0.01$), family history of LQTS-related cardiac event in a first-degree relative ($p=0.02$), diagnosis before four months of age ($p=0.01$) and a longer QTc ($p=0.0016$).

Conclusion: Clinical outcome is favorable in genetically confirmed non proband LQTS children, and similar to what has been previously described despite less frequent use of beta blocker and device therapies. Thus, beta blocker therapy should probably not be initiated systematically in such patients, especially when QTc duration does not exceed 460 ms. ICD implantation does not seem mandatory in non proband LQT3 children, at least in their first years of life.

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Optimal dosing of warfarin in a pediatric cohort: height, INR range, VKORC1 and CYP2C9 genotypes are the main contributors of the dose requirement

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Background: Managing vitamine K antagonist (VKA) therapy is challenging especially in children because of a narrow therapeutic range and a