



## HEMODYNAMICS IN CHD Report Summary

Project reference: 276987

Funded under: FP7-PEOPLE

Country: Turkey

### Periodic Report Summary - HEMODYNAMICS IN CHD (Mechanical regulation of congenital heart defects)

This project focuses on an important health problem, congenital heart defects (CHD). CHD refers to the variety of defects in the heart at birth. This health condition affects almost 1 % of the population, deteriorating the life expectancy and life quality of the patients and burdening excessive economic costs to countries. Current treatment strategies of many severe CHD types are based on correcting the blood circulation via high-risk operations during early childhood on an already developed heart. An alternative approach are the interventions on the abnormally developing heart during pregnancy or shortly after birth while the defect has not fully developed. The motivation here is the fact that, during development, the heart has the capability to remodel itself under increased / decreased loads. In order to develop effective approaches of that type, the factors affecting the embryonic development of CHD need to be clearly understood.

Despite excessive research attempts, the majority of CHD types cannot be linked to genetic mutations. On the other hand, since most CHD are related to heart valve problems and heart valves are structures ensuring unidirectional blood flow through the heart, it is widely accepted that abnormal hemodynamics (i.e. blood flow related forces) during heart development are a major source for CHD. Experimental studies on animal embryos can help to identify biological mechanisms affecting abnormal heart development driven by abnormal hemodynamics and test possible rescue strategies.

Chicken embryos have been widely used to study progression of CHD because of the similarity of chicken cardiac development with human cardiac development, ease of maintenance, ease of surgical interference and ease of visualisation of the heart. In this project, clinical relevant heart defects are created in chicken embryonic hearts during early heart development and subsequent abnormal development is investigated. As in human, chicken hearts are composed of four chambers (left / right atrias and left / right ventricles) and there are two atrioventricular (AV) and two outflow tract (OFT) valves in these hearts. Again as in human, left side of chicken heart works in systemic circulation and right side works in pulmonary circulation (two pump systems working in parallel). In most CHD cases, blood flow and morphology of structures are abnormal in either only left or in only right side of the heart. Therefore, the context of the current study was determined to disturb blood flow on either left or on right side of the heart at early stages of heart development, and then to quantify morphological (chamber sizes, valve sizes etc.) abnormalities while highlighting the hemodynamic environment via computational fluid dynamic (CFD) methods. The results hoped for are the correlations of characteristics of altered hemodynamics with morphological abnormalities. This information will be important to understand the progression of CHD and to come up with logical treatment strategies to restore these defects. Hemodynamic abnormality is created by either constricting the blood flow on the left (systemic side) or on the right side (pulmonary side) of the embryonic heart at early developmental stages. Two experimental techniques are used for this purpose: left atrial ligation (LAL) and right atrial ligation (RAL).

For LAL, a knot is tied at left atria of chicken embryos at embryonic day (ED) 4. At that stage, heart has not fully septated into left and right sections. Previous studies have shown that LAL at ED4, result in severely underdeveloped left ventricle and AV valves at ED10, when heart septation into left and right has been completed. Since these defects are characteristics of hypoplastic left heart syndrome (HLHS), phenotypes created via LAL are accepted as embryonic animal model of HLHS. Therefore, once the hemodynamic environment inside LAL performed chicken embryonic hearts is investigated, the progression of HLHS and similar left heart defects can be better understood. Similarly, for RAL, a knot is tied at right atria of chicken embryos at ED 5. At that stage, the heart has not fully septated into left and right sections. RAL is a technique that was recently developed by the investigator. Therefore, the obtained results will be first and important to show the progression of the defects in the right side of the heart.

The methodology to study effects of these defects on heart development is based on revealing hemodynamic alterations and morphological alterations and finding out the correlations between these two. Hemodynamics is studied by analysing B-mode and Doppler ultrasound images as well as generating CFD models. Heart morphology is studied by analysing 3D geometries generated by micro computed tomography (micro-CT). Ultrasound images are recorded right after the procedure (at ED4 for LAL and at ED5 for RAL) on an unseptated heart at the AV valve and OFT valve regions (unseptated heart, only one AV and one OFT valve) to see immediate changes in hemodynamics via flow constrictions. At ED7 when heart has septated into left and right sections, ultrasound images are again gathered on septated hearts at left / right AV canals and left / right OFTs. Similarly, 3D geometries are obtained via micro-CT right after the procedures (at ED4 for LAL and at ED5 for RAL) and at ED7. From ultrasound recordings, parameters to quantify hemodynamics and cardiac performance can be calculated. In this study, these parameters are determined to be peak velocity through valve, and average velocity through valve. Peak velocity levels help to determine changes in shear stress levels whereas average velocity levels help to determine changes in cardiac work. From the geometries generated via micro-CT, morphological abnormalities are determined. Here, sizes ratio of ventricle volumes and size ratios of AV valves are determined. The micro-CT geometries together with the flow profiles through valve sections will later be used to generate computational models of blood flow through AV and OFT valves.

After analysing ultrasound and micro-CT data, we found that, LAL results in an immediate decrease in shear stress in AV canal while keeping the cardiac work same. Left side of the heart eventually remodels (left AV valve and left ventricle underdevelops) under decreased shear stress while keeping cardiac work same. Right side of the heart is not affected from LAL. On the other hand, RAL does not cause an immediate change in shear stress levels and cardiac work. However, when heart is septated, shear stress levels and cardiac work is decreased in right side but not on the left side. Right AV valve but not RV remodels under disturbed flow. Left side is not affected from RAL. These results are important to show different remodelling for left and right side of the hearts under disturbed flows. CFD models that will be generated in the following term will highlight the hemodynamic environments and will enable to calculate shear stress levels for these models.

Once this project is completed, for the first time, a systematic approach to study CHD originating blood flow abnormalities on the left side or the right side of the heart will have been developed. The methodology to study mechanical signals that can trigger heart defects will hopefully be used by other researchers in the European Union (EU). Also, since the progression of congenital defects will be better understood, novel therapeutic approaches will be able to be developed in the future.

The results from this study are announced via the project website: [http://staff.dogus.edu.tr/cagatayyalcin/?page\\_id=33](http://staff.dogus.edu.tr/cagatayyalcin/?page_id=33)

## Related information

### Result In Brief

- [Resolution of congenital heart defects](#)

### Documents and Publications

- [Periodic Report - HEMODYNAMICS IN CHD \(Mechanical regulation of congenital heart defects\)](#)

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**Last updated on** 2013-08-14

**Retrieved on** 2014-09-26

**Permalink:** [http://cordis.europa.eu/result/rcn/57794\\_en.html](http://cordis.europa.eu/result/rcn/57794_en.html)

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