**GEORGE EMIL PALADE UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU MUREȘ**

**SCHOOL OF DOCTORAL STUDIES**

**-SUMMARY OF PHD THESIS-**

**Title:** Non-invasive determination of liver fibrosis in children with Glenn and Fontan operation

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**Introduction:**

Cyanogenic congenital heart malformations with single ventricle physiology represent one of the most complex and serious congenital heart conditions. Without surgical intervention, children with this type of malformation die in infancy. The discovery and use of staged palliative operations: in the first stage the systemic-pulmonary shunt or the Noorwood procedure, later the Glenn operation and the last step represented by the Fontan operation allowed these children to survive to adulthood. Along with the constant improvement of surgical techniques as well as pediatric cardiology and intensive care, the life expectancy of these children has progressively increased and the adverse effects of hemodynamic changes secondary to operations have become more and more evident. Survivors of the Fontan operation develop important complications over time, including: liver fibrosis (ranging from mild fibrosis to cirrhosis and hepatocellular carcinoma), plastic bronchitis, arrhythmias or renal failure. Biopsy is currently the gold standard for diagnosing liver fibrosis. However, the procedure can have numerous complications so that its use is limited, especially in the pediatric population. Considering the limitations of biopsy, in recent years certain non-invasive methods have been developed for the diagnosis of fibrosis, which are divided into imaging methods and serological methods.

**Objectives:**

The first study included 42 children, 21 patients with Glenn surgery and 21 healthy children included in the control group. The second study included 26 children, 13 Fontan patients and 13 healthy children.

The objectives of the two studies were the following:

- Determination of structural liver damage and signs of portal hypertension using abdominal ultrasound in patients with Glenn or Fontan surgery
- Determination of liver fibrosis in patients with Glenn and Fontan surgery by means of transient elastography and shearwave
- Determination of liver damage in patients with Glenn and Fontan operation by means of standard laboratory analyses
- Quantification of liver fibrosis and inflammation using serum biomarkers of fibrosis in Glenn and Fontan patients
- Correlation of elastography values with those of standard analyzes and serum biomarkers of liver fibrosis

**General methodology:**

The studies described in this paper were conducted prospectively and included pediatric patients (0-18 years) with Glenn or Fontan surgery admitted to the Pediatric Clinic I, Târgu-Mureș County Emergency Clinical Hospital and the Cardiology III Children's Clinic within the Institute of Cardiovascular Diseases and Transplant Târgu-Mureş between January 2019 and March 2022 as well as healthy children who were included in the control groups. After the inclusion of the patients in the groups, we performed a clinical examination with the determination of weight, height, body mass index and oxygen saturation. Medical records were reviewed and relevant demographic, anatomical, surgical, clinical and echocardiographic data were extracted. Later, laboratory analyses, abdominal ultrasound and liver elastography were performed on all patients. Laboratory analyzes and clinical data were used to determine biochemical liver fibrosis scores (Fibrotest, Actitest, APRI and FIB-4).

**Results:**

Glenn patients did not show significantly increased values of liver stiffness compared to the control group. In contrast, FibroTest, ActiTest and APRI fibrosis biomarkers were significantly higher in the Glenn group. In patients with Glenn surgery, we obtained a negative correlation between the post-operative time interval and liver stiffness values obtained by transient elastography.

Using shearwave and transient elastography, we obtained significantly increased liver stiffness values in Fontan patients compared to the Control group. Liver stiffness values determined by transient elastography were much higher than those determined by shearwave elastography. The values of liver stiffness were positively correlated with the time interval after Fontan operation and the values of transaminases and serum markers of liver fibrosis FibroTest, ActiTest and APRI were significantly higher in the Fontan group compared to the control group.

**General conclusions:**

Patients with a single ventricle physiology develop liver damage from the Glenn stage of palliation, demonstrated by the increased values of FibroTest, ActiTest and APRI serum fibrosis biomarkers. In patients with Glenn surgery, we obtained positive correlations between FibroTest, FIB-4 and the time interval after surgery indicating that the delay in performing the Fontan operation also leads to liver damage, possibly through prolonged hypoxia. This conclusion is also supported by the positive correlation between the age at the time of the Fontan operation and FibroTest, FIB-4, α-2-macroglobulin and GGT, respectively the liver stiffness values determined by transient elastography. Perioperative liver injury may increase the values of elastographic measurements, a fact suggested by the negative correlations of liver stiffness determined by transient elastography with the Glenn post-operative time interval.
Patients with Fontan operation showed increased values of liver stiffness compared to the healthy controls. Elastographic measurements can be altered by congestion so that changes in stiffness values over time in hemodynamically stable patients can provide clues to the progression of fibrosis. FibroTest and APRI fibrosis biomarker values were significantly higher in the Fontan population compared to the control group, suggesting the presence of fibrosis in this population. Transaminases and ActiTest values were also elevated, indicating increased necroinflammatory activity.

**Originality of the thesis:**

This work is the first in Romania in which liver disease was investigated in a population of patients with Fontan and Glenn surgery. Complex congenital cardiac malformations with single ventricle physiology are rare, extremely serious pathologies, and Glenn and Fontan palliative operations are complicated procedures, performed for only a few years in our country. The interdisciplinary character, on the border between two developing specialties - gastroenterology and pediatric cardiology, also gives originality to this thesis. Both studies described in this thesis are original due to the age of the population evaluated. Thus, these are among the few studies evaluating liver status in children with Fontan and Glenn operations using noninvasive markers and elastography. The observation that liver damage in single-ventricle patients may precede Fontan surgery has only recently been published, so Study 1, conducted in Glenn patients, is among the few conducted in this population. It is also the only study that investigated the role of FibroTest-ActiTest for the diagnosis of liver fibrosis and necroinflammatory activity in these patients. The study of liver stiffness in a group of children with Glenn surgery is the first of its kind in the literature to use two elastographic techniques, shearwave and transient elastography. The study on the group of children with Fontan operation also used both elastographic techniques, only one such study being published in the literature.