Relevance of the Cardiac Biomarkers in Children with Heart Disease Admitted for Severe Cardiac Pathology

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Heart disease in children can be congenital or acquired. Most congenital heart malformations have specific hemodynamics, producing either volume overload, pressure overload or both, that will finally determine myocardial cell damage, with complications like heart failure and sometime severe pulmonary hypertension. The understanding and management of pediatric patients with heart disease is mandatory in order to have the ability to influence the outcome. Cardiovascular biomarkers play a vital role in adult cardiology, influencing both the diagnosis and the prognostic, however there is still a gap in the pediatric field. We decided to study the relevance of cardiac biomarkers as: NT proBNP, Troponin T and hs-CRP, in the diagnosis and follow up of the pediatric patients with heart disease admitted for severe acute/chronic symptomes or patology, hoping that in future, cardiac biomarkers will be current used in the assessment of children with heart disease.

Keywords: biomarkers, Troponin, NT-proBNP, hs-CRP, heart disease, children

Biomarkers are characteristics of a biological state that can be used as indicators. The name of biomarkers comes from biological markers and it is an acronym. The Biomarkers Definitions Working Group of the National Institutes of Health defined biomarkers in 1998 as *a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*. [1] The WHO International Programme on Chemical Safety came with a new definition of biomarkers in 2001 *any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease* [2]. These substances can be molecules, proteins that are released into the body after an injury, at wich point the value of biomarkers increase with the pathological process and then return to normal when the injury stops. It seems to be a strong relation between biomarkers and outcome, influenced by medication [3]. A valid biomarker has to be measured rapidly, easy, even at the bedside, to be non-invasive and must to be very accurate, sensitive, specific and reproducible.

A large number of biomarkers have been studied in adult cardiology and became indications to be followed in the guidelines. The Guideline for the diagnosis of acute myocardial infarction included Troponin as a preferred biomarker. A high sensitive (hs) Troponin assay was developed to detect myocardial injury. Soon after, the interest for the implication of biomarkers in pediatric cardiology peaked. The *test of time* was won by three cardiac biomarkers: NT proBNP, high sensitive Troponin and hs-CRP. The problem with the biomarkers was to define the cutoff values, because, in children, they have to be age related and are still unvalidated. The problem is that different studies reported varied biomarker cutoff values. Therefore we chose to tackle the three most used cardiac biomarkers involved in pediatric cardiology.

Experimental part

Cardiac biomarkers in pediatric patients are not usual investigations, but when regarding the data from the literature, they are very important parameters that can reflect myocardial dysfunction, even in subclinical occurrence. The aim of our experimental study was to investigate the relevance of cardiac biomarkers in children with heart disease (congenital or acquired, complicated with heart failure and/or pulmonary arterial hypertension), who were usually admitted in the emergency room and to document the utility of this investigation, knowing the importance of cardiac biomarkers in adult heart disease, especially with acute presentation. The exclusion criteria were: children with congenital heart disease without complications, premature and neonates with patent ductus arteriosus (PDA), children with hypertension and children from the oncology department treated with anthracyclines.

Experimental part

Material and methods

The retrospective study included 30 patients with cardiac pathology, congenital heart disease complicated with heart failure and/or pulmonary arterial hypertension, and acquired heart disease, who were admitted in the Department of Pediatric Cardiology of the IIIrd Pediatric Clinic from the Emergency Children Hospital *Louis Turcanu* Timisoara. The patients were selected form a total of 389 cases admitted over a period of one year, between January 2016 – January 2017.

All these patients were investigated, with clinical examination, ECG, Echocardiography, selective Cardio-pulmonary X ray and selective Angio CT, to establish de cardiac diagnosis. The patients performed usual lab tests and cardiac biomarkers relevant for this study: NT-proBNP, cardiac Troponin T (cTnT) and high sensitive CRP (hs-CRP). For NT proBNP values we used the recommended values related with age, mentioned in table1. For the cTnT, the blood samples were collected on ice and the normal value was considered < 14 pg/mL(0.014 ng/mL). The hs-CRP normal value was considered < 500 mg/dL(5 mg/mL). The cardiac biomarkers were collected soon after the diagnosis was established and if modified, were rechecked until normalization.

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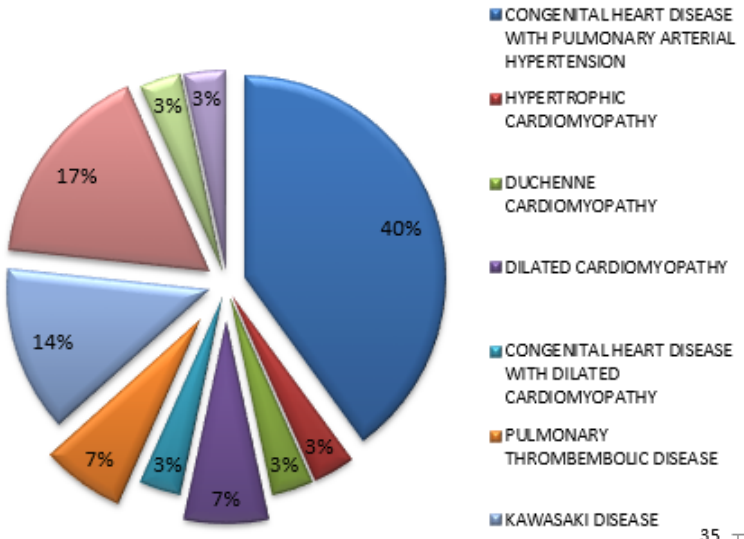


Fig. 1. Distribution of the pediatric patients with cardiac pathology involved in the cardiac biomarker study

Results and discussions

From a total of 389 pediatric patients admitted in the Cardiology Department of the IIIrd Pediatric Clinic, during a one year interval, we selected a number of 30 patients which performed cardiac biomarkers. These patients were diagnosed, after cardiac examination, with congenital heart disease with complications, like heart failure and/or severe pulmonary artery hypertension and children with acquired heart disease, as described in figure 1.

The ages of the patients were between 5 months and 18 years old and the sex was slightly dominated by females, with a 15:14 female to male ratio.

The results obtained in our patients are mentioned in figure 2, showing that the most sensitive biomarker was NT proBNP, followed by hs-CRP and cTnT. Not all patients had positive reaction for all three biomarkers, but there were diseases in which all three biomarkers were correlated. The myocardial injury increases with the number of cardiac biomarkers involved. In figure 3 the correlation between cardiac biomarkers and the cardiac pathology is presented.

Cardiac biomarkers are related with myocardial dysfunction. We performed cardiac biomarkers in 30 patients during a one year interval, mentioned in figure 1. From the study patients, a maximum of 12 children were diagnosed with congenital heart disease that developed complications such as pulmonary arterial hypertension and heart failure which was confirmed in the cath lab. They were followed by 5 patients with cardiomyopathies, including one girl with severe hypertrophic cardiomyopathy, with familial sudden cardiac death background, including her father, one boy with Duchenne muscular disease and secondary cardiomyopathy, who was admitted

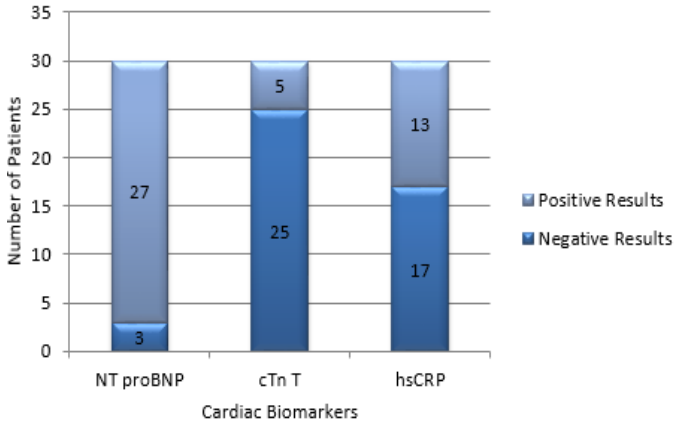
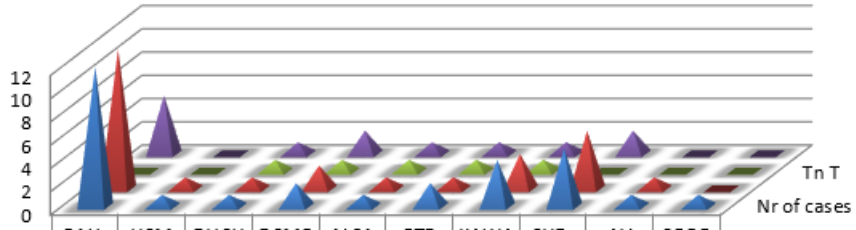


Fig. 2 Relation of positive cardiac biomarkers to total number of patients

for chest pain, mimicking acute myocardial infarction, 2 patients, one child and one adolescent with severe dilated cardiomyopathies and heart failure and one infant with a heart malformation, ALCAPA syndrome, meaning anomaly of the left coronary artery emerging from the pulmonary artery, that developed severe dilated cardiomyopathy. All the selected cardiomyopathies were severe cases. Other two patients were admitted for acute pulmonary thromboembolism, one boy who presented in the emergency department with cardiogenic shock and severe acute pulmonary hypertension and an adolescent presented with chest pain and mild respiratory failure. Another included pathology was Kawasaki disease with coronary aneurysms, three cases, from which one developed giant aneurysm of the left coronary artery with intracoronary thrombus formation. Five cases were children with congenital heart defects associating heart



	PAH-CHD	HCM	DUCHENNE CMP	DCMP	ALCAPA	PTE	KAWASAKI DISEASE	CHD-HF	AV FISTULA	CORONARY ANEURYSM
Nr of cases	12	1	1	2	1	2	4	5	1	1
NT pro BNP	12	1	1	2	1	1	3	5	1	0
Tn T	0	0	1	1	1	1	1	0	0	0
hs CRP	5	0	1	2	1	1	1	2	0	0

Fig. 3. Correlation between cardiac pathology in children and positive cardiac biomarkers

failure. The last two patients were particular cases, one girl discovered with a congenital giant aneurysm of the right coronary artery, without Kawasaki disease or Takayasu arteritis and one girl presented at the age of 3 with intense cyanosis, considered cyanotic heart disease, but was actually diagnosed with a giant intrapulmonary arteriovenous fistula. All of them had indications for biomarker investigations, to detect, treat and follow the myocardial dysfunction.

The NT proBNP was the most sensitive biomarker, that was positive in 27 patients, meaning 90% of the patients, followed by hs-CRP in 13 patients, meaning 43.3%, and cTnT, positive in 5 patients, representing 16.6% (fig. 2).

The correlations between de cardiac disease and the cardiac biomarkers are presented in figure 3. Analyzing the patients involved in the study, we can comment that in the largest group of 12 patients with congenital heart defects complicated with severe pulmonary hypertension, NT proBNP was modified in 100% of patients and this parameter correlated with the severity of the disease, therefore it became a good tool in monitoring the prognostic of this patients, as mentioned in the PAH Guidelines. In the same group, the hs-CRP was positive in just 5 cases, but the cTnT was completely negative.

The second large group was the cardiomyopathies, in which NT proBNP was positive in all five cases. Except the girl with familial hypertrophic cardiomiopathy, who was asymptomatic, all the other symptomatic patients presented positive results for cTnT and hs-CRP. Looking separately at every case, the 17 y/o boy with Duchenne cardiomyopathy was admitted for acute coronary syndrome, mimicking acute myocardial infarction with modified ECG. This patient was diagnosed and followed up in another county hospital and was completely unknown to us. Having positive cardiac biomarkers, he was treated as a myocardial infarction, including coronary angiography, which did not detect any modification for angioplasty. The diagnosis was myocardial infarction with non-obstructive coronary arteries, MINOCA. Following this patient, the cardiac biomarkers slightly decreased, but some remained in high values, such as liver enzymes. This made us review the case and complete the investigations with cardiac MRI, that differentiated the myocardial infarction from the specific modifications of Duchenne cardiomyopathy. The final diagnosis was Duchenne cardiomyopathy, because the ECG remained unchanged when compared with previous ECGs and cardiac biomarkers were constantly high in all the follow up examinations, all described as patterns of the muscular disease. The other two patients with severe dilated cardiomyopathy had all three cardiac biomarkers positive, because they were in NYHA IV heart failure. The infant with ALCAPA syndrome, a congenital heart disease where the left coronary artery emerges from the pulmonary artery and half of the heart is fed with desaturated blood, with the consequence of severe dilated cardiomyopathy, had all cardiac biomarkers positive, signaling the importance of the myocardial injury.

From the two patients with acute pulmonary embolism, only one had all three biomarkers positive, with the most impressive values of NT proBNP, over 10.000 pg/ml, because at admission he was in cardiogenic shock, with severe pulmonary hypertension, severe respiratory distress and NYHA IV heart failure. The other case with pulmonary embolism did not present respiratory or cardiac failure and all the cardiac biomarkers were normal.

Three out of four patients with Kawasaki disease had over limit values for NT proBNP, which was correlated with myocarditis; from these 3 cases, only one had all cardiac biomarkers positive and this was the patient that developed a giant coronary artery aneurysm, with thrombus formation inside. This patient was followed until the normalization of the cardiac biomarkers that reacted in the acute phase of the disease. The biomarkers in the last follow up were negative, but the coronary aneurysm with thrombus inside, just slightly decreased. The little boy remained in follow up program, under warfarin and aspirin treatment. One case of Kawasaki disease had negative results in all the cardiac biomarkers. However knowing the fact that Kawasaki disease is a generalized vasculitis that does not always affect the heart we can conclude that in the Kawasaki group, the cardiac biomarkers were extremely useful, proving the presence of myocardial cell injury and helped in detecting the patient with giant coronary artery aneurysm.

The last large group was patients with congenital heart disease complicated with heart failure, in which NT pro BNP was positive in all 5 cases, and hs-CRP in 2 cases. Correlated with the clinical status, the most severe cases frequently associated two biomarkers.

The patient with giant pulmonary arteriovenous fistula, was admitted for chronic cyanosis, 76% oxygen saturation, cardiac murmur and severe failure to thrive, but with a normal structural heart. Echocardiography detected a vascular modification in the lung and Angio CT confirmed the diagnosis. The only cardiac biomarker that was slightly increased was NT proBNP, as a result of chronic deoxygenation of the heart. Due to the pulmonary fistula there was a mixing of the oxygenated with deoxygenated blood at the lung level, the pulmonary veins returning into the left atrium with combined blood. This situation determined cardiomyocytes injury.

The last case was a girl detected with a giant right coronary artery aneurysm with a particular trajectory, but without other cardiac manifestations, no symptoms, only cardiac murmur, normal ECG and except for the right coronary artery aspect, normal echocardiography. This patient had negative cardiac biomarkers, meaning that at this moment there is no cardiac injury.

To see the relevance of the cardiac biomarkers in pediatric patients with cardiac involvement, we reviewed the literature to document their importance.

Cardiac Troponins

There are three cardiac troponins (cTn): T, I and C, from which, cardiac troponin T and I are only present in the cardiac muscle. They are released when a cardiac injury is present and it was proven that they increase in heart failure and cardiac myocyte damage, as a result of inflammatory cytokine, oxidative stress and neurohumoral activation. They were studied in the adult population with myocardial infarction and heart failure and proved to be better markers than muscle brain creatin kinase-MB (CK-MB), which was the previous used biomarker for cardiac muscle damage. Troponins have high specificity and sensitivity and are rapidly detected with high sensitivity Troponin assay. Translated to children, Troponins were studied as cardiac biomarkers in myocarditis, myocardial dysfunction, septic shock, congestive heart failure and congenital heart defects.

Cardiac troponin T (cTnT) was studied in children with myocarditis that developed on normal structural heart where 100% sensitivity and 85% specificity was found. Eisenberg, in a large retrospective cohort study, over 600 children, proposed a cutoff value of 0.01 ng/mL for cTnT to detect myocarditis [4]. The diagnosis can be excluded under this cutoff value in children without preexisting heart disease. Soongswang et collaborators found in their study

a median cTnT value of 0.88 ng/mL (0.04-3.11 ng/mL) in patients with myocarditis, but the same authors showed that cardiac cTnT level of 0.052 ng/mL is an appropriate cutoff point for the diagnosis of acute myocarditis [5]. Lauer specified in his study that the sensitivity of cTnT in diagnosing myocarditis is greater if the patient is tested soon after the onset of the symptomes, when there is only a supposition of myocarditis [6]. The conclusions of these studies were that cTnT determinantion is a very sensitive test in detecting myocardial cell damage in children with the suspected diagnosis of myocarditis.

Chest pain in pediatric patients is another symptom found in the emmegency department(ED) in which cTnT was used. A large study published by Brown and collaborators in ED of pediatrics, on a 7 year period, found that cTnT in pediatric patients with chest pain was positive for myocarditis and pericarditis, only one patient being discovered with miocardial infarction [7]. The conclusion was that Troponin investigation assay is recommended to be used in children with chest pain in ED.

Children with congenital heart disease develope cardiomyocyte injury due to volume or pressure overload. Hafez et collaborators used cTnI in evaluating the children with cyanotic and acyanotic heart disease and proved that the cTnI was significantly increased in both type of malformations ($p<0.05$) and has a significant correlation with oxygen saturation, ejection fraction and pulmonary to systemic blood flow (Qp/Qs) and pulmonary to systemic arterial pressure (Pp/Ps) ratios. The conclusion was that the incidence of myocardial damage in congenital heart disease is high and needs an early detection, for an early treatment, offering a good outcome for the patient [8]. A Scandinavian group report that cTnI is increased in pediatric patients with pressure overload due to aortic coartation and aortic and pulmonic valve stenosis, more than in volume overload due to atrial septal defect(ASD) or patent ductus arteriosus(PDA) and the situation returns to normal after surgical correction.[9] A Japanese group evaluate a large cohort of children with congenital noncyanotic heart defects, ASD and ventricular septal defect(VSD), with age between 2 m/o to 16.8 y/o, compared with normal children, using cTnI assay [10]. They found high leves of cTnI in the group with heart malformations and it seems to be the first to report the involvement of cTnI in children with heart disease. They also mentioned that cTnI levels in ASD group was significantly higher than in normal children, meaning that volume overload determined myocardial injury. VSD group also presented significantly increase in cTnI comparing with healthy children, meaning that ventricular volume overload added to right ventricular pressure overload, combined they induced myocardial injury. Strong corellation was described between cTnI with NT-pro BNP, which is a biomarker for heart failure and pulmonary hypertension. A few years later, Sugimoto confirmed the utility of cardiac biomarkers in children with congenital heart disease, but focused this time on the high sensitiv Troponin I levels in ASD and VSD [11].

Troponin was also investigated for the role of cardiac biomarker in Kawasaki disease(KD) and initially cTnI was considered not to have senzitivity and specificity for the cardiomyocyte involvement.[12] Since high sensitive troponin array (hs cTnI) developed, studies started to prove the presence of the myocardial injury starting from early stage of KD, but with an unexpected maximal elevation in the convalescent phase, indicating that cardiomyocyte injury persisted after the systemic inflamation ceased.[13] The normalisation of the hs cTnI is in the late convalescent stage, meaning 1-2 years after the onset of KD.

Another acquired heart disease is myocarditis and miocardial involvement in musckular dystrophy Duchenne/ Becker(DMD/BMD). A study from China compared the cardiac Troponins: cTnI with hs-cTnT in both diseases, showing that there is no differece between Troponins in myocarditis children, both of them rising significantly, but in DMD/BMD, hs-cTnT was more sensitif compared with cTnI [14].

Troponins cTnI and cTnT proved to be good biomarkers for detection the myocardial injury, but new generations of high sensitive troponins are much more important, detecting the injury sometime before a clinical expression. Time and new future researches will decide which one of the high sensitive Troponins is the best biomarker and in which disease.

BNP and NT-proBNP

In the classification there are 3 natriuretic peptides: atrial natriuretic peptide(ANP), produced in the atria, brain natriuretic peptide(BNP), produced in the ventricles and C natriuretic pedptide(CNP), produced in the brain. They were first described by de Bold.[15] BNP is B-type natriuretic peptide and NT-proBNP is N-terminal segment of Pro-BNP. The name of brain natriuretic peptide comes from the the first place it was discovered, in the pig brain. In humans it is produced in the ventricles, by the myocytes, in response to an increase in wall tension and in relation to the left ventricular filling pressures. The most stable from the two is NT-proBNP, 24 h in the blood at 20^0C, followed by BNP; the most instable is ANP. This means that the best detection is for NT-proBNP. Both of them, BNP and NT-pro BNP are peptides with a paracrin role, secreted by the cardiocytes as pre-pro-peptides, which are produced in the endoplasmatic reticulum, where they are also stored as atrial granules. The role of pre-pro-peptides is to mantain the salt and water homeostasis. Under different stimuly they are released after conversion into pro BNP, later cleaved by serin peptidase in BNP and NT-proBNP. BNP increase diuresis, natruresis and produces vasorelaxation and at the heart level has anti-proliferative and anti-hypertrophic properties. Normal value of NT-proBNP in adults is 0-300 ng/L. It is the most studied biomarker in relation with heart failure. Value ≥450 ng/L predicts heart failure in adults.

The BNP and NT-proBNP vary with age. The newborns have elevated BNP and NT-proBNP, due to the elimination of the placenta, redistribution of the blood volume in the heart, inducing volume overload and increase afterload, due to lung expansion and increase in the pulmonary blood flow and due to renal immaturity that decrease the elimination. After birth the BNP and NT-proBNT are high, maxinum in the first 4 days of life, reducing rapidly in the first 2 weeks of life. A diference between boys and girls apears in the second decade of life, higher BNP values can be found in girls. Nir et all. published in 2009 reference values for NT-proBNP in pediatric patients, based on combined data of four studies in children. They established the 95 percentile for NT-proBNP to be the upper limit of normal [16]. Every value over that limit is considered elevated in pediatric range. This reference values published by Nir were taken into consideration in furter studies (Table 1), last one published in 2016 [17].

BNP was used to detect and follow adult patients with heart failure, iskemic or noniskemic. In children, similarities with adults can be found only in patients with dilated cardiomyopathy as a dominant etiology for pediatric heart failure. It seems that persistent elevated BNP levels, despite adequate therapy, predicts a wrong long-therm outcome, with increased risk of death, hospitalization, even listing

Table 1

NT-proBNP 95TH PERCENTILE LEVEL IN NORMAL INFANTS, CHILDREN AND ADOLESCENTS FROM BIRTH TO 18 y/o

Age	Plasma NT-proBNP normal upper limit (pg/mL)
First 2 days	12.000
3-11 days	6.000
1 month – 1 year	650
1-2 years	400
2-6 years	300
6-18 years	160

NT-proBNP = N-terminal pro-brain natruretic peptide

for cardiac transplantation, comparing with patiens with lower levels. Increased NT-proBNP levels was found in 95% of children with modified Ross criteria for heart failure, and the levels varied significantly between mild, moderate and severe heart failure, determining a new classification of heart failure, combining modified Ross criteria with NT-proBNP values [18].

In patients with dylated cardiomyopathy, a value > 681pg/mL of NT-proBNP at 3 months from the onset, determines an increased risk of severe left ventricular dysfunction or may predict cardiac death. This study of Kim et al., recommended as a guide for long-term treatment to determine NT-proBNP at 3 mo after diagnose of dilated cardiomyopathy to predict the child's outcome[19]. BNP was increased in patient with heart failure, in comparison with children suffering from respiratory distress, fact proved by Kouloury et al [20].

Congenital heart disese was the cornerstone in NT-proBNP biomarker investigation. BNP and NT-proBNP are released in circulation by ventricular myocytes as a response to volume and pressure overload. In congenital heart defects with cyanosis, NT-proBNP was found to be significantly higher than in acyanotic and control group. NT-proBNP was significantly higher in symptomatic group, comparing with asymptomatic patients, and of course in the affected patients group, comparing with healthy patients. No difference was found between ASD and VSD in this study related with NT-pro BNP values [21]. Sugimoto mentioned that NT proBNP increase in congenital heart defects with left to right shunts, like ASD and VSD, and the levels are high when Qp/Qs is high. This situation changes after surgical correction, NT-proBNP turning to normal and proving that NT-proBNP was a marker of heart failure due to volume overload [11] Koura and collaborators measured the NT-proBNP in left to right shunt patients and found that it became increased when systolic dysfunction occus, rather than in dyastolic dysfunction, but highest in both dysfunctions. Alone, NT-proBNP cannot differentiate systolic from dystolic dysfunction and also is enable to separate impared relaxation from restrictive-like filling pattern [22].

In his review Eindhoven evaluated the utility of BNP in children with complex congenital heart disease, looking in the literature to collect data [23]. The implication of BNP and NT-pro BNP in congenital heart disease regarding the diagnose and the clinical decision making was not completely defined, but it was supposed that these biomarkers are of clinical importance because of the implication with proven usefulness in acquired heart disease, and also due to the simplicity of assesment. When comparing children with simple heart disease, such as ASD, VSD, PDA, with complex heart disease, in the complex heart disease, higher concentrations of NT-proBNP tend to be found [24]. In Tetralogy of Fallot, after surgical repair, the right ventricle starts to dylate due to pulmonary insufficiency, needing a valve implantation. The precise moment it happens is not known, in some children early after surgical repair, in other patients, late in life. NT-proBNP was significantly correlated with the right ventricle end diastolic dimensions, volume of the right ventricle, function of the right ventricle and severity of pulmonary insufficiency, being able to predict the moment for pulmonary valve implantation, but large studies are expected. In systemic right ventricle, when the systemic ventricle has right ventricle morphology, who is not prepared to pump as a left ventricle, and may lead to right ventricle dysfunction, NT-proBNP had a positiv correlation with right ventricle dysfunction. An early detection of right systemic ventricle deterioration is possible by monitoring NT-proBNP levels [25].

Pulmonary arterial hypertension represent a severe complication in children with congenital heart disease. Sometimes children are detected with cardiac malformations when the surgical time is exceeded, patients being unoperable because severe pulmonary hypertension is istalled. There are patiens that present pulmonary arterial hypertension postoperatively. Both of them need cardiac catheterization and echocardiography monitoring. It was found that NT proBNP best predicts hemodynamic imparement in these patients [26]. A sistematic review on this theme by Giannakoulas confirmed that natriuretic peptides in particular are simple and effective tools in detecting early right heart dysfunction, determining decisions for the early theraputic interventions and influencing the prognostic in patients with heart disease and pulmonary arterial hypertension [27]. Different papers documented that children with congenital heart disease and pulmonary arterial hypertension have elevated NT-proBNP levels [28, 29, 36]. BNP and NT-proBNB are leading cardiac biomarkers for pulmonary arterial hypertension, with a definite role in the assessment and in prognostic, as metioned in the European Society of Cardiology Guidelines for the diagnosis and treatment of pulmonary hypertension [30].

BNP and NT proBNP are valuable biomarkers in the diagnosis, treatment and prognostic of children with heart disease and in the future they will have increased importance in this pathology.

C Reactive Protein (hs-CRP)

C reactive protein is produced in the liver as a response to inflammation. It was detected in the serum of patients with acute inflammation, as a substance that reacted with the somatic *C* carbohydrate antigen of Pneumococcus, so this is where the name originates. Tillet and Francis discovered the C reactive protein in late 1930 [31]. Since then, many studies proved the implication in acute immune response, playing an important role in inflammation. A new generation of high sensitive or ultra sensitive C reactive protein(hs-CRP/us-CRP) assay identified the endothelial dysfunction in adult patiens with coronary artery disease. In pediatrics age was studied in obese children with metabolic syndrome, with the conclusion that hs-CRP could be used in early detection of cardiovascular risk in children [32]. In the same year with the previuos study it was found that hs-CRP is increased in patients with hypoxia associated with high levels BNP. Serum concentration of hs-CRP signifficantly correlated with Oxigen saturation and BNP levels [33]. A study from 2014 came to evaluate all three biomarkers: NT-proBNP, cTnI and hs-CRP in children with congenital heart disease. Hs-CRP was significantly higher in patients with heart disease in comparison with healthy control group [21].

Patients with unoperated congenital heart disease with left to right shunt, may develope severe pulmonary arterial hypertension. Serum hs-CRP together with NT-proBNP and Pentaxin 3 was studied in such a group. The results proved that hs-CRP was significantly increased in severe pulmonary hypertension group, ($p<0.01$). It seems that inflamation has an important role in the progression of the disease [34].

Serum hs-CRP could monitor sequelae in Kawasaki disease, due to low grade inflamation that may persist in patients with aneurysms [35].

Conclusions

In our retrospective study we proved that cardiac biomarkers were very usefull and necessary in the detection of myocardial injury and also in the management and prognosis of patients with heart disease, both congenital or aquired, with complications as heart failure or/and pulmonary arterial hypertension. NT pro-BNP is the most sensitive biomarker, followed by hs-CRP, as a reaction to heart inflamation. Troponin T reacted only in severe cases, and it was the only one we could apply. Studies in children needs to be extended, for a better understanding, but it is clear that the future belongs to biomarkers. Finding the specific biomarker, new theraputic targets will be identified. As in adults, we need to introduce cardiac biomarkers as a routine test in screening pediatric patients with acute cardiovascular involvement, in the emergency department. Further studies are expected to achive valid cutoff values age related and specific to cardiac disease, to allow a large aplication of the cardiac biomarkers in children.

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Manuscript received: 29.12.2017