UNIVERSITY OF MEDICINE AND PHARMACY
„VICTOR BABEȘ” TIMIȘOARA
FACULTY OF MEDICINE
Department XI Pediatrics

ARDELEAN V.O. ANDRADA-MARA

MODERN DIAGNOSTIC AND MONITORING TECHNIQUES IN PAEDIATRIC HEART DISEASE

-SUMMARY-

Scientific leader
PROF. UNIV.DR. DOROS GABRIELA SIMONA

T i m i ș o a r a
2 0 2 4

Table of contents

Introduction

Heart disease has been difficult to diagnose and has always been a leading cause of death in the pediatric population, but with the advent of echocardiography in the 1960s and 1970s, the diagnosis of heart disease became easier. After the 1970s echocardiography was deemed the perfect technique, the "gold standard" in cardiology.

The evolution of echocardiography was exponential, starting from 1952 with the appearance of the A-mode technique, then in the autumn of the same year Edler published his thesis on the M-mode, which is still used to calculate cardiac function today. Then, in 1957, Satomura discovered that Doppler echography could be used to calculate cardiac motion. In 1972 the first treaty on echocardiography was published. After these groundbreaking publications, echocardiography has evolved exponentially.

In 1998 the notion of myocardial strain was introduced, which was supposed to be a real help in detecting cardiac function, but there were no precise methods to determine it. With the advance of tissue Doppler (TDI), myocardial strain could be calculated, but it had a drawback, TDI is angle dependent.

Speckle tracking is an innovative technique that can determine cardiac function accurately, define myocardial strain and is independent of angle and varies very little intra and interobserver.

Over time, speckle tracking has been used in multiple pathologies and has been found to be much more accurate in calculating cardiac function, and moreover, it was the first indicator that predicted cardiac dysfunction. Thus, speckle tracking has been successfully used in adult cancer patients treated with anthracyclines to predict the occurrence of cardiotoxicity. Success in adults has prompted the study of speckle tracking in the pediatric population, studies are still limited but show real potential.

Current state of knowledge

In the general part I have conducted a review of the literature data on speckle tracking echography (STE). To begin with I have provided general data on speckle tracking and compared the method with other methods of assessing cardiac function on the market. In the next subchapter we have detailed the technique needed to apply the method, the terminology to understand the images we obtain after applying the method and I have provided images to exemplify the normal appearance with good cardiac function. Next, I have written a subchapter on result interpretation, being a new technique, which is mostly applied in adults, there are few studies for the pediatric population, but by thoroughly researching the literature I found a metaanalysis that included 2325 pediatric patients, which studied normal values for this age group, these data we adapted in the thesis. I also gave some examples of pathologies where speckle tracking echography can be used to detect changes in cardiac function.

The last chapter, which included seven subchapters, was dedicated to the use of speckle tracking echography in pediatric pathology. The first subchapter was dedicated to myocarditis, here we provided general data on myocarditis, as well as data from literature. I found supporting articles of the usefulness of speckle tracking in this pathology, many concluding that the results obtained from speckle tracking echography correlated with the results obtained by MRI, thus their recommendation was to introduce STE in the follow-up of patients with myocarditis. Given that STE provides a segmental overview of the left ventricle we investigated whether the method could be used in Kawasaki disease to determine the affected region when there are intracoronary thrombi, all articles found supported the use of the method for follow-up of these patients.

A large part of my PhD thesis was conducted during the SARS COV2 pandemic, and during the pandemic a new disease emerged that affected pediatric patients called pediatric multisystem inflammatory syndrome (PIMS), which is why we researched the usefulness of STE in the follow-up of these patients and found several studies that were conducted among these patients, and the conclusion was unanimous that STE is worth implementing for the diagnosis and management of patients diagnosed with PIMS.

I observed the usefulness of the method among inflammatory diseases, which is why I searched the literature for articles that used STE among patients with autoimmune diseases. The data supported that STE can detect a flare, especially in patients with systemic erythematosus lupus, moreover STE has been used in some studies as a predictor of the occurrence of cardiovascular complications.

In our hospital there is a nephrology department, which is why I had the opportunity to follow patients with chronic kidney disease, so we searched the literature for the applicability of STE among these patients. I found multiple articles which state that speckle tracking echocardiography would have great potential if implemented in the follow-up of patients with chronic kidney disease, as it can detect cardiac function disorders faster than any other echocardiographic method and moreover it can be used as a predictor of the occurrence of cardiovascular complications.

The next pathologies studied were cardiomyopathies, all the articles in the literature I found supported that STE was a real help in the diagnosis and management of patients with

dilated, hypertrophic and restrictive cardiomyopathies. Moreover, among patients with hypertrophic cardiomyopathy STE has been used as a predictor of arrhythmia occurrence.

When I searched the literature for the usefulness of speckle tracking in pediatrics, most articles were focused on oncologic pathology, meaning STE has been used successfully, to detect early cardiotoxicity among patients treated with chemotherapeutics, but especially those treated with anthracyclines.

Own contribution

The special part of the thesis includes three studies. The first study was conducted on the use of speckle tracking in various pathologies and the next two were focused on the usefulness of speckle tracking in oncological pathology.

After careful research of the literature, I found that speckle tracking echography has been used among pediatric patients with various pathologies, so I tried to enroll patients with the pathologies mentioned in my study, but being a small number of patients, which could not reveal statistically significant data, I decided to focus on the oncological patients. However, I decided to presented the data obtained on the small group of patients with different pathologies, because I mentioned the usefulness of STE in these diseases and had applicability according to the studies researched. The study of these patients is ongoing, so I cannot draw statistically significant conclusions.

The aim of our research is to demonstrate that there are alternative, non-invasive methods to follow cardiac complications in different pathologies, but especially for cardiotoxic effects of chemotherapeutic treatments, specifically anthracyclines, in the pediatric population.

The first study "Use of speckle tracking in pediatric pathology" is the ongoing study where I enrolled 35 patients with different pathologies, namely: myocarditis, systemic erythematosus lupus, chronic kidney disease, Kawasaki disease, PIMS, dilated cardiomyopathy, restrictive cardiomyopathy and hypertrophic cardiomyopathy. After dividing the patients by pathology, I studied the usefulness of STE on each pathology. In the case of myocarditis, I observed that the results were similar to those found in literature, STE correlated with MRI results and cardiac biomarkers.

I found STE to be of great use in pediatric multisystem inflammatory syndrome, as it also detected minor contractility changes and correlated well with cardiac biomarkers. Similarly with the data obtained from literature I was able to detect a lupus reactivation in a patient who presented for routine evaluation. For patients with chronic kidney disease, I observed that speckle tracking was useful in detecting cases with high cardiovascular risk, this data that was supported by articles found in literature. Patients with dilated cardiomyopathy were followed up by STE to track response to treatment, but we could not draw a clear conclusion as patients need to be followed up over a longer period of time, the same conclusion was reached for patients with hypertrophic cardiomyopathy. However, in the case of restrictive cardiomyopathies, STE was useful to detect the severity of the cases, thus out of the three enrolled cases the case with altered GLS did not survive, and the other two cases that survive, showed normal or slightly low GLS values.

In the second study, the primary objective was to determine the predictive role of STE parameters for anthracycline-induced cardiotoxicity in pediatric patients with oncological disease, the secondary objectives were to determine the correlation between STE results and traditional cardiac biomarkers and to observe differences between different types of anthracyclines. A total of 214 patients were enrolled in the study, of which 99 were included.

Of the 99 patients enrolled, 82 were treated with Doxorubicin and 17 were treated with Epirubicin. I compared the two groups according to their demographics age, sex, BMI, then according to oncological data: cancer type treatment protocol and cardiotoxicity rate, finally I evaluated myocardial toxicity according to cardiac biomarkers, echocardiographic values obtained and anthracycline type.

I found that there were statistically significant differences, across multiple parameters, when we compared the Doxorubicin-treated and Epirubicin-treated groups of patients, signifying that there are variations between their cardiotoxicity profiles. My results suggested that myocardial injury was more common among Doxorubicin-treated patients, these results correlated with cardiac biomarker values. I also found that the group of patients treated with Epirubicin had better cardiac function by both SMOD, MPI and GLS values which are considered predictive of the presence or absence of cardiotoxicity. Interestingly, our study found that GLS and SMOD had a significant negative correlation, while GLS and MPI had a significant positive correlation. This highlights the importance of considering a comprehensive set of indices for a more accurate assessment of cardiotoxicity.

The third study was designed to follow whether disease type and intensity of treatment have a significant impact on cardiac function measured by STE and MPI; to compare the sensitivity of STE and MPI with traditional echocardiographic methods for detecting early cardiac dysfunction; and to explore the potential of these measurements to predict long-term cardiac complications in this population group. A total of 145 patients were enrolled for this study, 99 patients with various oncological diseases and 46 healthy patients as controls.

Patients enrolled in the study and the control group were compared according to age, gender and body mass index. Additional factors were collected and analyzed: electrocardiogram (ECG) results, echocardiography results disease (ejection fraction and shortening fraction, GLS, Simpson's method of disc, myocardial performance index), presence of cardiotoxicity, cardiac biomarkers, disease type, protocol intensity, body surface area (m2), total anthracycline dose, cumulative dose of other chemotherapy agents (Cytarabine, Etoposide, Cyclophosphamide, Vincristine, Asparaginase, Ifosfamide, Methotrexate, Mercaptopurine, Oncaspar, Mitoxantrone) and radiotherapy received.

I found that cardiac function obtained by GLS, SMOD and MPI had lower values among cancer patients compared to the control group. I performed a regression analysis, which provided me with probability ratios for associations between different cardiac function measurements and the occurrence of cardiac toxicity. Only GLS had an odds ratio of 2.20, indicating that for each unit increase in GLS, the odds of cardiac toxicity occurrence were approximately double. However, this finding was not statistically significant. Myocardial Performance Index (MPI) showed a less marked association, with an odds ratio of 1.24, suggesting only a slight increase in the odds of cardiac toxicity for each unit increase in MPI. Simpson's method of discs (SMOD) had a similar odds ratio of 2.16, indicating a slightly more than twofold increase in the odds of cardiac toxicity for each unit increase in the SMOD measure. The combination of all three measures - GLS, SMOD and MPI - showed the highest odds ratio of 7.30, indicating a more than sevenfold increase in the odds of cardiac toxicity. Therefore, these results highlight the significant impact of cancer and its treatment on cardiac function in pediatric cancer patients. The present study's use of novel echocardiographic measures (GLS, SMOD, MPI) provides a valuable approach for the detection of early cardiac dysfunction and potentially for long-term cardiac prognosis in this population.

The last part of the thesis covers my experience with 3D printing. Following an international pediatric cardiology congress, I obtained a trial version of a program that produces 3D models from CT images. I was able to print four 3D models which were sectioned

in such a way as to highlight the malformations. The four printed pathologies were able to be closely studied by medical students training in our clinic. The malformations were presented verbally, then 2D echocardiographic images were presented, then tested to assess their level of understanding. After which 3D models of the malformations were given and the students confirmed that the information was much clearer with the real model of the heart. I also wish to implement the method in order to offer the 3D printed model of complex cardiac diseases to the cardiovascular surgeon, so as he can chose the optimal surgical correction for the patient.

General conclusions

Speckle tracking echocardiography is a new method of exploration in pediatric cardiac pathology that I have implemented for the first time in children, proving in this paper its efficiency in the diagnosis and monitoring of patients with various pathologies: myocarditis, Kawasaki disease, PIMS, systemic erythematosus lupus, chronic kidney disease and cardiomyopathies.

STE correlates with cardiac biomarkers and is a predictor of the progression of the patient's cardiac disease.

The study complements the data from the universal literature, but further work is needed to enroll more patients as in the universal literature.

The second and third studies confirm that:

- Cardiac function of patients treated with Epirubicin was better compared to patients treated with Doxorubicin.
- Cardiac function determined both by the new GLS method and by SMOD and MPI was worse in patients treated with Doxorubicin. However, ROC analysis did not support these echocardiographic markers as predictors of anthracycline-induced cardiotoxicity.
- I identified statistically significant correlations between the implemented assessment techniques GLS, SMOD and MPI and cardiac biomarkers.
- In the Doxorubicin group, cardiotoxicity tends to occur at significantly lower doses compared to Epirubicin.
- Comparing baseline values of cancer patients with a group of healthy children we found that the former group have lower cardiac function values.
- Type of neoplasia and intensity of treatment have significant impact on cardiac function.
- Early changes detected by GLS, SMOD and MPI were associated with long-term cardiac alterations.

3D printing of hearts of patients with complex malformations is for the first time performed in Romania. This innovative technology has been extremely well received in the university setting, with students and residents having a much broader understanding of malformations after the 3D models were presented. It is designed to benefit the patient for pre-operative preparation, allowing the surgeon to assess and decide the timing of surgical correction.

Implementation of STE in various cardiac pathology, SMOD and MPI together with STE in oncological pathology and 3D printing are new techniques that we have brought to pediatric cardiology, contributing to its development in Romania.

Originality and innovative contributions of the thesis

This paper is the first in Romania to address the use of novel, non-invasive methods to detect early cardiac dysfunction in various pathologies in children, but especially in pediatric cancer patients. In recent times echocardiography has evolved exponentially, thus facilitating the diagnosis and management of patients with cardiac disease. Speckle tracking is one of the newly discovered echocardiographic methods that has shown immense potential in the early detection of cardiac dysfunction in multiple pathologies, including cancer patients treated with anthracyclines. Among adult oncology patients, speckle tracking has been successfully used to detect cardiotoxicity. There are few studies in the international literature addressing this topic in the pediatric population.

The first study provided valuable and extremely useful information in practice by using STE in a spectrum of cardiac conditions in children. The novelty lies in the implementation of this method in children with wide applicability in pediatric pathology.

The following two studies conducted on chemotherapy-induced cardiotoxicity described in this thesis are original due to the paediatric age cohort of the study population. Thus, they are among the few studies using speckle tracking echocardiography for early detection of cardiac dysfunction among pediatric patients with anthracycline-treated oncological disease in our country.

Moreover, with the help of the first study on oncology patients we have shown that it is also important which type of anthracycline is chosen for treatment, with Doxorubicin having a higher percentage of cardiotoxicity compared to Epirubicin. We have also shown that it is important to combine echocardiography with cardiac biomarkers for the correct diagnosis of cardiotoxicity, since they are two complementary methods.

With the second study in oncology patients, we demonstrated that echocardiography alone can be used in the detection of anthracycline cardiotoxicity when more than one measurement is taken, not just the classical ones. That in other words, if the speckle tracking, myocardial performance index and Simpson's method values are low, the probability of the patient showing cardiotoxicity is quite high.

The present work is also innovative in that it is the first and only one to address cardiac 3D printing. Originally designed for teaching support, students and residents who received 3D cardiac models had a much better understanding of malformations compared to students who had only verbal and imaging presentations.

3D printing of cardiac models has huge potential, not only from a didactic point of view, but also to reduce the operating time of young patients with complex cardiac malformations, allowing the surgeon with the 3D model in sight to anticipate the type of surgical correction. We plan to further study this hypothesis through a future research project, in order to extend the usefulness of this method and implement it nationwide, helping the development of pediatric cardiology in our country as well.