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**The significance of echocardiographic indicators in the assessment of cardiac function in children diagnosed with myocarditis.**

**Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu**

**w dyscyplinie nauki medyczne**

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## **SUMMARY:**

Myocarditis is a rare disease involving complex immune processes that can result in damage to cardiomyocytes and impaired contractility. The condition could be characterized by an asymptomatic course, which can make an early diagnosis difficult. In some cases, patients may develop dilated cardiomyopathy after the acute phase, resulting in an uncertain prognosis.

The aim of the presented doctoral dissertation, consisting of a series of three publications, was to analyze the usefulness of echocardiography in the diagnostic algorithm for myocarditis in children, with particular emphasis on parameters used to assess left ventricular function. Additionally, an attempt was made to identify new echocardiographic parameters that may be characterized by greater diagnostic sensitivity in detecting myocarditis in adolescents with sparse clinical manifestations, thus enabling their differentiation from the healthy pediatric population. Consequently, a retro-prospective observational study of children diagnosed with myocarditis was conducted. At the time of inclusion in the study, patients underwent serum troponin I (TnI) testing, a 12-lead electrocardiogram (ECG), 24-hour Holter ECG monitoring, two-dimensional transthoracic echocardiography (TTE) with extension to assess left ventricle muscle performance index (LV MPI) and left atrial strain and function (LAS). In all cases, the diagnosis was confirmed by cardiac magnetic resonance (CMR) with assessment of late gadolinium enhancement (LGE) and myocardial oedema. The results of the tests conducted on children diagnosed with myocarditis were then compared with those of the control group, which exhibited no significant differences in terms of age or gender.

The first published study conducted was a retrospective analysis of clinical symptoms, laboratory test results, functional tests and imaging studies in 81 patients with mild and asymptomatic myocarditis. In all patients, the diagnosis was confirmed by CMR in accordance with the Lake Louise criteria. The acute phase of myocarditis was not characterized by any distinctive clinical picture in adolescent patients. Among the diagnostic tests performed, electrocardiography (ECG) and troponin I (TnI) concentration exhibited the highest sensitivity in establishing the initial diagnosis. The majority of patients (72%) exhibited normal left ventricular size and function on echocardiography, and the test's diagnostic sensitivity was only 28%. No significant correlation was found between cardiac marker levels (TnI, NT-proBNP) and left

ventricular systolic function ( $r = -0.07$ ,  $p < 0.05$ ), although a moderate statistically significant positive correlation was found between TnI concentration and left ventricular internal diameter in diastole ( $r = 0.42$ ,  $p < 0.05$ ). A significant proportion of the patient cohort, approximately 50%, were found to be overweight. Within this subgroup, persistent inflammatory changes were observed more frequently in the follow-up CMR examination after a period of 9 months. Furthermore, the study identified two distinct subgroups of patients within the study group. Group A was treated with angiotensin-converting enzyme inhibitors (ACE-I), while group B was not given any pharmacological treatment. The left ventricular internal diameter in diastole (LVIDd) and left ventricular ejection fraction (LVEF) values were then compared in the acute phase of the disease and after three months. A statistically significant reduction in LVIDd ( $51.1 \text{ mm} \pm 4.5 \text{ mm}$  vs  $48.8 \text{ mm} \pm 5.1 \text{ mm}$ ,  $p = 0.016$ ) and a statistically significant improvement in LVEF ( $56.8\% \pm 5.6\%$  vs  $67.6\% \pm 6.3\%$ ,  $p < 0.001$ ) were observed after three months of ACE-I treatment. These observations were not made in the subgroup not receiving treatment: LVIDd ( $47.5 \text{ mm} \pm 4.2 \text{ mm}$  vs  $47.4 \text{ mm} \pm 5.3 \text{ mm}$ ,  $p = 0.42$ ) and LVEF ( $66.6\% \pm 7.6\%$  vs  $69.5\% \pm 5\%$ ,  $p = 0.05$ ) were also analyzed.

The second publication included an analysis of echocardiographic parameters in 32 patients with myocarditis compared to 34 healthy children in the control group. In addition to standard echocardiographic parameters (LVEF, LVIDd), left ventricular function was assessed using the left ventricular myocardial performance index (LV MPI), evaluating it in four segments where changes in CMR most commonly were located in the acute phase of myocarditis. The study revealed that the sensitivity of the standard echocardiographic parameters: LVEF and LVIDd in the diagnostic process reached 34% and 6%, respectively. In contrast, the sensitivity of the LV MPI index was more than twice as high, at 75%. The analysis did not reveal any statistically significant differences in LVEF and LVIDd values between the study group and the control group. However, statistically significant differences were obtained between the mean LV MPI values in the study group compared to the values obtained in the control group for the intraventricular septum (IVS) basal segment ( $0.52 \pm 0.07$  vs.  $0.40 \pm 0.08$ ,  $p < 0.003$ ); for the basal segment of the lateral wall ( $0.48 \pm 0.02$  vs.  $0.40 \pm 0.08$ ,  $p < 0.019$ ); and for the middle segment of the IVS ( $0.50 \pm 0.01$  vs.  $0.39 \pm 0.09$ ,  $p < 0.001$ ). The investigation revealed no statistically significant difference for the basal segment of the inferior wall ( $0.40 \pm 0.02$  vs.  $0.42 \pm 0.08$ ;  $p =$

0.048). Furthermore, a positive, moderately statistically significant correlation was identified between LV MPI and LVIDd ( $r = 0.001$ ;  $p < 0.01$ ).

The third publication compared the results of echocardiographic examinations, taking into account the parameters of left atrial function in 30 adolescents with myocarditis and 30 children from the control group. A statistical analysis revealed that conventional echocardiographic parameters, utilized for the evaluation of systolic and diastolic left ventricular function, exhibited no statistically significant disparities between the study group and the control group. Patients diagnosed with myocarditis exhibited statistically significantly lower values of early diastolic velocity of the septal and lateral mitral annulus when compared to the control group ( $E'$  sep 12.16 cm/s vs. 13.6 cm/s;  $p < 0.01$ ;  $E'$  lat 15.66 cm/s vs. 17.9 cm/s;  $p < 0.018$ ). The values of left atrial wall strain (LAS) in all three phases differed statistically significantly between the study group and the control group. The strain in the reservoir phase (LASr) was 23.5% (14.4%–34.1%) as compared to 49.4% (40.1%–61.1%), with a  $p$ -value  $< 0.0001$ , in the conduit phase (LAScd) was -22% (-30.1% to -16.8%) vs. -37.1% (-48.2% to -27%), with  $p$ -value  $< 0.0001$ , in the systolic phase (LASct) was found to be -2% (-10.4% to -3.1%) compared with -11.25% (-17.8% to -9.8%),  $p < 0.0001$ . Patients diagnosed with myocarditis exhibited a higher left atrial filling index (LAFI) of 3.51 (2.76–4.67) in comparison to 1.75 (1.39–1.97);  $p < 0.05$ , and a higher left atrial stiffness index (LASI) of 0.26 (0.23–0.40) in contrast to 0.13 (0.11–0.15);  $p < 0.05$ , respectively.

The results of the study indicate a mild course of myocarditis in most adolescent patients. It has been observed that in overweight children, inflammatory changes in the heart persist longer, which may indicate a link between metabolic disorders and the course of the disease. Based on the results obtained, it can also be concluded that the use of angiotensin-converting enzyme inhibitors in children with myocarditis contributes to a faster normalization of left ventricular size and systolic function. Furthermore, the analysis showed that the left ventricular function index is useful in the diagnosis of myocarditis in adolescents. The data collected in the study suggest that in adolescents with mild myocarditis, left atrial function is impaired, as evidenced by reduced left atrial strain and increased stiffness what indicates left ventricular diastolic dysfunction.