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CARDIOMYOPATHY ASSOCIATED WITH VENTRICULAR PRE-EXCITATION OR DISSYNCHRONOUS CARDIOMYOPATHY IN PATIENTS WITH ASYMPTOMATIC AND SYMPTOMATIC WOLFF-PARKINSON-WHITE SYNDROME: PERSONAL EXPERIENCE IN PATIENT MANAGEMENT

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Aim. To study the causal relationship between the functioning of accessory pathway and changes in intraventricular hemodynamics in patients with dissynchronous cardiomyopathy.

Methods. The study included 83 patients with registered preexitation according to ECG data. Patients were divided into study and control group. The study group included 33 patients with diagnosed echocardiographic signs of dissynchronous cardiomyopathy (reduced ejection fraction (EF), increased chamber volume and/or decreased global longitudinal strain (GLS) of the left ventricle (LV)). The control group included 50 patients with Wolff-Parkinson-White syndrome/ phenomenon without dissynchrony.

Results. After radiofrequency ablation (RFA), patients in the study group showed natural normalization of the QRS complex width and LV GLS. The median QRS width before RFA was 110 ms [100; 120] and after RFA 70 ms [60; 80] ($p<0.0001$). The median LV GLS before RFA was -18.2% [-19.1; -17] and after RFA -21.3% [-23; -19.2] ($p<0.0001$). Despite the absence of statistically significant differences in the QRS width in patients in the study and control groups, statistically significant differences in the size and LV EF were revealed. In the study group, the median of end-diastolic volume (EDV) of LV (as a percentage of the parameter from the individual predicted norm) was 112% [102; 123] and EF was 64% [55; 65], and in patients from the control group 102% [97; 112] and 65% [64; 66], respectively. The level of significance of the differences for EDV was $p=0.0183$, for EF it was $p=0.0003$.

Conclusion. Risk factors of dissynchronous cardiomyopathy (age of patients, right-sided localization of accessory pathway, severity of ventricular preexcitation) are probably of important clinical significance, but are not specific.

Key words: Wolff-Parkinson-White syndrome; dyssynchrony; cardiomyopathy; pediatric population; global longitudinal strain

Conflict of interest: none.

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In patients with Wolff-Parkinson-White (WPW) syndrome, ventricular preexcitation caused by the presence of right-sided accessory atrioventricular pathways (APs) may lead to interventricular septal (IVS) dyssynchrony [1]. Due to dual ventricular activation via both the heart's normal conduction system (atrioventricular node and His bundle) and the APs, there is an electrical and mechanical eccentric activation of the ventricles, with premature contraction of the basal IVS relative to the rest of the myocardium. This results in disrupted synchrony of left ventricular (LV) myocardial contraction [2]. The IVS becomes thinned, resembling an aneurysmal deformity, with segmental dyskinesia and systolic bulging of the septum into the right ventricle (Figure 1). These changes contribute to the development of LV dyssynchrony, similar to what is observed in patients with left bundle branch block or chronic right ventricular pacing [3-5].

According to the literature, the development of cardiomyopathy (CMP) is more commonly observed in WPW patients without episodes of supraventricular tachycardia (SVT), or with only isolated episodes. This distinguishes dyssynchrony-induced CMP from the well-studied tachycardia-induced CMP. As with tachycardia-induced CMP, the dyssynchrony seen in WPW patients is usually reversible following radiofrequency catheter ablation (RFA) of the APs [6, 7].

It is believed that dyssynchrony-induced CMP occurs more frequently in younger patients, in those with

pronounced preexcitation on ECG, and in cases with right septal or right lateral AP localization [6]. However, CMP may also develop in adult patients [6, 8, 9], and left-sided APs do not preclude the onset of CMP [3].

The first report describing the development of dilated cardiomyopathy (DCMP) in children with WPW syndrome and dyssynchrony appeared in 2004. Nonetheless, many unresolved issues remain - particularly concerning the diagnosis of this condition - as there is still no universally accepted definition. Various terms can be found in the literature, such as “preexcitation-induced cardiomyopathy,” “symptomatic manifesting WPW phenomenon,” “ventricular dysfunction secondary to preexcitation,” and “ventricular preexcitation-associated cardiomyopathy” [6-9]. This inconsistency is largely due to the absence of a specific classification for this type of CMP in the current paediatric cardiomyopathy guidelines [10,11]. For the sake of clarity, this article uses the term dyssynchrony-induced cardiomyopathy.

In most of the available publications, the diagnosis of CMP in patients with Wolff-Parkinson-White (WPW) syndrome was established based on transthoracic echocardiography (TTE) findings - specifically, a left ventricular ejection fraction (LVEF) < 55% and a fractional shortening < 25% - in combination with clinical signs of heart failure (HF) [6]. More recently, speckle-tracking echocardiography (STE) has gained popularity for evaluating left ventricular systolic dysfunction. This method has demonstrated higher sensitivity for detecting contractile dysfunction of the LV, including at a “subclinical” level, compared to the traditional LVEF parameter [12,13]. Moreover, ventricular dyssynchrony itself may lead to inaccuracies in LVEF measurement [14].

Dyssynchrony-induced CMP generally has a favourable prognosis and, in most cases, resolves after RFA of the accessory pathway. Cases of reverse LV remodelling have also been described following spontaneous cessation of accessory pathway conduction, most frequently observed in children under 1 year of age [6,7]. The use of antiarrhythmic drugs - such as flecainide, amiodarone, and propafenone - can result in the suppression of conduction through the accessory pathway. However, literature suggests that pharmacological therapy offers only limited effectiveness, and many of these patients ultimately require RFA [6,15-18]. Given the increased risk of complications during RFA in patients weighing less than 15 kg [19], pharmacotherapy may be considered a temporary alternative in small children until they reach an optimal weight and developmental status suitable for safe ablation.

Study aim: To investigate the causal relationship between the function of an accessory pathway and the onset of intraventricular haemodynamic alterations leading to dyssynchrony-induced cardiomyopathy.

METHODS

Patient Characteristics

The study included 83 patients with documented ventricular pre-excitation based on ECG findings. All patients underwent evaluation and treatment between 2015 and 2025, and were divided into two groups: the main group and the control group.

The main group comprised 33 patients with echocardiographic signs of dyssynchrony-induced CMP, including reduced ejection fraction, chamber dilation, and/or reduced global longitudinal strain (GLS)of the left ventricle. Among these patients, 14 (42%) reported episodes of palpitations; however, only 5 (15%) had paroxysmal SVT documented on ECG. The remaining 19 patients (58%) were asymptomatic.

The control group consisted of 50 patients with WPW syndrome/phenomenon without echocardiographic evidence of ventricular dyssynchrony.

Exclusion criteria were as follows:

- Presence of congenital heart defects (CHDs), primary cardiomyopathies (hypertrophic, dilated, or restrictive), or laboratory-confirmed myocarditis;

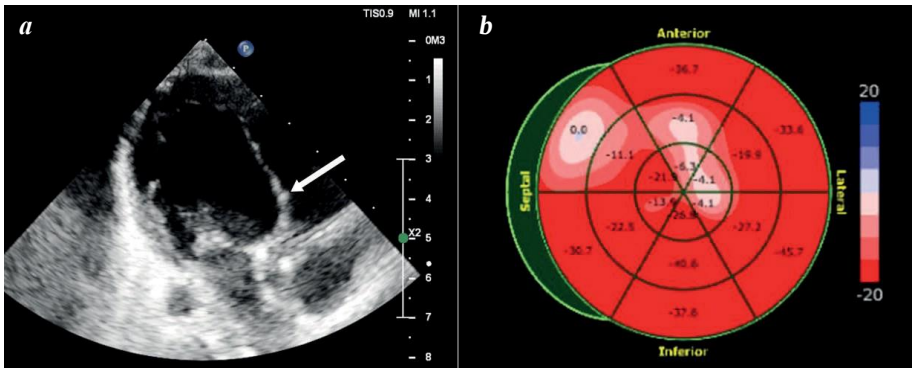

Fig. 1. Echocardiography (a) and speckle-tracking echocardiography (b): aneurysmal bulging of the interventricular septum (indicated by an arrow), accompanied by impaired longitudinal strain in the basal septal segment.

Table 1.

Clinical and Demographic Characteristics of the Patients

	Main group (n=33)	Control group (n=50)	p
Male sex, n (%)	17 (51.5)	28 (56)	0.689
PHA, years (Me [Q1; Q3])	14 [8;16]	11 [8;15]	0.462
PA (RFA), years (Me [Q1; Q3])	13 [8;15]	11 [9;16]	0.462
Manifest preexcitation, n (%)	26 (78.8)	36 (72)	0.487
Intermittent preexcitation, n (%)	7 (21.2)	14 (28)	0.492
Right-sided AP, n (%)	29 (87.8)	31 (62)	0.008
Left-sided AP, n (%)	6 (18.2)	18 (36)	0.074
Nodoventricular tract, n (%)	3 (9.1)	3 (6)	0.595

Note: PHA - primary hospitalisation age; PA - procedure age; RFA - radiofrequency ablation; AP - accessory pathway

• Presence of acute infectious diseases or exacerbations of chronic somatic conditions;
• Presence of arrhythmogenic CMP due to permanent or incessant tachyarrhythmias;
• History of endocrine disorders potentially associated with elevated average heart rate (e.g. hyperthyroidism, Addison's disease, pheochromocytoma, etc.);
• Lack of consent to participate in the study from the patients' parents or from the patients themselves if aged 15 or older.

All patients in both groups underwent RFA of the accessory pathway (AP). The procedure was considered successful if post-procedural ECG showed no signs of pre-excitation and no recurrence of tachycardia was observed during programmed stimulation. No RFA-related complications were reported during the early postoperative period.

Preoperative and postoperative evaluations (conducted 3-5 days after the procedure) included: 12-lead ECG to assess QRS duration; Holter ECG monitoring; TTE to evaluate chamber size, volume, and left ventricular systolic function; Speckle-tracking echocardiography to assess left ventricular GL.

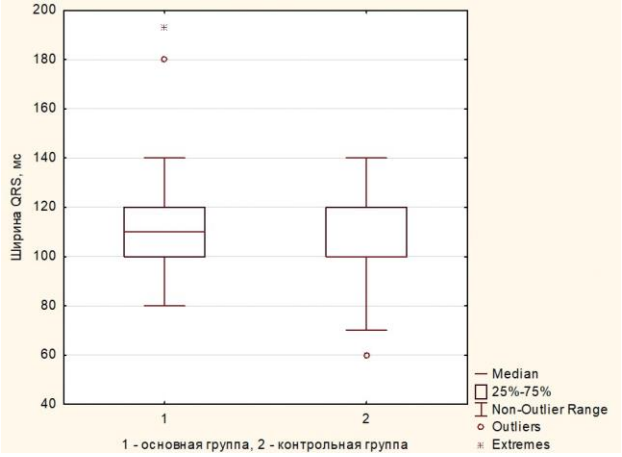

Fig. 2. Box plot of QRS width in the main and control groups before RFA.

Reference ECG parameters were derived from major global population-based paediatric ECG screening studies [20]. Holter ECG results were analysed in accordance with the standardised protocol [21]. Echocardiographic examinations were performed using the Affinity 70cv system (Philips, Netherlands) in line with the recommendations of the American Society of Echocardiography (ASE) [22].

In addition to standard chamber volume measurements, deviations in atrial volumes and left ventricular end-diastolic volume (EDV) from individual anthropometrically predicted normal values were assessed and expressed as percentages. This approach accounted for age and anthropometric heterogeneity among patients and was also suitable for longitudinal assessment of echocardiographic parameters as cardiac dimensions change with age and growth. These calculations were performed automatically using the "Child Heart" software application [23, 24].

LVEFwas measured using the Simpson's method, with values above 62-64%considered normal in children. GLS was analysed using QLAB software in accordance with the guidelines of the European Society of Cardiology (ESC), the European Association of Cardiovascular Imaging (EACVI), and the ASE) [25]. The GLS_Avg values were used in this study. A GLS_Avg threshold of -21% was adopted to indicate impaired systolic function.

Statistical analysis

Statistical analysis was performed using STATISTICA 10 software. Categorical variables are presented as absolute (n) and relative (%) frequencies, n (%). Continuous variables are expressed as medians (Me) and interquartile ranges [Q1; Q3], Me [Q1; Q3]. Differences between two related samples of quantitative variables were assessed using the Wilcoxon signed-rank test. Between-group comparisons of continuous variables were performed using the Mann-Whitney U test. The critical level of statistical significance for hypothesis testing in this study was set at 0.05.

Table 2.

Electrophysiological and Echocardiographic Characteristics of the Patients

	Main group (n=33)		Control group (n=50)	p
	Before RFA	After RFA		
QRS duration, ms (Me [Q1; Q3])	110 [100; 120]	70 [60; 80]	110 [100;120]	p_1<0.0001 p_2=0.6572
LV EDV, ml (Me [Q1; Q3])	78 [58; 88]	78 [54; 86]	72 [50; 90]	p_1=0.1952 p_2=0.5164
LV EDV %, (Me [Q1; Q3])	112 [102; 123]	105 [101; 118]	102 [97; 112]	p_1=0.1153 p_2=0.0183
LV EDI, ml/m² (Me [Q1; Q3])	54.82 [50.5; 60.6]	53.04 [50.5; 57.8]	51.195 [47.76; 55.13]	p_1=0.1624 p_2=0.0081
LV EF (B-mode), % (Me [Q1; Q3])	64 [55; 65]	64 [56; 65]	65 [64; 66]	p_1=0.2636 p_2=0.0003
LV GLS, % (Me [Q1; Q3])	-18.2 [-19.1; -17]	-21.3 [-23; -19.2]	-23.5 [-25.2; -21.9]	p_1<0.0001 p_2<0.0001

Nore: p1 - statistical significance level of the difference in the parameter within the WPW syndrome with dyssynchrony group before and after RFA; p2 - statistical significance level of the difference in the parameter between the main group (before RFA) and the control group; LV EDV - left ventricular end-diastolic volume; LV EDV% - percentage of the parameter relative to the individually predicted norm; LV EDI - left ventricular end-diastolic index; LV EF (B) - left ventricular ejection fraction by Simpson in B-mode; LV GLS - global longitudinal strain of the left ventricle.

RESULTS

The main group included 33 patients, comprising 17 boys (51.5%) and 16 girls (48.5%), aged from 9 months to 17 years. The median age was 14 [8; 16] years. The control group consisted of 50 patients, including 22 boys (44%) and 28 girls (56%), with ages ranging from 4 to 17 years and a median age of 11 [8; 15] years (Table 1). The absence of SVT episodes in some

patients, the rare occurrence of SVT episodes (lasting from several minutes to several hours and occurring from once per month to once per year), as well as normal 24-hour average heart rate values according to Holter ECG monitoring, suggest that preexcitation-related cardiomyopathy differs from tachycardia-induced cardiomyopathy.

In the main group, right-sided AP were significantly more common (p = 0.008). In two patients from the main group (6%) and two from the control group (4%), both right-sided and left-sided APs were identified simultaneously (Table 1).

ECG findings in both the main and control groups showed no significant difference in QRS duration (Figure 2). In the postoperative period, a consistent normalization of QRS duration was observed in patients from the main group. Among these patients, prior to the RFA, left ventricular enlargement was noted in only 5 patients (15.2%), and in 3 of them (9.1%) this was accompanied by atrial enlargement. Reduced LVEF was identified in 9 patients (27.2%).

Echocardiographic data demonstrated that patients with dyssynchrony had larger LV dimensions and lower LVEF compared to the control group (Figure 3). A statistically significant improvement in GLS of the LV was observed in the main group after the procedure. Improvements were also noted in LV contractility parameters (EF in B-mode using Simpson's method) and LV size (end-diastolic volume, EDVi), although these changes did not reach statistical significance (Table 2).

DISCUSSION

Exploring the causal relationship between the functioning of AP and the development of dyssynchrony-related, preexcitation-associated CMPis a relatively new area of research in arrhythmology. Despite an increasing number of recent publications on this topic, many questions remain unanswered.

According to the literature, dyssynchrony-induced CMP is more frequently observed in patients with the WPW phenomenon in the absence of SVT episodes or with only isolated episodes. These findings are consistent with our results, where 79% of patients had no history of tachycardia episodes based on clinical history and Holter ECG data.

Due to the lack of standardised diagnostic criteria and the absence of this condition in current CMP classifications, seven patients in the main group had previously been followed in other institutions under the diagnosis of dilated CMP with a comorbid WPW phenomenon. At the time of admission to our department, the therapy these patients had been receiving (various combinations of ACE inhibitors, beta-blockers, diuretics, mineralocorticoid receptor antagonists, digoxin, and cardiometabolic agents) had no significant clinical effect. In the majority of our patients (n = 24, 72.7%), only subclinical contractile impairment was identified - namely, a reduction in GLS despite preserved EF and normal LV dimensions. This suggests that reliance on the standard echocardiographic protocol alone may lead to underdiagnosis of dyssynchrony and the early manifestations of dyssynchrony-related CMP in children with WPW syndrome.

A.Miyazaki et al. (2022) noted that preexcitation-associated CMP more commonly develops in infants and young children, although cases have also been reported in adults aged 18-59 years [6]. In some infants, rapid progression of ventricular dysfunction occurs shortly after birth [26, 27]. In our study, dyssynchrony and contractile dysfunction were more frequently detected in school-aged children. The current prevalence of dyssynchrony-related CMP among patients with WPW phenomenon/ syndrome remains unknown, partly due to the fact that some patients undergo successful RFA of the APs prior to CMP onset. Others are diagnosed with idiopathic dilated CMP [6, 26], undergo HF therapy, or even end up on the waiting list for heart transplantation or implantation of a ventricular assist device [28, 29].

In line with previous studies [30], right-sided AP localisation was most commonly observed in our cohort. Although left-sided APs can also contribute to CMP development, they appear to do so less frequently.

According to current paediatric guidelines for RFA, in patients with WPW phenomenon and ventricular dysfunction secondary to preexcitation that is refractory to medical therapy, RFA is recommended with a class IIa indication, even for patients weighing less than 15 kg [9]. There are published cases of RFA being performed in infants as young as 2 and 4 months, who presented no episodes of SVT but experienced rapidly progressing LV dysfunction and HFafter birth. In one case, BiVAD implantation was required prior to ablation, but the device was removed 30 days after successful RFA, following the normalisation of echocardiographic parameters [29]. In another case, treatment with amiodarone proved ineffective [31].

In the literature, there are reports on the use of pharmacological therapy (amiodarone, flecainide, propafenone) in WPW syndrome as an alternative management strategy for small children until they reach the physical parameters necessary for performing RFA. In our practice, only one female patient received amiodarone therapy, which had been initiated following an episode of SVT . This patient had previously been observed in other clinics with a primary diagnosis of dilated cardiomyopathy and a concomitant diagnosis of WPW syndrome. Despite the administration of heart failure therapy and amiodarone, a single SVT episode was recorded, and the clinical and instrumental signs

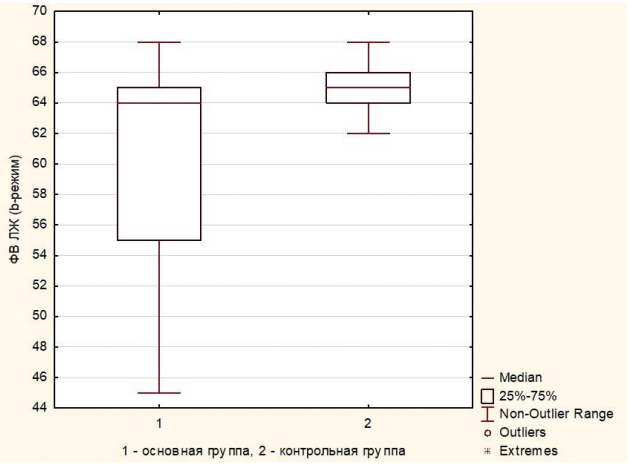

Fig. 3. Box plot of LV ejection fraction (Simpson method, B-mode) in the main and control groups before RFA.

of cardiomyopathy persisted. The patient was first admitted to our department at the age of 9 months, but RFA was only performed at 2 years and 10 months of age, once her body weight reached 16 kg. Complete reverse remodelling of the left ventricle was achieved only two years after RFA [32].

Recovery of cardiac function after RFA of an AP occurs over variable periods, ranging from several days to several years [6]. There are reports of cases in which restoration of LV function required more than three years. The factors that correlate with the duration and degree of functional recovery after RFA include the degree of baseline LV dysfunction and the patient's age (especially over 6 years). Accordingly, children older than 6 years with severe heart failure may experience only partial recovery of LV function following RFA [7, 8].

In our cohort, recovery of LV function was more often observed in the early postoperative period, likely due to the fact that most patients exhibited only subclinical contractile impairment (i.e. abnormal GLS values). Among patients with baseline LV remodelling (LV dilatation and reduced contractility), restoration of function was observed within 6 months to 3 years after RFA (Figure 4). The recovery of LV function after RFA, together with the initial presence of preexcitation on ECG, supports the role of eccentric myocardial activation in the development of dyssynchrony-induced CMP with a dilated phenotype and distinguishes CMP in patients with WPW from idiopathic DCM [6, 7].

The identified risk factors - such as patient age, right-sided AP localisation, and the extent of ventricular preexcitation - are likely to have important clinical implications, although they are not disease-specific. Therefore, identifying new predictors of dyssynchrony-induced CMP in patients with WPW phenomenon is essential for establishing prognosis and guiding treatment strategies.

According to the literature, LV dyssynchrony and abnormal motion of the interventricular septum precede LV remodelling (volume increase, reduced ejection fraction), which may mimic idiopathic DCM [33]. Hence, the prevalence of WPW patients with DCM-like features is lower than that of patients with dyssynchrony alone.

In our study, to assess LV function, we used both the EF and GLS. This approach was chosen because GLS is more reproducible than other strain parameters (such as circumferential or radial strain). Moreover, longitudinal strain analysis via speckle-tracking echocardiography is now widely available and integrated into most modern echocardiographic systems, enabling direct in-device measurement without the need to export images for offline analysis.

The bull's-eye plot (polar map) analysis enables assessment of longitudinal strain in each myocardial segment individually and also provides a global average strain value (GLS_Avg). In patients with WPW syndrome, special attention is paid to the basal and mid-myocardial segments, as APs are typically localised in these regions, and evaluation of apical segments is often limited due to suboptimal tracking.

The colour scale of the polar map ranges from dark red (representing high negative strain or shortening - i.e. normal function) to blue (representing positive strain or stretching - i.e. dysfunction). Affected segments usually show either low negative strain (light pink) or positive strain (blue). G. Abdelmohsen et al. demonstrated that segments adjacent to the AP exhibit an early strain peak, as they receive electrical impulses prematurely, resulting in significant dyssynchrony [3].

The contribution of genetic abnormalities to the development of dyssynchrony-induced CMP remains an open question. The available literature does not provide data on genotype-phenotype correlations in patients with WPW syndrome/phenomenon and dyssynchrony-induced CMP. Only M. Emmel et al. have expressed doubts regarding a genetic aetiology of this condition. The authors based their assumption on the absence of a family history among their patients and the recovery observed following cessation of AP conduction [1].

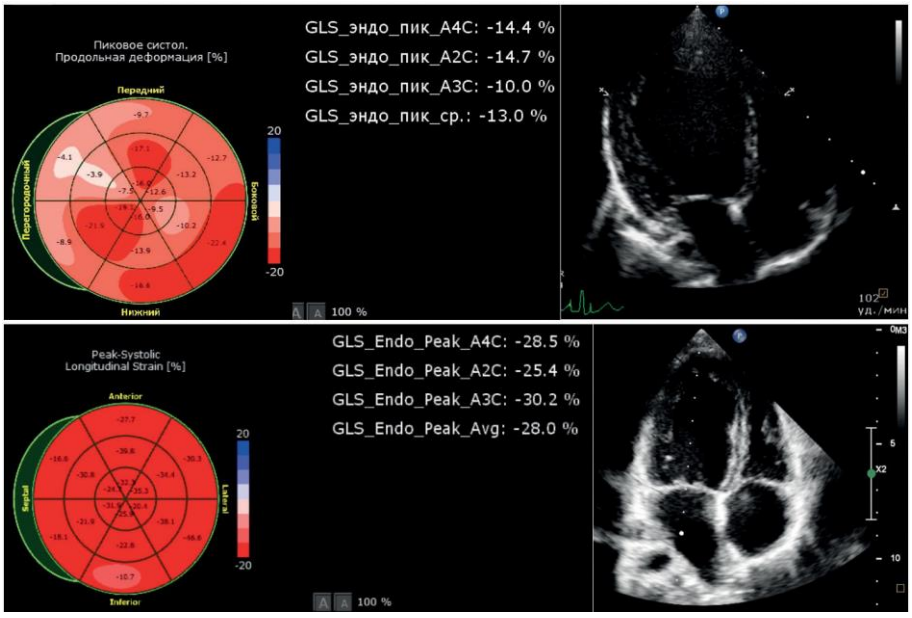

Fig. 4. Examples of echocardiographic measurements: speckle-tracking echocardiography, 18-segment polar map (left), transthoracic echocardiography (right). Dilatation of the left ventricle and reduced longitudinal strain (GLS) in the basal and mid segments of the anteroseptal region in a female patient with a right-sided AP before RFA (aged 9 months) (top). Normalisation of left ventricular size and longitudinal strain 2 years and 9 months after AP RFA (bottom)

However, it is well recognised that the clinical course of diseases may be influenced not only by mutations in specific genes but also by the presence of other genetic factors capable of modifying the effects of such mutations (modifier genes). The influence of genetic modifiers may aggravate disease severity (by increasing susceptibility or worsening progression), or

conversely, they may play a protective role in mitigating clinical manifestations.

CONCLUSION

The presence of pre-excitation and reverse remodelling of the left ventricle following cessation of accessory pathway conduction not only confirms the direct role of eccentric myocardial activation in the development of dyssynchrony-induced cardiomyopathy, but also distinguishes it from dilated CMP. Currently, there is a pressing need to standardise the diagnostic criteria and classification of pre-excitation-induced CMP in patients with the Wolff-Parkinson-White phenomenon.

We believe that in patients with WPW syndrome or phenomenon, echocardiographic assessment should routinely include Speckle-tracking echocardiography, which enables the detection of *subclinical* myocardial contractility impairments that may not be identified using conventional echocardiographic protocols. Early identification of such abnormalities should prompt timely RFA of the AP to prevent the progression of CMP and improve patient prognosis.

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