Cardiac Morphofunctional Characteristics of Individuals with ERP

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Based on electrocardiographic (ECG), electrophysiological, epicardial, and non-invasive electroanatomical mapping studies, the inferior and/or lateral part of the left ventricle (LV) is involved in individuals with early repolarization pattern (ERP) . In Brugada syndrome (BrS), which is also a form of J-wave syndrome, structural changes were described in the outflow tract of the right ventricle (mild fibrosis, decreased connexin-43 expression, increased collagen content, or fibro-adipose infiltration), while wall motion abnormalities and mild dilatation have been noted in imaging studies. These structural changes are more frequently observed in patients who have died of sudden cardiac death (SCD). It is reasonable to assume that morphological changes, presumably similar to BrS, are also present in individuals with ERP, in myocardial regions involved in pathomechanism.

early repolarization pattern morphofunctional changes echocardiography

1. Conventional Echocardiography

Echocardiography (ECHO) represents the most common non-invasive imaging technique that provides useful information about the structure and function of the heart: it is highly sensitive and specific in regard to the diagnosis of structural heart diseases and possible substrates for sudden cardiac death (SCD); it can be considered the first-line imaging technique for the primary prevention of SCD [1]. Certain cardiac parameters differ depending on age, gender, and body surface area (BSA), even in the absence of heart disease [2][3][4]: it is important to consider this fact when planning the methodology and interpreting the results of any morphological study.

Quattrini et al. investigated the cardiac characteristics associated with ERP in elite athletes from the Italian national team, during their training for the Olympic Games: by analyzing the ECHO parameters, they found that left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall thickness (LVPWT), and left ventricular mass (LVM) were greater in individuals with ERP; there was no significant difference between the individuals with ERP (the ERP+ group) and those without ERP (the ERP- group), in regard to the other structural and functional parameters [5].

Reinhard et al. studied the ECHO characteristics related to ERP in healthy athletes, for 6 years. The age of the population was 21 ± 5 years, and ERP was present in 17% of cases. The individuals with ERP+ were predominantly male. The study found that ERP was not associated with the type of sport performed; however, a trend was observed between the prevalence of ERP and the dynamics of the sport. Among the ECHO parameters, in the ERP+ group, the relative heart volume was higher in males, while the LVPWT proved to be greater in the

female population. All the other studied ECHO parameters were similar in the two groups. Left ventricular geometry (normal shape, concentric remodeling, concentric hypertrophy, eccentric hypertrophy) also occurred in the same proportion in the two groups. The correlation between high-risk subgroups of ERP (inferior type, J wave > 2 mV, notching type, or horizontal/descending ST slope) and ECHO parameters were also examined. Notching-type ERP was associated with greater left atrial diameter (LAD), LVM, and relative heart volume [6].

In 2015, Serra-Grim et al. published the results of a retrospective study, covering nearly 40 years, that followed the parameters of 299 professional football players. The study analyzed the clinical and ECHO parameters associated with ERP: the percentage of ERP+ individuals was 34.1%; the ejection fraction (EF), LVPWT, interventricular septum (IVS), and LAD were similar between the ERP+ and ERP- individuals; only the LVEDD differed, being significantly higher in the ERP+ group [7].

A Swedish study investigated the associations between ERP and cardiac structure and function, as well as the response of ERP to strenuous exercise. The participants were men over the age of 45, doing cross-country running. A total of 151 individuals participated in the study, of which 67 were in the ERP+ group. All the subjects underwent a detailed pre- and post-race cardiological examination, including transthoracic ECHO. The study analyzed relatively few ECHO parameters, and found only one parameter that differed between the two groups: the ratio (E/A) between peak early diastolic transmitral flow velocity (E) and peak late diastolic transmitral flow velocity (A), which was higher in the ERP+ group before the exercise. During the post-run examination, this difference between the groups was not detectable [8].

In a retrospective study, Miragoli et al. analyzed the data of young, healthy athletes who underwent routine cardiological examination at the University Hospital of Parma between 2006 and 2017. Data from 414 subjects, aged 12 to 17 years, were processed. The participants' electrocardiograms and ECHO data were also collected. The results showed no significant differences between the groups, when the left ventricular diameters and volumes were examined. At the same time, in the ERP+ group, the degree of left ventricular hypertrophy was more pronounced, as evidenced by greater IVS, LVPWT, and LVM. In addition, the relative wall thickness (RWT) and LVM/BSA ratio were also higher. These results suggest concentric remodeling, so ERP was considered a possible marker for geometrical remodeling of the LV [9].

The Gutenberg Health Study was a population-based cohort study in Germany, designed as a prospective, observational, single-center study, to investigate cardiovascular risk factors. As part of the study, Trenkwalder et al. investigated the association between cardiac morphofunctional parameters and the presence of ERP, using a large number of cases (6784 men, 7094 women). The population ranged in age from 35 to 74 years, with a balanced gender ratio. The standard ECHO characteristics of ERP+ individuals were compared with those of ERP- individuals. Analysis of structural parameters in the male population revealed a significant difference in LVEDD, left ventricular end-systolic diameter (LVESD), and LVM, which were smaller in the ERP+ group. Among the markers of LV diastolic and systolic function, the E/A ratio and peak velocity of the early diastolic mitral annular motion (E') parameters were significantly higher, and the E/E' ratio was lower. The left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and stroke volume were also smaller. There was no

significant difference between the groups in the male population, in terms of IVS, LVPWT, RWT, deceleration time, and EF parameters [10]. As with ERP+ men, ERP+ women had smaller LVEDD and LVESD, but LVM was similar between the groups. In contrast to the men, the women in the ERP+ group had greater IVS, LVPWT, and RWT. In the female population, the parameters of LV function showed significantly smaller LVEDV and stroke volume in the ERP+ group, whereas LVESV showed only a trend towards a smaller value in the ERP+ group; however, the EF, deceleration time, E', E/A ratio, and E/E' ratio were the same in both groups [10].

Ilkhanoff et al. investigated the relationship between ERP and ECHO parameters in the middle-aged population across 25 years, as part of the CARDIA study. From their results, individuals who maintained ERP during the research period had significantly smaller LVEDD, LVESD, and LVM. According to the authors' interpretation, the persistence of ERP from young adulthood was related to favorable structural and functional parameters [11].

In their comprehensive study, Szabó et al. examined the echocardiographic characteristics of young men with ERP, evaluating a total of 31 parameters: in this study, the control group of the ERP+ population had similar BSA. There was a significant difference in only two parameters: the LVESV was smaller, and a mild mitral regurgitation was more common in the ERP+ group. The increased incidence of mitral regurgitation in the ERP+ group was investigated and demonstrated for the first time, although the study was performed on a relatively small number of cases [12].

According to some studies, the presence of LV false tendons is also associated with ventricular arrhythmias [13]. In their study, Liu et al. hypothesized that the presence of these fibromuscular structures might be related to the presence of ERP. According to their results, the dimensions and volumes of the left atrium, LV, and right ventricle were similar in the ERP+ and ERP- groups. The frequency of false tendons was also the same in both groups, but transverse tendons were more frequent than longitudinal tendons in the ERP+ group [14].

2. Speckle Tracking Echocardiography

Speckle tracking echocardiography (STE) is a relatively new, non-invasive imaging technique that can objectively assess global and regional myocardial function. STE can be used to determine the so-called deformation parameters (e.g., global longitudinal strain) that characterize well the mechanics of the myocardial segments. STE has a higher diagnostic value in detecting cardiac dysfunction than conventional two-dimensional (2D) ECHO [15] [16].

In their study, Gülel et al. selected a control group of individuals with ERP, based on age and body mass index. In addition to 2D ECHO examination, STE was used to characterize the myocardium. Only one functional parameter differed between the two groups: the E/E' ratio, which was smaller in the ERP+ group. No other differences were found between the groups, in regard to the standard ECHO parameters. When the LV deformation parameters were analyzed, no significant differences were found between the ERP+ and ERP- groups regarding the LV longitudinal parameters. Analysis of the circumferential deformation parameters showed that the early diastolic strain rate (SRE) at the level of the apex and the global SRE were higher in the ERP+ group. In addition, for the

radial deformation parameters, peak strain and SRE differed between the groups, being lower in the ERP+ subjects [17].

Çöllüoğlu et al. compared the cardiac characteristics of 50 ERP+ and 50 ERP- healthy athletes. In addition to the 2D ECHO examination, the functional parameters of the LV were also analyzed, using STE. Right ventricular dimension, infero-lateral wall thickness, aortic root diameter, LAD, RWT, and LVESV were larger in the ERP+ group, and the tranmitral E-wave was smaller. The results of 2D STE also showed a significant difference between the two groups, with respect to several parameters. In the ERP+ group, the global longitudinal strain was smaller, and the strain rate, measured in the apical three-chamber view, was also smaller in the ERP+ group. The groups' global circumferential strain and strain rate parameters were similar [18].

3. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (cMRI) is a rapidly developing non-invasive imaging technique that can be used to describe the structure and function of the heart in detail. The advantage of cMRI over conventional ECHO examination is that it characterizes the structure of the heart more comprehensively, and provides unique information about myocardial scarring, viability, and mass. Many experts consider cMRI to be the method of choice for assessing myocardial function [19][20].

The Dallas Heart Study examined the relationship between ERP and LVM. More than 3000 men and women participated in the study, and the cardiac parameters were determined by cMRI. Certain factors that may affect cardiac parameters, such as blood pressure and BSA, were similar in the ERP+ and ERP- groups. In the ERP+ population, LVM was greater in both men and women. There were no differences between the groups, in regard to other parameters [21].

In a recently published study, the presence of J-point elevation in individuals with hypertrophic cardiomyopathy was shown to increase the risk of ventricular arrhythmias and SCD [22]. In addition, Azevedo et al. hypothesized that in individuals with hypertrophic cardiomyopathy, ERP+ individuals have greater LVM. In their retrospective study, Azevedo et al. reviewed the cMRI scans of 85 individuals. Larger LVEDV and LVM were observed in ERP+ patients, whereas the EF was smaller. The baseline parameters of the two groups were similar [23].

Table 1 summarizes the studies that have investigated the structural and functional parameters associated with ERP.

Table 1. Characteristics of studies investigating cardiac morphological and functional parameters in individuals with ERP, from different patient populations.

Study	Imaging Technique	n	Age, Years	Men, %	ERP, %	Parameter Difference *
Athletes						

Study	Imaging Technique	n	Age, Years	Men, %	ERP, %	Parameter Difference *
Quattrini et al. [5]	ECHO	704	25 ± 5	62	14.0	3
Reinhard et al. [6]	ECHO	623	21 ± 5	60.7	17.3	5
Serra-Grim et al. [7]	ECHO	299	20 ± 6.4	66	31.4	1
Aagaard et al. [8]	ECHO	151	50.9 ± 4.9	100	44.3	1
Miragoli et al. [9]	ECHO	414	13.6 ± 1.8	72	22.0	3
Çöllüoğlu et al. [18]	ECHO, STE	100	35.0 ± 11.5	49	50	9
General population						
Trenkwalder et al. [10]	ECHO	13878	54.6 ± 11	48.9	6.6	12
Ilkhanoff et al. [11]	ECHO	1701	25.2 ± 3.5	41.9	-	3
Szabó et al. [12]	ECHO	62	22.5 ± 1.5	100	48.3	2
Liu et al. [14]	ECHO	77	31.6 ± 7.2	96.1	42.8	1
Gülel et al. [17]	ECHO, STE	60	25.5 ± 6.2	75	58.3	5
McNamara et al. [21]	cMRI	2753	43 ± 9.5	45.1	9.9	1
Patients with HCM						
Azevedo et al. [23]	cMRI	85	56 ± 15	62.3	10.5	3

ECHO—echocardiography; cMRI—cardiac magnetic resonance imaging; STE—speckle tracking echocardiography; n—population size; ERP—early repolarization pattern; HCM—hypertrophic cardiomyopathy; * number of parameters showing significant difference when comparing ERP+ and ERP− groups, including results of comparisons between different subgroups.

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