Cardiology in the Young

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Analysis of the influencing factors associated with dyssynchrony and cardiac dysfunction in children with ventricular pre-excitation

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Original Article

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Abstract

Objective: To investigate the correlation between ventricular pre-excitation-related dyssynchrony, on cardiac dysfunction, and recovery. *Methods and Results:* This study included 76 children (39 boys and 37 girls) with a median age of 5.25 (2.67–10.75) years. The patients with pre-excitation-related cardiac dysfunction (cardiac dysfunction group, n = 34) had a longer standard deviation of the time-to-peak systolic strain of the left ventricle and larger difference between the maximum and minimum times-to-peak systolic strain than those with a normal cardiac function (normal function group, n = 42) (51.77 ± 24.70 ms versus 33.29 ± 9.48 ms, $p < 0.05$; 185.82 ± 92.51 ms versus 111.93 ± 34.27 ms, $p < 0.05$, respectively). The cardiac dysfunction group had a maximum time-to-peak systolic strain at the basal segments of the anterior and posterior septa and the normal function group at the basal segments of anterolateral and posterolateral walls. The prevalence of ventricular septal dyssynchrony in the cardiac dysfunction group was significantly higher than that in the normal function group (94.1% (32/34) versus 7.7% (3/42), $p < 0.05$). The patients with ventricular septal dyssynchrony (n = 35) had a significantly higher prevalence of intra-left ventricular systolic dyssynchrony than those with ventricular septal synchrony (n = 41) (57.1% (20/35) versus 14.6% (6/41), $p < 0.05$). During follow-up after pathway ablation, the patients who recovered from intra-left ventricular dyssynchrony (n = 29) had a shorter left ventricular ejection fraction recovery time than those who did not (n = 5) ($\chi^2 = 5.94$, $p < 0.05$). Among the patients who recovered, 93.1% (27/29) had a normalised standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain within 1 month after ablation. *Conclusion:* Ventricular pre-excitation may cause ventricular septal dyssynchrony; thus, attention must be paid to intra-left ventricular dyssynchrony and cardiac dysfunction. Whether intra-left ventricular systolic dyssynchrony can resolve within 1 month may be a new early predictor of patient prognosis.

The key mechanism of ventricular pre-excitation-related cardiac dysfunction is electrical–mechanical dyssynchrony caused by ventricular pre-excitation, which may lead to remodelling and progressive dilation of left ventricle and cardiac dysfunction.[1] Affected patients usually develop a specific type of dilated cardiomyopathy. This type of dilated cardiomyopathy has been referred to as pre-excitation-induced dilated cardiomyopathy.[2,3] Previous studies have shown that pre-excitation-related cardiac dysfunction mostly occurs in patients with right-dominant accessory pathways.[4] However, not all right-sided pre-excitation leads to cardiac dysfunction.[5] Even for pathways at the same location, the effects on cardiac function are incongruent. The exact mechanism for such a difference is uncertain, and controversy exists over the pathogenic risk factors.[5–7] Additionally, no studies have yet investigated the relationship between recovery from ventricular dyssynchrony and cardiac dysfunction after the abolishment of pre-excitation. Therefore, this study aimed to investigate the effects of pre-excitation-related dyssynchrony on cardiac dysfunction and identify the factors influencing cardiac function recovery to aid in early diagnosis and selection of the proper timing for the implementation of therapeutic interventions.

Participants

The clinical data of 76 consecutive children with persistent right-sided pre-excitation who underwent catheter ablation between September 2017 and January 2020 in the Pediatric Cardiology Department of the First Hospital of Tsinghua University were analysed. All patients met the indications for catheter ablation.[8,9] The patients were divided into a pre-excitation-related cardiac dysfunction group (cardiac dysfunction group) and a normal cardiac function

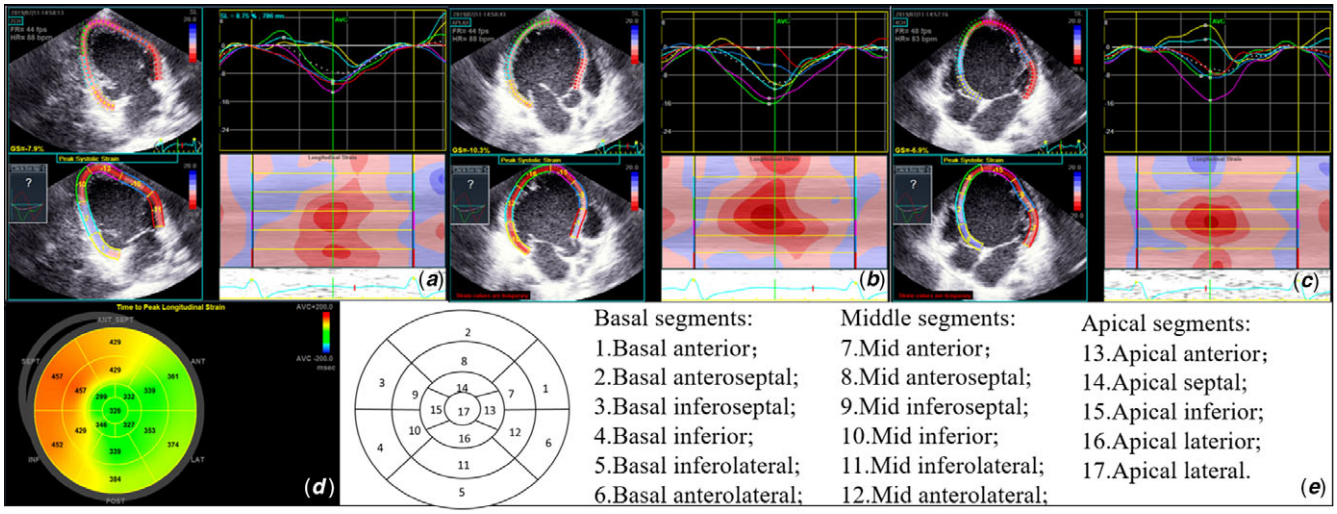

Figure 1. Strain–time curves of the left ventricular (LV) long-axis apical two, three and four chamber views measured via two-dimensional speckle tracking imaging in a patient with ventricular pre-excitation (VPE) related cardiac dysfunction. (***a***) Strain–time curves of the apical two-chamber view. (***b***) Strain–time curves of the apical three-chamber view. (***c***) Strain–time curves of the apical four chamber view. The strain value was positive (yellow and blue) at the septum and negative at all other segments. The septum presented diastole, while the other segments contracted; this phenomenon was interpreted as ventricular septal dyssynchrony (classical pattern). (***d***) The bull's-eye plot of the LV time-to-peak systolic strain (Ts) shows a delayed ventricular septal Ts (yellow) and dyssynchrony of the other segments in LV (green). (***e***) The bull's-eye plot shows the sections of the left ventricle.

group (normal function group). The diagnostic criteria for pre-excitation-related cardiac dysfunction were as follows: (1) 12-lead electrocardiography showing pre-excitation of the right pathway; (2) echocardiography showing left ventricular dilation and/or cardiac dysfunction; (3) normal cardiac anatomical structure; and (4) normalisation or improvement of the ventricular size and cardiac function after successful blocking of pathway anterograde conduction via catheter ablation.[2,3] The exclusion criteria included intermittent pre-excitation, tachycardiomyopathy, CHD, hypertrophic cardiomyopathy, primary hereditary dilated cardiomyopathy, non-compaction of the ventricular myocardium, and a positive family history of cardiomyopathy.

Methods

Pre-operative process

Anti-arrhythmic drugs were withdrawn for at least five half-lives before ablation. Twelve-lead electrocardiography was performed to measure the QRS interval under pre-excitation conditions. Three-day electrocardiography monitoring was performed in each patient before echocardiography, which showed a persistent sinus rhythm and pre-excitation with no tachycardia onset.

Evaluation of the cardiac size and function

Transthoracic echocardiogram (GE Healthcare, Wisconsin, USA; Vivid E9 ultrasound system, 3.5-Hz frequency probe) was used to evaluate the left ventricular size and function. The left ventricular diastolic diameter was measured on the parasternal left ventricular long-axis section. The left ventricular end-diastolic volume and ejection fraction were calculated using the biplane Simpson's method. The corrected left ventricular end-diastolic volume/body surface area (m^2) and left ventricular diastolic diameter Z scores were used to evaluate the left ventricular size. Left ventricular diastolic diameter Z scores higher than the mean plus two standard deviations (X + SD (Z score > 2)) for the same body surface were considered to indicate enlargement. Left ventricular ejection fractions of ≤ 55% were regarded to indicate cardiac dysfunction.

Evaluation of ventricular dyssynchrony

Interventricular and left ventricular wall motion dyssynchronies were evaluated as follows: we used two-dimensional speckle-tracking imaging and tissue Doppler imaging to collect apical long-axis two-, three-, and four-chamber views with a frame rate of 60–90 frames/s. We obtained data by performing offline analysis and measurement using EchoPAC 7.0.

Interventricular mechanical delay was measured via tissue Doppler imaging as the absolute difference in the time-to-systolic peak between the basal segments of the left and right lateral walls. Three measurements were performed, and the average value was calculated. An interventricular mechanical delay of > 40 ms indicated interventricular dyssynchrony.[5,10]

We used two-dimensional speckle-tracking imaging to perform two-dimensional strain analysis (Fig 1a–c). The epicardial boundary was drawn manually or using a software. The width of the area of interest was adjusted manually to match the endocardial and epicardial boundaries. The tissue grey scale tracked the position and movement of the myocardium acoustic speckles in the area of interest frame by frame during the entire cardiac cycle. The strain values for 17 segments of the left ventricle were measured according to the motion trajectory of the speckles. Measurements with more than one segment of inadequate tracking within at least one apical view were excluded. The time-to-peak systolic strain of the left ventricle was defined as the interval between the onset of the QRS wave and left ventricular longitudinal systolic strain peak value during the cardiac cycle. The standard deviation of the time-to-peak systolic strain for the 17 segments along the left ventricular long axis was calculated (Fig 1d and e). The locations demonstrating the maximum time-to-peak systolic strain and difference in the maximum time-to-peak systolic strain in the left ventricle between the two groups were recorded. The global strain values and average three-, four-, and two-chamber strain values were obtained individually.[11] A standard

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Table 1. Clinical data for patients with or without cardiac dysfunction before ablation

	VPE-related cardiac dysfunction group	Normal function group	p-Value
n	34	42	
Age (years)	2.88 (1.66–8.25)*	6.85 (3.79–11.77)	0.01
Weight (kg)	21.89 ± 17.85*	32.79 ± 20.22	0.02
QRS duration(ms)	127.88 ± 19.22*	116.28 ± 13.96	0.01
LVEF (%)	41.66 ± 13.47*	61.98 ± 3.49	0.001
LVDd (mm)	46.76 ± 15.79*	38.29 ± 6.20	0.01
LVEDV/m^2	101.06 ± 69.28*	44.72 ± 6.99	0.001
LVDd Z scores	14.85 ± 13.98*	−0.95 ± 0.48	0.001

LVDd = left ventricular diastolic diameter; LVEDV/m^2 = left ventricular end-diastolic volume /body surface area (m^2); LVEF = left ventricular ejection fraction; VPE = ventricular pre-excitation .
*Compared with control group $p < 0.05$.

deviation of the time-to-peak systolic strain of > 40 ms or a difference between the maximum and minimum times-to-peak systolic strain of > 150 ms indicated intra-left ventricular dyssynchrony.[5,10]

Ventricular septal dyssynchrony was evaluated as follows: we used two-dimensional speckle-tracking imaging to perform two-dimensional left ventricular strain analysis. Apical long-axis two-, three-, and four-chamber strain–time curves were obtained (Fig 1a–c). Septal dyssynchrony was defined as paradoxical segmental dilation of the ventricular septum during systole, as shown by the strain–time curves of one or more sections.[12] Figure 1c shows the classical septal dyssynchrony pattern and strain–time curves of the apical four-chamber view measured on two-dimensional speckle-tracking imaging in a patient with cardiac dysfunction. The strain value was positive (yellow and blue) at the septum and negative at all other segments. Paradoxical diastole of the septum was present, while the other segments were contracting; this phenomenon was interpreted as ventricular septal dyssynchrony.

Intracardiac electrophysiological study and catheter ablation (radiofrequency/cryoablation)

The methods were the same as those reported in a previous literature.[13]

Follow-up

The patients were followed up after 7 days and 1, 3, 6, 9, and 12 months and every 4–6 months thereafter. Electrocardiography and echocardiography were performed at each visit to identify any recurrence of pre-excitation and evaluate the left ventricular diastolic diameter and ejection fraction. Normalisation of intra-left ventricular dyssynchrony was defined as a standard deviation of the time-to-peak systolic strain of ≤ 40 ms and a difference between the maximum and minimum times-to-peak systolic strain of ≤ 150 ms. The end point of follow-up was a left ventricular ejection fraction of > 55% and normalisation of the left ventricular diastolic diameter during two successive visits.

Statistical analysis

Statistical analysis was performed using SPSS 22. Continuous variables were presented as means ± standard deviations or medians (25–75%). The two groups were compared using an independent/paired Student's t-test or non-parametric test. Categorical variables were presented as percentages or ratios. The chi-square test was used to perform the analysis. Receiver operating characteristic curves were used to evaluate the predictive value of the parameters associated with dyssynchrony for the development of pre-excitation-induced dilated cardiomyopathy as well as their sensitivity and specificity. Left ventricular ejection fraction recovery between the two groups after ablation was compared using the Kaplan–Meier test (log-rank method). Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Clinical characteristics

This study included 76 children (39 boys and 37 girls) with a median age of 5.25 (2.67–10.75) years and weight of 27.83 ± 19.87 kg. Thirty-four children were divided into the cardiac dysfunction group and 42 children into the normal function group. The median age of the patients in the cardiac dysfunction group was 2.88 (1.66–8.25) years (Table 1).

The left ventricular diastolic diameter and left ventricular end-diastolic volume/m^2, left ventricular diastolic diameter Z score, and QRS interval in the cardiac dysfunction group were significantly larger, higher, and longer than those in the normal function group, respectively (Table 1). The global strain values and average three-, four-, and two-chamber strain values in the cardiac dysfunction group were significantly lower than those in the normal function group ($p < 0.05$). These results indicated that the cardiac systolic function of the patients in the cardiac dysfunction group decreased compared with that in the normal function group (Fig 2).

Among the patients with cardiac dysfunction, 82.4% (28/34) had taken anti-heart failure medications, including cardiotonic, diuretic, and reverse remodelling drugs, for a median duration of 9 (2–25) months. All 76 children underwent catheter ablation (radiofrequency ablation: n = 62; cryoablation: n = 14). The success rate was 100%, while the recurrence rate was 2.6% (2/76). All recurrent cases were successfully ablated on the second attempt. No complications were associated with ablation. In the cardiac dysfunction group, 79.4% (27/34) of the patients had right free wall pathways, while 20.6% (7/34) had right septal pathways. In the normal function group, 47.6% (20/42) had right free wall pathways, while 52.4% (22/42) had right septal pathways.

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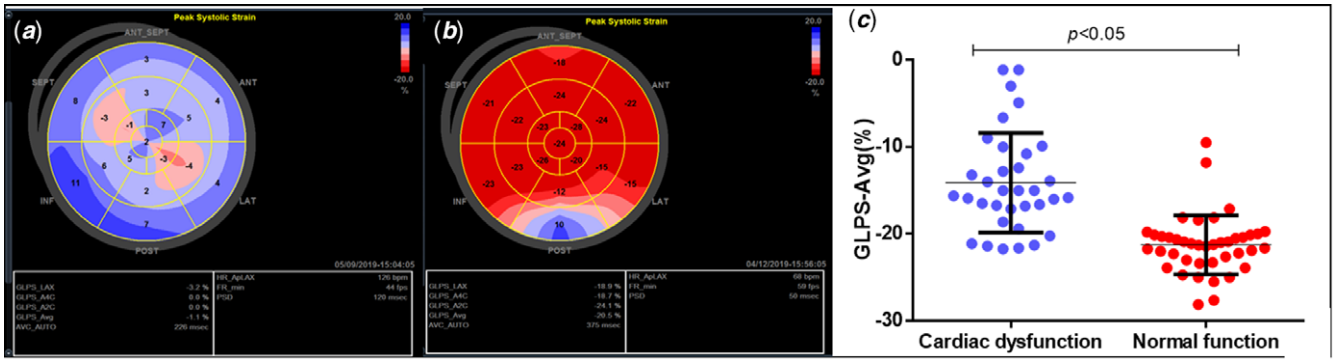

Figure 2. Bull's-eye plot of myocardial systolic strain and comparison of the average global systolic strain value between the ventricular pre-excitation (VPE)-related cardiac dysfunction and normal functional groups before ablation. (***a***) A patient with VPE-related cardiac dysfunction. The bull's-eye plot shows decreased systolic strain values in all segments of the left ventricle (LV, blue and pink). (***b***) A patient with normal cardiac function. The bull's-eye plot shows decreased systolic strain values in the inferior wall of the LV (blue and pink) and normal values in the other segments (red). (***c***) GLPS-Avg: Average global longitudinal peak systolic strain value.

Association between ventricular dyssynchrony and cardiac function

Interventricular dyssynchrony was identified in both cardiac dysfunction and normal function groups. However, there was no significant difference in the interventricular mechanical delay between them (56.32 ± 29.06 ms versus 57.14 ± 22.66 ms, $p > 0.05$).

The standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain in the cardiac dysfunction group were significantly longer and larger than those of in the normal function group, respectively (51.77 ± 24.70 ms versus 33.29 ± 9.48 ms, $p < 0.05$; 185.82 ± 92.51 ms versus 111.93 ± 34.27 ms, $p < 0.05$, respectively) (Fig 3a and b). The prevalence of intra-left ventricular systolic dyssynchrony in the cardiac dysfunction group was significantly higher than that in the normal function group (55.9% (19/34) versus 16.7% (7/42), $p < 0.05$) (Fig 3c).

Difference in the maximum left ventricular time-to-peak systolic strain and its association with cardiac function

The maximum time-to-peak systolic strain in the anterior wall (basal, middle, and apical segments), septum (basal, middle, and apex of the anterior and posterior basal septal segments), inferior wall (basal, middle, and apical segments), and cardiac apex (Fig 4a and c) significantly differed between the cardiac dysfunction and normal function groups ($p < 0.05$).

The cardiac dysfunction group had the maximum left ventricular time-to-peak systolic strain at the basal segments of the anterior and posterior septa, and the normal function group at the basal segments of the anterolateral and posterolateral walls (Fig 4b).

Association between ventricular septal dyssynchrony and intra-left ventricular systolic dyssynchrony

The prevalence of ventricular septal dyssynchrony in the cardiac dysfunction group was significantly higher than that in the normal function group (94.1% (32/34) versus 7.7% (3/42), $p < 0.05$). The patients were further divided into ventricular septal dyssynchrony ($n = 35$) and ventricular septal synchrony ($n = 41$) groups. The standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain in the ventricular septal dyssynchrony group were longer and larger than those in the ventricular septal synchrony group, respectively(51.52 ± 24.22 ms versus 32.55 ± 9.12 ms, $p < 0.05$; 182.97 ± 91.39 ms versus 110.32 ± 34.27 ms, $p < 0.05$, respectively).

The prevalence of intra-left ventricular systolic dyssynchrony in the ventricular septal dyssynchrony group (positive classical pattern) was significantly higher than that in the ventricular septal synchrony group (negative classical pattern (57.1% (20/35)versus 14.6% (6/41), $p < 0.05$) (Fig 3d).

Predictive value of the dyssynchrony parameters for cardiac dysfunction

The risk threshold values of the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain for the development of pre-excitation-related cardiac dysfunction were evaluated via the receiver operating characteristic curve analysis($n = 76$). The risk threshold value of the standard deviation of the time-to-peak systolic strain for predicting the development of cardiac dysfunction was 42.74 ms, with a sensitivity of 55.9% and specificity of 88.1% ($p < 0.05$). The area under curve value was 0.75, with a 95% confidence interval of 0.64–0.86 (Fig 4). The risk threshold value of the difference between the maximum and minimum times-to-peak systolic strain was 129.50 ms, with a sensitivity of 70.6% and specificity of 76.2%. The area under curve value was 0.79, with a 95% confidence interval of 0.68–0.89 (Fig 5).

Association between cardiac dysfunction recovery and changes in intra-left ventricular systolic dyssynchrony

The median post-ablation follow-up duration for the 34 patients in the cardiac dysfunction group was 12 (10.25–18) months. The left ventricular diastolic diameter and left ventricular diastolic diameter Z scores decreased, while the left ventricular ejection fraction increased after ablation. The mean overall myocardial strain value increased. The standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain decreased significantly after ablation (51.77 ± 24.70 ms versus 33.95 ± 14.70 ms, $p < 0.05$; 185.82 ± 92.51 ms versus 115.59 ± 65.86 ms, $p < 0.05$) (Table 2).

The 34 patients with pre-excitation-induced dilated cardiomyopathy were followed up to observe the relationship between left ventricular ejection fraction recovery and intra-left ventricular systolic dyssynchrony recovery. The median time for the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain was 1 week. The median time to left ventricular ejection fraction recovery was 3 months. The patients were again further divided into

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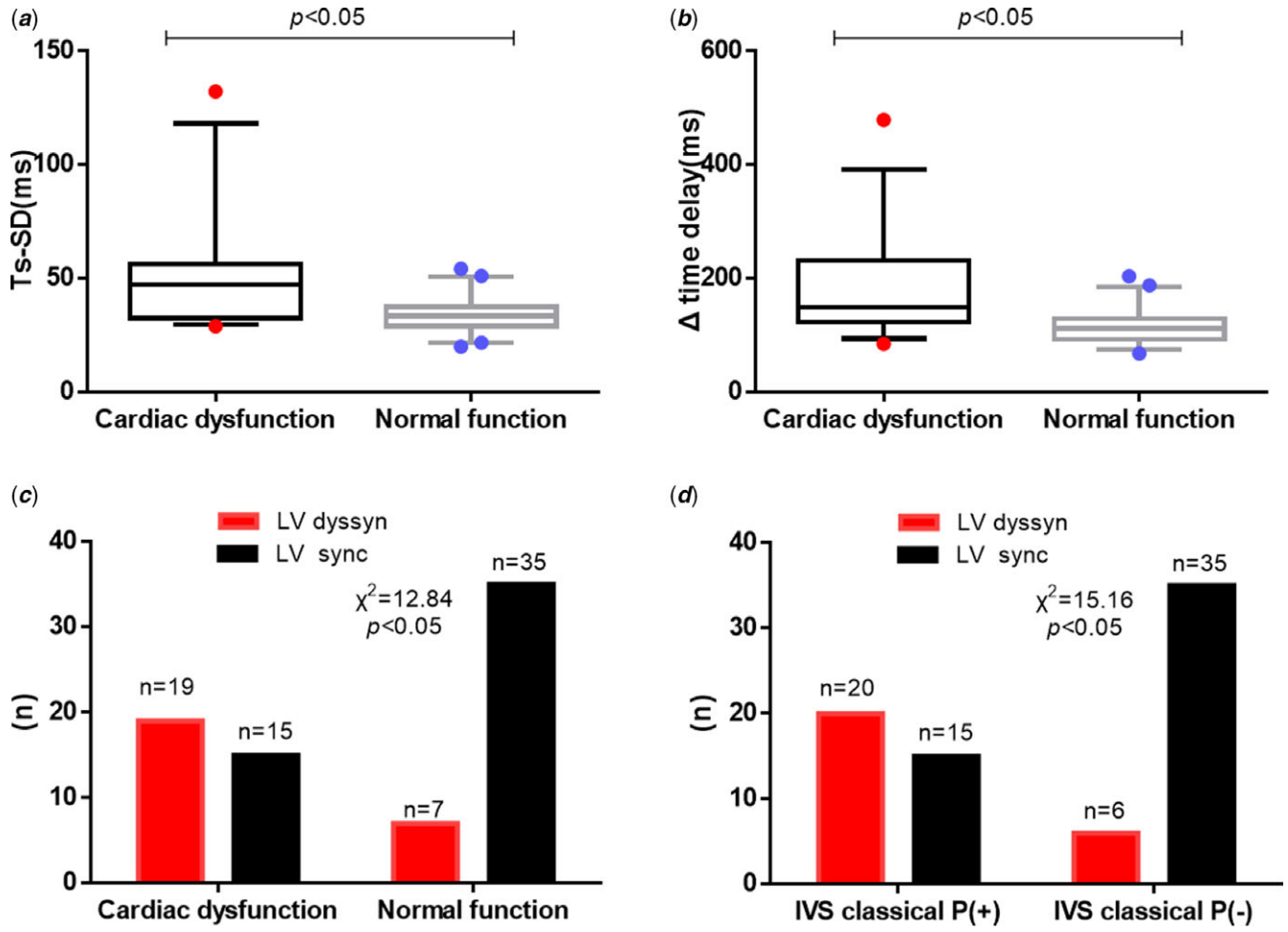

Figure 3. Difference in intra-left ventricular (LV) dyssynchrony and its relationship with ventricular septal dyssynchrony in both the ventricular pre-excitation (VPE)-related cardiac dysfunction and normal function groups. (***a***) Ts-SD: standard deviation of the time-to-peak systolic strain. (***b***) Δ time delay: difference between the maximum and minimum times-to-peak systolic strain. (***c***) LV dyssyn: intra-LV systolic dyssynchrony. LV sync: intra-LV systolic synchrony. (***d***) IVS classical P(+): ventricular septal classical pattern (dyssynchrony). IVS classical P (-): ventricular septal synchrony.

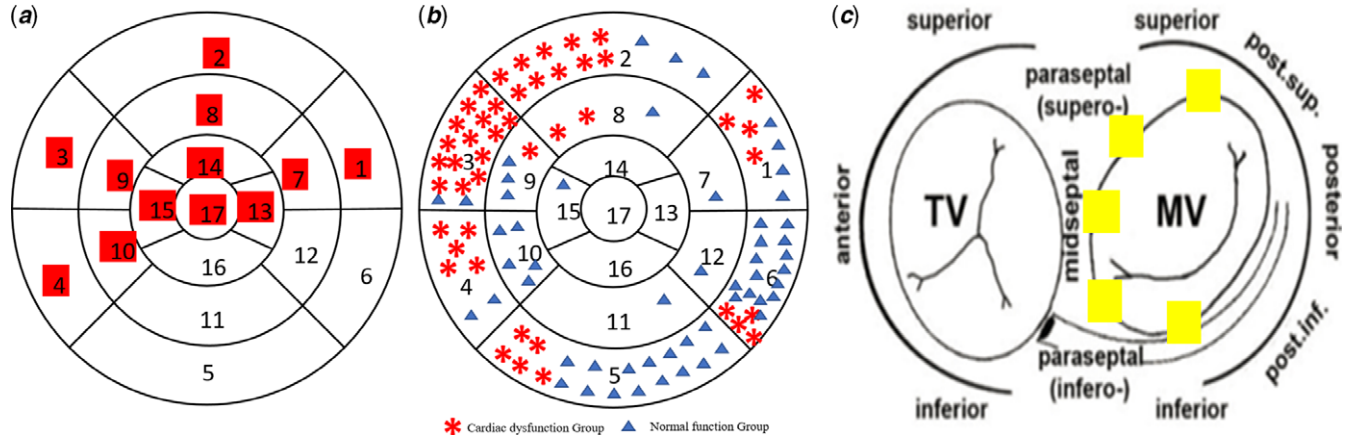

Figure 4. Difference in the time-to-peak systolic strain (Ts) between the ventricular pre-excitation related cardiac dysfunction and normal function groups. (***a***) The bull's-eye plot shows the distribution of the locations with differences in the Ts between both groups. (***b***) Distribution of the maximum Ts in the left ventricle. (***c***) Distribution of the difference in the Ts between the two groups.

normalised (n = 29) (85.3%, 29/34) and non-normalised groups (n = 5) (14.7%, 5/34) according to dyssynchrony recovery. The left ventricular ejection fraction recovery time in the normalised group was shorter than that in the non-normalised group ($\chi^2 = 5.94$, $p < 0.05$). Among the 29 patients in the normalised group, 93.1% (27/29) had a normalised standard deviation of the time-

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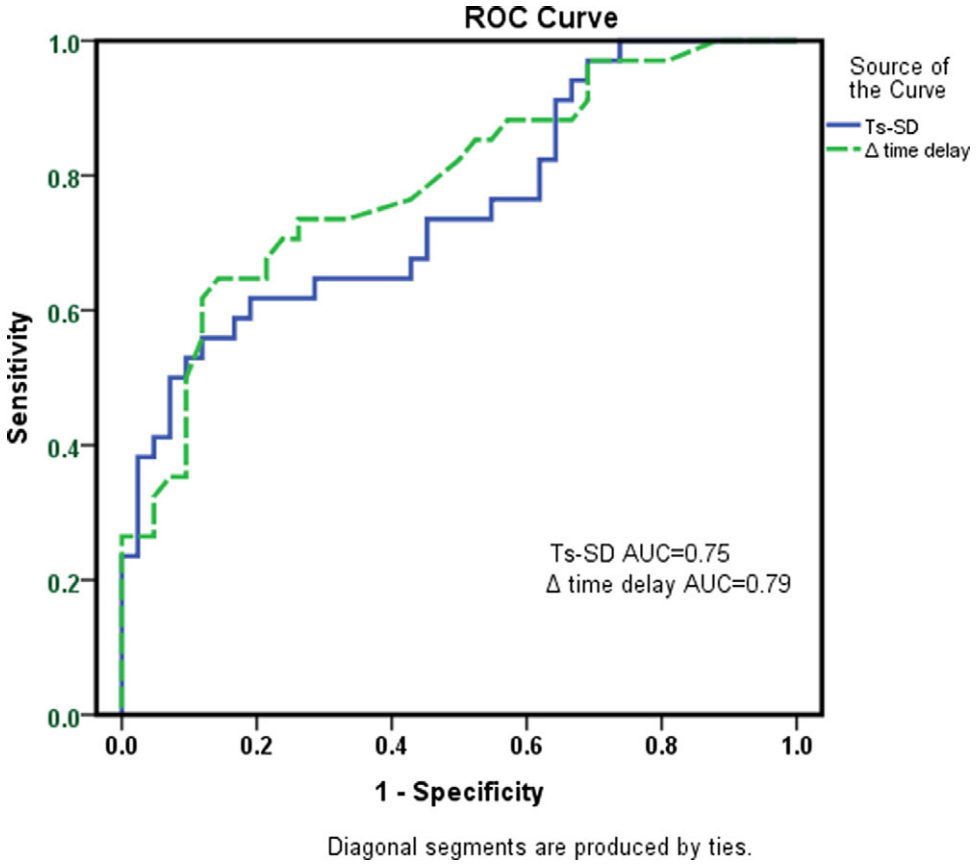

Figure 5. Receiver operating characteristic curve for evaluating the predictors of ventricular pre-excitation-related cardiac dysfunction.

Table 2. Comparison of parameters of cardiac ventricular dyssynchrony before and after catheter ablation for children with VPE-related cardiac dysfunction (n = 34)

	n	Pre-CA	Post-CA	p-value
LVDd(mm)	34	46.76 ± 15.79*	42.50 ± 17.41	0.02
LVDd Z scores	34	14.85 ± 13.98*	9.50 ± 14.05	0.001
LVEF (%)	34	41.66 ± 13.47*	50.06 ± 15.94	0.001
GLPS-Avg (%)	34	−14.16 ± 5.74*	−16.02 ± 5.56	0.01
Ts-SD (ms)	34	51.77 ± 24.70*	33.95 ± 14.70	0.001
Δ time delay (ms)	34	185.82 ± 92.51*	115.59 ± 65.86	0.003

CA = catheter ablation; GLPS-Avg = average global longitudinal peak systolic strain value; LVDd = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction ; Ts-SD = standard deviation of the time-to-peak systolic strain; VPE = ventricular pre-excitation; Δ time delay = difference between maximum and minimum times-to-peak systolic strain.
*Compared between pre- and post-accessory pathway ablation $p < 0.05$.

to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain within 1 month after ablation; the recovery of the left ventricular ejection fraction was later than the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain. Among the five patients in the non-normalised group, the median time for the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain decreased (74.66 ms versus 50.12 ms and 273 ms versus 145 ms, respectively). However, the intra-left ventricular systolic dyssynchrony and left ventricular ejection fraction did not recover during the follow-up. The relationship between the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain and left ventricular ejection fraction recovery over time is shown in Fig 6.

Discussion

In 1976, Francis et al. firstly reported pre-excitation with concomitant ventricular wall dyskinesia. With the increasing number of reported cases, it has been demonstrated that this type of ventricular wall dyskinesia may cause left ventricular remodelling, progressive dilation, and dysfunction.[14,15] The key mechanism for pre-excitation-related cardiac dysfunction is pre-excitation-induced electrical–mechanical dyssynchrony. Based on previously reported cases, pre-excitation-induced dilated cardiomyopathy occurs only in patients with right-sided pathways.[4] However, persistent pre-excitation at similar locations do not always lead to cardiac dysfunction. However, the mechanisms underlying the inhomogeneous effects of similar abnormal conduction on cardiac function are not completely understood. This study was performed to evaluate systolic dyssynchrony of the interventricular, intraventricular, and different segments of the left ventricle using tissue Doppler imaging and two-dimensional speckle-tracking imaging to investigate dyssynchrony parameters closely related to pre-excitation.[2,16,17] Our analyses showed that ventricular pre-excitation may cause ventricular septal dyssynchrony, and attention must then be paid to intra-left ventricular dyssynchrony and cardiac

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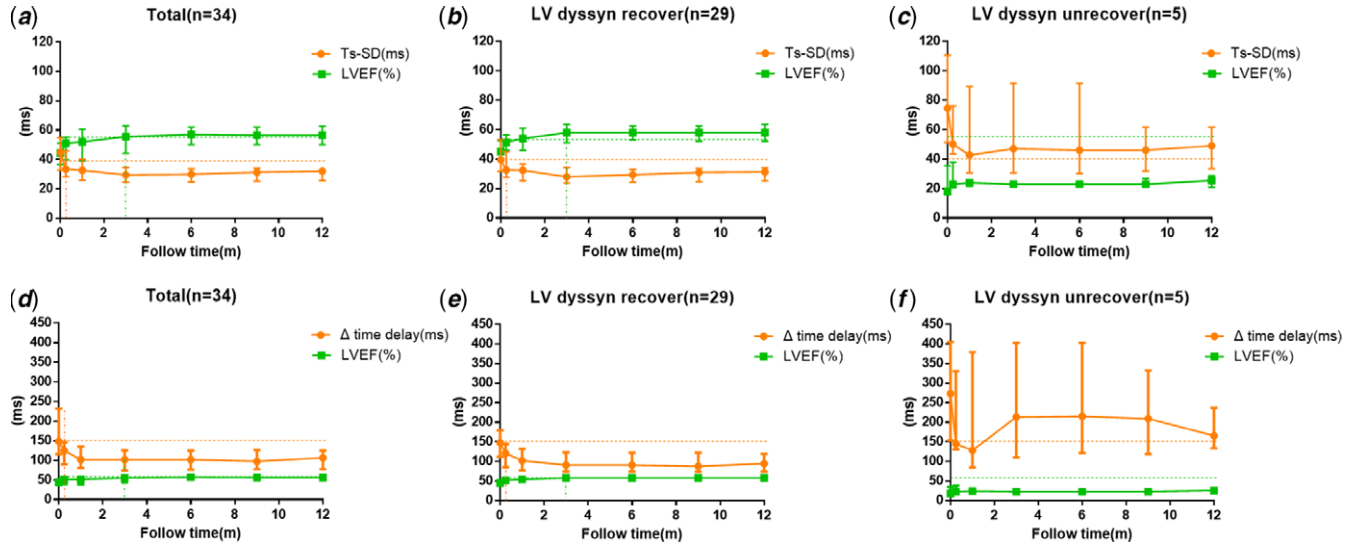

Figure 6. Trends of the standard deviation of the time-to-peak systolic strain (Ts-SD), difference between the maximum and minimum times-to-peak systolic strain (Δ time delay), and left ventricular ejection fraction (LVEF) in the patients with ventricular pre-excitation (VPE)-related cardiac dysfunction after ablation. (***a*** and ***d***) Total: all patients with VPE-related cardiac dysfunction (n = 34). (***b*** and ***e***) left ventricular (LV) dyssyn recover: patients with recovered intra-LV systolic dyssynchrony (n = 29). (***c*** and ***f***) LV dyssyn unrecover: patients with unrecovered intra-LV systolic dyssynchrony (n = 5).

dysfunction. A standard deviation of the time-to-peak systolic strain of the left ventricle of > 42.74 ms and a difference between the maximum and minimum times-to-peak systolic strain of > 129.50 ms are the risk threshold values for the development of cardiac dysfunction in patients with pre-excitation. Whether intra-left ventricular dyssynchrony can resolve within 1 month may be a new early predictor of patient prognosis. Application of these findings may benefit children with pre-excitation with a potential risk of cardiac function injury and aid in early diagnostic and therapeutic interventions for these patients.

Previous studies have shown that left ventricular systolic delay with interventricular dyssynchrony may lead to cardiac dysfunction.[18] However, our study showed that interventricular dyssynchrony occurred in both the cardiac dysfunction and normal function groups. There was no significant difference in the interventricular mechanical delay between them. This finding indicates that interventricular dyssynchrony may not be a pathogenic factor in pre-excitation-induced cardiac dysfunction.

Dai et al.[5] reported nine cases of childhood pre-excitation-induced dilated cardiomyopathy with intra-left ventricular systolic dyssynchrony (standard deviation of the time-to-peak systolic strain: 45.4 ± 25 ms). They suggested that intra-left ventricular systolic dyssynchrony might be a risk factor for the development of pre-excitation-induced dilated cardiomyopathy. Our study investigated whether intra-left ventricular systolic dyssynchrony is an influencing factor for cardiac dysfunction by comparing intra-left ventricular systolic dyssynchrony parameters between patients with cardiac dysfunction and those with normal function. The analyses showed that the standard deviation of the time-to-peak systolic strain (51.77 ± 24.70 ms) and difference between the maximum and minimum times-to-peak systolic strain (185.82 ± 92.51 ms) in the cardiac dysfunction group indicated significant intra-left ventricular systolic dyssynchrony, which was not identified in the normal function group (33.29 ± 9.48 ms and 111.93 ± 34.27 ms, respectively). These results are concordant with those reported in the literature,[5] indicating that intra-left ventricular systolic dyssynchrony is a pathogenic factor for pre-excitation-induced cardiac dysfunction. The possible mechanism might be that long-term discordant left ventricular myocardial contraction and inefficient cardiac pumping would lead to changes in excitation–contraction coupling and myocyte survival. It can cause left ventricular reconstruction, secondary left ventricular enlargement, and cardiac dysfunction.[12,19] Our study evaluated the risk values of the standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain for the development of pre-excitation-induced cardiac dysfunction; we propose that a standard deviation of the time-to-peak systolic strain of > 42.74 ms and a difference between the maximum and minimum times-to-peak systolic strain of > 129.5 ms were the risk threshold values for the development of pre-excitation-related cardiac dysfunction. For children with right-sided pre-excitation, whose standard deviation of the time-to-peak systolic strain and difference between the maximum and minimum times-to-peak systolic strain reach the risk threshold values, the possibility of cardiac dysfunction should be considered. Close follow-up and early intervention should be implemented.

The comparison of dyssynchrony of the different segments of the left ventricle between both groups showed a delayed time-to-peak systolic strain in the ventricular septum and adjacent anterior and inferior walls in the patients in the cardiac dysfunction group. A delayed time-to-peak systolic strain was identified in the anterolateral and posterolateral walls of the normal function group. This indicates that dyssynchrony of the ventricular septum, especially delayed time-to-peak systolic strain of the ventricular septum, might contribute to cardiac dysfunction. This corroborates the findings of Iwasaku et al.[20] and Fukunag et al.,[21] who reported that ventricular septal systolic strain occurred later than left ventricular lateral wall systolic strain in patients with pre-excitation-induced dilated cardiomyopathy. Our study further investigated the relationship between ventricular septal dyssynchrony and intra-left ventricular systolic dyssynchrony, and the difference between the cardiac dysfunction and normal function groups. The analyses showed that ventricular septal dyssynchrony might affect intra-left ventricular systolic dyssynchrony (57.1% versus 14.6%) and is related to the development of pre-excitation-induced dilated cardiomyopathy (94.1% versus 7.7%). This is concordant with the

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findings of Kown et al.[12] that septal dyskinesia was the only factor (not age at diagnosis, pathway location, and QRS interval) associated with pre-excitation-related cardiac dysfunction. A possible underlying mechanism might be that right-sided pathways (including pathways in the right free wall and right septum) could pre-excite the right ventricle and lead to earlier right ventricular contraction compared with the left free wall and stretching of the septum to move towards the anterior chest wall. Thus, the resulting paradoxical and attenuated septal motion would cause delayed systolic strain in the ventricular septum and adjacent areas.[21] A delayed local electrical excitation may cause discordant myocardial contractions and inefficient cardiac pumping. The late-systole myocardium would bear a larger tension and shearing force; thus, the myocardial energetic metabolism would be further altered.[19] This leads to left ventricular systolic dyssynchrony and cardiac dysfunction.[12] In our cardiac dysfunction group, 79.4% had right free wall pathways, while 20.6% had right septal pathways. It seemed that patients with right free wall accessory pathways would be more likely to have left ventricular dysfunction than those with right ventricular septal accessory pathways, assuming that transseptal conduction from the septal pathways would mitigate late septal times-to-peak strain. However, owing to disparities in insertion locations, conduction velocities, and directions of the right pathways, the degree of right ventricular and septal pre-excitations may be inhomogeneous. This might be the reason for the disparities in abnormal ventricular septal motion and different degrees of cardiac dysfunction. Therefore, for children with abnormal ventricular septal motion, especially those with concomitant delayed systolic strain, cardiac dysfunction should be suspected.

The left ventricular diastolic diameter, standard deviation of the time-to-peak systolic strain, and difference between the maximum and minimum times-to-peak systolic strain of the patients in the cardiac dysfunction group decreased, and the left ventricular ejection fraction increased significantly after ablation. Our analyses showed a significant amelioration of intra-left ventricular systolic dyssynchrony, decrease in the left ventricle, and improvement of cardiac function after pathway ablation. Additionally, the recovery of the left ventricular ejection fraction was later than that of intra-left ventricular systolic dyssynchrony, which supported the finding that cardiac dysfunction was caused by pre-excitation. The analyses also showed that intra-left ventricular systolic dyssynchrony might persist even after successful blocking of pathway conduction, thus delaying the recovery of cardiac dysfunction. The possible explanations are as follows. Firstly, the phenomenon of myocardial memory exists when pre-excitation causes abnormal myocardial repolarisation. Such myocardial memory might persist for a period after pathway ablation and delay the recovery of intra-left ventricular systolic dyssynchrony.[22] Secondly, local myocardial fibrosis may occur at the location where pre-excitation pre-excites, thus affecting intra-left ventricular systolic dyssynchrony.[23,24] Thirdly, similar to late cardiac dysfunction caused by tachycardiomyopathy, secondary intra-left ventricular systolic dyssynchrony may develop after long-term severe cardiac enlargement and myocardial fibrosis caused by cardiac dysfunction.[25,26] This type of intra-left ventricular dyssynchrony is difficult to resolve even after successful ablation of the pathways.

This study showed that among the patients whose intra-left ventricular dyssynchrony was resolved during follow-up, 93.1% recovered within 1 month after ablation. The left ventricular ejection fraction recovered after intra-left ventricular systolic dyssynchrony recovery with excellent prognosis. We propose that the duration of intra-left ventricular dyssynchrony recovery owing to myocardial memory is within 1 month, which is concordant with the literature reporting that myocardial memory might recover within 1 month.[27] A duration of recovery of over 1 month may be associated with myocardial fibrosis or late cardiac dysfunction; therefore, early therapeutic interventions should be considered for pre-excitation-related cardiac dysfunction to prevent myocardial fibrosis and late cardiac dysfunction.

Conclusion

Ventricular pre-excitation may cause ventricular septal dyssynchrony, and attention must be paid to intra-left ventricular dyssynchrony and cardiac dysfunction, especially when the systolic strain of the ventricular septum is delayed. A standard deviation of the time-to-peak systolic strain of the left ventricle of > 42.74 ms and a difference between the maximum and minimum times-to-peak systolic strain of > 129.50 ms are the risk threshold values for the development of cardiac dysfunction in patients with pre-excitation. Intra-left ventricular dyssynchrony may persist even after successful ablation of the pathways, which may affect the recovery of cardiac dysfunction. Whether intra-left ventricular dyssynchrony can resolve within 1 month may be a new early predictor of patient prognosis.

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Conflict of Interest. None.

Ethical standards. All procedures were performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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