Heart and Vessels

# Deep insight into cardiac dysfunction in children and young adults with Wolff-Parkinson-White syndrome using speckle tracking imaging

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| **Suggested Reviewers:** | |

# Deep insight into cardiac dysfunction in children and young adults with Wolff-Parkinson-White syndrome using speckle tracking imaging

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**Abstract**

Although ventricular pre-excitation via accessory pathways (APs) causes cardiac dysfunction in children and young adults with Wolff-Parkinson-White (WPW) syndrome, the underlying cardiac dysfunction mechanisms are unclear. This study aimed to characterize cardiac dysfunction and clarify sensitive cardiac dysfunction indicators in WPW syndrome patients classified by the APs location with a layer-specific strain analysis. Twenty-four patients with WPW syndrome with a mean age of 14.1 years (6.9–21.6 years) (11 cases: type A with a left-sided AP ([WA group]), 13 cases: type B with a right-sided AP [WB group]) and 37 age-matched normal controls (N group) were examined. We measured the left ventricle (LV), basal, papillary, and apical circumferential strain (CS), and longitudinal strain (LS) using a layer-specific strain with speckle tracking imaging. Dyssynchrony was also measured based on the timing of the radial strain at each segment. Peak endomyocardial basal and papillary CS was lower in both the WA and WB groups compared to the N group. Peak mid-myocardial and epimyocardial basal CS and peak mid-myocardial papillary CS were lower only in the WB group compared to the N group. Peak LS in all three layers was lower only in the WB group compared to the N group. There were no significant differences between groups in terms of LV ejection fraction (EF) and dyssynchrony index. Layer-specific strain decreased in more sites in the WB group despite the normal EF value. Layer-specific strains are sensitive indicators for the detection of the early stages of cardiac dysfunction.

**Keywords**

Wolff-Parkinson-White syndrome, Layer-specific strain, Speckle tracking Imaging, Dyssynchrony

Cardiac dysfunction

## Introduction

In patients with manifest Wolff-Parkinson-White (WPW) syndrome, the ventricles are electrically and mechanically pre-excited via an accessory pathway (AP), which directly connects the atria and the ventricles. This may cause eccentric ventricular activation via the AP and normal conduction system, resulting in an asynchronous ventricular depolarization and cardiac dysfunction in some patients [1, 2]. The cardiac function in patients with manifest WPW syndrome depends largely on the degree and site of the pre-excitation.

Recently, it has been reported that some pediatric and adult patients, especially those with a right-sided AP and overt ventricular pre-excitation can develop LV dysfunction and dilated cardiomyopathy (DCM) [3-5]. In a study conducted at our institution, Fukunaga also reported a case of WPW syndrome with right-sided AP and DCM-like changes [6]. However, those reports only included patients with right-sided AP who needed radiofrequency catheter ablation (RFCA). Therefore, the cardiac function has not been fully elucidated in patients who do not need RFCA and the process by which cardiac dysfunction develops is not clear.

In Japan, first- and seventh-grade children are screened for heart disease using electrocardiography (ECG) at school. WPW syndrome is one of several conditions frequently detected through school-based cardiovascular screening programs. Diagnosis is based on delta wave detection on ECG. Therefore, institutions in Japan have many opportunities to evaluate cardiac function in WPW

syndrome, even in patients without abnormal physical examination findings or other symptoms, such as palpitations or cardiac failure.

A recent development in cardiac dysfunction detection is the layer-specific strain analysis, which allows separate quantification of the deformation of the endocardial, mid-cardial, and epicardial layers of the myocardium. This new sensitive indicator effectively detects cardiac dysfunction in various cardiac diseases [7-9]. Our institution has also reported the usefulness of layer-specific strain as an early marker of cardiac dysfunction in various cardiac diseases [10, 11]. However, to the best of our knowledge, no previous study has analyzed the LV layer-specific strain in patients with manifest WPW syndrome, especially those who do not need RFCA. Therefore, we aimed to assess the details of LV dysfunction in patients with manifest WPW syndrome (classified by the location of APs using layer-specific strain analysis), including those who do not need RFCA. We also aimed to determine the possibility of early cardiac dysfunction detection.

## Methods

### Study Population

We prospectively recruited 24 consecutive patients, aged 6.9–21.6 years, with manifest WPW syndrome who regularly visited the outpatient clinic between April 2014 and March 2020. Patients were diagnosed with WPW syndrome through school-based cardiovascular screening and presented

to our hospital. After reviewing their ECGs, only patients with a QRS width greater than or equal to 120 ms and a PR time of less than 120 ms were included in this study. Even in the absence of palpitations or cardiac dysfunction, patients still visited the outpatient clinic once a year. Patients with other diseases and post-AP ablation were excluded. The patients were classified according to the location of APs based on the algorithm reported by Arruda et al. [12]: type A-group (WA) with a left-sided AP; type B-group (WB) with a right-sided AP. The localization of APs was confirmed in 11 patients using electrophysiological studies consistent with the localization of the 12-leads ECG. Age-matched healthy individuals were recruited from Juntendo University and Shizuoka Children's Hospital as normal controls for LV myocardial mechanical analysis. These subjects were either healthy volunteers or children undergoing echocardiography to evaluate innocent murmurs: normal-group (N). They had no history of cardiovascular disease and showed normal sinus rhythm on ECG and normal findings on echocardiography. All participants or their guardians provided written informed consent, and the study was approved by the Institutional Review Board of Juntendo University and Shizuoka Children's Hospital.

**Echocardiography**

Echocardiography was performed using a Vivid E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with an appropriate M5S or 6S probe for patient size. Images were optimized for gain,

compression, depth, and sector width and acquired at frame rates of 70–96 frames/s. Apical 4- and 2-chamber views and parasternal short-axis views at the basal, papillary, and apical ventricular levels were acquired. In each plane, images from three consecutive cardiac cycles were acquired during a breath-hold at end-expiration, if possible. For younger children, we selected three cardiac cycles at end-expiration on the respiratory tract. Chamber quantification was performed following the European Association of Cardiovascular Imaging recommendations [13]. LV wall thickness (WT), interventricular septum end-diastolic diameter (IVSd), and posterior wall end-diastolic diameter (PWd) were measured from the parasternal long-axis views. Mean WT was calculated as (IVSd+PWd)/2. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were calculated from the apical 4- and 2-chamber views using the modified biplane Simpson's rule. The LV diastolic function was quantified using the ratio between the E-wave velocity of the pulsed-wave Doppler mitral flow and the early diastolic velocity of the septum and LV free wall at the mitral annulus level (e' wave) on tissue Doppler imaging.

**Left Ventricle Deformation Analysis**

The analysis was performed offline with the aid of a commercially available software package (EchoPAC 113 1.0; GE Vingmed Ultrasound AS, Horton, Norway). Two observers (S.A. and Y.H.), blinded to the clinical data, performed strain analysis. The strain was measured using 2D speckle-

tracking echocardiography as previously described[14]. The system used for this study allows the calculation of mean strain values for the total WT and three separate myocardial layers (endomyocardium, midmyocardium, and epimyocardium) [14]. The dyssynchrony index was measured as the standard deviation of time to peak-systolic strain for all six radial strain segments (RS) at basal, papillary, and apical levels. All data were measured at least three times, and the averages were reported [15].

**Statistical Analysis**

Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and non-normally distributed variables as median (range). All group differences were assessed using one-factor analysis of variance with a post-hoc comparison using the Tukey-Kramer method for normally distributed data or the Steel-Dwass test for non-normally distributed data. Intra- and interobserver agreements for the LV layer-specific strain were calculated using the Bland-Altman approach, including the calculation of mean bias (average difference between measurements) and the lower and upper limits of agreement (95% limits of agreement of mean bias) in five randomly selected patients and five controls. The variation coefficient was also determined (i.e., the SD of the difference between paired samples divided by the average of the paired samples). Statistical analyses were performed using JMP software (version 14.2.0; SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was

considered statistically significant.

## Results

### Feasibility

**Table 1** shows the characteristics of the study participants. The median age of the 24 patients (15 males) at echocardiography was 14.1 years (range, 6.9–21.6 years). The diagnoses were 24 cases of WPW syndrome, WA in 11 patients, and WB in 13 patients. Height, body weight, age, and the number of cases were similar in the patient and control groups. E-wave velocity and e' at the septum were lower in the WB group than the N group. No significant differences were found between patients and controls for LVEF, e' at the LV free wall, or mean E/e' at the septum and LV free walls. **Table 2** shows the dyssynchrony index of the study participants. The dyssynchrony index at the basal, papillary, and apical levels showed no significant difference between the groups.

### Left Ventricle Strain Pattern

The basal circumferential strain showed that peak endomyocardial basal CS was lower in both the WA and WB groups compared to the N group (**Figure 1, Table 3**). Peak mid-myocardial and epimyocardial basal CS was lower in the WB group than the N group. The papillary circumferential strain showed that the peak endomyocardial papillary CS was lower in both the WA and WB groups

than the N group (**Figure 1, Table 3**). Peak mid-myocardial papillary CS in the WB group was lower than the N group. Peak epimyocardial papillary CS did not differ significantly between the groups. The apical circumferential strain showed that the peak apical CS in all three layers did not differ significantly between the groups (**Figure 1, Table 3**). Longitudinal Strain showed that peak LS in all three layers in the WB group was lower than the N group (**Figure 1, Table 3**).

**Reproducibility**

**Table 4** presents the results for intra- and interobserver variability. Significant differences were not observed in the variability of the endomyocardial, mid-myocardial, and epimyocardial CS scores at the basal, papillary, and apical levels or for LS.

**Discussion**

To our knowledge, the present study is the first to use layer-specific strain analysis to examine the characteristics and the differences in cardiac dysfunction between two groups of WPW syndrome classified according to APs location. There were three main findings in this study (Figure 2). First, LS was lower in the WB group, and CS was lower in many layers in the WB group. However, only endocardial CS at the basal and papillary levels was lower in the WA group. Second, when focused on the same plane, impairment of LV peak strain occurs from the endomyocardial CS and subsequently expands towards the epimyocardial CS. Third, when focused on each of the three short-axis planes,

CS impairment begins at the basal level and expands towards the apex.

**Left Ventricle Dysfunction Assessed by Conventional Echocardiographic Parameters**

LVEF was used as the conventional measure of cardiac dysfunction, which was defined as a decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in LVEF of at least 10% to less than 55% without accompanying signs or symptoms [16].

No patient showed decreased LVEF at the time of the study. Furthermore, no significant difference was found between patients and controls despite decreasing myocardial deformation in many layers. Thus, this study showed that myocardial deformation analysis is a more sensitive indicator for the early detection of cardiac dysfunction than conventional measurements.

**Influence of Accessory Pathway Location on Left Ventricle Dysfunction**

Evidence is now emerging that LV dyssynchrony disturbs myocardial regional workload and wall stress, which may result in wall motion abnormalities, myocardial perfusion defects, changes in coronary blood flow and regional molecular abnormalities, increased LV cavity volume, and asymmetrical changes in LV WT [17]. In WPW with right-sided AP, the right ventricle is excited prematurely. Therefore the right ventricle (RV) contracts first, before LV contraction, causing left

ventricular bundle branch block (LBBB) type abnormality on ECG. In addition, the APs are located closer to the sinus node in WB than in WA. Therefore, during sinus rhythm, ventricular excitation via the APs is much faster in WB than in WA. More cells are depolarized via the APs in WB than in WA at the myocardial cells level. This suggests that because asynchronous contraction between the two ventricles is more pronounced in WB than in WA, the decline in cardiac function is more apparent in WB than in WA. Indeed, WPW syndrome has been reported to cause abnormal septal motion, characterized by an early systolic posterior motion, a subsequent anterior movement in mid-systole, and the usual posterior septal motion beginning in late systole, particularly in WPW with right-sided AP [2, 18].

Tomaske et al. reported that the AP's location was inferoparaseptal in 65%, superoparaseptal in 17.5%, and septal in 17.5% of patients [19]. Surprisingly, more than 50% of their patients showed a reduced LV function, defined as EF of less than 55%, before RFCA. Dai et al. reported abnormal interventricular septal motion and LV dyssynchrony may develop in patients with right-sided AP before LV dysfunction [20]. Bradley et al. reported that LV function decreased in patients with LBBB due to asynchronous motion (18). There is the possibility that similar mechanisms caused the LV dysfunction in the WB group in terms of delayed electrical activation in the LV compared to the RV [19, 20]. Furthermore, a right-sided AP caused the development of DCM [5]. The measurement of RS in each segment is considered useful as an indicator of dyssynchrony [15]. Seo et al. reported that

indicators improve significantly before and after RFCA in WPW syndrome [21]. In our study, we found no significant differences between the groups in terms of dyssynchrony index, although WPW syndrome with right-sided AP showed decreased strain, consistent with previous reports [19, 20]. The reason for the lack of significant differences in the dyssynchrony index may be that our patients were much younger compared to the previous study. If we evaluated our patients in the future, we might find a worsened dyssynchrony index.

**Impairment of Endocardial Circumferential Strain before Epicardial Circumferential Strain**

Several studies have suggested the vulnerability of the endocardial layers in various diseases. Yu et al. reported that, subendocardial circumferential deformation is sensitive to anthracycline in childhood cancers survivors [22]. In patients with ischemia [23] or hypertension, the endocardial layers' vulnerability has been proposed. Hamada et al. reported that endocardial CS is a powerful predictor of cardiac events in patients with chronic ischemic cardiomyopathy [24]. Our institution has also reported similar results in chemotherapy-induced cardiac dysfunction [11], which may be due to endocardial layers vulnerability.

The present study demonstrated that potential myocardial damage occurs in the endocardial layers before the mid-myocardial and epicardial layers in WPW syndrome patients. This is concordant with reports on other diseases. Similar mechanisms might cause LV dysfunction in WPW.

**Impairment of Basal Circumferential Strain before Apical Circumferential Strain**

Streeter et al. reported the rate of circumferentially to longitudinally oriented fibers is 10:1, with its ratio increasing towards the base and decreasing towards the apex [25]. This suggests that the effect of impaired contraction in the circumferential direction is more prominent at the basal level than at the apex. Furthermore, the Laplace law supports the idea that the larger cavity radius at the base is more affected than the LV apex by interventricular pressure in the heart with subclinical myocardial damage [26]. Studies at our institution have reported that cardiac dysfunction in childhood cancer survivors progresses from the base to the apex [10, 11]. Furthermore, the excitation time at the base is most likely to vary between ventricles. Theoretically, asynchronous contractions should be most pronounced in the basal slice, and mechanical stress causing myocardial stress might be larger. It may place more of a load on the myocardium at the base than at other levels. Dai et al. reported that in a WPW syndrome with LV dyssynchrony with right-sided AP, basal strains decreased [20]. These findings support our results that impairment in basal and papillary CS occurs before apical CS occurs.

**Impairment of Circumferential Strain Before Longitudinal Strain**

In contrast to LS, endocardial CS is more sensitive for early detection of LV systolic dysfunction in long-term cancer survivors [22]. The wall of the human heart has a well-defined distribution of fibers,

with the angle varying from approximately 90° (in the circumferential direction) at the endocardial surface to approximately −90° at the outer surface [25]. The fibers' angle at 15% inside the LV endocardium is only 20°, suggesting that damage to the endocardial layer may affect both the longitudinally and circumferentially oriented fibers [25]. Furthermore, the ratio of circumferentially to longitudinally oriented fibers increases towards the base and decreases towards the apex [25]. When myocardial damage occurs only in the endocardial layers, LS remains stable until the damage approaches the epicardial layers [25], as myocardial deformation of each layer is dependent on active function within the layer and passive motion from adjacent layers [27]. These findings suggest that contraction impairment affects CS more than LS, especially in young patients, when myocardial damage is not severe. These reports support the fact that in our study, WPW syndrome with right-sided AP was impaired to the mid-cardial layer and showed a decrease in longitudinal strain. In contrast, WPW syndrome with left-sided AP was only impaired to the endocardial layer and did not show a decrease in LS.

**Clinical Implications**

Endocardial CS at the basal level is considered a more useful and sensitive indicator of cardiac dysfunction than conventional parameters. Future studies with larger numbers of patients and repeated cardiac deformation evaluation may evaluate the accurate time course of the cardiac dysfunction and

detect it earlier in patients with WPW syndrome. These findings have important clinical implications and may allow for early therapeutic interventions, such as RFCA, for subclinical LV dysfunction and potentially improve myocardial deformation impairment. Furthermore, this parameter could allow a better evaluation of the therapeutic effects of medications or RFCA.

**Study Limitations**

First, this study included a small number of patients. Future studies with larger sample sizes are necessary to provide a robust conclusion on cardiac dysfunction time course in patients with WPW syndrome. Nevertheless, this study was enough to identify layer-specific strain differences in WPW syndrome. Second, patients with WPW syndrome were only classified into two AP locations. Tomaske et al. reported that WPW syndrome with an AP of the right septum or posterior septum might cause LV dyssynchrony and jeopardize overall LV function [19]. Finally, we did not evaluate post-treatment changes, such as RFCA. In the future, studies with larger sample sizes, a more detailed classification based on the APs location, and pre-and post-treatment evaluation will allow us to elucidate the mechanisms of cardiac dysfunction in WPW syndrome.

**Conclusions**

This study demonstrates that impairment of endocardial circumferential deformation was the initial

cardiac abnormality seen in patients with WPW syndrome. This impairment then extends from the endocardium towards the epicardium and the base towards the apex. The present findings provide novel insight into the characteristics of patients with WPW syndrome.

**Conflict of interest:** None

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## References


1. Klein GJ, Yee R, and Sharma AD(1989) Longitudinal electrophysiologic assessment of asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. N Engl J Med 320: 1229-33.

2. Demaria AN, Vera Z, Neumann A, and Mason DT(1976) Alterations in ventricular contraction pattern in the Wolff-Parkinson- White syndrome. Detection by echocardiography. Circulation 53: 249-57.

3. Shan Q, Jin Y, and Cao K(2007) Reversible left ventricular dyssynchrony and dysfunction resulting from right ventricular pre-excitation. EP Europace 9: 697-701.

4. Nelson GS, Curry CW, Wyman BT, Kramer A, Declerck J, Talbot M, Douglas MR, Berger RD, McVeigh ER, and Kass DA(2000) Predictors of Systolic Augmentation From Left Ventricular Preexcitation in Patients With Dilated Cardiomyopathy and Intraventricular Conduction Delay. Circulation 101: 2703-09.

5. Udink ten Cate FE, Kruessell MA, Wagner K, Trieschmann U, Emmel M, Brockmeier K, and Sreeram N(2010) Dilated cardiomyopathy in children with ventricular preexcitation: the location of the accessory pathway is predictive of this association. J Electrocardiol 43: 146-54.

6. Fukunaga H, Akimoto K, Furukawa T, Takahashi K, Kishiro M, Shimizu T,

Kamiyama H, and Sumitomo N(2013) Improvement in non-tachycardia-induced cardiac failure after radiofrequency catheter ablation in a child with a right-sided accessory pathway. Heart and Vessels 28: 802-07.

7. Llesuy SF, Milei J, Gonzalez Flecha BS, and Boveris A(1990) Myocardial damage induced by doxorubicins: Hydroperoxide-initiated chemiluminescence and morphology. Free Radical Biology and Medicine 8: 259-64.

8. Ishizu T, Seo Y, Enomoto Y, Sugimori H, Yamamoto M, Machino T, Kawamura R, and Aonuma K(2010) Experimental validation of left ventricular transmural strain gradient with echocardiographic two-dimensional speckle tracking imaging. Eur J Echocardiogr 11: 377-85.

9. Adamu U, Schmitz F, Becker M, Kelm M, and Hoffmann R(2009) Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. Eur J Echocardiogr 10: 303-8.

10. Yamada M, Takahashi K, Kobayashi M, Yazaki K, Takayasu H, Akimoto K, Kishiro M, Inage A, Yoshikawa T, Park I-S, Nakanishi K, Kawasaki S, and Shimizu T(2017) Mechanisms of Left Ventricular Dysfunction Assessed by Layer-Specific Strain Analysis in Patients With Repaired Tetralogy of Fallot. Circulation Journal 81: 846-54.

11. Yazaki K, Takahashi K, Shigemitsu S, Yamada M, Iso T, Kobayashi M, Akimoto K, Tamaichi H, Fujimura J, Saito M, Nii M, and Shimizu T(2018) In-Depth Insight Into the Mechanisms of Cardiac Dysfunction in Patients With Childhood Cancer After Anthracycline Treatment Using Layer-Specific Strain Analysis. Circulation Journal 82: 715-23.

12. Arruda MS, McClelland JH, Wang X, Beckman KJ, Widman LE, Gonzalez MD, Nakagawa H, Lazzara R, and Jackman WM(1998) Development and Validation of an ECG Algorithm for Identifying Accessory Pathway Ablation Site in Wolff-Parkinson-White Syndrome. Journal of Cardiovascular Electrophysiology 9: 2-12.

13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, and Voigt J-U(2015) Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging 16: 233-71.

14. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, and Vered Z(2004) Two-dimensional strain-a novel software for real-

time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 17: 1021-9.

15. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, and Bax JJ(2008) Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. J Am Coll Cardiol 51: 1944-52.

16. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, and Keefe D(2002) Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience. Journal of Clinical Oncology 20: 1215-21.

17. Cheng A, Helm RH, and Abraham TP(2009) Pathophysiological mechanisms underlying ventricular dyssynchrony. Europace 11: v10-v14.

18. Francis GS, Theroux P, O'Rourke RA, Hagan AD, and Johnson AD(1976) An echocardiographic study of interventricular septal motion in the Wolff-Parkinson-White syndrome. Circulation 54: 174-78.

19. Tomaske M, Janousek J, Razek V, Gebauer RA, Tomek V, Hindricks G, Knirsch W, and Bauersfeld U(2008) Adverse effects of Wolff-Parkinson-White syndrome with right septal or posteroseptal accessory pathways on cardiac function. Europace 10:

181-89.

20. Dai C, Guo B, Li W, Xiao Y, Jin M, Han L, and Dong J(2018) The effect of ventricular pre-excitation on ventricular wall motion and left ventricular systolic function. EP Europace 20: 1175-81.

21. Seo M-K, Chang S-A, Kim H-K, Shin D-H, Choi E-K, Kim Y-J, Oh S, Cho G-Y, Sohn D-W, Oh B-H, and Park Y-B(2011) Synchronicity of LV Contraction as a Determinant of LV Twist Mechanics. JACC: Cardiovascular Imaging 4: 338-47.

22. Yu W, Li SN, Chan GCF, Ha SY, Wong SJ, and Cheung YF(2013) Transmural strain and rotation gradient in survivors of childhood cancers. Eur Heart J Cardiovasc Imaging 14: 175-82.

23. Becker M, Ocklenburg C, Altiok E, Futing A, Balzer J, Krombach G, Lysyansky M, Kuhl H, Krings R, Kelm M, and Hoffmann R(2009) Impact of infarct transmurality on layer-specific impairment of myocardial function: a myocardial deformation imaging study. Eur Heart J 30: 1467-76.

24. Hamada S, Schroeder J, Hoffmann R, Altiok E, Keszei A, Almalla M, Napp A, Marx N, and Becker M(2016) Prediction of Outcomes in Patients with Chronic Ischemic Cardiomyopathy by Layer-Specific Strain Echocardiography: A Proof of Concept. J Am Soc Echocardiogr 29: 412-20.

25. Streeter DD, Spotnitz HM, Patel DP, Ross J, and Sonnenblick EH(1969) Fiber Orientation in the Canine Left Ventricle during Diastole and Systole. Circulation Research 24: 339-47.

26. Attias D, Macron L, Dreyfus J, Monin JL, Brochet E, Lepage L, Hekimian G, Iung B, Vahanian A, and Messika-Zeitoun D(2013) Relationship between longitudinal strain and symptomatic status in aortic stenosis. J Am Soc Echocardiogr 26: 868-74.

27. Sarvari SI, Haugaa KH, Zahid W, Bendz B, Aakhus S, Aaberge L, and Edvardsen T(2013) Layer-Specific Quantification of Myocardial Deformation by Strain Echocardiography May Reveal Significant CAD in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome. JACC: Cardiovascular Imaging 6: 535-44.

【Figure Legends】

Figure 1.

Comparison of the LV layer-specific strain analysis of (**A**) basal circumferential strain (CS), (**B**) papillary CS, (**C**) apical CS, and (**D**) longitudinal strain (LS). Yellow, patients with Wolff-Parkinson-White syndrome type A; red, patients with Wolff-Parkinson-White syndrome type B; blue, normal controls. *Significant difference between patients with WA-group and normal group, $P<0.05$. **Significant difference between patients with WA-group and normal group, $P<0.01$. †Significant difference between patients with WB-group and normal group, $P<0.05$. ††Significant difference between patients with WB-group and normal group, $P<0.01$.

Figure 2.

Impariment of LV myocardial deformation in patients with WPW syndrome.

WB group: Basal CS at all layers (red circle), Papillary CS at the endo and midmyocadial layers (red circle) and LS at all layers (red curves) are decreased. WA group: basal and papillary endomyocardial CS (red circle) are decreased.

Table

| Table 1. Baseline Characteristics of Study Group of Patients With Wolff-Parkinson-White syndrome and Healthy Controls | | | |
|---|---|---|---|
| | **WA-group** | **WB-group** | **N-group** |
| **Total number (males)** | **11 (7)** | **13 (8)** | **37 (24)** |
| **Age (years)** | **12.2±3.5** | **15.8±4.7** | **14.7±5.0** |
| **Height (cm)** | **149.2 (116.0-172.5)** | **161.3 (121.9-178.0)** | **151.3 (116.6-183.0)** |
| **Weight (kg)** | **43.1±15.2** | **55.4±17.8** | **46.7±16.4** |
| **BMI (kg/m$^2$)** | **18.6 (15.9-22.3)** | **20.6 (15.1-29.0)** | **19.6 (14.8-30.0)** |
| **BSA (m$^2$)** | **1.33±0.33** | **1.57±0.34** | **1.40±0.31** |
| **NYHA** | **I** | **I** | **I** |
| **SBP (mmHg)** | **97.8 (88-128)** | **109 (90-126)** | **107.2 (82-127)** |
| **DBP (mmHg)** | **50.4 (40-70)** | **62.3 (50-90)** | **61.3 (42-84)** |
| **IVSD (mm)** | **6.1** | **6.6** | **6.1** |

| | | | |
|---|---|---|---|
| | **(5.0-8.4)** | **(5.5-8.4)** | **(4.8-8.4)** |
| **PWd (mm)** | **6.2±0.3** | **6.5±1.2** | **6.4±0.9** |
| **Mean wall thickness (mm)** | **6.2**<br>**(5.2-7.9)** | **6.5**<br>**(5.1-8.2)** | **6.3**<br>**(4.9-8.5)** |
| **QRS (msec)** | **127.4** ** <br>**(123-146)** | **137.8** ††<br>**(121-154)** | **88.7** ** ††<br>**(73-112)** |
| **BNP (pg/mL)** | **11.2±6.2** | **15.7±7.2** | **-** |
| **LVEF (%)** | **67.3±3.7** | **64.0±3.9** | **66.7±5.2** |
| **E-wave velocity (cm/s)** | **94.4**<br>**(70-115)** | **81.5**<br>**(52-116)** | **95**<br>**(58-133)** |
| **A-wave velocity (cm/s)** | **49.1±11.8** | **45.3±8.2** | **43.3±10.6** |
| **E/A ratio** | **2.02**<br>**(1.23-3.27)** | **1.84** †<br>**(1.16-2.60)** | **2.33** †<br>**(1.43-4.28)** |
| **Septal e' (cm/s)** | **13.7±1.4** | **12.8±2.3** † | **14.7±2.5** † |
| **Septal a' (cm/s)** | **5.7±0.9** | **6.2±1.5** | **6.7±1.5** |
| **LV FW e' (cm/s)** | **17.1**<br>**(13.0-21.3)** | **16.4** †<br>**(12.0-25.0)** | **18.8** †<br>**(14.3-24.0)** |
| **LV FW a' (cm/s)** | **5.5** * | **6.3** | **6.6** * |

| | | | |
|---|---|---|---|
| | **(4.3-6.0)** | **(3.3-9.3)** | **(4.0-9.7)** |
| **mean E/e'** | **6.33**<br>**(4.68-7.73)** | **5.66**<br>**(4.49-6.88)** | **5.87**<br>**(4.04-8.15)** |

Table 1.

*Significant difference between patients with WA-group and normal group, P<0.05. **Significant difference between patients with WA-group and normal group, P<0.01. †Significant difference between patients with WB-group and normal group, P<0.05. ††Significant difference between patients with WB-group and normal group, P<0.01.

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; FW, free wall; HR, heart rate; IVSd, intraventricular septum end-diastolic diameter; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; PWd, posterior wall end-diastolic diameter; WA, Wolff-Parkinson-White syndrome type A; WB, Wolff-Parkinson-White syndrome type B

| Table2. Dyssynchrony Index of Patients With Wolff-Parkinson-White syndrome and Healthy Controls | | | |
|---|---|---|---|
| | **WA-group** | **WB-group** | **N-group** |
| **TBasRS (sd)** | **13.7 (0-24.1)** | **11.7 (4.2-40.7)** | **12.1 (1.5-50.3)** |
| **TPapRS (sd)** | **9.9 (1.7-41.5)** | **5.3 (0.5-23.6)** | **4.1 (0-12.2)** |
| **TApiRS (sd)** | **20.9 (1.6-48.8)** | **15.6 (1.4-48.6)** | **14.6 (1.4-46.8)** |
| **SDRS/mean TBasRS** | **0.14 (0-0.24)** | **0.13 (0-0.67)** | **0.12 (0-0.73)** |
| **SDRS/mean TPapRS** | **0.11 (0.02-0.41)** | **0.06 (0-0.27)** | **0.05 (0-0.13)** |
| **SDRS/mean TApiRS** | **0.18 (0.02-0.52)** | **0.18 (0-0.60)** | **0.15 (0.02-0.54)** |

Table 2.

There were no significant difference between the groups.

SD, standard deviation; TApiRS, time to peak-systolic strain for all 6 segments in radial strain at apical levels; TBasRS, time to peak-systolic strain for all 6 segments in radial strain at basal levels; TPapRS, time to peak-systolic strain for all 6 segments in radial strain at papillary levels; WA, Wolff-Parkinson-White syndrome type A; WB, Wolff-Parkinson-White syndrome type B.

| Table 3. Intraobserver and Interobserver Variability of Layer-Specific Strain | | | | |
|---|---|---|---|---|
| **Variable** | **Bias** | **LLA** | **ULA** | **CV** |
| **Intraobserver** | | | | |
| **Endocardial basal CS** | **-0.010** | **-1.527** | **1.507** | **3.44** |
| **Midmyocardial basal CS** | **-0.013** | **-0.822** | **0.795** | **2.47** |
| **Epicardial basal CS** | **-0.087** | **-1.243** | **1.070** | **4.85** |
| **Endocardial papillary CS** | **0.033** | **-3.978** | **4.045** | **8.46** |
| **Midmyocardial papillary CS** | **0.347** | **-2.150** | **2.843** | **7.41** |
| **Epicardial papillary CS** | **0.517** | **-1.070** | **2.103** | **7.06** |
| **Endocardial apical CS** | **0.095** | **-3.230** | **3.420** | **5.53** |
| **Midmyocardial apical CS** | **0.205** | **-1.775** | **2.185** | **4.47** |
| **Epicardial apical CS** | **0.202** | **-1.707** | **2.111** | **5.84** |
| **Endocardial LS** | **-0.853** | **-2.311** | **0.604** | **3.68** |
| **Midmyocardial LS** | **-0.687** | **-1.759** | **0.386** | **3.02** |
| **Epicardial LS** | **-0.547** | **-1.580** | **0.486** | **3.23** |
| **Interobserver** | | | | |
| **Endocardial basal CS** | **-0.010** | **-2.128** | **1.935** | **4.60** |

| | | | | |
|---|---|---|---|---|
| **Midmyocardial basal CS** | **-0.233** | **-1.448** | **0.981** | **3.68** |
| **Epicardial basal CS** | **-0.400** | **-3.240** | **2.440** | **11.74** |
| **Endocardial papillary CS** | **-0.793** | **-4.940** | **3.354** | **8.60** |
| **Midmyocardial papillary CS** | **0.093** | **-2.000** | **2.186** | **6.16** |
| **Epicardial papillary CS** | **0.640** | **-1.593** | **2.873** | **9.98** |
| **Endocardial apical CS** | **-1.391** | **-5.532** | **2.749** | **6.72** |
| **Midmyocardial apical CS** | **-0.172** | **-1.953** | **1.610** | **3.98** |
| **Epicardial apical CS** | **0.618** | **-1.987** | **3.224** | **8.07** |
| **Endocardial LS** | **-1.253** | **-3.447** | **0.940** | **5.49** |
| **Midmyocardial LS** | **-0.917** | **-2.293** | **0.460** | **3.85** |
| **Epicardial LS** | **-0.653** | **-1.480** | **0.173** | **2.57** |

Table 3.

CS, circumferential strain; CV, coefficient of variation; LLA, 95% lower limit of agreement; LS, longitudinal strain; ULA, 95% upper limit of agreement.

Figure

Click here to access/download;Figure;Figure1.jpg

**Figure 1. Correlation of Layer-Specific Strain Between Patients and Controls**

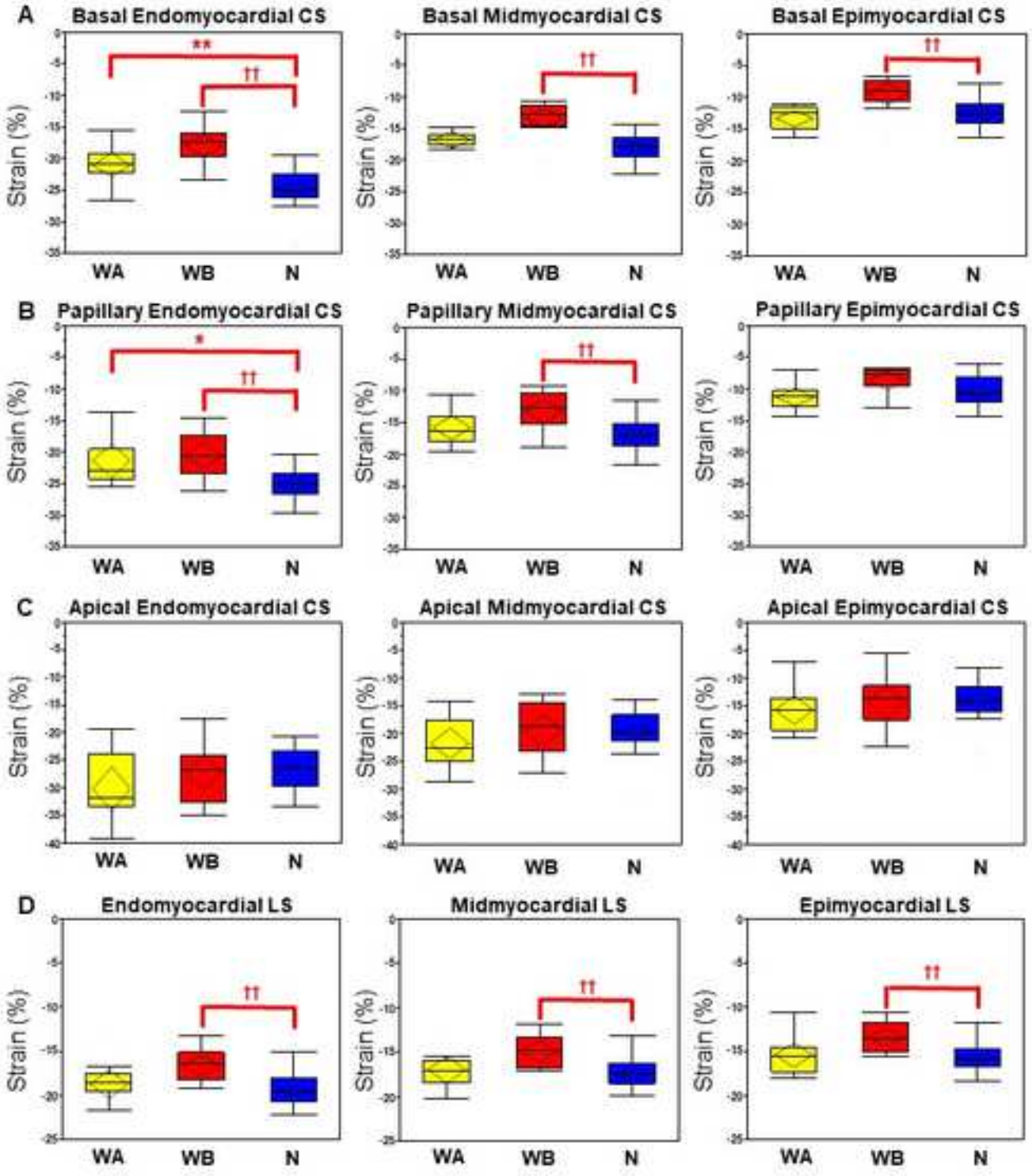
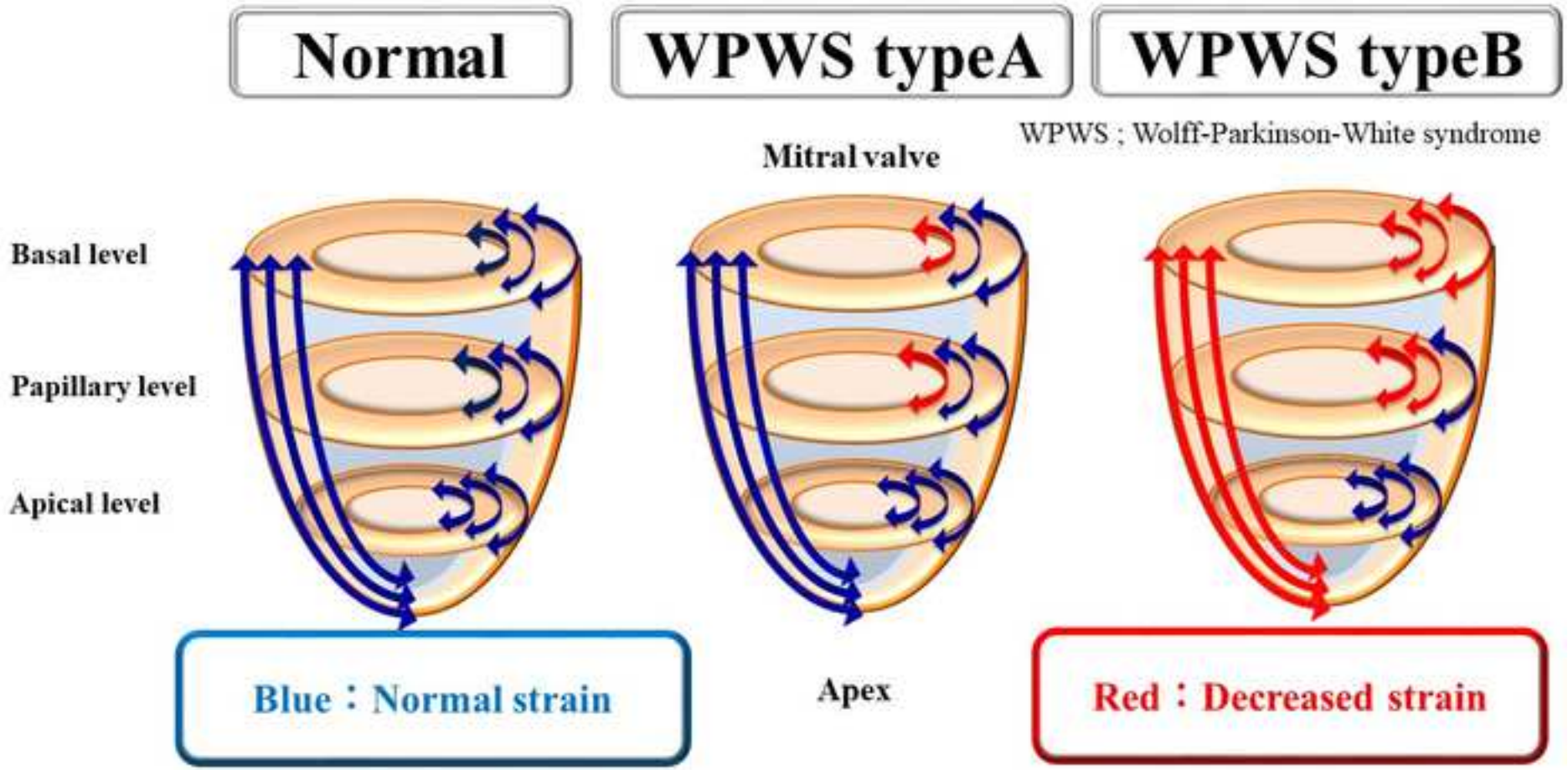


**Figure.2 Summary of Characteristics of Cardiac Dysfunction between Patients and Controls**



[Date of submission]

Nobuhisa Hagiwara
Editor-in-Chief
*Heart and Vessels*

Dear Editor

I wish to submit an original clinical research article for publication in *Heart and Vessels*, titled "Deep insight into cardiac dysfunction in children and young adults with Wolff-Parkinson-White syndrome using speckle tracking imaging." The paper was coauthored by Satoshi Akimoto, Hideo Fukunaga, Azusa Akiya, Yu Hosono, Takeshi Iso, Sachie Shigemitsu, Noboru Tanaka, Haruna Tabuchi, Hidemori Hayashi, Gaku Sekita, and Toshiaki Shimizu.

In this study, we investigated the characteristics of cardiac dysfunction in patients with WPW syndrome classified by the location of APs using a layer-specific strain analysis. Our study population included 24 patients with WPW syndrome (mean age of 14.1 years) (11 cases: type A with a left-sided AP [WA-group], 13 cases: type B with a right-sided AP [WB-group]) and 37 age-matched normal controls (N-group). We measured the left ventricle (LV) basal, papillary, and apical circumferential strain (CS), and longitudinal strain (LS) using a layer-specific strain with speckle tracking imaging. Dyssynchrony was also measured based on the timing of the radial strain at each segment.

We believe that our study makes a significant contribution to the literature because we found that compared to the N group, the peak endomyocardial basal and papillary CS was lower in both the WA and WB groups, the peak mid-myocardial and epimyocardial basal CS and peak mid-myocardial papillary CS was lower in the WB group only. The peak LS in all three layers was lower in the WB group only. Furthermore, there were no significant between-group differences for LV ejection fraction (EF) or dyssynchrony index.

Further, we believe that this paper will be of interest to the readership of your journal because we have demonstrated that layer-specific strains are sensitive indicators for the detection of the early stages of cardiac dysfunction.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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