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LV dyssynchrony as assessed by phase analysis of gated SPECT myocardial perfusion imaging in patients with Wolff-Parkinson-White syndrome

Chun Chen,

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing, Jiangsu 210029, China

Dianfu Li,

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing, Jiangsu 210029, China

Changqing Miao,

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing, Jiangsu 210029, China

Jianlin Feng,

Department of Nuclear Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

Yanli Zhou,

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing, Jiangsu 210029, China

Kejiang Cao,

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing, Jiangsu 210029, China

Michael S. Lloyd, and

Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

Ji Chen

Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, USA

Chun Chen: chenchunjsnj@163.com; Dianfu Li: lidianfu@gmail.com

Abstract

Purpose—The purpose of this study was to evaluate left ventricular (LV) mechanical dyssynchrony in patients with Wolff-Parkinson-White (WPW) syndrome pre- and post-radiofrequency catheter ablation (RFA) using phase analysis of gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).

Methods—Forty-five WPW patients were enrolled and had gated SPECT MPI pre- and 2–3 days post-RFA. Electrophysiological study (EPS) was used to locate accessory pathways (APs) and categorize the patients according to the AP locations (septal, left and right free wall). Electrocardiography (ECG) was performed pre- and post-RFA to confirm successful elimination

of the APs. Phase analysis of gated SPECT MPI was used to assess LV dyssynchrony pre- and post-RFA.

Results—Among the 45 patients, 3 had gating errors, and thus 42 had SPECT phase analysis. Twenty-two patients (52.4 %) had baseline LV dyssynchrony. Baseline LV dyssynchrony was more prominent in the patients with septal APs than in the patients with left or right APs ($p<0.05$). RFA improved LV synchrony in the entire cohort and in the patients with septal APs ($p<0.01$).

Conclusion—Phase analysis of gated SPECT MPI demonstrated that LV mechanical dyssynchrony can be present in patients with WPW syndrome. Septal APs result in the greatest degree of LV mechanical dyssynchrony and afford the most benefit after RFA. This study supports further investigation in the relationship between electrical and mechanical activation using EPS and phase analysis of gated SPECT MPI.

Keywords

Myocardial perfusion imaging; Phase analysis; LV dyssynchrony; Wolff-Parkinson-White syndrome; Radiofrequency catheter ablation

Introduction

Most accessory pathways (APs) are direct myocardial connections between the atrium and ventricle that bypass the atrioventricular node. They arise almost anywhere along the mitral or tricuspid annuli and occur in about 0.1–0.3 % in the general population [1]. An AP that conducts anterogradely, or from the atrium to the ventricle, is termed a manifest AP because it is readily apparent on surface electrocardiogram (ECG). A manifest AP, because it depolarizes the ventricle from a site separate to the normal conduction system, results in the characteristic ECG findings of a delta wave and short PR interval (<0.12 s) [1, 2]. The presence of altered depolarization from electrical preexcitation may also result in mechanical dyssynchrony. It has been shown by echocardiography that Wolff-Parkinson-White (WPW) syndrome with right septal or posteroseptal APs can cause left ventricular (LV) mechanical dyssynchrony and jeopardize LV function [3, 4]. Gated blood pool imaging has also been used to localize APs and to assess ventricular contraction patterns and LV dyssynchrony associated with WPW syndrome [5–8].

Radiofrequency catheter ablation (RFA) of AP is an established treatment for patients with symptomatic WPW syndrome; however, its application in asymptomatic patients remains controversial [9]. A recent study showed that LV dyssynchrony in asymptomatic WPW syndrome is a risk factor for development of dilated cardiomyopathy [10]. The utility of RFA for reducing or eliminating preexcitation-induced dyssynchrony is unclear. Reliable tools to measure LV dyssynchrony in relation to the AP location before and after RFA may provide valuable prognostic information in patients with WPW syndrome. Although echocardiography and gated blood pool imaging have shown promising results in this clinical application, alternative techniques may be needed because of their limitations. Echocardiography involves significant user interactions and requires expertise to obtain reliable and consistent results. The PROSPECT trial reported that the high variability of echocardiographic dyssynchrony parameters was the major reason for their modest accuracy to predict cardiac resynchronization therapy (CRT) response [11]. Gated blood pool imaging involves complicated procedures when analyzing 3-D images [12, 13].

Phase analysis of gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been developed to assess LV dyssynchrony [14]. It is an automatic, 3-D technique to assess LV dyssynchrony and has been shown to have great reproducibility and repeatability [15, 16]. Phase analysis of gated SPECT MPI has been

shown to correlate well with echocardiography and gated blood pool SPECT in measuring LV dyssynchrony [17–19] and to predict response to CRT in heart failure patients [20]. Moreover, recent studies showed that phase analysis of gated SPECT MPI has sufficient spatial and temporal resolution to examine specific regional mechanical activation over the LV for optimizing CRT LV lead implantation in heart failure patients [21] as well as assessing the effect of alcohol septal ablation in patients with hypertrophic cardiomyopathy [22].

Phase analysis of gated SPECT MPI has not yet been applied to patients with WPW syndrome. The purpose of this study was to evaluate LV mechanical dyssynchrony in patients with WPW syndrome pre- and post-RFA using phase analysis of gated SPECT MPI.

Materials and methods

Patients

The study population included patients between 18 and 65 years old, all with supraventricular tachycardia symptoms and manifest AP on surface ECG, who underwent RFA in the First Affiliated Hospital of Nanjing Medical University between April 2009 and December 2010. Patients with structural heart disease (e.g., atrial septal defect, Ebstein's anomaly, coronary artery disease, or hypertrophic cardiomyopathy) that may influence LV mechanical synchrony were excluded. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients who participated in this study.

Electrocardiogram

Twelve-lead ECG during sinus rhythm was conducted in all patients before and after RFA with a Mac 5000 System (GE Medical Systems, Milwaukee, WI, USA). QRS durations were measured either manually or by a computerized ECG system analysis of intervals. The areas of QRS wave were measured manually from ECG recordings. A small compartment on the ECG recording paper was defined as 1×1 mm. The whole areas of QRS wave were summarized on all 12 leads.

Electrophysiological study and RFA

The electrophysiological study (EPS) and RFA procedure were performed according to the standard techniques. Briefly, three quadric-polar electrode catheters were inserted percutaneously and introduced to high right atrium, His bundle position and right ventricular apex via the femoral vein. A decapolar catheter was advanced to the coronary sinus vein through the subclavian vein. Manifest preexcitation was defined as the presence of a delta wave on surface ECG and an intracardiac His-ventricle time of less than 35 ms. By standard mapping methods and techniques [23], the site of the AP was identified and ablated. RFA was considered successful if both antegrade and retrograde AP conduction were abolished for at least 30 min after RFA during the procedure. Long-term success of RFA was defined as the absence of tachycardia recurrence and preexcitation pattern on surface ECG.

The site of successful ablation of the AP for each patient was recorded on fluoroscopy according to the method mentioned above (also in [23]). All of the patients were categorized into three subgroups according to the sites of the APs in the septal wall, right free wall, or left free wall, respectively.

Gated SPECT MPI

All enrolled patients underwent resting gated SPECT MPI scans pre-RFA and 2–3 days post-RFA. ^{99m}Tc -Sestamibi doses ranged from 25 to 30 mCi depending on the patient weight or body mass index. The scans were performed 60 min post-injection. A Philips CardioMD system (Philips Medical Systems, Milpitas, CA, USA) was used to acquire the MPI data with 20 % energy windows centered at 140 keV. A total of 64 projections (24 s/projection, total acquisition time of 14 min) were obtained over a 180° circular orbit. The MPI data were acquired as 8 frames per cardiac cycle and stored in a 64×64 matrix with 6.4 mm/pixel. All of the gated SPECT MPI data were reconstructed using a manufacturer-provided filtered backprojection program (AutoSPECTPlus™, Philips Medical Systems) and then filtered by a Butterworth low-pass filter with a cutoff frequency of 0.5 Nyquist and an order of 5. All reconstructed data were reoriented to generate gated short-axis images, which were then submitted to the phase analysis software in the Emory Cardiac Toolbox (Emory University, Atlanta, GA, USA) for LV dyssynchrony assessment and to Quantitative Gated SPECT (Cedars-Sinai Medical Center, Los Angeles, CA, USA) for LV function assessment.

Phase analysis of gated SPECT MPI has been described extensively and summarized in a recent review article [24]. Briefly, regional maximal count detection was performed in 3-D for each temporal frame of the gated short-axis image. Then, the first-harmonic Fourier function was used to approximate the discrete sample points into a continuous wall-thickening curve. For each region, the wall-thickening curve provided a phase angle that represented the onset of mechanical contraction of the region. Once the phase angles of all regions were obtained, a phase distribution was generated to provide information on mechanical dyssynchrony for the entire ventricle. The phase distribution was displayed in a polar map as well as in a histogram as in Fig. 1. For a normal subject, the entire LV starts contraction almost at the same time, so that the phase polar map is nearly uniform and the phase histogram is narrow and highly peaked. Phase standard deviation (PSD) (the standard deviation of the phase distribution) and phase histogram bandwidth (PHB) (the width of the band including 95 % of the samples over the LV) are two quantitative indices that have been shown to measure LV global dyssynchrony. According to our previous study [25], the normal value of PSD was $9.3 \pm 1.9^\circ$, and the normal value of PHB was $29.1 \pm 5.4^\circ$. In this study, the normal limits of PSD and PHB were determined by the mean plus 2 standard deviations of the normal distribution, i.e., 13.1 and 39.9° , respectively.

Echocardiography

Standard echocardiograms were acquired using an ultrasound machine (Vivid 7, GE Medical Systems, Milwaukee, WI, USA) with an M4S probe. Patients were examined in the left lateral decubitus position, and images were acquired at end expiration in order to minimize global cardiac movement. Standard grayscale 2-D images were acquired in the two-chamber and four-chamber apical views, as well as the parasternal short-axis view at the level of the mitral valve, papillary muscles, and apex levels. All of the images were recorded with a 2-D frame rate of 50 frames/s to allow for reliable analyses. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured from the apical two-chamber and four-chamber views, and LV ejection fraction (LVEF) was calculated using the Simpson rule.

Statistical analysis

Comparisons among patients with septal, right, and left APs were conducted using one-way analysis of variance (ANOVA) test. The paired *t* test was used to compare QRS duration, whole QRS area, PSD, and PHB before and after RFA in the entire cohort as well as in the subgroups. The unpaired *t* test with unequal variance was used to compare QRS duration,

whole QRS area, PSD, and PHB between the subgroups. A p value less than 0.05 was considered statistically significant. The statistical analysis was done using MedCalc statistical software.

Results

Demographics and baseline characteristics

Forty-seven subjects were recruited in the study. Two subjects were excluded because no APs were found during EPS although there were resemble delta waves on their body surface ECG. Thus 45 patients (age=41.5±9.8 years, male/female=30/15, echocardiographic LVEF=63.8 ± 4.7 %) were enrolled in our study. Forty-four of them had a normal size of the LV and a LVEF more than 55 % without symptoms of congestive heart failure prior to RFA, except for one patient who had a LVEF of 40 % and a dilated LV (LV diameter=56 mm) with mild symptoms of heart failure (New York Heart Association class II). At 3 months after successful RFA, the heart failure symptoms of this patient disappeared, and the LV reduced to a normal size (LV diameter=52 mm) with a normal LVEF (59 %). None of the patients suffered from incessant tachycardia, rapid conduction of atrial fibrillation via AP, or other arrhythmias that might contribute independently to LV dysfunction.

RFA findings

RFA was successfully performed in all patients without any complications. Preexcitation recurred in one patient 1 day after RFA and in two patients a month later and required repeated ablation, which was successful in the three patients. According to the results of RFA, the 45 patients were categorized into 3 subgroups according to the AP locations in the right free wall ($N=13$), septal wall ($N=16$), and left free wall ($N=16$), respectively. One patient had three APs, and two patients had two APs. These multiple APs were distributed around the tricuspid ring. The patients with multiple APs were assigned to one of the three subgroups according to the AP that contributed to the predominant preexcitation vector. The patient with reduced LVEF (40 %) pre-RFA had the AP in the right anteroseptal wall and was assigned to the septal subgroup.

Electrocardiogram findings

Delta waves were absent in all patients after RFA. Table 1 shows the QRS duration and whole QRS area pre- and post-RFA. Significant reduction in QRS duration and whole QRS area post-RFA was observed in the entire population as well as in the patients with and without baseline LV dyssynchrony. There were no significant differences in QRS duration and whole QRS area between the patients with and without baseline LV dyssynchrony. This finding indicates that mechanical dyssynchrony is not necessarily associated with electrical dyssynchrony and is concordant with other studies [26, 27].

SPECT findings

There were gating errors in three patients (one in the septal group and two in the left group). Therefore, the SPECT findings were obtained from 42 patients. Among the 42 patients included in the SPECT analysis, 22 had significant baseline LV dyssynchrony as determined by PSD and/or PHB greater than the normal limits in our previous study [25], i.e., 13.1 and 39.9°, respectively. In these 22 patients with baseline LV dyssynchrony, 14 patients had both abnormal PSD and PHB, 3 patients had abnormal PSD, and 5 patients had abnormal PHB, respectively. The other 20 patients had both PSD and PHB less than the normal limits.

Table 1 shows the LV function parameters assessed by gated SPECT MPI. Significant improvement was observed in LVEDV and LVESV, but not in LVEF after RFA, indicating some degrees of LV reverse remodeling due to RFA in these patients. At baseline, the

patients with LV dyssynchrony had significantly larger LVEDV and LVESV and significantly smaller LVEF than the patients without LV dyssynchrony, indicating that LV dyssynchrony is associated with poorer LV function.

Table 2 shows the LV dyssynchrony parameters pre- and post-RFA. Significant improvement in LV synchrony post-RFA was observed in the entire cohort as well as in the patients with baseline LV dyssynchrony, but not in the patients without baseline LV dyssynchrony. Post-RFA, only one patient with baseline LV dyssynchrony still had abnormal PSD (13.2°), and all others had the LV dyssynchrony parameters in the normal range. Post-RFA, the patients with baseline LV dyssynchrony had significantly larger PSD and PHB than the patients without baseline LV dyssynchrony.

Table 3 shows the LV dyssynchrony parameters pre- and post-RFA according to the AP location. Among the 42 patients included in the SPECT analysis, 13 patients had APs at the right free wall (right subgroup), 15 patients had APs at the septal wall (septal subgroup), and 14 patients had APs at the left free wall (left subgroup), respectively. Baseline LV dyssynchrony was found in 6 patients in the right subgroup, 11 patients in the septal subgroup, and 5 patients in the left subgroup, respectively. The septal subgroup had significantly larger PHB than the other two subgroups. Significant improvement in LV synchrony post-RFA was observed in the septal subgroup, but not in the other two subgroups.

Two patient examples of improved LV synchrony after RFA are shown in Fig. 1.

Discussion

This is the first systematic analysis of LV mechanical dyssynchrony in patients with WPW syndrome pre- and post-RFA using phase analysis of gated SPECT MPI. This study revealed several important findings. First, we have demonstrated that 52.4 % (22/42) of the WPW patients in our study had baseline LV dyssynchrony as assessed by phase analysis of gated SPECT MPI and that LV dyssynchrony in WPW patients could be reduced in varying degrees by elimination of the preexcitation. This finding supported the hypothesis that altered mechanical activation caused directly by AP is a causative factor for LV mechanical dyssynchrony. This finding is concordant with other studies using other imaging modalities [3, 4, 28–30].

This study also demonstrated that the amount of LV dyssynchrony caused by AP depended on AP location. The subgroup of patients with AP along the septal wall had substantially worse baseline LV mechanical dyssynchrony and derived the most improvement in LV synchrony after RFA. This finding is in agreement with echocardiographic studies that showed right septal or posteroseptal AP caused LV dyssynchrony and jeopardized LV function, and LV synchrony and function improved after RFA [3, 4, 28–30]. Similarly, a study using gated blood pool imaging reported that no significant changes in LV dyssynchrony were observed following ablation of APs in the right free wall or left free wall [8]. One explanation for this finding relates to the relationship between degree of preexcitation and AP location. Left free wall pathways are the most remote from the sinus node and are thus often activated relatively late with respect to conduction down the normal AV node. This results in less preexcitation than APs that are closer to the sinus node and consequently alter normal ventricular depolarization to a greater degree.

Echocardiography and gated blood pool imaging have been used to assess patients with WPW syndrome. However, these techniques have some limitations. Echocardiography involves significant user interactions and requires expertise to obtain reliable and consistent results. The PROSPECT trial reported that the high variability of echocardiographic

dyssynchrony parameters was the major reason for their modest accuracy to predict CRT response [11]. Gated blood pool imaging involves complicated procedures when analyzing 3-D images [12, 13]. Our analysis used a novel, reliable imaging modality to assess LV dyssynchrony. Phase analysis of gated SPECT MPI is 3-D and largely automatic [14], having good reproducibility and repeatability [15, 16]. This study supported that phase analysis of gated SPECT MPI is a viable alternative technique to assess the effect of RFA on LV dyssynchrony in patients with WPW syndrome.

There are several limitations in our study. First, onset of mechanical activation was not compared quantitatively among different LV regions in relation to electrical preexcitation measured by EPS. Second, gated SPECT MPI cannot image the right ventricle with sufficient counts; therefore, phase analysis of gated SPECT MPI can only assess LV dyssynchrony. Cardiac dyssynchrony may happen between the right and left ventricles (interventricular dyssynchrony) in patients with WPW syndrome. Third, this is a proof of concept study with a relatively small number of patients. The findings in this study are descriptive and exploratory and need to be validated in a large-scale study.

Conclusion

Phase analysis of gated SPECT MPI demonstrated that LV mechanical dyssynchrony can be present in patients with WPW syndrome. Septal APs result in the greatest degree of LV mechanical dyssynchrony and afford the most benefit after RFA. This study supports further investigation in the relationship between electrical and mechanical activation using EPS and phase analysis of gated SPECT MPI.

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Fig. 1.

Patient examples. a Patient with an AP in the left free wall. The phase polar map pre-RFA shows a preexcitation region in the lateral wall as reflected by lower phase values. Preexcitation is not present in the phase polar map post-RFA. The phase histogram post-RFA is narrower than that pre-RFA. Post-RFA PSD decreased from 14.8 to 9.5°, and PHB decreased from 45 to 31°, indicating improvement in LV synchrony in this patient. b Patient with an AP in the septal wall. The phase polar map pre-RFA shows a preexcitation region in the septal wall as reflected by lower phase values. Preexcitation is not present in the phase polar map post-RFA. The phase histogram post-RFA is narrower than that pre-RFA. Post-RFA PSD decreased from 13.8 to 10.4°, and PHB decreased from 52 to 36°, indicating improvement in LV synchrony in this patient

Table 1

QRS duration, whole QRS area, and LV function pre- and post-RFA

	<i>N</i>	Pre-RFA	Post-RFA	<i>p</i>
QRS duration (s)				
Entire population	42	0.162±0.022	0.099±0.013	<0.0001
With baseline LV dyssynchrony	22	0.165±0.021	0.104±0.013 *	<0.0001
Without baseline LV dyssynchrony	20	0.159±0.022	0.094±0.011 *	<0.0001
Whole QRS area (mm ²)				
Entire population	42	147.60±62.77	80.13±29.00	<0.0001
With baseline LV dyssynchrony	22	161.70±63.15	86.30±25.64	<0.0001
Without baseline LV dyssynchrony	20	142.68±60.17	76.31 ±32.86	<0.0001
LVEDV (ml)				
Entire population	42	92.1±28.5	86.9±25.5	<0.01
With baseline LV dyssynchrony	22	104.4±27.6 *	98.6±25.1 *	<0.05
Without baseline LV dyssynchrony	20	78.7±23.3 *	74.1±19.4 *	<0.01
LVESV (ml)				
Entire population	42	36.7±17.9	34.2±14.9	<0.05
With baseline LV dyssynchrony	22	44.3±19.0 *	40.0±4.5 *	<0.05
Without baseline LV dyssynchrony	20	28.4±12.1 *	28.0±13.0 *	NS
LVEF (%)				
Entire population	42	61.3±8.9	63.1±8.9	NS
With baseline LV dyssynchrony	22	58.9±8.3 *	62.0±9.5	NS
Without baseline LV dyssynchrony	20	65.5±7.0 *	63.9±8.9	NS

Data are given as mean ± standard deviation; *p* values were calculated by comparing pre-RFA and post-RFA parameters in the same group using the paired *t* test

The patients with and without baseline LV dyssynchrony were compared using the unpaired *t* test with unequal variance.

**p*<0.01. The lack of an asterisk indicates no statistical significance

Table 2

LV dyssynchrony pre- and post-RFA

	<i>N</i>	Pre-RFA	Post-RFA	<i>p</i>
PSD (°)				
Entire cohort	42	11.9±3.9	9.5±2.0	<0.01
With baseline LV dyssynchrony	22	14.8±2.2 ^{**}	10.2±1.5 [*]	<0.01
Without baseline LV dyssynchrony	20	8.6±2.2 ^{**}	8.7±2.2 [*]	NS
PHB (°)				
Entire cohort	42	38.2±11.1	30.6±5.1	<0.01
With baseline LV dyssynchrony	22	46.7±7.6 ^{**}	32.4±4.5 [*]	<0.01
Without baseline LV dyssynchrony	20	28.8±4.9 ^{**}	28.7±5.1 [*]	NS

Data are given as mean ± standard deviation; *p* values were calculated by comparing pre-RFA and post-RFA parameters in the same group using the paired *t* test

The patients with and without baseline LV dyssynchrony were compared using the unpaired *t* test with unequal variance.

^{*}
p<0.05;

^{**}
p<0.01. The lack of an asterisk indicates no statistical significance

Table 3

LV dyssynchrony pre- and post-RFA according to the AP location

	<i>N</i>	Pre-RFA	Post-RFA	<i>p</i>
PSD (°)				
Right free wall	13	11.0±4.0	8.8±2.4	NS
Septal wall	15	13.3±3.9	10.1±1.7	<0.01
Left free wall	14	11.1±3.4	9.5±1.9	NS
PHB (°)				
Right free wall	13	35.1±10.7	28.8±5.3	NS
Septal wall	15	44.0±12.7 [*]	33.1±4.7 [*]	<0.01
Left free wall	14	34.8±7.0	29.6±4.5	NS

Data are given as mean ± standard deviation; *p* values were calculated by comparing pre-RFA and post-RFA parameters in the same group using the paired *t* test

The patients with different subgroups according to the AP location were compared using the unpaired *t* test with unequal variance.

^{*} *p* < 0.05. The lack of an asterisk indicates no statistical significance. The septal subgroup had significantly larger PHB than the right and left subgroups (both *p* < 0.05). There was no significant difference in PHB between the right and left subgroups