Background—Cardiac memory refers to a change in ventricular repolarization induced by and persisting for minutes to months after cessation of a period of altered ventricular activation (eg, resulting from pacing or preexcitation in patients with Wolff-Parkinson-White syndrome). ECG imaging (ECGI) is a novel imaging modality for noninvasive electroanatomic mapping of epicardial activation and repolarization.

Methods and Results—Fourteen pediatric patients with Wolff-Parkinson-White syndrome and no other congenital disease, were imaged with ECGI a day before and 45 minutes, 1 week, and 1 month after successful catheter ablation. ECGI determined that preexcitation sites were consistent with sites of successful ablation in all cases to within a 1-hour arc of each atrioventricular annulus. In the preexcited rhythm, activation-recovery interval (ARI) was the longest (349 ± 6 ms) in the area of preexcitation leading to high average base-to-apex ARI dispersion of 95 ± 9 ms (normal is ≈ 40 ms). The ARI dispersion remained the same 45 minutes after ablation, although the activation sequence was restored to normal. ARI dispersion was still high (79 ± 9 ms) 1 week later and returned to normal (45 ± 6 ms) 1 month after ablation.

Conclusions—The study demonstrates that ECGI can noninvasively localize ventricular insertion sites of accessory pathways to guide ablation and evaluate its outcome in pediatric patients with Wolff-Parkinson-White syndrome. Wolff-Parkinson-White is associated with high ARI dispersion in the preexcited rhythm that persists after ablation and gradually returns to normal over a period of 1 month, demonstrating the presence of cardiac memory. The 1-month time course is consistent with transcriptional reprogramming and remodeling of ion channels. (Circulation. 2008;118:907-915.)

Key Words: ablation ■ electrocardiography ■ cardiac memory ■ imaging ■ Wolff-Parkinson-White syndrome

Cardiac memory (CM)1 is the phenomenon of repolarization changes induced by long-standing altered cardiac activation (eg, pacing) that persist for a period of time after normal activation has been restored. The mechanism of CM is a remodeling process that alters the molecular determinants of action potential duration such as membrane density and kinetic properties of ion channels.2 As pacing therapy becomes increasingly prevalent in heart failure, bradycardia, heart block, and congenital heart defects, the effects of CM induced by a long-standing changed activation sequence are of important scientific and clinical interest. The Wolff-Parkinson-White (WPW) syndrome3 involves a long-standing altered activation sequence, different from normal sinus rhythm, as a result of ventricular preexcitation from the ventricular insertion site of an atrioventricular accessory pathway (AP). As such, it mimics long-standing ventricular pacing and provides a natural model for studying repolarization changes associated with long-term altered ventricular activation. Importantly, AP ablation provides a model of activation and repolarization changes and their time course after cessation of pacing and restoration of normal sinus rhythm.

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Symptomatic Patients with WPW syndrome are treated by transvenous catheter ablation of the AP. APs are located mostly around the atrioventricular anuli, with the rare exception of Mahaim fibers.4 Noninvasive localization of AP around the atrioventricular anuli before catheterization can facilitate invasive catheter mapping. Current noninvasive techniques for localization of APs include algorithms based on the ECGI data.
on the delta wave and QRS morphologies on the 12-lead ECG. Although easy and fast, a number of studies have shown inconsistencies and inaccuracies in these ECG algorithms, especially in the pediatric population. Moreover, in a smaller number of cases, multiple APs may exist, which makes localization from 12-lead ECG even more difficult.

ECG imaging (ECGI) is a novel noninvasive imaging modality that reconstructs epicardial potentials (voltage maps), electrograms, activation (isochrones), and repolarization sequences from 250 simultaneously recorded body surface ECGs and an accurate heart-torso anatomy obtained from an ECG-gated thoracic computed tomography (CT) scan (Figure 1). ECGI has been extensively validated in canine experiments and in humans with intraoperative mapping data. It has been applied to image normal and abnormal cardiac electrophysiology (both activation and repolarization) in humans. ECGI could localize ventricular pacing sites in patients undergoing cardiac resynchronization therapy with an accuracy of 7±3 mm (using the CT coordinates of the pacing leads as the gold standard). These capabilities suggest its suitability for the noninvasive determination of the preexcitation region in patients with WPW syndrome before catheter mapping and ablation, thereby guiding the procedure and possibly shortening it and reducing its associated iatrogenic risks. The objective of the present study is 2-fold: to evaluate ECGI as a noninvasive preablation procedure for locating the region of preexcitation in patients with WPW syndrome and to image activation and repolarization before ablation and at several time points after ablation to study the time course of activation and repolarization changes in the context of CM.

Methods
The study population consisted of 14 WPW pediatric patients (6 male, 8 female patients; age, 12±3 years) who were referred to St. Louis Children’s Hospital for ablation between January 2006 and May 2007; all of them had nonintermittent preexcitation (delta wave) on the surface 12-lead ECG, with transthoracic echocardiograms demonstrating structurally normal hearts. They were all symptomatic and subsequently underwent successful catheter ablation. A day before catheterization and ablation, each patient underwent an ECGI study with 200 conductive-carbon electrodes arranged in strips. Body-surface markers were adhered to the patient’s torso to document the position of the strips with respect to anatomic markers like the sternal notch, nipples on the front, and any identifiable birthmarks on the back. Body-surface potentials were recorded in the baseline resting rhythm during the first ECGI study. Because the carbon electrodes are transparent to x-ray, they did not interfere with fluoroscopy during the catheter electrophysiology study. Body-surface potentials were
recorded during supraventricular tachycardia (SVT)\textsuperscript{3} (induced during the electrophysiology study as part of the procedure). ECGI maps of anterograde ventricular activation and retrograde atrial activation (only when a clear retrograde P wave could be seen on the body-surface ECG) were reconstructed offline. After successful ablation (loss of delta wave and testing with adenosine), the clock position (schematic in Figure 2B) of the ablation catheter at the site of success was documented in the 60° left anterior oblique fluorangiogram and was compared with the preablation ECGI localization. Another ECGI recording was made 45 minutes after successful ablation with the patient still in the same supine position and in normal sinus rhythm without preexcitation. Patients were followed up with ECGI using the same methods 1 week and 1 month after ablation with the body-surface potentials recorded at the baseline resting rhythm. The study protocol was reviewed and fully approved by the Human Research Protection Office at Washington University. Informed written consent was obtained from all subjects before the study.

Statistical Analysis
ARI and ARId numerical data are presented as mean±SD, with these measures taken over the entire patient population (n=14). The relationship between the epicardial activation maps at different time points after ablation and the epicardial ARI maps before and after ablation is determined by Pearson’s product-moment correlation coefficient (r).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Epicardial Potentials and Activation
Figure 3A shows the preablation epicardial potential map in subject W1 during early activation in the preexcited rhythm. The earliest epicardial breakthrough, indicated by a local potential minimum (deep blue, asterisk), was observed in the left posterior area at 7 o’clock around the epicardial aspect of the mitral annulus (MA) 8 ms after onset of the delta wave on the body-surface ECG. The epicardial potential map during the initial phase of repolarization (Figure 3B; 181 ms
after onset of delta wave) followed a pattern similar to that during early activation but with reversed polarity, with the minimum replaced by a potential maximum (red). The preablation ECGI isochrone map (Figure 3C) showed early activation (red, asterisk) initiating from the same area, confirming the presence of an activation source (AP) in this region. These results consistently indicated a left posterior insertion site of the AP, 7 o’clock around the MA. ECGI isochrone map (Figure 3D) of the patient in postablation isochrone map (Figure 3D) showed the latest epicardial activation (white, Figure 5B) in the left posterior atrial wall. Activation spread out uniformly from this area, with the minimum replaced by a potential maximum (red). The early repolarization potential map exhibited 2 discrete potential maxima (red, asterisk; Figure 3J) replacing the 2 minima observed during early activation. The preablation isochrone map showed an elongated area of early activation (red; Figure 3K) in the left lateral and posterolateral areas. The presence of 2 potential minima during early activation (and 2 maxima during early repolarization) established the possibility of the presence of 2 discrete APs (later confirmed during the ablation procedure; the Table). Postablation ECGI maps of retrograde atrial activation were constructed in 5 subjects in whom a clear retrograde P wave was discerned after the QRS on the body-surface ECG during SVT. 

Retrograde Atrial and Anterograde Ventricular Activation During SVT

ECGI maps of retrograde atrial activation were constructed in 5 subjects in whom a clear retrograde P wave was discerned after the QRS on the body-surface ECG during SVT. Examples of ECGI activation maps during SVT are shown in Figure 5 for a left-sided and a right-sided pathway. A retrograde atrial activation map for subject W1 (left posterior ventricular insertion) is shown in Figure 5A and 5B. Earliest activation (white, Figure 5B) was in the left posterior atrial wall. Activation spread out uniformly from this area, with the
anterior lower right atrium activating last (deep blue, Figure 5A). Figure 5E and 5F shows the retrograde atrial activation map for subject W5 (right-sided midseptal AP). The sequence of retrograde atrial activation in this case was distinctly different from that of subject W1. The lower right atrium was the first to activate (white, light pink), from where activation propagated to the top of the right atrium and to the posterior side. The latest areas to activate (blue) were the left lateral atrial wall and the left atrial appendage. The earliest sites of retrograde atrial activation were consistent with the earliest site of ventricular activation before ablation. The anterograde ventricular activation showed early anterior RV epicardial activation (red, orange, Figure 5E and 5G) in apical (W1) or paraseptal (W5) areas. The latest area to activate was the posterolateral RV base (W1) or the LV basal lateral area (W5). The ECGI activation map of anterograde ventricular conduction during SVT was found to be similar \( (r=0.98) \) to the normal sinus rhythm activation map after ablation, indicating that in SVT, anterograde conduction involved the atrioventricular node and His-Purkinje system exclusively and was independent of the location of the AP.

**Electrograms and ARI**

ECGI epicardial ARI maps (computed by ARI method) before and 45 minutes, 1 week, and 1 month after successful AP ablation are shown in Figures 6 and 7. The insets show the electrogram from the preablation preexcitation site (asterisk, Figures 6 and 7). For all patients except W6, the epicardial electrogram at the preexcitation site showed an r-S activation morphology (insets in Figure 6A, 6E, 6I, 7A, and 7E); the small positive r wave reflects the intramural activity as the activation wave front propagates from an endocardial site toward the epicardium. An r-S electrogram on the epicardial preexcitation site indicated endocardial AP insertion. For patient W6, complete absence of this small positive deflection and a pure QS-wave morphology of the electrogram at the preexcitation site (inset, Figure 7I) indicated that the activation source was epicardial or subepicardial. This, together with the proximity of the epicardial breakthrough to the CS, suggested a left posterior epicardial pathway associated with the coronary venous system (either in the CS or its branches). The T wave in the electrogram at the preexcitation site was inverted (insets, Figures 6A, 6E, 6I, 7A, 7E, and 7I). Forty-five minutes after ablation, the electrogram morphology during activation changed from r-S (or QS) to q-R. In contrast, the T-wave inversion persisted and remained (though to a lesser degree) even a week after ablation (insets, Figures 6B, 6C, 6F, 6G, 7B, 7C, 7F, 7G, 7J, and 7K). The T wave became flatter with a small positive deflection a month after ablation (insets, Figures 6D, 6H, 6L, 7D, 7H, and 7L). In the preexcited rhythm, the basal annular area had a high ARI (red, Figures 6A, 6E, 6I, 7A, 7E, and 7I) with the longest ARI at the preexcitation site (349±6 ms; same for both the ARI method and alternative method) with an ARId of 95±8 ms (ARI method) and 85±9 ms (alternative method). The ARI distribution remained unchanged 45 minutes after ablation \( (r=0.91) \) despite the major changes in the activation sequence (Figures 3 and 4). The ARId decreased after a week (Figures 6C, 6G, 6K, 7C, 7G, and 7K) but was still high(79±9 ms [ARI method] and 66±9 ms [alternative method]).
method]). ARId was restored to close to normal values (45 ± 9 ms [ARI method] and 39 ± 7 ms [alternative method]) a month after ablation (Figures 6D, 6H, 6L, 7D, 7H, and 7L). Activation sequences a week and a month after ablation were the same as the one 45 minutes after ablation (normal sinus rhythm).

Comparison With Sites of Successful Ablation

After successful ablation, the clock position of the ablation catheter was documented in the left anterior oblique projection of the fluoroangiogram using the clock diagram shown in Figure 2B. The Table compares the ECGI-localized site of preexcitation, the predicted location of the AP from the

Figure 5. ECGI-imaged retrograde atrial and anterograde ventricular activation during induced SVT in subjects W1 (left posterior AP) and W5 (midseptal AP). The left 2 panels in each row show the retrograde atrial activation in anterior (first panel) and posterior (second panel) views of the atria. The area of earliest retrograde activation is shown in white; the isochronal lines of retrograde atrial activation are depicted in black. Inset, Lead V2 of ECG during SVT, with the red lines marking the start and end of the retrograde P wave after the QRS complex. The right 2 panels in each row show the anterograde ventricular activation in anterior (third panel) and left posterior (fourth panel) views of the ventricular epicardium. Earliest activation (red, orange) takes place in the anterior RV epicardium in apical or paraseptal region and activation propagates in an apex-to-base fashion, latest activation (blue) is in posterolateral RV base or LV base, consistent with a normal ventricular activation sequence. Ao indicates aorta; RA, right atrium; LA, left atrium; and LAA, left atrial appendage.

Figure 6. ECGI-imaged ARI maps before and after ablation in subjects W1, W2, and W3 presented in the left posterior view of the epicardium. Each row shows the epicardial ARI map before ablation (first panel) and 45 minutes (second panel), 1 week (third panel), and 1 month (fourth panel) after ablation. The inset in each panel shows the noninvasively reconstructed epicardial electrogram from the preablation site of earliest preexcitation (asterisk). Before ablation (first panel), the epicardial preexcitation site (asterisk) has the longest ARI (red). In general, the annular basal area near the site of preexcitation has a longer ARI (red, orange) compared with remote locations, creating an abnormally high ARId. Epicardial ARI distribution remains unchanged 45 minutes after ablation (second panel). Changes in epicardial ARI take place after 1 week (third panel) and 1 month (fourth panel), resulting in a gradual reduction of ARId. The insets show the changes in the T-wave morphology of the epicardial electrogram at the preablation site of preexcitation (asterisk) during the course of this remodeling process.
12-lead ECG–based Arruda algorithm, and the site of successful ablation. ECGI-localized preexcitation sites were consistent with the successful ablation site to an accuracy of an hour’s arc. In 3 cases (subjects W3, W4, and W6), ECGI provided a clinically meaningful improvement in the pathway localization. It identified multiple pathways in subject W3. It pinpointed 1 pathway to the right posterior septum in subject W4 that could have been on either side of the septum according to the Arruda algorithm. It also correctly identified 1 left posterior epicardial pathway (subject W6) that appeared to be a right posteroseptal insertion from the ECG-based algorithm.

### Discussion

#### Noninvasive Localization of the AP

Although the conventional ECG-based Arruda algorithm (valid only for single APs) provides a broad subjective idea of the AP location, the ECGI prediction is more focused and corresponds better with the sites of successful ablation. ECGI is able to distinguish between endocardial and epicardial APs (from electrogram morphology). It also is able to determine the presence and locations of dual pathways before ablation. The spatial pattern of epicardial potentials during early activation (5 to 10 ms after the onset of the delta wave) is mirrored with reverse polarity in the initial repolarization phase, implying that there is no or minimal involvement of conduction system in the propagation of the preexcitation wave front. Hence, even for endocardial APs (12 of 14), the insertion site corresponds closely to the site of earliest epicardial activation (epicardial breakthrough). The study shows that ECGI can be used successfully for noninvasive localization of target ablation sites before catheter ablation in patients with WPW syndrome. It also shows that ECGI can be used as a follow-up tool after ablation to determine whether normal activation had been restored. This concept of preablation localization of target areas and postablation follow-up with ECGI can be extended to other arrhythmias or substrate-based ablation procedures in the future.

#### CM and Repolarization Changes

One important result of the study is the observation of abnormal repolarization in patients with WPW syndrome, resulting in altered epicardial apicobasal ARI. Epicardial apicobasal recovery in normal LV is characterized by an epicardial ARI of 40 to 50 ms, the posterolateral base having a longer ARI compared with the apex. ECGI repolarization images in normal adults have shown an LV epicardial basal ARI of 280 to 300 ms during resting normal sinus rhythm. The LV epicardial basal ARI in the resting WPW left-sided and posteroseptal preexcited rhythm is significantly longer at 337 to 355 ms, leading to an abnormally large ARI of 86 to 112 ms. A previous study provided direct evidence for endocardial ARI prolongation over the preexcited area in patients with manifest WPW, which persisted without any significant change minutes after ablation. Our study shows that in contrast to the fast return of activation to sinus rhythm after AP ablation, the repolarization pattern remains abnormal and unaltered. One week after ablation, the epicardial apicobasal recovery gradients decrease but are still abnormally high; they decrease to normal values only after 1 month. This time course is consistent with “long-term” CM. Suggested mechanisms for long-term CM include attenuation of the expression of the transient outward current (Iₒ) as a result of altered gene transcription by continued downregulation of the cAMP response element binding protein, altered kinetics of L-type calcium channel (I₅ᵥ), and changes in the density and kinetics of the rapid delayed rectifier potassium current (Iₖr). Experiments in canine models have shown that prolonged ventricular pacing downregulates nuclear cAMP response...
element binding protein, with the change being maximal at the pacing site and diminishing with distance. Consistent with this finding, our ECGI ARI maps (Figures 6 and 7, first and fourth columns) show a maximal ARI difference between preablation and postablation rhythms at the preexcitation region (27%) with only an 8% change at remote apical locations. This spatial pattern and the long time course of resolution after ablation (1 month) suggest that CM in the human heart may be associated with transcriptional reprogramming.

Plotnikov et al17 showed that inducibility of CM in canine pacing experiments increases with age and correlates directly with the accentuation of the epicardial action potential notch attributed to the age-related evolution of Ito. The interpatient consistencies in the preablation ARI value at the preexcitation region and the time course of resolution after ablation do not indicate age dependence of inducibility or resolution of CM within the limited age spread of the patients included in this study. We could not find any data in the literature on age-related evolution of Ito in the human ventricular myocyte. However, data from atrial myocytes suggest that Ito is expressed in the human atria from early infancy and does not exhibit significant developmental changes.

Memory-related body-surface T-wave changes in patients with WPW syndrome were studied19 with vectorcardiography. Vectorcardiography also was used to study the development and resolution of CM induced by a week of maximal RV endocardial pacing in humans,20 reporting a resolution time of 1 month. Although vectorcardiography records the manifestation of CM in the body-surface T wave, ECGI maps cardiac activation and repolarization changes caused by the myocardial remodeling processes that underlie CM. The present study shows persistent ARI prolongation over the preablation epicardial region of preexcitation both before and after ablation. Soon after ablation, the activation sequence has reverted to normal as depicted by the ECGI isochrone maps (fourth column, Figures 3 and 4). However, the deeper T wave of the epicardial electrogram (insets, first column, Figures 6 and 7) at the preablation preexcitation site still tracks the preablation inverted r-S wave (insets, first column, Figures 6 and 7), and the epicardial ARIs remain unchanged from their preablation distribution, returning to normal gradually over a time course of 1 month, consistent with long-term CM.

Clinical Implications

The demonstrated ability of ECGI to locate the region of WPW preexcitation more accurately than the ECG-based Arruda algorithm suggests its utility in guiding ablation of AP and evaluating its outcome noninvasively. The study shows that the altered activation sequence of the preexcitation rhythm is accompanied by high dispersion of repolarization, which resolves over a period of 1 month after conversion to normal sinus rhythm. It is well established21 that high dispersion of repolarization provides a substrate for unidirectional conduction block and reentrant arrhythmias. The results of the present study may apply to other clinical situations such as cardiac pacing in which a high dispersion of repolarization in a structurally abnormal heart might provide a possible mechanistic basis for pacing-induced proarrhythmia.22,23

Study Limitations

The patient population (n=14) included in the study is small, and ECGI AP localization is compared with the predicted pathway location from only 1 ECG algorithm. Within these limitations, ECGI provides a clinically relevant improvement in pathway localization in 3 of 14 cases (21%). The present study also lacks quantitative measures of the accuracy of ECGI localization relative to the site of successful catheter ablation. A quantitative measure of localization error requires an exact and accurate method of registration between the ECGI CT anatomy and electrophysiological fluorangiograms that can be implemented in the clinical setting of the electrophysiology laboratory. Moreover, ECGI localized the preexcitation site on the epicardial aspect of the atrioventricular annulus, whereas in most cases, the ablation site was endocardial, beneath this epicardial site.

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Disclosures

Dr Rudy chairs the scientific advisory board and holds equity in CardiolInsight Technologies (CIT). CIT does not support any research conducted by Dr Rudy, including that presented here.

References

ECG imaging, a noninvasive imaging modality for cardiac electrophysiology, determines the locations of Wolff-Parkinson-White accessory pathways with greater accuracy than the conventional ECG-based Arruda algorithm. This capability makes ECG imaging an effective tool for guiding accessory pathway ablation procedures, possibly shortening their time and reducing the associated iatrogenic risks. ECG imaging also can be used to evaluate the outcome of ablation. The study shows that persistent preexcitation, which constitutes a natural model for prolonged ventricular pacing from the accessory pathway insertion site, leads to high dispersion of repolarization and a prolonged activation-recovery interval (action potential duration) at the preexcited (paced) region. The abnormal repolarization gradients resolve over a period of 1 month after a return to normal sinus rhythm by successful ablation. This time course is consistent with long-term cardiac memory, possibly involving transcriptional changes that trigger remodeling processes that alter the molecular determinants of action potential duration. The results of this study may apply to other clinical situations like cardiac pacing in which a high dispersion of repolarization in a structurally abnormal heart might provide a possible mechanistic basis of pacing-induced proarrhythmia reported in the literature.

CLINICAL PERSPECTIVE

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Cardiac Memory in Patients With Wolff-Parkinson-White Syndrome: Noninvasive Imaging of Activation and Repolarization Before and After Catheter Ablation
Subham Ghosh, Edward K. Rhee, Jennifer N. Avari, Pamela K. Woodard and Yoram Rudy

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