Determination of Human Ventricular Repolarization by Noncontact Mapping
Validation With Monophasic Action Potential Recordings

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Background—Noncontact mapping (NCM) has not been validated as a clinical technique to measure ventricular repolarization. We used NCM to determine repolarization characteristics by analysis of reconstructed unipolar electrograms (UEs) at the same sites as monophasic action potential (MAP) recordings in the human ventricle.

Methods and Results—MAPs were recorded from a total of 355 beats at 46 sites in the left or right ventricle of 9 patients undergoing ablation of ventricular tachycardia guided by NCM (EnSite system). Measurements were made during sinus rhythm, constant right ventricular pacing, and ventricular extrastimuli during restitution-curve construction. The EnGuide locator signal was used to document MAP catheter locations on the endocardial geometry. UE-determined activation-recovery interval (ARI) measured at the maximum derivative of the T wave (Wyatt method) and the minimum derivative of the positive T wave (alternative method) was correlated with MAP measured at 90% repolarization (MAP90%) at the same sites. ARI correlated with MAP90% during steady state by the Wyatt method ($r=0.83$, $P<0.001$) and the alternative method ($r=0.94$, $P<0.001$). Restitution curves constructed from MAP and UE data exhibited the same characteristics, with a mean correlation coefficient of 0.95 (range, 0.90 to 0.99, $P<0.001$). The error between ARI and MAP90% was greater over a shorter diastolic coupling interval but was not influenced by distance of the sampling site from the multielectrode array.

Conclusions—NCM accurately determines steady-state and dynamic endocardial repolarization in humans. Global, high-density, NCM data could be used to characterize abnormalities of human ventricular repolarization. (Circulation. 2004;110:1343-1350.)

Key Words: electrophysiology • mapping • ventricles • potentials

Dispersion of repolarization is a well-recognized arrhythmogenic substrate. Substantial experimental evidence supports its role in the initiation and maintenance of reentrant ventricular arrhythmias.1–3 Monophasic action potential (MAP) catheters may be used to directly measure endocardial repolarization in a variety of disease states.4–7 Although it is possible to determine global endocardial repolarization patterns with electroanatomic mapping,8,9 contact measurement is still limited by the small area of coverage, need for sequential measurements, and technical requirement for good myocardial contact.

Noncontact mapping (NCM) reconstructs >3000 unipolar electrograms (UEs) over the entire endocardial surface of a cardiac chamber in a single beat. Previous validation studies were confined to assessment of intracardiac activation,10,11 and therefore, NCM has not yet been validated as a clinical tool to characterize repolarization changes. In the present study, we compared repolarization timings measured by reconstructed UEs with MAP recordings recorded simultaneously at the same sites in the human left or right ventricle. We applied validated principles that were used in contact UEs12 to estimate activation-recovery intervals (ARIs) from the UEs.13

Methods

Patients

Nine patients (3 female; mean age, 54 years) who presented with monomorphic ventricular tachycardia to the Wessex Cardiac Unit, Southampton, United Kingdom, were prospectively enrolled into the study (Table 1). They all underwent evaluation with clinical history, physical examination, 12-lead ECG, transthoracic echocardiography, and left ventricular and coronary angiography. The mean left ventricular ejection fraction was 0.57±0.16. The study was performed with patients in the postabsorptive, nonsedated state immediately after NCM-guided ablation of left or right ventricular tachycardia. All patients had given written consent before the study. The Southampton and Southwest Hampshire local research ethics committee granted ethical approval of this study.
Noncontact Mapping
The technique of NCM with the EnSite 3000 system (Endocardial Solutions Inc) has been described previously. The system consists of a 64-multielectrode array (MEA) mounted on a 7.5-mL inflatable balloon on a 9F catheter, an amplifier system, and a Silicon Graphics Workstation. For left ventricular study, the MEA was introduced under fluoroscopic guidance from the left femoral vein. A 7F, 4-mm-tip deflectable ablation catheter (Stinger, Bard) was then introduced into the ventricle via the same route as the MEA catheter. The system calculated the position of the ablation catheter relative to the fixed, known position of the ring electrodes at either end of the MEA. By dragging the ablation catheter tip along the endocardial surface and constantly passing a 5-kHz locator signal to the EnGuide locator signal was directed through the MAP catheter and MEA in left ventricle during data acquisition (anterior-posterior view). Open arrow indicates tip of MAP catheter. Bipolar pacing catheter is placed in right ventricular apex.

MAP Recordings
The onset of the MAP was determined at the fastest upstroke of the MAP potential or, if seen, the fast negative slope of a rapid biphasic deflection that superimposed on the initial phase of the MAP. The MAP duration was measured at 90% repolarization (MAP90%). Activation time was defined as the interval from the onset of QRS or pacing stimulus from surface ECG to the onset of MAP90%. Recovery time for MAP recordings was defined as the sum of local activation time and MAP90%.

Restitution Curves
Constant right ventricular pacing (S1) with a bipolar, woven catheter (Bard EP Inc) at the right ventricular apex was performed for 2 minutes at cycle lengths of 400 and 600 ms with a pulse width of 2-ms duration and a stimulus strength of twice diastolic threshold. After steady state had been established, an extrastimulus (S2) was introduced at every 10-beat cycle. The coupling interval of S1–S2 was decremented by 40 ms every cycle from steady state to 400 ms, by 20 ms every cycle down to 300 ms, and by 10 ms every cycle from 300 ms until refractoriness. Action potential durations from MAP and UE recordings were determined from the same sites (Figure 3). MAP90% and ARI timings after abrupt shortening in S1–S2 coupling.

Definitions
Reconstructed UEs
Three different morphologies of UE T wave were defined: positive, negative, and biphasic. ARI was measured between the time of dV/dtmax of the QRS and the dV/dtmax of the T wave in the UE of all T-wave morphologies (Wyatt method). For positive T wave, an additional method for determining end of repolarization by measuring recovery at the dV/dtmax of the T wave for comparison (alternative method) was used. Activation time was defined as the interval from the onset of QRS or pacing stimulus from surface ECG to the onset of ARI. Recovery time was taken as the sum of local activation time and ARI.

Figure 1. MAP catheter and MEA in left ventricle during data acquisition (anterior-posterior view). Open arrow indicates tip of MAP catheter. Bipolar pacing catheter is placed in right ventricular apex.
intervals were plotted against the preceding diastolic intervals as restitution curves. For direct comparison of the degree of action potential duration shortening during electrical restitution measured by the 2 methods, MAP90%, ARI, and diastolic intervals were presented as percentages of steady-state values.\textsuperscript{16}

**Data Analysis**

Data were analyzed with the Silicon Graphics workstation with the standard Precision software (version 4.0) installed. A custom-designed template was used to simultaneously display the following waveforms on the screen from the same selected endocardial site: surface ECG, MAP recording, UE, and its first derivative ($dV/dt$). Measurements were made manually from electrograms displayed on a Silicon Graphics color monitor at 200 mm/s resolution. The use of horizontal (timing) and vertical (amplitude) electronic calipers from the workstation allows timing of activation and repolarization to be determined to an accuracy of 1 ms and comparison of MAP recordings and UEs of the same beat to be made (Figure 2A). The distance of each sampling site of the geometry from the center of the MEA was documented by using a preset workstation algorithm. In addition, 3 paired recordings on average were randomly selected at widely spaced intervals from each site for comparison. Recording bandwidth was set at 0.1 to 300 Hz for MAP and UE recordings. No adaptive, notch, or spatial filters were used. For measurement of the minimum derivative ($dV/dt_{\text{min}}$) of QRS and the maximum derivative ($dV/dt_{\text{max}}$) of the UE T wave, the filter bandwidth was selected at 0.1 to 25 Hz to reduce noise in the $dV/dt$ channel. Use of this filter setting is justified for 2 reasons. First, compared with phase 0 of the MAP, the UE has a significantly slower component in the QRS complex during activation. Second, the amplitudes of $dV/dt_{\text{max}}$ and $dV/dt_{\text{min}}$ of the T wave are sufficiently small so that they are unlikely to be significantly affected by the filter setting. For analysis of restitution curves, we compared changes in action potential durations as determined by ARI and MAP90% during electrical restitution as percentages of steady-state values because their baseline absolute values may not be equal.

**Statistical Analysis**

Three randomly chosen, paired MAP and UE recordings were taken from each site to measure activation time, MAP90%, ARI, and repolarization time determined by the 2 methods. Comparison of the means of these paired timings for all sites was made by the Pearson correlation coefficient test, simple linear regression analysis, and 95% confidence intervals. Error for MAP and UE measurements was calculated by (UE timing – MAP timing). Bland-Altman statistics were used to present the agreement between MAP and UE timings.

![Figure 2](image-url)
for 3 T-wave polarities by plotting the differences between ARIs and MAP90% against their means. Continuous data were presented as mean±SD and compared with the paired Student t test. A probability value of <0.05 was considered statistically significant.

**Results**

A total of 10 studies were performed in 9 patients. One patient (No. 6) had a study repeated because of recurrence of ventricular tachycardia requiring a second NCM-guided ventricu lar tachycardia ablation. Of the 50 ventricular endocardial sites from which 370 beats with satisfactory MAP recordings were made, 4 sites containing 12 beats were excluded because of a flat or complex UE T wave that did not conform to the inclusion criteria. During electrical restitution, 3 beats were excluded because of flattening of the UE T wave at short S1–S2 coupling intervals such that the end of repolarization could not be determined. Therefore, a total of 355 paired MAP and UE recordings were analyzed: 168 during steady state and 187 during electrical restitution.

**Steady State**

One hundred sixty-eight beats were recorded from 46 endocardial sites in the study patients (mean of 5 sites per patient). Seventeen sites were analyzed during right ventricular pacing only, 21 were analyzed in sinus rhythm only, and 8 sites were analyzed during both sinus rhythm and right ventricular pacing. The T-wave polarities of the UEs were negative in 86 of the analyzed beats, positive in 58, and biphasic in 24. The overall site-specific correlation between MAP-determined and UE-determined activation and repolarization time is shown in Table 2. Paired comparison of repolarization time is also shown as linear regression plots in Figure 4. The MAP and UE activation and repolarization data were closely correlated during sinus rhythm and constant right ventricular pacing. When ARIs were measured, a close correlation with MAP90% was found for each of the T-wave polarities (Table 3). The error comparing ARIs with MAP90% was relatively small for the negative T wave (0±11 ms) and the biphasic T wave (4±19 ms). However, the error was significantly larger for the positive T wave, especially with the Wyatt method (−47±12 ms). This error was reduced (10±15 ms) by applying the alternative method for determining ARI for positive T wave (Figure 5). Errors up to a maximum of 98 ms were found with the Wyatt method to measure ARI compared with MAP90%.

**Electrical Restitution**

One hundred eighty-seven paired recordings from MAP and NCM data were made at each coupling interval during construction of electrical restitution curves from 11 sites in 6 patients. Comparison at individual sites showed a mean correlation coefficient of \( r = 0.95 \) (range, 0.90 to 0.99, \( P < 0.001 \)). The mean difference between MAP90% and ARI measurement with the alternative method during electrical restitution was \( 2 ± 2 \% \) (of steady-state durations). When the
Wyatt method was used for measurement of the positive T wave, mean error was increased to 7/11006% because of an underestimation of ARI compared with MAP90%. Errors were significantly greater at shorter diastolic intervals (Figure 6).

**Distance From MEA**

The mean distance of the sampling sites of MAP recordings on the geometry from the center of the MEA was 41/1006 ± 10 mm (range, 23 to 73). There was no significant relation between ARI and MAP90% timing difference and increasing distance from the center of the MEA with either the Wyatt method (r=0.09, P=0.12) or the alternative method (r=0.06, P=0.21) (Figure 7).

**Discussion**

We have demonstrated in this study that ARIs determined by UEs are closely correlated with MAP recordings during sinus rhythm, constant pacing, and abrupt changes in the preceding diastolic interval. Moreover, a significantly high correlation was found for each of the 3 T-wave polarities.

UE measurements on the endocardial surface by contact catheters have been validated as an accurate representation of local refractory periods and transmembrane action potential durations in the dog,13,15 swine,9 and human12,17 heart. Some investigators used intramural plunge needles for measurements in experimental heart preparations,3 whereas others used sock arrays of 50 to 80 button electrodes to record on the epicardium of the beating heart.12 We have adopted these validated principles from contact UE measurements to the NCM reconstructed electrograms and their first derivatives to compare local repolarization timings with MAP recordings.

Although the NCM electrograms are reconstructed by an inverse solution, the close correlation between ARIs and MAP90% with small errors in our study is similar to other reports from the dog endocardium15 and human epicardium12 measured with contact UEs. The correlation in local repolarization time between UE and MAP recordings is notably strong with both Wyatt and alternative methods. This accuracy of repolarization time measurement is important in the study of arrhythmogenic mechanisms because it is the heterogeneity of instantaneous local repolarization that underlies phase 2 reentry and initiation of ventricular arrhythmias.3,18

In agreement with Chen et al.,12 the Wyatt method considerably underestimates ARI for the positive T wave in our report, despite a good correlation with MAP90% (r=0.86).
With this method, the error between MAP90% and ARI for the positive T wave was 47 ± 12 ms. In contrast, the alternative method of ARI estimation provided closer correlation with the positive T wave (r = 0.95), with an error of 10 ± 15 ms. Although the theoretical basis for this observation remains to be determined, it is consistent in the human endocardium and epicardium and has been reproduced from contact and noncontact electrograms. The disparity with the results of Haws and Lux may be explained by differences between species and that they took dV/dt_{min} of the transmembrane action potential as the end of repolarization instead of MAP90%. Furthermore, the Wyatt method is derived from the 1-dimensional classic cable theory. It is possible that in the 3-dimensional cardiac chamber, in which the polarity of the T wave represents the spatial direction of repolarization wavefronts, the minimum derivative of a positive T wave might be physiologically analogous to the maximum derivative of a negative T wave that repolarizes in an opposite direction.

We have also demonstrated that UE-determined changes in ARIs during construction of restitution curves exhibited the same characteristics as MAP90%. The percentage shortenings of MAP90% and ARI were closely correlated, but greater errors have been observed, particularly with the Wyatt method for estimation of ARI at short diastolic intervals. This may have important implications not only for measurement of global endocardial repolarization patterns during steady state but also in the calculation of restitution slopes in the range of diastolic intervals where errors are highest. Compared with the alternative method, the Wyatt method could overestimate restitution slopes at sites with a positive T wave.

**Figure 5.** Agreement between MAP and reconstructed UE repolarization timings. Bland-Altman plots show timing difference (with 95% confidence limits) versus mean for paired recordings. A, Positive T wave (closed circles indicate Wyatt method; open circles indicate alternative method); B, Negative T wave; C, Biphasic T wave.

**Figure 6.** Correlation of restitution curves. A, Restitution curves constructed by MAP and reconstructed UE from single endocardial site with positive T wave (r = 0.94, P < 0.001). Alternative method was used for this comparison. B, Error between MAP90% and reconstructed ARI by both Wyatt and alternative methods for all recordings versus diastolic interval (mean ± SD). *P < 0.05 comparing Wyatt method with alternative method.
dispersion of repolarization has been implicated in ventricular arrhythmogenesis for several decades, but the ideal method of multisite intracardiac measurement in humans has remained elusive to the electrophysiologist. Our report supports the potential role of NCM as a clinical tool to study ventricular arrhythmogenic mechanisms in vivo and that an algorithm could potentially be constructed based on simple, defined criteria to calculate global, simultaneous repolarization timings in any cardiac cycle. A recent study proposed that human endocardial restitution slopes could be determined by MAP recordings, and their response to adrenergic stimulation appeared to reflect experimental findings. We have not validated reconstructed T-wave morphology with contact electrograms at the same sites as MAP recordings. This is because MAP recording involves endocardial pressure such that the myocardium subjacent to the electrode tip is inactivated and the ST segments of contact UEs in the vicinity are invariably elevated. However, MAP durations have not been directly compared with reconstructed T-wave morphology but with timing measurements of UE derivatives. In our study, the mean distance of MAP recording sites from the MEA (41 mm) was greater than those in previous reports. Despite our attempts to make recordings closer to the MEA, the inflated balloon within the left ventricle prevented stable alignment of the MAP catheter with the endocardium and measurement of satisfactory MAP potentials. Nevertheless, our results suggest that NCM could provide accurate representation of relatively distant repolarization data.

Clinical Implications
Dispersion of repolarization has been implicated in ventricular arrhythmogenesis for several decades, but the ideal method of multisite intracardiac measurement in humans has remained elusive to the electrophysiologist. Our report supports the potential role of NCM as a clinical tool to study ventricular arrhythmogenic mechanisms in vivo and that an algorithm could potentially be constructed based on simple, defined criteria to calculate global, simultaneous repolarization timings in any cardiac cycle. A recent study proposed that human endocardial restitution slopes could be determined by MAP recordings, and their response to adrenergic stimulation appeared to reflect experimental findings. We therefore speculate that NCM could be used to measure global ventricular response to electrical restitution or pharmacological interventions in humans and to evaluate methods of risk stratification in patients with inherited or acquired conditions that predispose to life-threatening ventricular arrhythmias.

Limitations
We have not validated reconstructed T-wave morphology with contact electrograms at the same sites as MAP recordings. This is because MAP recording involves endocardial pressure such that the myocardium subjacent to the electrode tip is inactivated and the ST segments of contact UEs in the vicinity are invariably elevated. However, MAP durations have not been directly compared with reconstructed T-wave morphology but with timing measurements of UE derivatives. In our study, the mean distance of MAP recording sites from the MEA (41 mm) was greater than those in previous reports. Despite our attempts to make recordings closer to the MEA, the inflated balloon within the left ventricle prevented stable alignment of the MAP catheter with the endocardium and measurement of satisfactory MAP potentials. Nevertheless, our results suggest that NCM could provide accurate representation of relatively distant repolarization data.

Conclusions
Reconstructed UEs from NCM accurately defined endocardial repolarization characteristics. Measurements with current software configuration during the resting state, constant pacing, and electrical restitution were closely correlated with MAPs at the same sites. High-density, noncontact repolarization data could allow the study of global dynamic changes of repolarization in the clinical setting.

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Disclosure
Drs Yue and Betts have participated in a scientific study for Endocardial Solutions.

References


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