Intraventricular Electrogram Analysis for Ventricular Tachycardia Detection: Statistical Validation

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THRONE, R.D., ET AL.: Intraventricular Electrogram Analysis for Ventricular Tachycardia Detection: Statistical Validation. *Time-domain analysis of intraventricular electrogram morphology during ventricular tachycardia (VT) and sinus rhythm or atrial fibrillation (SR/AF) has been proposed as a method for increasing the specificity of pathological tachycardia detection by antitachycardia devices. However, few studies have validated the use of such analysis with statistical methods. When statistical methods have been utilized, it has been assumed that the distribution of the values derived from analysis of the intracardiac electrograms have had a normal (gaussian) distribution. In this study, we sought to determine whether: (1) the distribution of values derived from analysis of intracardiac electrogram during SR/AF and VT is gaussian or nongaussian; and (2) the discrimination of monomorphic VT from SR/AF using SR/AF templates can be validated statistically. Two previously proposed time-domain methods—correlation waveform analysis (CWA) and area of difference (AD)—were selected for evaluation of 29 patients with 33 distinct, sustained monomorphic VTs. An initial SR/AF template was used to analyze subsequent SR/AF and VT passages with a minimum of 50 consecutive depolarizations using a "best-fit" alignment. The values derived from each analysis were examined subsequently for skewness (asymmetry) and kurtosis (shape) using two-tailed tests ($P < 0.02$). For passages of SR/AF, a normal (gaussian) distribution was present in only 24% (CWA), and 45% (AD); for passages of VT, normal distribution was present in only 58% for both CWA and AD. Using appropriate statistical testing with nonparametric tolerance intervals, CWA and AD discriminated VT from SR/AF in 29 out of 33 (88%), and 30 out of 33 (91%) instances, respectively, with 95% confidence. Thus, the assumption of a gaussian distribution for values derived from time-domain analysis of intraventricular electrograms for VT detection is not uniformly valid. Both CWA, which is independent of both baseline and amplitude fluctuations, and AD, which is not independent of these fluctuations, have similar performance when validated with appropriate statistical methods. (PACE, Vol. 13, December, Part I 1990)*

statistical validation, correlation waveform analysis, area of difference, nonparametric tolerance intervals, ventricular tachycardia detection

Introduction

Although implantable devices appear to improve survival for patients whose dysrhythmias are refractory to antiarrhythmic medical therapy, present implantable devices for detection and treatment of tachycardias use simple analog circuits, and lack specificity in ventricular tachycardia (VT) recognition.[1-7] Methods for detection of VT have been based primarily on timing information derived from rate.[8-16] The identification of differences in intraventricular electrogram morphology during sinus rhythm (SR) and VT have been proposed to increase the accuracy of VT dis-

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crimination.[12,17-24] These algorithms have usually been tested on short (10–15 seconds) passages of the dysrhythmias.[12,18,23-26] Some investigators have limited their analysis to as few as 10 SR and 10 VT depolarizations.[21]

Few studies to date have validated the results of electrogram morphology analysis with statistical methodology, though paired Student's *t*-tests have been used in one study.[21] However, paired Student's *t*-tests assume an underlying normal distribution of the derived similarity measures. However, the actual distribution of the values derived from time-domain methods proposed for VT detection has never been determined. Therefore, whether the results of intraventricular electrogram analysis for discriminating VT can, in fact, be appropriately validated with statistical confidence has not heretofore been demonstrated.

In this study, we analyzed two previously proposed template-matching techniques for discriminating ventricular electrograms during VT from ventricular electrograms during SR/AF: correlation waveform analysis (CWA);[23,25,26] and area of difference (AD).[20-22] CWA is an analytic method that is independent of electrogram baseline and amplitude fluctuations, whereas AD is dependent upon both fluctuations. The goals of this study were to determine whether: (1) the values derived from analyzing passages of VT and SR/AF with CWA and AD have a gaussian (normal) or nongaussian distribution, and (2) VT can be distinguished with statistical certainty from SR/AF using these two different time-domain methods.

Methods

Electrophysiology Study

Bipolar (1 cm) distal ventricular endocardial electrograms were recorded during elective clinical cardiac electrophysiology studies as previously reported.[23,25,26] Three 6 French quadrapolar electrode catheters (USCI, Billerica, MA, USA) with an interelectrode distance of 1 cm were introduced and advanced under fluoroscopic guidance to the high right atrium (or right atrial appendage) and right ventricular apex. Two catheters were positioned in the right ventricular apex with one dedicated to pacing, and the other to obtaining recordings from the distal electrode pair. All recordings were made with the patients lying supine.

Ventricular electrograms were recorded on FM magnetic tape (Hewlett-Packard Models 3968 and 3964A, [San Diego, CA, USA]) from distal bipolar endocardial electrodes positioned in the right ventricular apex using amplifiers with filter settings of 0.5–500 Hz (Siemens Mingograf-7, Siemens-Elema, Solna, Sweden) or 1–500 Hz (PPG Biomedical Systems, Lenexa, Kansas, USA). Tape speed was $3\frac{3}{4}$ inches per second with a bandwidth of 0–1,250 Hz.

Data sets typically consisted of an initial passage of SR or atrial fibrillation (AF) with at least eight normal depolarizations, two or three subsequent 30-second passages during SR/AF, and a passage of monomorphic VT with at least 50 depolarizations. An SR/AF ventricular electrogram template was constructed by signal averaging eight normal ventricular depolarizations from SR/AF. This template was then compared to the ventricular electrograms in the remaining passages of SR/AF and the passage of VT using each of the template-matching techniques described below. A software trigger (peak detector) was used for the detection of waveforms. The best fit (within an 11 msec window) alignment was used for evaluating the algorithms.[25,26] All passages were digitized at 1,000 Hz.

Algorithms Analyzed

The following notation is used in all algorithms:

N = the number of points in the template.
t_i = template points.
s_i = the signal points to be processed.
$\bar{t}$ = the template average.
$\bar{s}$ = the signal average.
ρ = the value of the similarity measure.

CWA

CWA[23,25,26] uses the correlation coefficient ρ as a measure of similarity between the template and waveform under analysis. The correlation coefficient is independent of both amplitude and baseline changes between the template and the signal under analysis. Mathematically the correlation coefficient is defined as:

$$\rho = \frac{\sum_{i=1}^{i=N} (t_i - \bar{t})(s_i - \bar{s})}{\sqrt{\sum_{k=1}^{k=N} (t_k - \bar{t})^2}\sqrt{\sum_{k=1}^{k=N} (s_k - \bar{s})^2}}$$

$$= 1 - \frac{1}{2}\sum_{i=1}^{i=N}\left(\frac{t_i - \bar{t}}{\sqrt{\sum_{k=1}^{k=N} (t_k - \bar{t})^2}} - \frac{s_i - \bar{s}}{\sqrt{\sum_{k=1}^{k=N} (s_k - \bar{s})^2}}\right)^2$$

To avoid the square root computation, we equivalently use

$$\wp = sign(\rho)\rho^2$$

where $sign(\rho)$ is ± 1 depending on the sign of ρ.

AD

The AD[20–22] measures the absolute difference in amplitude of sample points in the template and the waveform under analysis with a similarity measure given by

$$AD = \sum_{i=1}^{i=N} |t_i - s_i|$$

The area of difference is usually reported as a percentage change of the absolute deviation of the template points from the baseline, i.e.,

$$\wp = AD(\%) = \frac{\sum_{i=1}^{i=N} |t_i - s_i|}{\sum_{i=1}^{i=N} |t_i|} \times 100\%$$

Testing the Hypothesis of Normality

The data was initially examined to determine whether the hypothesis of normality of the distribution of similarity values (V) should be rejected or accepted. Two distinct tests for normality were used. First, the skewness (asymmetry) of the distribution of V values during the SR/AF passages or during the VT passage was tested ($P < 0.02$) using a standared two-tailed test.[27] Second, the kurtosis (shape) of the distribution of $\wp$ values during the SR/AF passages or during the VT passage was tested ($P < 0.02$) using Geary's method.[27,28] This was also a two-tailed test.

Statistical Validation with Nonparametric Tolerance Intervals

Statistical validation with nonparametric tolerance intervals[27] assume only that the similarity values V are from a continuous, though unknown, probability distribution function. Therefore, it can be used to validate methods whose results produce either gaussian (normal) or nongaussian distributions.

Nonparametric tolerance intervals are constructed using the ranges of the observed values of V to estimate, with a given confidence level, bounds within which ζ% of all V will occur with 95% confidence. If the intervals for VT do not overlap with the corresponding intervals for SR/AF for a particular algorithm under analysis, the algorithm is declared to successfully separate at least ζ% of the SR (or AF) depolarizations from at least ζ% of the VT depolarizations with 95% confidence.

The values derived from an ideal analysis of intraventricular electrograms would separate all VT depolarizations from all SR/AF depolarizations with 100% certainty. However, this expectation may be neither realistic nor practical due to the possibility of phenomena such as sinus capture or fusion beats occurring during VT. In some cases, the local (bipolar) intraventricular electrogram wave fronts may even have characteristics which are similar when SR/AF is compared to VT.

In this study, $\zeta = 90$ and 75, bounding 90% and 75% of the values of $\wp$ during SR/AF and VT, respectively. The minimum confidence level was set at 95%.

Results

Testing Hypothesis of Normality

Tables I and II summarize the results of testing the hypothesis of normality using two-tailed tests for skewness and kurtosis ($P < 0.02$). Table I summarizes the results for SR/AF, while Table II

Table I.

Accept/Reject Hypothesis of a Normal Distribution	CWA	AD
Reject: Skewness alone	6 (21%)	6 (21%)
Reject: Kurtosis alone	3 (10%)	2 (7%)
Reject: Skewness and kurtosis	13 (45%)	8 (27%)
Accept	7 (24%)	13 (45%)

Summary of testing the hypothesis of an underlying normal distribution of similarity values $\wp$ during sinus rhythm or atrial fibrillation against skewness and kurtosis using a two-sided test ($P < 0.02$). There are 29 possible sinus rhythm/atrial fibrillation instances.

Table II.

Accept/Reject Hypothesis of a Normal Distribution	CWA	AD
Reject: Skewness alone	7 (21%)	9 (27%)
Reject: Kurtosis alone	2 (6%)	3 (9%)
Reject: Skewness and kurtosis	5 (15%)	2 (6%)
Accept	19 (58%)	19 (58%)

Summary of testing the hypothesis of an underlying normal distribution of similarity values ρ during monomorphic ventricular tachycardia against skewness and kurtosis using a two-sided test ($P < 0.02$). There are 33 possible ventricular tachycardia instances.

summarizes the results for VT. The top row of the tables identifies the template-matching technique used. The number of instances the normality hypothesis was rejected due to skewness, kurtosis, or both skewness and kurtosis, is summarized separately. The number of instances where the normality hypothesis was accepted is summarized at the bottom of the two tables.

For the SR/AF passages (Table I), the normality hypothesis was accepted in 7 out of 29 (24%) to 13 out of 29 (45%) instances, respectively, while for the VT passages (Table II) the normality hypothesis was accepted in 19 out of 33 (58%) instances for both methods.

Distinguishing VT from SR/AF

Table III summarizes the results of comparing 90% and 75% tolerance intervals for CWA and AD. The first row of the table indicates the number of instances (out of 33) in which 75% of all SR/AF depolarizations could not be distinguished from 75% of all VT depolarizations. The second row indicates the number of instances in which at least 75% (but < 90%) of all SR/AF depolarizations could be distinguished from at least 75% (but < 90%) of all VT depolarizations. The final row indicates the number of instances in which at least 90% of all SR/AF could be distinguished from at least 90% of all VT depolarizations. CWA and AD could distinguish 90% of the SR/AF depolarizations from 90% of the VT depolarizations with 95% confidence in 29 out of 33 (88%) and 30 out of 33 (91%) instances, respectively. There were at most 2 out of 33 (6%) instances that could not be distinguished when 75% of all SR/AF depolarizations were compared to 75% of all VT depolarizations.

Discussion and Conclusion

In examining the results of CWA and AD for distinguishing ventricular electrograms during VT from those during SR/AF, the assumption that the distribution of similarity values is uniformly normal (gaussian) does not appear to be valid. Therefore, the application of statistical methods which assume an underlying normal distribution of similarity values for the purpose of validating a proposed technique for distinguishing VT from SR/AF may not be appropriate. While the use of nonparametric tolerance intervals does not require any assumption about the underlying distribution of values derived from intracardiac electrogram analysis, it is necessary that the passages under analysis be "representative" passages of both SR/AF and VT and have sufficient duration to permit valid statistical assessment.

Despite considerable differences in computational complexity, for the patient population studied and the statistical analysis method used, both of the template-matching algorithms analyzed in this study had similar statistical performance in distinguishing ventricular electrograms during SR or AF fibrillation from electrograms during VT.

The algorithms examined in this study utilized intraventricular electrograms from electrode catheters acutely placed in supine patients at rest during clinical EPS studies. Distribution analysis and statistical assessment of the effects of changes in patient position, sympathetic tone, antiarrhythmic drugs, exercise, and chronic leads is not known at present. Other time-domain methods, including those which depend upon

Table III.

% Intervals Distinguished	CWA	AD
<75	0 (0%)	2 (6%)
≥75, <90	4 (12%)	1 (3%)
≥90	29 (88%)	30 (91%)

Summary of separation of VT tolerance intervals from the corresponding SR/AF tolerance intervals (95% confidence level). There are 33 VT instances.

Table IV.

Pt	Sex	Heart Disease	Drugs	SR/AF QRS Morphology	VT QRS Morphology
1	M	None	None	SR-RBBB	RBB-S/L
2	F	None	Iso	SR-Normal	LBB-I/L
3	M	None	Iso	SR-Normal	RBB-S/R
4	F	None	Am	SR-Normal	RBB-S/R
5	M	None	None	SR-RBBB	LBB-I/R
6	M	CAD	None	SR-Normal	LBB-S/L
7	M	CAD	None	SR-Normal	RBB-S/R
8	M	CAD	None	SR-Normal	LBB-I/R
9	M	CAD	None	SR-RBBB	LBB-S/R
10	M	CAD	None	SR-IVCD	RBB-I/R
11	M	CAD	None	ST-IVCD	LBB-S/L
12	M	CAD	None	AF-LBBB	LBB-S/L
13	M	CAD	None	AF-LBBB	RBB-S/L
14	M	CAD	None	AF-RBBB	LBB-I/L
15	M	CAD	Iso	SR-RBBB	LBB-I/L
16	M	CAD	Proc	SR-Normal	RBB-S/R
17	M	CAD	Proc	SR-Normal	RBB-S/R
18	M	CAD	Proc	SR-RBBB	LBB-S/R
19	M	CAD	Proc	SR-IVCD	RBB-S/R
20	M	CAD	Am	SR-IVCD	RBB-I/R
21	M	CAD	Am	SR-IVCD	LBB-S/L
22	M	CAD	Am	SR-IVCD	†RBB-S/R †LBB-S/L †RBB-S/R
23	M	CAD	Am	SR-IVCD	LBB-S/L RBB-S/R
24	M	CAD	Am	SR-LBBB	LBB-S/L
25	M	CAD	Am Me	SR-LBBB	LBB-I/R
26	M	CAD	En	SR-RBBB	RBB-S/L
27	F	CAD	Qu	SR-Normal	LBB-S/R RBB-S/R
28	M	CAD	Qu	AF-IVCD	RBB-S/L
29	M	CAD	Qu Me	SR-RBBB	RBB-S/R

Patient data for statistical study. †These are different VT morphologies. CAD = Coronary Artery Disease; Iso = Isopril, Am = Amiodarone, Proc = Procainamide, En = Encainide, Me = Mexiletine, Qu = Quinidine.

electrogram baseline fluctuation alone, amplitude fluctuation alone, or which utilize other template-electrogram alignment strategies, will require similar analysis and assessment in order to validate their results with statistical confidence.

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