ORIGINAL ARTICLE

ASSESSMENT OF NON-INVASIVE MARKERS IN IDENTIFYING PATIENTS AT RISK OF INDUCIBLE VENTRICULAR ARRHYTHMIAS

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Background: A number of non-invasive tools have been tested to assess arrhythmogenic risk in different patients groups. Some of them could possibly predict the inducibility of ventricular tachycardia (VT) by programmed ventricular stimulation (PVS). **Methods:** The study has been conducted at Al-Kadhimia Teaching Hospital, Baghdad/Iraq. 26 patients suspected to have ventricular arrhythmias as underlying cause to their symptoms and planned for PVS were included between May 2004 to December 2005. In one patient electrophysiologic (EP) study could not be performed because he was in slow well tolerated VT and thus was omitted from the study. QRS-dispersion (QRSd), QT-dispersion (QTd), short-term heart rate variability (HRV) and heart rate turbulence (HRT) were measured in all the 25 patients prior to their admission for PVS. The patients were divided in 2 groups according to the result of the invasive EP study: Group I (n=17) included the patients in whom ventricular arrhythmia (VA) couldn't be induced by PVS. Group II (n=8) included the patients in whom sustained VA was induced by PVS. **Results:** A higher mean QRSd, QTd and QRSd+QTd was found in group II in comparison with Group I. A significant difference was noticed in mean QRSd and QRSd+QTd (p=0.038 and 0.0167 respectively) but not in QTd (p=0.161). A significant difference between the two groups was noticed in mean short-term HRV (p=0.014). Mean turbulence onset (TO) value was higher (p=0.014) and mean turbulence slope (TS) value were lower (p=0.544) in Group II, but the difference was significant only in mean TO. **Conclusion:** QRS dispersion, short-term heart rate variability and turbulence onset may be important risk stratifying parameters regarding arrythmogenic liability.

Keywords: ventricular arrhythmia, programmed ventricular stimulation, non-invasive arrhythmic risk markers

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INTRODUCTION

The electrophysiological evaluation of ventricular tachycardia (VT) in man began in 1972[1] and since then programmed electrical stimulation (PES) has been accepted as a procedure to study VT safely. Programmed ventricular stimulation (PVS) has become a procedure with diagnostic, prognostic and therapeutic objectives.[2] Ventricular tachyarrhythmia induction is usually accomplished with propagated right ventricular stimuli and is often facilitated by minimising the extra stimulus coupling interval.[3]

The principal goals of the electrophysiologic study in the evaluation of VT are[4]:

1. Confirming the diagnosis of VT
2. Defining the mechanism of arrhythmia
3. Localising the site of origin of VT
4. Evaluating the efficacy of pharmacologic and non pharmacologic therapeutic methods

PES of the ventricle is widely used to provoke sustained VT in patients who have had clinical events of unsustained VT, syncope, or resuscitated sudden cardiac death.[5] It has even been applied to assess arrhythmic potential in patients who have not had but may be at increased risk for ventricular arrhythmias[6] but the results of PVS should be interpreted with caution in such patients especially when using aggressive stimulation protocol[7].

The non-invasive tools available for assessing arrhythmogenic risk, e.g., heart rate variability, repolarisation indices and many others all show promise but are far from definitive or reliable.[8] Some non-invasive parameters could possibly predict the inducibility of VT by PVS which in turn may serve as a reference test for new non-invasive methods of risk stratification for ventricular arrhythmias. For this purpose we choose to assess the value of QRS-dispersion (QRSd), QT-dispersion (QTd), short-term heart rate variability (HRV) and heart rate turbulence (HRT) in predicting ventricular arrhythmia (VA) inducibility by PVS.

SUBJECTS AND METHODS

The study population consisted of 26 patients admitted for VT induction during electrophysiology (EP) study in Al-Kadhimia Teaching Hospital, Baghdad/Iraq, between May 2004 to December 2005. The patients were suspected to have ventricular arrhythmias as underlying cause to their symptoms. In one patient EP study could not be performed because he was in slow well tolerated VT and thus was omitted from the study.

The characteristics and clinical features of the study population are listed in Table-1.

The purpose of the test and procedure were explained to the patient. All antiarrhythmic drugs and aspirin were withdrawn at least 2–3 days before the study. All patients gave written informed consent. They were studied in the cardiac catheterization laboratory in the resting, non-sedated state. All patients prior to the EP study underwent a complete review of medical history. Clinical examination of the heart, peripheral pulse, measurement of blood pressure, as well as blood electrolytes analysis, chest X-ray, ECG, holter monitoring and echocardiogram were performed.

During Electrophysiological study continuous monitoring of the heart was done by connecting the patient to a monitor (Hellige SMU 611, Germany). Surface ECG was recorded simultaneously with the intracardiac electrocardiogram by surface electrodes connected to a multichannel page monitor (EIZO Flex Scan FX.E7S, JAPAN) of the Electrophysiology (EP) device (Bard Electrophysiology. CR Bard, Inc. USA). A Radionics Pace-1A stimulator, Burlington, USA was used for intracardiac stimulation. For analysis of the data the OS2 software was used.

Quadripolar Electrode catheters (ST. Jude Medical and Cordis Webster. 6F) were passed percutaneously through the right femoral vein by (Seldinger technique) and positioned under fluoroscopic control. A syringe with a (16) gauge needle was inserted under slight negative pressure in the femoral vein then a guide wire (Cordis, Johnson and Johnson Co.) was put in the needle and followed under fluoroscopy screen (O≡C Medical System Inc. lKXlk Workstation. USA). A dilator (Cordis, Johnson & Johnson Co.) was inserted over the guide wire. The guide wire was then pulled and a sheet was put to provide an access for the catheter. Three quadripolar catheters per patient were used. One of the catheters was positioned into the right atrium. The other one was used to record His bundle potential. The third catheter (used for recording and stimulation) passed through the right atrium to reach the right ventricular apex (RVA) and when needed the position was changed to right ventricular outflow tract (RVOT). The speed of the monitor for the intracardiac electrogram recording was 100 mm/Sec.

For the induction of VT in all patients a current of 5 mA with a pulse width of 2 ms, ventricular pacing in 10 beats train at two cycle lengths 400 and 600 ms (S1S1) was used. S1S2 is the coupling interval of the first ventricular extrastimulus (ES), S2S3 is the coupling interval of the second ES, and S3S4 is the coupling interval of the third ES. The sequence of the protocol was in the following manner:

I- RVA stimulation:

1. S1S1= 600 ms, S1S2= 350 ms, S2S3= 300 ms
2. S1S1= 400 ms, S1S2= 250 ms, S2S3= 220 ms
3. Ventricular burst pacing for 30 beats at a cycle length of 300 ms
4. S1S1= 600 ms, S1S2= 350 ms, S2S3= 300 ms, S3S4= 250 ms
5. S1S1= 400 ms, S1S2= 250 ms, S2S3= 220 ms, S3S4= 200 ms
6. S1S1= 400 ms, S1S2= 600 ms, S2S3= begin at 400 ms and decrease by 50 ms steps to 200 ms.

II- RVOT stimulation:

Repeat the above steps in the RVOT if sustained VT was not induced with RVA stimulation.

The end point of the protocol was induction of sustained VT or VF or completion of the protocol.

After the EP study the patients were divided in two groups. Group I include the patients in whom ventricular arrhythmia couldn't be induced; and Group II include the patients in whom sustained ventricular arrhythmia was induced.

The measurements of QTd and QRSd were performed by the same investigator from a 12-lead ECG obtained prior to PVS. Both ECG variables were measured from the computer screen directly. QRS duration was measured in all 12 leads. The QT interval was measurable in more than 8 leads in all patients. QTd (QT maximum - QT minimum) and QRSd (QRS maximum - QRS minimum) were calculated based on QT and QRS measurements. Both ECG variables were measured from two complexes in each lead with high gain (8 times normal) and speed (50 mm/sec) to facilitate more precise discrimination. The end of the T-wave was measured where it intersected the isoelectric TP baseline. In cases of low T-wave amplitude, gain was further increased (16 times or 32 times normal) so that the end of the T-wave could be visually identified. In the presence of a U-wave, the end of the T-wave was obtained from the nadir between the T- and U wave peaks. In the presence of biphasic T-waves, the intersection of the late stage of the T-wave with the isoelectric TP baseline was used as the end of the T-wave. QTd and QRSd were not measured in 3 out of 25 patients because of bundle branch blocks.

Both heart rate variability and heart rate turbulence were measured through cardiac Holter Monitoring System (GE Medical systems, Seer MC, Milwaukee WI, USA and Cardiosoft Holter V1.20). The duration of the holter recording analysed was 24 hours during which the patient was allowed to go home.

Short term HRV was measured through measuring beat to beat RR intervals in ms from 11 beat strip (10 RR intervals) during the sleeping time of the patient using the holter recording. Short term HRV was defined as the difference between maximum and minimum RR intervals. The value was corrected to mean heart rate of 75 beats/min as following:

HRV= 800 (ms)×measured HRV (ms)/mean of 10 RR intervals (ms)

10 sets of 10 RR intervals were chosen and short term HRV was measured for each set, then the mean of short

term HRV was calculated (modified from Bikkina *et al*[9]). HRT quantifies heart rate changes by 2 parameters, turbulence onset (TO) and turbulence slope (TS). TO is the amount of sinus acceleration following a ventricular premature complex (VPC), TS is the rate of sinus deceleration that follows the sinus acceleration. RR intervals are plotted versus beat number, with 2 normal beats preceding and 20 normal beats succeeding the VPC beat and compensatory pause. TO is the percentage difference between the heart rate immediately following VPC and the heart rate immediately preceding VPC. It is calculated using the equation:

$$TO = ((RR1+RR2)-(RR-2+RR-1))/(RR-2+RR-1)\times 100$$

with RR-2 and RR-1 being the first two normal intervals preceding the PVC and RR1 and RR2 the first two normal intervals following the VPC. Initially, TO was determined for each individual VPC, followed by the determination of the average value of all individual measurements. Positive values for TO indicate deceleration; negative values indicate acceleration of the sinus rhythm.

To obtain TS (ms/beat), the slopes of RR change were calculated by fitting each 5 beat RR sequence following the compensatory pause (RR[1]~RR[5], RR[2]~RR[6], ..., RR[16]~RR[20]) with a straight line. The maximum of the 16 slopes were taken to be TS. TO<0 and TS>2.5 was considered normal. Each VPC which showed at least 5 sinus RR sequences before and 20 sinus RR sequences after the VPC were included in the count. The HRT was measured when at least 5 VPC were present in the holter record. HRT was not measured in 6 patients because the criteria for the VPC were not fulfilled.

Statistica and Excel statistical packages were used. The results were expressed as Mean±SD. Student's *t*-test was used to compare parametric values, Chi-square test was used to compare the nonparametric values, and $p \leq 0.05$ was taken as significant.

RESULTS

In 8 out of the 25 patients studied, sustained monomorphic VT could be induced, while non-sustained polymorphic VT was induced in 2 patients. 6 (75%) of the sustained arrhythmia were induced through using a beat train of 400 ms cycle length (CL) and 2 ES, the other 2 (25%) were also induced by a beat train of 400 ms CL, but with 3 ES. The non-sustained polymorphic VT was induced by a beat train of 400 ms CL with 3 ES. The site of induction of these arrhythmias was RVA in 5 (62.5 %) patients and RVOT in 3 (37.5%) patients. The arrhythmias induced were terminated by ATP in 5 (62.5%) patients and by DC shock in 3 (37.5%) patients.

The mean QRSd was (41.86±13.81 ms), mean QTd (49.5±19.10 ms), mean value of QRSd+QTd (91.36±26.58 ms), mean value of short-term HRV (32.47±13.17 ms), mean value of TO (-0.83±2.5%), and that of TS (5.77±5.40 ms/beat).

Group I had 17 patients, and Group II consisted of 8 patients. A comparison of the findings between the two groups is shown in Table-2.

Table-1: Characteristics and clinical feature of the study population (n=25)

Age Range	24–72 Year
Mean Age	51.76 Years
Male:female ratio	4:1
Presenting symptom	
Palpitation	2 (8%) patients
Syncope	11 (44%) patients
Dizzy spells	12 (48%) patients
Ejection fraction	31–76% (mean 47.36%)
Cardiomyopathy	
Dilated	5 (20%) patients
Ischemic	16 (64%) patients
None	4 (16%) patients

Table-2: Comparison between group I and II

	Group I (n=17)	Group II (n=8)	*p*
Age (Yr)	49.65±11.90	56.25±7.63	0.109
Male/female ratio	13/4	7/1	0.52
Presenting symptom			
Palpitation	2 (11.76%)		0.346
Syncope	6 (35.29)	5 (62.5%)	
Dizzy spells	9 (52.94%)	3 (37.5%)	
Ejection fraction (%)	51.94±14.44	37.63±6.50	0.0024
Cardiomyopathy			0.2
Dilated	4 (23.52%)	1 (12.5%)	
Ischemic	9 (52.94%)	7 (87.5%)	
None	4 (23.52%)		
QRSd* (mSec)	38.27±14.40	49.57±9.07	0.038
QTd* (mSec)	45.60±19.09	57.86±17.50	0.161
QRSd+QTd* (mSec)	83.87±28	107.43±14.23	0.0167
Short-term HRV (mSec)	36.48±12.72	23.96±10.16	0.017
HRT*			
Turbulence onset	-1.78±2.13%	1.22 ± 2.04%	0.014
Turbulence slope	6.35±5.20 ms/beat	4.53 ± 6.11ms/beat	0.544

QRSd=QRS dispersion, QTd=QT dispersion, HRV=Heart Rate Variability, HRT=Heart Rate Turbulence. *QRSd, QTd and QRSd+QTd were not measured in 2 patients of group I and 1 patient of group II because of left bundle branch block. HRT was not measured in 4 patients of group I and 2 patient of group II because the criteria chosen for the ventricular premature complex were not fulfilled.

DISCUSSION

One of today's major cardiology challenges is identification of patients at risk of ventricular arrhythmias and sudden cardiac death. The use of invasive electrophysiologic studies helps select patients at particularly high risk for those arrhythmias especially in patients with chronic ischemic heart disease.[10–13] In patients with non-ischemic cardiomyopathy, however, both positive and negative predictive values of this technique are unclear. Patients with ischemic heart disease and left ventricular systolic dysfunction constitute most of patients who present with sudden cardiac death. But even in patients with coronary disease, the risk of sudden death depends on multiple

variables in addition to ejection fraction and depending on the presence of other risk factors, for example, patients with EF 30% to 40% may have total mortality and sudden death risks that exceed those of some patients with EF 30%.[14]

In this study we evaluated the role of QT-dispersion, QRS-dispersion, HRV and HRT in predicting VT inducibility during PVS. In our study population, the majority of patients (16 out of 25) have coronary artery disease, 10 patients with an ejection fraction (EF) of less than 40% (7 patients with ischemic heart disease and 3 with dilated cardiomyopathy). VA was inducible in 7 patients with coronary artery disease and 1 patient with idiopathic dilated cardiomyopathy (DCM). Non-sustained polymorphic VT was induced in 2 patients with idiopathic dilated cardiomyopathy. In patients with no underlying heart disease, no arrhythmia was induced. In the study of Oritz *et al*[15], a lower inducibility rate of VT by PVS was noticed in patients with idiopathic DCM. The substrate for VT in the DCM is less well understood and probably a different mechanism is responsible for VT, some of which may not be reproduced by programmed stimulation and the potential for induction of multiple morphologies in cases with such a diffuse substrate may exist.[15]

We found that neither age nor gender has an effect on inducibility of VT by PVS in the two groups of patients. Mean EF was significantly lower in group II. Previous studies that included patients regardless of the measured left ventricular EF (as the present study) have noted associations between a lower EF and inducible ventricular tachycardia.[16–18] The higher percentage of patients with IHD in group II, shows the importance of PVS in those patients for risk stratification.

QRSd and QRSd+QTd may help predict VT inducibility by PVS in the patients selected. Many investigators have evaluated QT dispersion as a marker of heterogeneous re-polarisation of the myocardium and as an indicator of risk for VT in different clinical settings.[19–24] In all these studies there was a difference in the method of measurement of QTd which could be the cause of the difference in their results. Also a dilemma arises when the QT intervals are not measurable in all 12 leads, and it is not possible to tell whether any of the omitted leads contain the extreme QT values necessary for QT dispersion.[25]

Short-term HRV may be a better predictor of sympathovagal balance and therefore a better tool for assessing the risk for development of malignant VA and sudden death. Bikkina *et al*[9], have suggested that a diminished short-term HRV (less than 50 ms) could be a strong predictor of VT inducibility. They also suggested that short-term HRV may have more power than low left ventricular EF in predicting inducible VT.[9] The study of Perkiomaki *et al*[26], was specifically designed to differentiate between patients with clinical and electrophysiological presentation of stable monomorphic VT or VF and carefully matched postmyocardial infarctions patients without arrhythmic propensity. This study showed that QTd is increased in patients with vulnerability to both stable and unstable arrhythmia, but low HRV is observed only in patients with VF and not in patients with stable monomorphic VT versus matched postinfarction patients. The HRV had a high positive predictive accuracy for detecting vulnerability to unstable ventricular tachyarrhythmia. But there was no correlation between the measures of HRV and QTd. They supported the notion that abnormal autonomic balances favor vulnerability to VF or unstable ventricular tachyarrhythmias, or both.[26] The fibrillation threshold of the ventricle decreases with sympathetic activity and increases with vagal activity. Sympathetic activity has been reported to be enhanced and parasympathetic activity reduced in patients with acute myocardial infarction. It has been demonstrated that patients with acute myocardial infarction and diminished HRV have a greater propensity for developing VF.[9] The difference in the method of measurement of short-term HRV between the present study and that of Bikkina *et al*[9] is the timing of the measurement. In our study short-term HRV was measured at the time when the patient was asleep excluding external influences on the autonomic nervous system. In addition, short-term HRV was measured in 10 sets of 10 RR intervals while in the study of Bikkina *et al*[9], the measurement was done just before EP study in one set of 10 RR intervals. The study of Schmidt *et al*[27], showed that HRT is a consistent phenomenon in low risk patients with IHD. The absence of this phenomenon indicates a significantly increased risk of subsequent mortality. They found that turbulence onset and slope in combination are the strongest holter-based risk predictor. HRT is a phenomenon triggered by a minimum endogenous stimulus to which the reflex responses are possibly more organised and systematic.[27] The study of Ghuran *et al*[28], showed that TS and combined TS and TO both produced moderately high relative risk values for cardiac arrest in patients survivors of acute myocardial infarction. In the present study, there was a significant higher value of mean TO (more than zero) in group II as compared to group I. Although, mean TS was less in Group II in comparison with Group I but the value remained within the normal range (>2.5 ms/beat). This could mean that TO has a higher predictive power for VT inducibility than TS in our patients group. This difference from previous studies could be due to the small number of patients in group II in whom HRT parameters were measured. The mechanisms linking the absence of HRT to mortality are not obvious. Probably, the TO and TS assessment reflects specific aspects of cardiac autonomic status. The preserved vagal tone is anti-arrhythmic and probably

constitutes autonomic anti-arrhythmic protection. Thus, by measurement of the HRT, a direct manifestation of this protection may be captured when responding to a potentially pro-arrhythmic ventricular premature beat. If an absent response to ventricular premature beat in patients with high values of TO and low values of TS is a manifestation of lost anti-arrhythmic protection, the chronotropic response to ventricular premature beat might be the mechanistic link between impaired autonomic balance and cardiac mortality.[27] Although, the difference between the two groups in the presenting symptoms was not significant, the higher percentage of syncope in Group II may probably indicate that syncope is a clinical sign of deleterious prognosis.

CONCLUSION

QRS dispersion, short-term heart rate variability and turbulence onset may be important risk stratifying parameters regarding arrythmogenic liability. QRS dispersion plus QT dispersion may improve the predictive power of QRS dispersion. Those parameters can increase the arrythmogenic risk stratifying efficacy of already accepted factors such as ejection fraction and programmed ventricular stimulation especially in patients with ejection fraction between 30–40%. Multicentre studies on a larger population of patients are needed to evaluate the prognostic ability of QRSd, QTd, short-term HRV and HRT concerning ventricular arrhythmic risk.

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