Europace (2007) 9, 1203–1208
doi:10.1093/europace/eum228

Electrocardiographic markers of structural heart disease and predictors of death in 2332 unselected patients undergoing outpatient Holter recording

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Received 30 April 2007; accepted after revision 14 September 2007; online publish-ahead-of-print 25 October 2007

KEYWORDS
Risk stratification;
Sudden death;
Ventricular fibrillation;
QRS complex duration;
QRS interval;
Ventricular ectopic beat;
Ventricular premature beat;
Heart rate variability;
Myocardial infarction

Aims To test the hypothesis that the QS interval of ventricular ectopic beats (VEBs) (ventricular ectopic QS interval, VEQSI) would provide a marker for the presence of structural heart disease and a predictor of mortality.

Methods and results We interviewed and examined 2332 patients undergoing Holter ECG monitoring for clinical indications. In persons with VEBs, the morphologies were counted and the QS interval was measured for each of these morphologies. The duration of the broadest VEB, measured from the QRS onset in the derivation showing the earliest onset to its end in the derivation showing the latest termination, was taken as that patient's VEQSI. Survival was ascertained from public health records. Of 15 electrocardiographic variables pre-selected as potential prognostic indicators, VEQSI demonstrated the strongest association with the presence of structural heart disease ($P = 0.013$). Thirty-four persons died in 16 ± 4 months follow-up. Univariate predictors of mortality are age, history of myocardial infarction, maximum heart rate, QS interval, the number of VEB morphologies, and the VEQSI. On multivariate analysis, only age ($P < 0.001$) and the number of VEB morphologies ($P = 0.02$) predicted mortality.

Conclusion VEQSI predicts the presence of structural heart disease. The number of VEB morphologies in a Holter recording predicts all-cause mortality.

Introduction

Of the many electrocardiographic indices proposed as markers of risk of death, only the QS interval has shown a consistent predictive value in large prospective studies.[1–3] In the presence of an intact conduction system, the QRS complex remains narrow even in the presence of ventricular dilatation. As ventricular ectopic beats (VEBs) are conducted through the ventricles with limited participation of the specialized conduction tissue, we speculated that the QS interval of VEBs (ventricular ectopic QS interval or VEQSI) might provide a better index of the risk of death than the QS index of conducted beats.

Early studies on the use of the ambulatory ECG to measure risk of death concentrated on the frequency of VEBs and on the presence or absence of ventricular tachycardia (VT).[4,5] More recently, heart rate variability (HRV) has received attention as a means of predicting risk of mortality.[6–8] We measured these indices in a population of patients attending for ambulatory ECG monitoring for a variety of clinical indications, and compared them with the VEQSI measured in the same recordings as predictors of mortality. We also considered the number of morphologies of VEB as this seemed likely to constitute a significant confounding variable in analysing the predictive value of VEQSI.

Methods

We interviewed unselected patients attending for 24 h Holter ECG monitoring for clinical indications at 'Policlinico Tor Vergata' between February 2003 and October 2004. A clinical history was taken and cardiovascular examination performed by a physician training in cardiology or by a final-year medical student as the monitor was being applied. The selection of patients was based solely on the availability of the interviewing physician or student

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on the day in question. The patient was asked to bring relevant medical documentation when returning the following day for removal of the recorder.

From the documentation returned by the patient, information gleaned from the patient interview and examination and a search of the computerized archive of our echocardiography laboratory and from hospital admission records, the interviewing physician or student determined whether the patient had structural heart disease defined as a history of acute myocardial infarction (AMI) or valvular or congenital heart disease or heart failure or a reduced left ventricular ejection fraction (LVEF) or evidence of familial heart muscle disease or a history of any form of cardiac surgery. A history of hypertension or arrhythmia alone was not considered to constitute the evidence of structural heart disease.

As a comparison group, we identified those patients whose data suggested an absence of any cardiac pathology. The interviewing physician or medical student designated a patient as 'apparently normal' if they did not have any evidence of structural heart disease, and had no history of hypertension or sustained arrhythmia and were not receiving any medications suggestive of a history of a cardiovascular disorder including beta blocking agents, anti-arrhythmic drugs or aspirin.

Holter recording and analysis

Dedicated nurses applied Holter recording systems with meticulous skin preparation. A seven electrode three-channel system was connected to give ECG derivations approximating to limb lead II and chest leads V1 and V5. All recordings were performed at a sampling frequency of 1 kHz using a three-channel device with solid-state memory (Rozinn Cardio ID RZ153, Rozinn Electronics Inc., Glendale, NY, USA).

Analysis was performed on a workstation running commercial Holter analysis software (Rozinn Holter for Windows, Rozinn Electronics Inc, Glendale, NY, USA). All recordings were analysed by the same physician, an experienced cardiac electrophysiologist who performed careful manual over-reading to eliminate artefacts and to correct the automated identification of VEBs and their classification by morphology. The interpreting physician was not present during the patient interview. At the time of Holter analysis, the physician was unaware of the full clinical characteristics of the patient, having only a single line summary of information necessary to generate a clinical report. Any Holter containing <18 h of good quality recording was excluded from analysis.

We prospectively selected 15 Holter ECG variables for evaluation including VEQSI, QS interval, three measures of heart rate (mean, minimum and maximum rate), four variables relating to ventricular ectopy (VEB frequency, number of VEB morphologies, number of episodes of VT and maximum frequency during VT), and three time domain (standard deviation of NN intervals, SDNN; root meam square standard deviation, RMSSD and HRV triangular index) and three frequency domain indices of HRV (high, low and very low frequency power). The indices were selected on the basis of published studies regarding Holter predictors of sudden cardiac death[1–8] or as potential confounding variables in evaluating the prognostic importance of VEQSI.

All VEBs in each recording were inspected. VEBs were considered to be of the same morphology if they had the same sequence of deflections (expressed as Q, q, R, r, S, s, R', r', S, s') in all three derivations with the amplitude of each deflection differing by $<25\%$ when expressed as a proportion of the amplitude of the conducted QRS complex preceding the VEB.

The number of morphologies of VEB in each recording was counted, up to a maximum of six morphologies. For each VEB morphology, regardless of the number of morphologies, the QS interval was measured on a single QRS complex representative of that morphology and chosen for the clarity of its onset and termination. Measurements were made using electronic callipers on a simultaneous three-derivation ECG segment represented on screen at 3.5 s per screen and at the maximum gain setting of the system. We measured from the start of the QRS in the derivation showing the earliest onset to the end of the QRS in the derivation showing the latest termination. The duration of the broadest VEB was considered to be the VEQSI of that patient. The QS interval of a conducted QRS complex was measured in the same way, choosing a broad QRS complex in patients with intermittent bundle branch block, a spontaneous beat in patients with periods of pacing, and always using a complex with a good clarity of onset and termination.

HRV was characterized using the same commercial Holter analysis software (Rozinn Holter for Windows, Rozinn Electronics Inc, Glendale, NY, USA) after careful editing to assure accurate identification of all normal beats and freedom from artifacts. Recordings of imperfect quality and patients in persistent atrial fibrillation or atrial tachycardia or with a persistently high frequency of ectopic beats were excluded from HRV analysis, as were recordings with persistent pacing of any modality. Recordings containing periods of pacing or periods of arrhythmia were accepted if all such episodes had been identified by the system and thus excluded from HRV analysis.

Follow-up

Survival was ascertained from the computerized records of the 'Comune di Roma', a regional archive of data derived from death certification. In the case of patients who had died during the period of follow-up, the date of death was noted. At the time of our search, the records contained information on deaths occurring before the end of 2004.

Statistical analysis

Continuous variables are shown as average $\pm$ SD, categorical ones as absolute and relative frequency. Comparison of variables was assessed by a *t*-test or Mann–Whitney non-parametric test, as appropriate. Correlations between distributions were performed by the Pearson method, showing the correlation coefficient (R) and its significance. Multivariate predictors of the presence of known structural heart diseases were identified using logistic regression analysis. Predictors of Death were analysed using Cox Regression analysis; potential predictors were inserted into the multivariable model, where $P < 0.1$ in univariate analysis.

Analyses were performed with SPSS 12.0 statistical package (SPSS Inc, Chicago, IL, USA). Significance was set at $P < 0.05$.

Results

During the study period, we performed Holter ECG monitoring on over 4000 outpatients of whom 2811 were recruited to the study, others were excluded because the interviewing researcher was not available on the day of their attendance. Of these, 479 were subsequently excluded because the recording was not of satisfactory quality or duration.

Clinical characteristics and electrocardiographic findings

The demographic details of our Holter ECG population have previously been described.[9] Patients were 49% male, aged 60 ± 16 years. The majority of the study subjects were healthy persons referred for the evaluation of mild symptoms such as palpitation or dizzy spells, but 479 (21%) had evidence of structural heart disease (*Table 1*). Persons with structural heart disease were significantly older than the remainder of the group (67 ± 11 vs. 59 ± 17 years, $P < 0.001$).

Table 1 Patient characteristics ($n = 2332$)

	n (%)	Age	*P*	VEB morphologies	*P*	VEQSI (ms)	*P*
Apparently normal	971 (42%)	53 ± 18	–	1.5 ± 1.4	–	151 ± 17	–
Any structural heart disease	479 (21%)	66 ± 11	<0.001	2.8 ± 1.6	<0.001	163 ± 19	<0.001
History of AMI	196 (8%)	67 ± 9	<0.001	3 ± 1.6	<0.001	166 ± 20	<0.001
Valvular or congenital heart disease, normal LVEF	103 (4%)	64 ± 16	<0.001	2.5 ± 1.6	<0.001	158 ± 16	<0.001
Reduced LVEF of any cause	207 (9%)	67 ± 12	<0.001	2.9 ± 1.7	<0.001	164 ± 20	<0.001
Hypertension without other heart disease	622 (27%)	66 ± 11	<0.001	2 ± 1.5	<0.001	154 ± 17	0.014
Use of anti-arrhythmic drugs	186 (8%)	66 ± 10	<0.001	2 ± 1.5	<0.001	161 ± 22	<0.001
Use of beta receptor blocking drugs	326 (14%)	64 ± 12	<0.001	2.3 ± 1.6	<0.001	159 ± 19	<0.001

The number of ventricular ectopic beat (VEB) morphologies and the ventricular ectopic QS interval (VEQSI) measurements are mean ± SD. Each category of cardiovascular disease is compared with the group without known cardiovascular disease and not receiving cardiovascular medications using a non-paired *t*-test or a Mann–Whitney *U* test.

AMI, Acute myocardial infarction; LVEF, Left ventricular ejection fraction.

Table 2 Association between pre-selected ECG indices and the presence of structural heart disease and correlation with left ventricular ejection fraction on multivariate analysis

	Structural heart disease		LVEF	
	Odds ratio	*P*	*R*	*P*
Basic measurements				
Mean heart rate	1.02	0.4	–	–
Maximum heart rate	0.97	0.04	0.094	0.004
Minimum heart rate	–	–	−0.061	0.065
QS interval	1.00	0.82	−0.21	<0.001
Ventricular ectopy				
VEB frequency	1.00	0.79	−0.12	<0.001
VEB morphologies	1.01	0.92	−0.32	<0.001
VEQSI	1.03	0.01	−0.30	<0.001
Episodes of VT	–	–	−0.10	0.002
Max. VT frequency	1.01	0.07	–	–
Heart rate variability				
SDNN	01.00	0.70	0.073	0.042
HRV triangular index	0.98	0.55	–	–

The absence of a correlation on univariate analysis is represented as '–'. The HRV indices other than SDNN and HRV triangular index have been omitted as none proved significant on univariate analysis.

VEB, ventricular ectopic beat; VEQSI, ventricular ectopic QS interval; VT, ventricular tachycardia.

VEBs were present in 79% of Holter recordings including 91% of those performed in patients with structural heart disease. Of the 15 electrocardiographic features prospectively investigated as possible markers of structural heart disease, logistic regression analysis identified VEQSI and maximum heart rate as the only variables that independently distinguished between persons with structural heart disease and those with apparently normal hearts, of which VEQSI was the more powerful predictor (*Table 2*, *Figure 1*). Compared to apparently normal subjects those with structural heart disease had a higher VEQSI (163 ± 19 vs. 151 ± 17) and lower maximum heart rate (114 ± 19 vs. 122 ± 23). Using a dichotomy limit of VEQSI ≥170 ms, the index had a sensitivity of 0.41 and a specificity of 0.83 in identifying the presence of structural heart disease in our population.

Left ventricular function

Of the 2332 patients whose data were analysed, a measurement of LVEF was available from an imaging study performed within 1 year before the Holter recording in 913 cases (39%) including 279/446 (63%) of patients with structural heart disease. In none of these cases was there evidence of a substantial event such as AMI or cardiac surgery between the time of LVEF measurement and the time of the Holter recording. In almost all cases, LVEF was measured by echocardiography. Of the 16 electrocardiographic variables evaluated as potential markers of LV dysfunction (*Table 2*), the number of VEB morphologies ($R = -0.318$, $P < 0.001$) and VEQSI ($R = -0.302$, $P < 0.001$) correlated most closely with LVEF (*Figure 2*).

Correlations between electrocardiographic variables

There was a strong correlation between VEQSI and the number of VEB morphologies ($R = 0.42$, $P < 0.001$). There was a modest correlation between VEQSI and conducted QS interval ($R = 0.27$, $P < 0.001$), and between the number of VEBs and the number of VT episodes ($R = 0.26$, $P < 0.001$). Other than these and correlations within the set of heart rate variables (mean, minimum and maximum heart rate and rate of fastest VT) and within the set of HRV variables, no other correlation achieved a Pearson coefficient of >0.2.

Predictors of mortality

In 16 ± 4 months subsequent to the qualifying Holter recording, 34 persons died. On univariate analysis, predictors of all cause mortality were age, history of MI, maximum heart rate, QRS index, the number of VEB morphologies, and the VEQSI. On multivariate analysis, only age and the number of VEB morphologies were predictive of mortality (*Table 3*).

Discussion

Our study demonstrates that the number of morphologies of VEB in a Holter recording is a predictor of all-cause mortality. Of the other 14 electrocardiographic variables tested, only VEQSI, conducted QS interval, and maximum

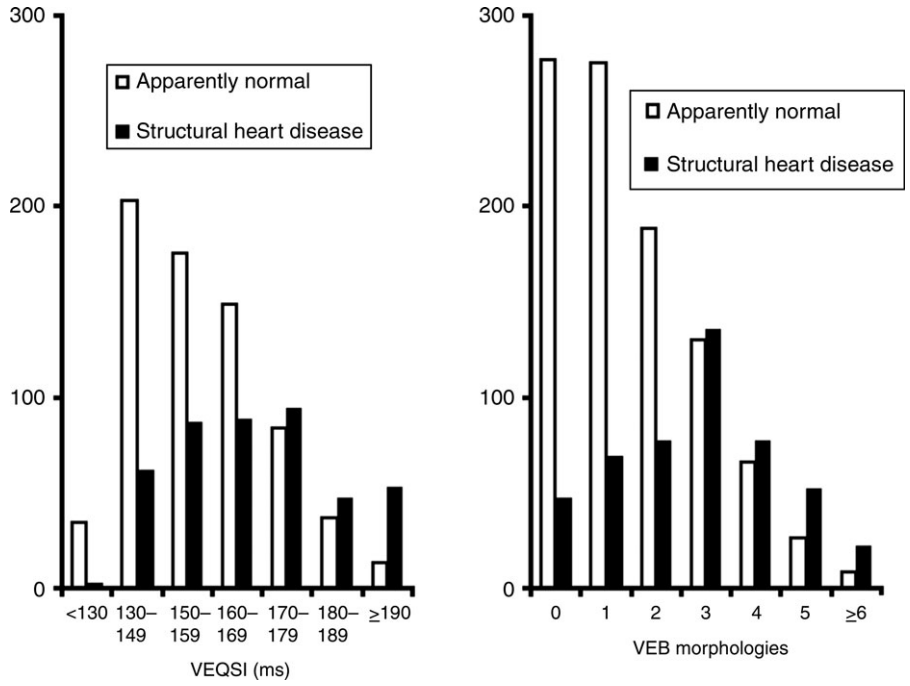

Figure 1 Frequency distribution histogram of ventricular ectopic QS interval and of the number of ventricular ectopic beat morphologies per nominal 24 h Holter ECG in persons with evidence of structural heart disease and those with apparently normal hearts.

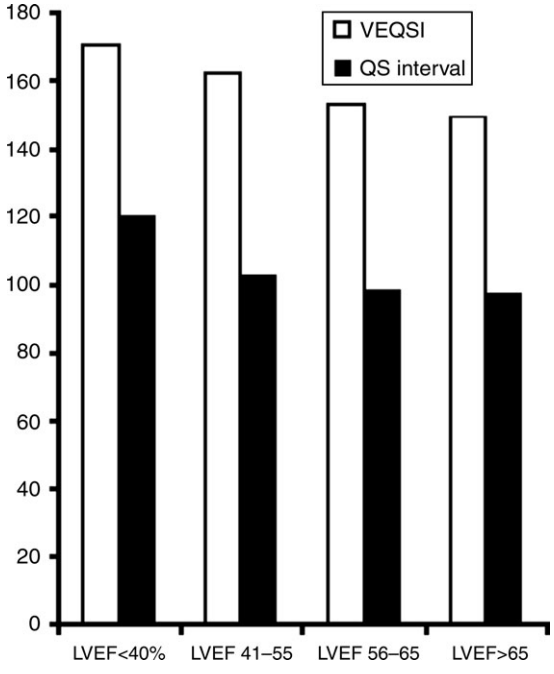

Figure 2 Relationship between ventricular ectopic QS interval, conducted QS interval and left ventricular ejection fraction.

heart rate show a trend towards association with mortality. Of these, VEQSI shows most promise. Our data show that VEQSI is a marker for the presence of structural heart disease and is correlated with left ventricular (LV) function. In our series, it is the most powerful independent electrocardiographic predictor of the presence of structural heart disease.

Ventricular ectopy as a predictor of cardiac mortality

The presence of multiple VEB morphologies has traditionally been regarded as a predictor of adverse outcome in coronary artery disease. In the classification of ventricular ectopy proposed by Lown and Wolf,[10] the finding of 'multiform' ectopic beats placed the patient in the third of five grades. Only the presence of couplets, of VT or of VEBs of great prematurity was considered of greater importance. Although this grading scheme was widely used for many years, no clear confirmation has emerged for the importance of the number of VEB morphologies, and some evidence suggests that it is of little importance.[11] Of the criteria used in the Lown classification, only the presence of non-sustained VT is still widely considered to be important.[12]

Counting the morphologies of VEBs in a Holter recording is tedious and to some extent subjective. The QRS axis changes with posture and in a 24 h recording changes in position are inevitable.VEBs arising from the same point in the heart may appear quite different when the patient is supine and when upright. In this study, we sought to minimize this effect by judging the similarity of VEBs with reference to an adjacent conducted QRS complex. We expect that it will be difficult for any automated Holter analysis system to measure the number of VEB morphologies in a reproducible way.

VEB morphology and structural heart disease

A correlation between VEB morphology and structural cardiac disease was documented by Moulton *et al.*[13] who used 12 lead recordings of short duration recorded at the time of cardiac catheterization. They categorized patients on the basis of VEB morphology into Group 1, in whom the ventricular ectopic QRS was smooth or displayed notching

Table 3 Clinical and electrocardiographic characteristics and association with mortality

	Survived ($n = 2298$)	Died ($n = 34$)	Hazard ratio	P
Clinical variables				
Age (years)	60 ± 16	74 ± 8	1.07	<0.001
History of AMI	190 (8%)	6 (18%)	1.41	0.46
Basic Holter measurements				
Maximum heart rate (bpm)	121 ± 24	112 ± 21	0.99	0.63
QS interval (ms)	100 ± 19	107 ± 23	1.10	0.76
Ventricular ectopy				
VEB morphologies	1.9 ± 1.6	3.4 ± 1.7	1.32	0.02
VEQSI (ms)	155 ± 18	164 ± 22	1.10	0.45

All of the Holter ECG features listed in *Table 2*, as well age, sex, history of AMI, RMSSD, left ventricular ejection fraction (LVEF) and three frequency domain HRV variables, were tested for association with death. Only the variables associated with mortality on univariate analysis are presented. The hazard ratios (HR) returned by Cox Regression analysis are expressed per year of age, per beats per minute for heart rate, per 10 ms increment of QS interval or ventricular ectopic QS interval (VEQSI), and per morphology of VEB.

of $\leq$40 ms, and Group 2 in whom the ventricular ectopic QRS displayed notching of $>$40 ms. They noted that VEBs of Group 2 were associated with greater LV dilatation and that VEBs of this type were generally of greater duration than those of Type 1.

Moulton *et al*. noted that VEBs of persons with structural heart disease were of greater duration. They suggested a dichotomy limit of 160 ms in the identification of patients with LV dilatation, but found that a morphological classification based on the presence of notching of the ectopic QRS complex was more sensitive than a classification based on duration. We quantified the duration but not the notching of the VEB because of the practical difficulty in measuring notching in a reproducible way.

Conducted QS interval

In populations with a high prevalence of left bundle branch block, the QS interval has emerged as an important predictor of sudden cardiac death and of benefit from implantable cardioverter (ICD) therapy, possibly because a broader QRS reflects the greater distance traversed by a wave of depolarization in a dilated left ventricle or slowed conduction through diseased myocardium. In persons with an intact conduction system, the QRS complex is narrow irrespective of the state of the myocardium. In persons without bundle branch block and in patients with right bundle branch block, the QS interval of conducted beats does not predict cardiac mortality.[3] In our series, conducted QS interval showed a limited correlation with the presence of structural heart disease, and no ability to predict death. This may reflect the fact that this was a relatively healthy ambulant population with a low prevalence of left bundle branch block.

Ventricular ectopic QS interval

In most persons suspected of having an elevated risk of sudden cardiac death, 24 h Holter ECG monitoring reveals the presence of VEBs. As these arise in the ventricles and are conducted in a manner largely independent of the specialized conduction tissues, the duration of the resulting QRS should depend only on the site of origin, the degree of ventricular dilatation and the velocity of conduction in the ventricular myocardium. It should therefore reflect the state of the myocardium more closely than the QS interval of conducted beats, which is influenced more by the state of the His-Purkinje system. Our data support this hypothesis.

As VEB morphology depends on the site of origin of the VEB, we would expect VEQSI to be linked to the number of VEB morphologies present in a recording as persons with multiple sites of origin are more likely to have one site of origin located far from the midline of the heart and capable of producing a broader QRS complex. This effect could be augmented by the error involved in any biological measurement. The more morphologies are measured, the more likelihood there is that a high value will be returned in error. Our data suggest that there is a correlation between VEQSI and the number of VEB morphologies in a recording. Of these two measurements, our data suggest that the VEB morphology count has greater prognostic power but we found VEQSI the easier to perform as little subjectivity was involved. We expect that the automation of measurement will also prove easier for VEQSI.

Screening for persons at risk of sudden death

Randomised clinical trials have established that ICD therapy can improve survival in persons at high risk of sudden cardiac death.[1] The existence of effective preventative therapy makes it imperative that patients at risk of sudden death be identified. Current guidelines on the use of ICD therapy in the primary prevention of sudden death base their selection criteria almost exclusively on LVEF, in accordance with the entry criteria of the relevant clinical trials. Unfortunately, the use of a single dichotomy limit for LVEF is unsatisfactory regardless of the cut-off value used.[14]

There is evidence that the conducted QS interval[1] and T wave alternans[15] can provide additional information about the likelihood that an individual will receive benefit from the implantation of an ICD. Other electrocardiographic indices have been proposed as markers of risk of death, including the dispersion of the QT interval, HRV and the presence of late potentials in the signal averaged ECG. Although each of these was shown to predict death in initial studies, none has shown a consistent and powerful predictive value in multivariate analysis across larger prospective studies.[16–18] The failure of traditional HRV measurements

is confirmed in the current study in which the Holter recordings were edited meticulously to assure a standard of measurement higher than that obtained in routine practice. HRV analysis in the form of heart rate turbulence requires further evaluation but this also has demonstrated only limited independent predictive value, at least in recordings of short duration.[19]

The field of electrocardiographic prediction of death is littered with failed methodologies and conflicting evidence. Although no single method has proved satisfactory, there is evidence that risk factors can be combined to give an estimate of risk more accurate than any one index can provide.[12] We believe that VEQSI may have a role in a combined scoring scheme of this type.

Conclusions

The current study suggests that VEQSI correlates with the presence and severity of structural heart disease and exhibits a trend towards association with the risk of death. The number of VEB morphologies is also a marker of reduced LVEF, and correlates with all-cause mortality.

The number of VEB morphologies found in a nominal 24 h Holter recording and the VEQSI show promise in the assessment of an individual's risk of death in addition to prognostic information provided by measurement of LVEF.

Limitations

The population studied was unselected and incompletely characterized. The non-electrocardiographic data were limited to that performed by the patients' physicians, and available to the patient or present on our hospital computer system at the time of the Holter recording. These data may have been incomplete in some cases. Cardiac imaging data were not available for all subjects and the data available were derived from different imaging methods performed in different centers without a uniform protocol.

The physician performing the measurement of VEQSI and other electrocardiographic variables could not be blinded to all of the clinical information because of the need to generate a clinical report for the Holter recording in parallel with the research study. This could have introduced interpretation bias.

Mortality figures and cause of death were derived from death certification. The cause of death listed on the death certificate could not be verified independently nor could we determine how the cause of death was ascertained by the certifying physician. The coding system did not permit the identification of the mode of death, only the underlying pathological processes, so we do not know which if any of the deaths occurred suddenly.

Acknowledgements

We are indebted to Tiziana De Santo and Raffaele Pulvirenti of Medtronic Italy for statistical help and to the Department of Epidemiology of ASL Roma E for access to their archives.

Conflict of interest: none declared.

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