Research methods

Simultaneous assessment of electrocardiographic parameters for risk stratification: validation in healthy subjects

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Background. **Sudden cardiac death represents a major public health problem, but in the general population the identification of those subjects at very high risk remains poor. Simultaneous multiparametric ECG analysis can improve the identification of high-risk patients.**

Methods. **Five-min ECG recordings at a 5 MHz sampling rate (extended length-XL-ECG, Mortara Instruments, Milwaukee, WI, USA) were acquired in 105 healthy subjects (age range 21 to 80 years), equally distributed for age decades and sex, and three additional recordings, 30 min apart, were repeated in 30 subjects on the second day. The following parameters were recorded and analyzed: the RR interval, QRS duration, QT interval corrected according to the Bazett and Fridericia formulae, QT dispersion, T wave complexity, activation-recovery interval dispersion, standard deviation of the RR intervals, filtered QRS duration, the square root of the mean voltage of the last 40 ms of the filtered QRS, and the length of time that the terminal vector magnitude complex remains < 40 μV.**

Results. **QRS duration, activation-recovery interval dispersion, and filtered QRS differed in the two sexes. The standard deviation of the RR intervals, T wave complexity and QT dispersion were significantly correlated with age. The reproducibility was good for each parameter.**

Conclusions. **The XL-ECG allows the simultaneous calculation of eight adequately reproducible different parameters the values of which are in agreement with those of the literature. Thus, XL-ECG is a reliable time- and cost-saving tool.**

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Introduction

Sudden cardiac death represents a major public health problem, but in the general population the identification of those subjects at very high risk remains poor despite the progress in the understanding of the underlying mechanisms[1].

The electrophysiologic study turned out to be of limited value for the identification of patients either affected by idiopathic cardiomyopathy[2,3] or by ischemic heart disease[4] who are prone to life-threatening ventricular arrhythmias, and, although a positive electrophysiologic study dictates prophylactic implantable cardioverter-defibrillator therapy[5], the 2-year mortality rate after a negative electrophysiologic study can be as high as 28%[6] to 32%[7].

Similarly, the predictive value of noninvasive methods for the evaluation of the risk of life-threatening arrhythmias is low, preventing their routine use in the clinical workout of patients[8]. Furthermore, it has been shown that the combined evaluation of several noninvasive risk parameters can significantly increase the predictive power of the same test[9-11]. As an example, in the recent ATRAMI study[12], a decreased heart rate variability (HRV) and a decreased baroreflex sensitivity carried similar prognostic values, but the combination of the two identified a group of patients with a 17% higher 2-year mortality among the population whose overall mortality was 4%.

Biomedical research and technological improvements have led to the recent introduction of a system, namely the "extended-length electrocardiogram" (XL-ECG, Mortara Instruments, Milwaukee, WI, USA), which enables the measurement of a num-

ber of different ECG parameters of arrhythmic risk by analyzing short standard ECG recordings. The aim of the present study was to describe the distribution of each parameter in the normal population, to identify the confidence limits and to analyze the possible relationships with age and sex, in order to obtain a pool of data for comparison with those reported in the literature. The reproducibility of the measurements provided by the system was another of the main issues addressed in the study.

Methods

We enrolled 105 healthy subjects with a similar age distribution between genders (51 males, 54 females, age range 21 to 80 years). All subjects had an unremarkable past medical history and their physical examination, echocardiogram, exercise tolerance test, and laboratory findings were all normal. No patient was taking any medications before and during the whole study period. All subjects gave their informed written consent to participate in the study, which conformed to the Declaration of Helsinki and was approved by the local Ethics Committee.

Data acquisition. After 20 min of rest (equilibration period), a standard 10 s 12-lead ECG, and a 5-min recording of the 12-lead XL-ECG were recorded and stored onto a memory card using the Portrait® ECG apparatus (Mortara Instruments). The choice of a 5-min recording, from the possible range of 2 to 60 min, was made since this time was considered short enough for subject comfort and compliance, and long enough to allow for analysis of almost all the ECG predictors of risk[13]. The standard position for the 10 ECG electrodes was used for the 12-lead XL-ECG recordings. To reduce muscle noise, the arm leads were placed on top of the shoulders (the acromion) and the leg leads on the anterior superior iliac crest. Data of 8 ECG leads (I, II and V_1 through V_6) were acquired at a sampling rate of 1000 Hz per lead (5000 Hz for the signal-averages). All ECG data were acquired and stored at a voltage resolution of 16 bits. The 5-min recording generates a data file 5.24 Mb in size. The Portrait® ECG apparatus has a built-in PCMCIA card slot that can accommodate Compact Flash cards holding up to 64 Mb of data (enough for 12 subjects). After acquisition, the data were transferred from the flash card to the hard disk of a PC desktop. Custom software was used to analyze the 5 min of data for the 8 parameters listed below. Leads III, aVR, aVL and aVF were calculated from leads I and II using standard formulae[14].

The following parameters were calculated:

• resting heart rate. It was calculated as the average RR interval in the 5-min ECG recording. Despite being the easiest cardiovascular parameter to assess, its regulation, physiological and pathophysiological significance are complex. The heart rate may provide important information on life expectancy[15]. In fact, a relative hyperadrenergic tone due to abnormalities of the autonomic nervous system is suspected in the mechanism of sudden death, and an elevated heart rate at rest was confirmed as being an independent risk factor for sudden death in middle-aged men[16];

• QRS duration. The QRS duration was measured in all leads from the earliest onset to the latest offset and the median value was calculated. The resolution was 1 ms and the filter range was 0.05 to 300 Hz;

• HRV. A reduced R-R (cycle length) variability has been shown to be a predictor of subsequent arrhythmic deaths[17,18]. Most measurements of HRV have been made with 24-hour ambulatory ECG data, but it has been shown that the results in the time domain of 5-min recordings are representative of longer recordings[19,20]. The parameter used as a clinical prediction tool is the standard deviation of the time interval between normal beats (SDNN)[21];

• signal-averaged ECG. The purpose of signal averaging is to decrease the level of noise that contaminates the ECG. After signal averaging, the QRS duration can be determined more accurately, and low-voltage high-frequency waveforms can be seen at the end of the QRS complex in many patients with serious ventricular arrhythmias. We measured the signal-averaged ECG on a vector magnitude signal derived from 8 leads, rather than from the Frank XYZ leads. Twenty-five and 40 Hz were used as high-pass filters. The three measured parameters were: 1) the filtered QRS duration (FQRS); 2) the low amplitude (< 40 μV) signal duration in the terminal portion of the FQRS (LAS); and 3) the square root of the mean voltage (RMS) of the last 40 ms of the FQRS[22];

• QT interval. The third longest value of the QT interval among the 8 recorded leads was used as the global QT interval. The heart rate-corrected QT (QTc) was evaluated by using the Bazett [$QTc = QT/(R\text{-}R)^{1/2}$] and Fridericia [$QTc = QT/(R\text{-}R)^{1/3}$] formulae[23];

• QT interval dispersion (QTd). An increased QTd has been reported as a noninvasive marker of an electrophysiological arrhythmogenic substrate and it has been associated with a higher risk of ventricular arrhythmias and of sudden death in various cardiac disorders[24-28]. This parameter is determined by subtracting the shortest from the longest QT value among 8 leads, chosen as follows according to the recommendations of de Bruyne et al.[29]: the 6 precordial leads, the limb lead with the shortest QT and the limb lead with the median QT;

• T wave complexity index. It has been proposed that the complexity of the T wave reflects the degree of abnormal repolarization and hence the risk of arrhythmias[30]. This method is based on principal component analysis applied to the 12 leads as opposed to the many leads used during body surface mapping[30,31]. Compared with other methods available for characterization

of the QT interval, this method does not require identification of the end of the T wave. The analysis allows the identification of a set of 8 values that represent the relative magnitude of the spatial components of repolarization. The evaluation of the relative contribution of these components provides an estimate of the spatial complexity of repolarization. The T wave complexity index utilized in this study was calculated[31] as the ratio of the second value to the first multiplied by 100 and is thus expressed as a percentage. Such an approach should allow a comparison between the morphology of the T wave across the 12 leads and the quantification of T wave abnormalities in an observer-independent way[31]. On this basis, the analysis applied to the 12-lead ECG could distinguish normal from abnormal repolarization patterns. It is therefore tempting to speculate that this analysis as applied to standard 12-lead ECG may help identify patients with an abnormal repolarization who are at a higher risk of ventricular arrhythmias. This approach should provide several advantages over the existing methods for the quantification of repolarization: 1) it produces an index that provides information on the spatial dispersion of repolarization, 2) it is independent of the subjective definition of the QT interval duration, and 3) it is entirely automatic and does not require repetitive and time consuming calculations;

• activation-recovery interval (ARI) dispersion. Lux et al.[32] first described the ARI. It is defined as the time from the most negative dV/dt during the QRS complex (the intrinsic deflection) to the most positive dV/dt during the T wave. In animal studies, ARIs calculated from electrograms recorded on the heart surface had a close 1:1 correlation with the duration of the action potentials recorded from the cells underlying the recording electrode. Recent studies with a simulated human torso suggested that the ARI is a good estimate of the underlying action potential duration in surface leads[33-35]. This parameter was measured only in the precordial (V_1-V_6) leads. The ARI dispersion (the longest ARI minus the shortest) is the parameter of interest.

To assess the reproducibility of this method, the ECG recordings were repeated in 30 subjects on the following day. Three different consecutive recordings, 30 min apart, were performed and analyzed.

Statistical analysis. The mean, the standard error (SE), the standard deviation (SD), the confidence interval of the mean and the 5th and 95th percentiles of the weighted mean (tolerance limits) of each parameter were computed. The correlation with age and heart rate were analyzed by Pearson's r. Differences for sex were computed using the Student's t-test for unpaired data. Age subgroups were analyzed using ANOVA followed by the Bonferroni t-test. Normal probability (P-P) plots of standardized residuals were used to assess the robustness of the adjusted predicted values. The reproducibility was assessed using the limits of agreement and the Bland-Altman correlation coefficient between the difference and average of each couple of values[36,37]. An SPSS statistical package for Windows 10.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

Table I shows the mean values ± SD, 95% mean confidence intervals (95% CI), the 5th and 95th percentiles of the R-R interval, QRS duration, QT interval, QTc interval and ARI dispersion. Sex differences for the R-R interval, QRS duration and ARI dispersion are reported in table II: the R-R interval and QRS duration were significantly higher in males while ARI dispersion showed higher values in females.

SDNN was significantly correlated with age ($r = -0.344$, $p < 0.0001$), and with the R-R interval ($r = 0.497$, $p < 0.0001$, $SDNN = 0.0816 \times R\text{-}R - 20.976$). When adjusted for the R-R, SDNN remained age-dependent ($r = -0.215$, $p = 0.028$). The mean values ± SD, mean 95% CI, 5th and 95th percentiles of SDNN and the R-R adjusted SDNN are reported in table III. Similarly, the T wave complexity was significantly correlated with age ($r = 0.302$, $p = 0.002$) and with the R-R in-

Table I. Mean values, mean 95% confidence intervals (CI), 5th and 95th percentiles of the cycle length interval (R-R), QRS duration (QRS), QT interval (QT), corrected QT interval (QTc), and activation-recovery interval dispersion (ARId) in the 105 healthy subjects included in the study.

Parameter	Mean ± SD	95% CI		Percentiles	
		Lower	Upper	5th	95th
R-R (ms)	881 ± 134	885	907	693	1098
QRS (ms)	85 ± 12	83	88	64	106
QT (ms)	382 ± 29	376	387	338	435
QTcB (ms)	409 ± 30	403	415	355	458
QTcF (ms)	399 ± 26	394	404	352	440
ARId (ms)	83 ± 34	76	89	14	125

QTcB = QT corrected according to the Bazett formula; QTcF = QT corrected according to Fridericia formula; SD = standard deviation.

Table II. Mean values, mean 95% confidence intervals, 5th and 95th percentiles of the cycle length interval, QRS duration, and activation-recovery interval dispersion reported as a function of sex.

Parameter	No. subjects	Mean ± SD	95% CI		Percentiles	
			Lower	Upper	5th	95th
R-R (ms)						
Female	54	849 ± 117	817	881	678	1031
Male	51	914 ± 144	874	955	730	1149
p	0.012					
QRS (ms)						
Female	54	80 ± 11	77	83	62	102
Male	51	91 ± 12	87	94	71	112
p	< 0.0001					
ARId (ms)						
Female	54	89 ± 28	81	97	17	128
Male	51	76 ± 38	65	86	7	124
p	0.042					

Abbreviations as in table I.

Table III. Mean values, mean 95% confidence intervals, 5th and 95th percentiles of the standard deviation of all cycle length intervals (SDNN) and of the standard deviation of all cycle length intervals adjusted for the R-R by age decade.

Parameter	No. subjects	Mean ± SD	95% CI		Percentiles	
			Lower	Upper	5th	95th
SDNN (ms)*						
20-29	26	62 ± 23	53	72	28	115
30-39	27	56 ± 24	47	66	22	107
40-49	21	42 ± 14	36	49	20	71
50-59	15	42 ± 16	33	51	22	69
> 60	16	43 ± 22	31	54	21	91
Total	105	51 ± 22	47	55	22	92
R-R adjusted SDNN (ms)**						
20-29	26	53 ± 10	49	57	36	68
30-39	27	52 ± 15	46	58	33	91
40-49	21	50 ± 8	46	54	35	69
50-59	15	51 ± 9	46	56	38	67
> 60	16	46 ± 9	41	51	35	61
Total	105	51 ± 11	49	53	36	69

Abbreviations as in table I. * = ANOVA F = 4.704, p = 0.002; 20-29 vs 40-49 p = 0.011, vs 50-59 p = 0.036, vs > 60 p = 0.034; ** = ANOVA F = 1.165, p = NS.

terval (r = -0.228, p = 0.020, T wave complexity = 5.926 × R-R + 29.642). When adjusted for the R-R interval, the T wave complexity remained age-dependent (r = -0.217 p = 0.026). The mean ± SD values, mean 95% CI, 5th and 95th percentiles of the T wave complexity and the R-R adjusted T wave complexity are reported in table IV. QTd was age-dependent (r = 0.317, p = 0.001). The mean ± SD values, mean 95% CI, 5th and 95th percentiles of QTd are reported in table V.

Table VI shows the mean ± SD values, mean 95% CI, 5th and 95th percentiles of the late potentials. The RMS and LAS calculated both at 25 and 40 Hz did not show any correlation with age and heart rate, while the FQRS showed higher values in males than in females (p < 0.0001).

As reported in tables VII and VIII, the reproducibility, as assessed using the limits of agreement and the Bland-Altman correlation coefficient, was good for all the measured parameters.

Discussion

In the present study we performed a multiparametric ECG analysis in normal subjects in order to study the distribution, in the normal population, of all the ECG parameters describing the susceptibility of the heart to life-threatening arrhythmias and to sudden cardiac death, and in order to build a database of normal values for comparison with those of the literature[18-35]

Table IV. Mean values, mean 95% confidence intervals, 5th and 95th percentiles of the T wave complexity and of the T wave complexity adjusted for the R-R by age decade.

Parameter	No. subjects	Mean ± SD	95% CI		Percentiles	
			Lower	Upper	5th	95th
T wave complexity (%)*						
20-29	26	13 ± 6	11	15	6	29
30-39	27	15 ± 11	10	19	5	48
40-49	21	16 ± 11	11	21	7	52
50-59	15	15 ± 7	11	19	4	24
> 60	16	22 ± 9	17	27	8	37
Total	105	16 ± 9	14	18	6	32
R-R adjusted T wave complexity (%)**						
20-29	26	15 ± 2	15	16	12	19
30-39	27	10 ± 3	14	17	6	19
40-49	21	16 ± 2	15	17	12	19
50-59	15	16 ± 2	15	17	12	18
> 60	16	17 ± 2	16	17	14	19
Total	105	16 ± 2	15	16	12	19

Abbreviations as in table I. * = ANOVA F = 2.708, p = 0.034; 20-29 vs > 60 p = 0.023; ** = ANOVA F = 0.994, p = NS.

Table V. Mean values, mean 95% confidence intervals, 5th and 95th percentiles of QT dispersion by age decade.

Parameter	No. subjects	Mean ± SD	95% CI		Percentiles	
			Lower	Upper	5th	95th
QT dispersion (ms)						
20-29	26	35 ± 17	27	42	8	68
30-39	27	39 ± 30	27	51	9	134
40-49	21	31 ± 20	22	40	1	82
50-59	15	31 ± 24	17	44	9	71
> 60	16	68 ± 25	55	81	18	91
Total	105	40 ± 26	34	45	10	89

Abbreviations as in table I. ANOVA F = 7.162, p < 0.0001; 20-29 vs > 60 p < 0.0001, 30-39 vs > 60 p = 0.002, 40-49 vs > 60 p < 0.0001, 50-59 vs > 60 p < 0.0001.

Table VI. Signal-averaged ECG parameters in the 105 healthy subjects included in the study. Sex differences of the filtered QRS are also reported.

Parameter	No. subjects	Mean ± SD	95% CI		Percentiles	
			Lower	Upper	5th	95th
FQRS 25 Hz						
Female	54	92.4 ± 9.1	89.9	94.9	77	105
Male	51	102.8 ± 12.5*	99.3	106.3	85	128
	105	97.5 ± 12.0	95.1	99.8	80	117
FQRS 40 Hz						
Female	54	90.0 ± 9.5	87.4	92.6	76	104
Male	51	97.7 ± 9.5*	95.1	100.4	84	116
	105	93.8 ± 10.2	91.8	95.7	77	114
LAS 25 Hz	105	31.8 ± 9.0	30.1	33.6	18	51
LAS 40 Hz	105	34.2 ± 9.4	32.3	36.0	21	55
RMS 25 Hz	105	50.2 ± 34.0	43.7	56.8	14	136
RMS 40 Hz	105	40.9 ± 29.0	35.3	46.5	11	96

FQRS = filtered QRS duration; LAS = low amplitude signals: length of the time interval during which the terminal vector magnitude of the FQRS remains < 40 μV; RMS = square root of the mean voltage of the last 40 ms of the FQRS. Other abbreviations as in table I. * = p < 0.0001.

Table VII. Reproducibility (limits of agreement and Bland-Altman r) of the cycle length intervals, the standard deviation of all cycle length intervals, the QRS duration, the QT duration, the QT dispersion, the ARI dispersion and the T-wave complexity in 30 of the healthy subjects included in the study.

Parameter	Baseline	Comparisons	Mean ± SE difference	% Variation	95% CI		Bland-Altman	
					Lower	Upper	r	p
R-R (ms)	910 ± 23	1 vs 2	26 ± 19	3 ± 2	-13	65	-0.244	0.229
		1 vs 3	29 ± 21	4 ± 2	-15	72	-0.192	0.348
		1 vs 4	31 ± 22	4 ± 3	-15	77	-0.155	0.449
SDNN (ms)	67.3 ± 8.2	1 vs 2	0.8 ± 2.1	3 ± 5	-3.4	5.1	0.002	0.991
		1 vs 3	-1.6 ± 3.0	2 ± 6	-7.7	4.6	-0.236	0.245
		1 vs 4	-2.9 ± 3.0	0 ± 6	-9.0	3.3	-0.260	0.200
QRS (ms)	88.7 ± 3.3	1 vs 2	0.6 ± 0.8	1 ± 1	-1.1	2.3	-0.089	0.666
		1 vs 3	-0.2 ± 1.0	0 ± 1	-2.3	2.0	-0.214	0.294
		1 vs 4	-0.2 ± 1.0	0 ± 1	-2.3	1.8	-0.203	0.319
QT (ms)	391 ± 6	1 vs 2	7 ± 3	2 ± 1	0	14	-0.375	0.059
		1 vs 3	8 ± 5	2 ± 1	-1	18	-0.199	0.330
		1 vs 4	11 ± 4	3 ± 1	3	18	-0.375	0.059
QTd (ms)	38.2 ± 4.1	1 vs 2	2.0 ± 2.7	20 ± 14	-3.5	7.5	-0.329	0.101
		1 vs 3	2.4 ± 3.0	20 ± 14	-3.8	8.6	-0.147	0.474
		1 vs 4	6.4 ± 6.8	30 ± 20	-7.5	20.3	-0.085	0.679
ARId (ms)	86.3 ± 5.5	1 vs 2	-3.7 ± 2.7	-5 ± 4	-9.3	1.8	-0.051	0.803
		1 vs 3	-5.3 ± 3.7	-6 ± 4	-13.0	2.4	-0.121	0.556
		1 vs 4	-4.7 ± 2.9	-3 ± 4	-10.7	1.4	-0.384	0.053
TWC (%)	17.1 ± 1.5	1 vs 2	0.2 ± 0.8	5 ± 5	-1.4	1.9	-0.308	0.126
		1 vs 3	-0.1 ± 0.8	3 ± 6	-1.4	1.9	-0.207	0.311
		1 vs 4	0.3 ± 0.9	6 ± 5	-1.3	2.6	-0.209	0.305

TWC = T wave complexity. Other abbreviations as in tables I and III. Baseline data and differences are reported as mean ± SE; % variation as mean ± SE of difference/baseline value * 100.

Table VIII. Reproducibility (limits of agreement and Bland-Altman r) of the signal-averaged ECG parameters in 30 of the healthy subjects included in the study.

Parameter	Baseline	Comparisons	Mean ± SE difference	% Variation	95% CI		Bland-Altman	
					Lower	Upper	r	p
FQRS 25 Hz	106.6 ± 4.5	1 vs 2	-1.5 ± 2.3	-1 ± 2	-6.2	3.2	-0.245	0.227
		1 vs 3	-4.5 ± 2.6	-4 ± 2	-9.8	0.7	-0.386	0.051
		1 vs 4	-2.3 ± 2.4	-2 ± 2	-7.3	2.6	-0.318	0.113
LAS 25 Hz	35.2 ± 2.4	1 vs 2	1.0 ± 1.9	1 ± 5	-2.9	4.9	0.214	0.293
		1 vs 3	-0.6 ± 1.8	-1 ± 5	-4.3	3.2	-0.143	0.485
		1 vs 4	-0.8 ± 1.6	-1 ± 4	-4.2	2.6	-0.287	0.156
RMS 25 Hz	42.9 ± 5.4	1 vs 2	8.7 ± 5.5	24 ± 18	-2.7	20.1	-0.011	0.959
		1 vs 3	7.6 ± 5.2	29 ± 18	-3.0	18.2	-0.120	0.561
		1 vs 4	7.7 ± 5.0	29 ± 17	-2.5	17.9	-0.214	0.294
FQRS 40 Hz	103.1 ± 4.1	1 vs 2	4.8 ± 2.4	-4 ± 2	-9.6	0.1	-0.125	0.543
		1 vs 3	-5.2 ± 2.2	-5 ± 2	-9.7	-0.7	-0.184	0.368
		1 vs 4	-1.7 ± 1.8	-1 ± 2	-5.5	2.0	-0.109	0.594
LAS 40 Hz	40.6 ± 2.3	1 vs 2	-3.2 ± 1.7	-8 ± 4	-6.7	0.3	-0.071	0.730
		1 vs 3	-3.5 ± 2.0	-8 ± 4	-7.5	0.5	-0.184	0.369
		1 vs 4	-1.4 ± 1.7	-3 ± 4	-5.0	2.1	-0.123	0.550
RMS 40 Hz	33.7 ± 4.7	1 vs 2	7.6 ± 4.4	45 ± 22	-1.5	16.6	-0.203	0.320
		1 vs 3	5.2 ± 3.5	33 ± 18	-1.9	12.4	-0.099	0.631
		1 vs 4	2.0 ± 3.3	26 ± 18	-4.8	8.8	-0.269	0.183

Abbreviations as in tables I and VI. Baseline data and differences are reported as mean ± SE; % variation as mean ± SE of difference/baseline value * 100.

and for use in the future as reference. Eight parameters of arrhythmic risk ranging from the simplest, i.e. resting heart rate, to the most sophisticated and newest, i.e ARI, were evaluated noninvasively after a single 5-min surface ECG recording. The reproducibility of the measurements was carefully evaluated in order to assess the reliability of the recording approach and of the algorithms of analysis.

As well known, heart rate is associated with the prognosis. In the general population resting heart rate showed an independent predictive value for all-cause mortality, coronary deaths and sudden cardiac death after adjustment for some clinical variables such as age[38]. This independent value of heart rate was further confirmed in patients with arterial hypertension[39]. These data are in accordance with other population-based studies, such as the Paris Prospective Study in which resting heart rate was specifically associated with sudden death[40]. In the study by Wijbenga et al.[41] it was shown that in patients with heart failure resting heart rate was, at univariate analysis, associated with mortality or heart transplant.

The prognostic implications of an increased QRS duration have been scarcely investigated. Recently, Silvet et al.[42] showed that QRS prolongation (> 110 ms) is associated with an increase in mortality, and this is independent of the ejection fraction, cardiac rhythm and age. In a subset analysis, its impact seemed more prominent in the elderly and in those subjects with a more preserved left ventricular function. The QRS duration was found to be a good predictor of the prognosis in patients with chronic heart failure[43].

HRV is considered a noninvasive marker of the autonomic nervous system modulation[19], and a low HRV has been shown to have a prognostic value in the general population[44] and in patients with myocardial infarction[45]. In the MPIP study[46] including 24-hour recordings, a striking relationship between SDNN and mortality was documented in post-myocardial infarction patients: in fact, the finding of an SDNN < 50 ms was associated with a 5.3-fold increase in the relative risk of mortality compared to patients with an SDNN ≥ 100 ms. In dilated cardiomyopathy, Fouchier et al.[47] found, in 24-hour ECG recordings, that a reduced SDNN (a cut-off level of 100 ms) and ventricular tachycardia predicted sudden cardiac death and/or arrhythmic events. Although a decreased HRV is a risk factor for arrhythmic events, HRV by itself lacks the positive predictive accuracy necessary for adequate risk stratification in a clinical setting. The combination of a decreased HRV (evaluated in 24-hour recordings) with other risk factors substantially improves the power for risk stratification. In the recent ATRAMI study[12,48], either a decreased HRV or a decreased baroreflex sensitivity carried similar prognostic values, but the combination of decreased values of both identified a group with a 17% higher 2-year mortality in a population whose overall mortality was 4%. Moreover, in the EMIAT study[9], even though the overall mortality was not reduced by amiodarone treatment, patients with both a depressed HRV and a low left ventricular ejection fraction benefited significantly in terms of a reduction both in arrhythmic events and in the total cardiac mortality. In the present investigation, values of SDNN, calculated in 5-min periods, were slightly different from those assessed throughout the 24-hour period[18,19]. This is not surprising, since theoretically the SDNN should vary with time. In fact, our data are comparable with those reported in other studies including short recordings[21,49,50]. Moreover, our data confirm the previously described relation between SDNN and both age and sex[51,52].

The value of late potentials as a prognostic indicator of the occurrence[53] of ventricular tachycardia and sudden cardiac death has been reported both in patients with coronary artery disease as well as in those with nonischemic dilated cardiomyopathy[54]. The relatively low positive predictive accuracy of signal-averaged ECG as a stand-alone test indicates that it should also be used together with other diagnostic methods[55].

The presence of heterogeneity in the recovery of ventricular refractory periods is to be considered an important factor for the development of arrhythmias, and the measurement of the QT interval remains a reliable, albeit gross, index for the quantification of ventricular repolarization despite its well-known methodological limitations[30]. In fact, it is known that the manual determination of the end of the T wave is often difficult[56] and that the morphology of the T wave itself strongly influences any human measurement of the QT interval as well as any computer algorithm. The close link between the QT interval and heart rate makes it necessary to correct the QTc by some correction formulae. In the present investigation we used two different formulae (Bazett and Fridericia) in order to better characterize the behavior and the significance of this parameter.

A more specific measurement of ventricular repolarization inhomogeneity, the QTd, defined as the greatest interlead variability of the QT interval, is presumed to represent a noninvasive ECG measurement of ventricular repolarization inhomogeneity and a clinical marker of the arrhythmogenic risk. Many studies addressed the value of the QTd in the prediction of ventricular arrhythmias in various clinical conditions (ischemic heart disease[24], heart failure[57] and hypertrophic cardiomyopathy[58]), but the results have been controversial[59-61]. This is possibly due to difficulties in the manual measurement of the QT interval and to the influence of the respiratory movements and of the autonomic tone, and to other factors.

The T wave complexity index is a newly-developed parameter recently introduced from 12-lead ECG and from 12-lead digital Holter recordings. This method has been shown to differentiate normal subjects from patients with the long QT syndrome[56], hypertrophic cardiomyopathy[30], and arrhythmogenic right ventricu-

lar dysplasia[62]. In the present investigation we measured the T wave complexity in a large cohort of normal subjects in order to calculate normal values.

The ARI dispersion is a newly developed parameter, firstly described by Lux et al.[33-35]. In animal studies, the ARI, calculated from electrograms recorded on the heart surface, had a close 1:1 correlation with the duration of the action potentials recorded from cells underlying the recording electrode. Recent studies with a simulated human torso suggest that the ARI is a good estimate of the underlying action potential in surface leads as well[33-35]. So far, studies in humans are lacking; thus the clinical significance of this parameter remains incompletely understood.

The results of our study demonstrate that a 5-min surface ECG recording can be confidently proposed as a new method of measuring all the parameters which define the arrhythmic risk of the individual patient, that the algorithms of analysis made available by technology are reliable, and that the reproducibility of measurements is good. The short duration of the acquisition time inevitably influenced some measurements, particularly the SDNN, the values of which were slightly different from those measured over 24 hours in Holter recordings[19] which were still comparable to those measured in short recordings[21,51]. More interestingly, we found some correlation between the parameters and simple variables such as heart rate, sex and age, which will need to be considered in the clinical risk stratification workout of patients. Some of these correlations were already known; in fact, our data confirmed the relation between SDNN and both age and sex[51,52]; other correlations, such as the higher values of ARI dispersion and of the FQRS in females however, were demonstrated for the first time.

In conclusion, with the use of the XL-ECG system, we defined the normal values of all those ECG parameters estimating the susceptibility of the heart to life-threatening arrhythmias. We also described their distribution in the normal population and their correlations with demographic parameters. This work was preparatory for the noninvasive evaluation of the pathophysiological substratum of life-threatening arrhythmias and sudden cardiac death in the clinical setting. This new approach, based on 5-min surface ECG recordings, proved to be reliable, easy to set up, comfortable for the patients and effective in terms of time and cost saving.

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