THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

PROCEEDINGS OF THE ROMANIAN ACADEMY, Series A,
Volume 4, Number 1/2003, pp. 00–00

BIOENGINEERING SPOTS HEART REPERCUSSIONS OF MENTAL PROCESSES: sudden cardiac death *corde indemno* is preventable

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Abstract. The chronic psychosocial stress (CPS) is strongly suspected to be involved in the etiology of sudden cardiac death (SCD) without myocardial lesion ("white" postmortems) accounting for at least 9 percent of the mortality by cardiovascular diseases (CVD) in Romania – one of the highest in Europe. Neurocardiology and cardiovascular bioengineering have made available sensitive "rhythmological" tools able to distinguish among heart repercussions of various states of vigil awareness, e.g. between attention strain and emotional stress. Informational contents of RR time-intervals or QT interval series as derived from high temporal resolution ECG facsimiles have been revealed using spectral analysis and more recently by methods of non-linear dynamics. Discriminatory capability of artificial neural networks has been called to distinguish between normal and pathologic RR spectra in relation with underlying psycho-somatic states. The major application is detection and limitation of risk for malignant cardiac arrhythmias entailed by CPS in cardiac patients and especially in subjects with sporadic arrhythmic complaints on a normal clinical and paraclinical background, who are not dealt with by conventional medical care. Clinical studies based upon the armamentarium of information science & technology can offer a unique insight towards states of the mind, even if within the limits of structural science only, for now. On medium term, the above alliance can detect SCD risk in vague-symptomatic non-cardiac subjects and timely devise countermeasures to save valuable lives at socially acceptable costs even for today Romania.

BACKGROUND

Terminal events like rapidly developing ventricular fibrillation or sudden cardiac arrest result from a disturbance in the delicate and complex time relationship between cardiac depolarization, the firing of myocardial (ventricular) cells as signaled by the QRS complex in electrocardiogram (ECG), and their repolarization electrically echoed by QT interval. Such a disturbance may be triggered by known conditions as ischaemia or damage to an area of cardiac muscle, a chemical or metabolic insult or an emotionally traumatic incident. It also may occur without any observable cause at any age life.

Patients suffering from chronic, potentially fatal diseases, such as carcinoma of the pancreas, hepatic cirrhosis or reticulum cell sarcoma, whose serum chemistry was carefully maintained in the normal range, were found alert and comfortable one evening with normal vital signs like heart rate, blood pressure and electrocardiogram and, on the next morning, were reportedly found dead. In such a study [1], 12 such patients have been subjected to continuous ECG monitoring up to the time of their death from ventricular fibrillation or cardiac arrest. In each of them death was preceded by disturbances in cardiac conduction and repolarization. Subsequent autopsy showed no significant cardiac lesion pointing to deregulation of brain-originated heart control in relation with psychical consequences of the main disease.

Somehow opposite is the failure to die of patient whose potentially fatal coronary heart disease is complicated by a sudden massive stroke that reduce him/her to a vegetative existence that, with good care, may continue for years. An abnormal ECG may turn normal following the stroke, thereby suggesting that the forebrain is involved in the regulation of the heartbeat.

Recommended by Mihai DRĂGĂNESCU
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In otherwise healthy subjects sudden deaths have been reported from fright and social exclusion as well. To punish social deviants ancient Greeks practiced ostracism that was frequently leading to death. They wrote the name of the guilty on an *ostreion*, an oyster shell, and threw it out to sea; the death of the condemned soon followed, without any obvious cause.

In the same vein, Wolf and Bruhn have reported a proclivity for fatal myocardial infraction in individuals from Roseto - an Italian American enclave, who eventually have been alienated to some extent from their culture or social setting [1].

SUDDEN CARDIAC DEATH CORDE INDEMNO IN ROMANIA

Romania features one of highest CVD mortality in Europe, actually occupying the 3rd worst place after Russian Federation and Latvia.

Clues based on short series of postmortem data, scarcely available due to the consistent refusal of autopsy with our cultural model, suggest that about 15 percent of hospital SCD casualties have no heart lesion [2]. It is already known that SCD stands for about 60 percent of CVD mortality [3]. Taken together these numbers lead to 9 percent of Romanian CVD mortality unexplained by a heart condition detectable at postmortem.

Psychosocial stress exacerbated after the 1989 revolutionary turnover is strongly suspected to have created circumstances for hastening terminal events in more patients and for triggering lethal arrhythmic accidents in a significant number of healthy individuals (from conventional medicine standpoint). It is worth to notice that the typical SCD candidate is mid-age (40 to 60), not known as a cardiac patient, presents signs of chronic stress generated by long lasting no-solution or difficult-to-be-solved life problems, sometimes hardly involved in societal reform stirring fierce opposition, did not develop auto-protection strategies based on philosophical or religious experiences, and has perhaps some genetic proclivity toward arrhythmic heart troubles. This person is usually simply overlooked by weak preventive care Romania can now afford while conventional cardiology is far unable to offer him/her medicine protection or behavioral advice. In this context, finding socially acceptable means to detect SCD risk in such people and, if the case presents, to institute adequate life protection has an ethical significance as well.

INSIGHT BROUGHT ABOUT BY THE ADVENT OF EFFICIENT SOFTWARE FOR QT INTERVAL MEASUREMENT

First efficient algorithms for automatic software measurements of beat by beat QT intervals in high temporal resolution ECG facsimiles were published in 1992 [4] and urged experimental & clinical research addressing an old wish of clinical physiology, that is getting a continuous noninvasive access to the force of ventricular contraction – a most important vital parameter whose adequate handling can make difference between survival and death. Such a promise QT and other systolic time-intervals (yet relying on pressure rather than electrical sensing) were holding for several decades.

So, early experimental work in open chest, anesthetized dog conducted by Huang et al [5] put face to face direct intra-myocardial pressure and QT traces got by the above algorithms under various mechanical and pharmacological interventions; closely parallel patterns have documented the indexation value of QT interval measure for the force of ventricular contraction on a beat by beat basis.

Of keen interest, in virtue of a serious rare condition involving high SCD risk – *the long QT syndrome*, was the time-constant (τ_{QT}) of the RR – QT system modelable by a low pass AC transfer network combined with a DC non-linear transfer (cf. to Bazett's equation) between mean RR and mean QT interval. The true τ_{QT} was got in young (19-20 years) healthy males who underwent step change of heart rate (HR, number of RR intervals per minute) by invasive right atrial pacing (RAP) in clinic [6]. Other day HR was manipulated by pharmacological autonomic blockade to get τ_{QT} while RR was decreasing with τ_{RR}. τ's were exponentially approximated in RR&QT plots derived from thoracic ECGs digitized at 1 ms. Under mid-signal input RR-QT behaves linearly: adjacent RR up-steps produce τ_{QT} close to 48 s (Table 1). During blockade involving large RR inputs, $[\tau_{QT} - \tau_{RR}] <$ true τ_{QT} on RAP, disclosing system nonlinearity.

Table 1. Determining the time-constant of the RR-QT system. RAP=right atrial pacing; SIN = sinusal (normal) rhythm; ATRO=atropine (vagal) blockade; PROP=propranolol (sympathetic) blockade; mean± standard deviation (SD) in ms.

	RAP to RAP, n=4	**SIN to RAP, n=6**	**RAP to SIN, n=5**	**ATRO, n=9**	**PROP + ATRO, n=12**
RR_{in}	751±7.5	1049.5±41.0	514.2±64.7	926.6±135.4	651.4±137.1
RR_{fin}	610±18.0	822.2±47.4	948.2±95.3	495.1±50.9	571.9±72.0
τ_{RR}[s]	0	0	0	23.3±8.5	24.5±5.0
τ_{QT}[s]	48.0±1.8	46.6±8.5	54.9±14.2	63.6±6.6	65.5±7.9

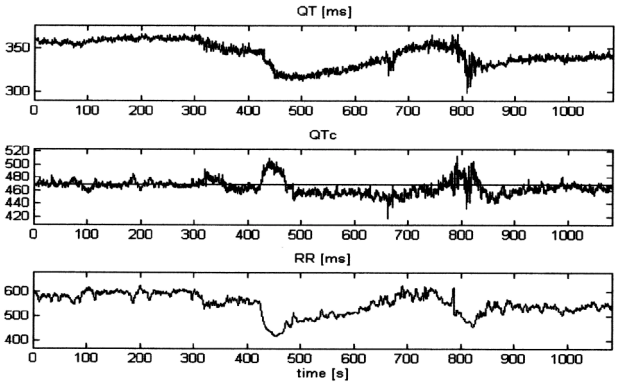

Fig. 01. Beat by beat traces of true QT interval, QT corrected For RR influence, and RR interval. Remark ordinate scaling: QT variability is about 1/10 of RR variability.

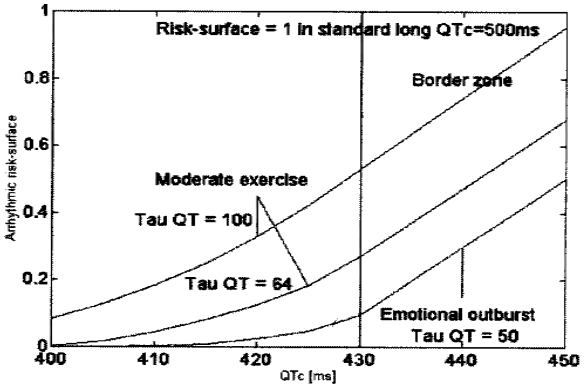

Fig. 02. Risk surfaces got by computer simulation.

Fig. 01 shows QTc (QT corrected cf. Bazett) dynamics in diabetic woman diagnosed with with borderline long QT (QTc =469 ms), during a mild HR transition to standing (1st event): QTc remains 45 s around 510 ms, just exceeding the standard long QT "arrhythmia risk surface" (area closed by the QTc curve and the long-QT threshold) for QTc = 500 ms. Computer simulation was done for QTc overshoots that occur with HR transitions observed on short-term (5 min) moderate stress in healthy. Fig. 02 shows dependence of risk surface in man on basal QTc in an "emotional outburst" molded on RAP-to-RAP data (τ_{RR} = 2 s, τ_{QT} = 50 s), and in "moderate exercise induction" as under ATRO (τ_{RR} = 24 s, while normal τ_{QT} = 64 s or prolonged τ_{QT} = 100 s). Thus, long time constant of RR- QT system entails *functional* long-QT episodes during every day life of healthy, whose risk surfaces appear close to patent long-QT patients. Superposition of adverse extra-stimuli on a vulnerable episode may lead to arrhythmic life threatening events.

BEAT-BY-BEAT QT VARIABILITY: THE SPECTRAL APPROACH

Beat by beat QT variability amounts to 1/10 of that of RR. QT spectral power derived from high resolution ECG clusters in the same way as in the more known RR spectrum [4], that is within 0.1 Hz, low frequency (LF) or “sympathetic” band (standardized now at 0.04-0.15 Hz; earlier also called Traube-Hering-Mayer, THM band) and “respiratory” HF band around the breathing rhythm (standardized 0.15-0.4 Hz). Question arose whether QT- LF power relates to RR interval’s LF modulation, mostly brought by right cardiac vagus, or, differently, whether QT-LF reflects sympathetic control of ventricles. This is important since chronic exacerbation of sympathetic drive to ventricles, rather than to atria, is currently held responsible for life-threatening arrhythmias.

A study [7] reported a clinical setting involving 10 healthy male subjects (ss), aged 19-20, who spent 10 min in relaxed dorsal decubitus, before fixed right atrial pacing (RAP) in 7 min steps, as follows: 1) just above sinus-rhythm (RAP min) when relaxed; 2) RAP at 100, or 110 beat/min (b/m) when stimulus fell on T-wave tail, always relaxed, in 8 ss; 3) mental stress (MS) by applying a Kraepelin arithmetic test, while RAP at 100 or 110 b/m, in 8 ss. QTs were software derived within ± 1.12 ms of values got with manual

tangent method. After re-sampling at 500 ms, the most stationary 3 min epochs were Fourier-transformed and LF power (ms^2) was summed over 0.05 to 0.15 Hz. Results in table 2 showed that stabilizing RR by RAP during relaxed rest dramatically spoils QT-LF; superimposing MS over steady RAP significantly augments QT-LF. So, QT-LF spectral power has a double subordination: during relaxed rest it follows mostly RR-LF fluctuation; during mental stress a RR-independent factor is added, which presumably reflects the sympathetic status of ventricles. The latter promised more pertinent evaluation of RR and QT spectra in terms of arrhythmia risk stratification in both myocardial infarction patients and non-cardiac subjects with stress-dependent sporadic rhythm disturbances.

Table 2 (see the text).

	Baseline	**RAP min**	**RAP 100**	**RAP 110**	**RAP100 + stress**	**RAP110 + stress**
Mean RR	974 ± 124	779 ± 62	602 ± 5.0	566 ± 2.8	602 ± 5.2	566 ± 2.8
Mean QT	376 ± 26.7	356 ± 16.1	324 ± 8.2	308 ± 0.9	326 ± 11.7	308 ± 3.0
RR-LF	1196 ± 941.7	1.35 ± 2.1	1.1 ± 1.3	0.16 ± 0.1	2.5 ± 1.2	0.66 ± 0.69
QT-LF	**1.39 ± 0.59**	**0.50 ± 0.45**	**0.59 ± 0.4 (aggregated)**		**1.19 ± 0.69**	
SIGN TEST	p = 0.002		p = 0.0078			

Table 3 (see the text).

Setting \ Variable	**Mean RR** [ms]	**RR-LF** [ms^2]	**QT-LF** [ms^2]	**IV QT-LF** [ms^2]
Stress	740 ± 124	631 ± 545	1.62 ± 1.42	0.53 ± 0.64
Wilcoxon p	**0.0017**	**NS**	**0.0211**	**0.0133** $^{\otimes}$
Baseline	*842 ± 144*	*556 ± 502*	*0.93 ± 0.82*	*0.38 ± 0.65*
Wilcoxon p	**0.0017**	**0.0017**	**NS**	**NS**
Propranolol	989 ± 158	1030 ±693	0.80 ± 0.36	0.24 ± 0.11
Wilcoxon p	**0.0017**	**0.0017**	**0.0207**	**NS**
Prop&Atropine	567 ± 57	1.2 ± 0.8	0.46 ± 0.32	0.35 ± 0.25
Wilcoxon p	**0.0592**	**0.0057**	**NS**	**0.0564** $^{\otimes}$
Prop&Atro&Stress	578 ± 49	2.9 ± 3.2	0.57 ± 0.32	0.38 ± 0.21
Remarks			**P&A**vs**B: 0.031**	**P&A&S**vs**P: 0.0499**

While sympathetical message is beyond any question within the QT-LF band, the neural system(s) involved remain(s) unclear since every efferent traffic to the heart is 0.1 Hz modulated, whereas both α_1 and β_1, and, still, muscarinic stimulation can affect repolarization in myocardial fibers. Sympathetic and/or vagal vehicle may be consequential for QT-LF reading in terms of stress-dependent arrhythmia and sudden death risk in cardiac patients.

The study addressing that issue [8] enrolled 14 healthy males, aged 19-20,who went through: 1) baseline (B) in relaxed supine (10 min); 2) mental stress (S) by a recorded Kraepelin arithmetic test (5 min); 3) intravenous (i.v.) propranolol (P) 0.4 mg/kg infused in 15 min; 4) atropine (A) 0.02 mg/kg in 2 min; 5) 10 min rest; 6) repeated S. RR by QT mean squared coherence (MSC) spectrum was computed to get QT-LF's idio-ventricular fraction (IV QT-LF) by removing RR-coherent influences; in fact each QT-LF power-line was multiplied by {1 –MSC} at that frequency.

Results in table 3 (averages ± SD) with 2-tailed Wilcoxon p ($^{\otimes}$1-tailed to test IV QT-LF stress-responses) for comparisons inter-lines or as shown. IV QT-LF is significantly higher in P&A&S versus P only, when α_1-only-mediated stress effects and norepinephrine release over-activation by muscarinic blockade are perhaps synergetic. Decrease of QT-LF under P&A versus both B and P reflects dramatic fall of RR-LF due to vagal blockade. An adrenergic mechanism appeared involved in QT-LF response to mental stress. Moreover, while QT-LF features ordinarily a better sensitivity to stress, its IV fraction is robust vis-à-vis of confusing influences from either RR-LF or up and downs in mean RR.

CROSS-SPECTRAL RR BY QT REFINES THE CLINICAL MESSAGE

There was already shown that an RR-independent factor specifically related to sympathetic drive to ventricles (or idio-ventricular sympathetic control, IVSC) may act upon QT variability together with its modulation by RR, as a function of situation.

In principle, RR*QT coherence spectrum can track the consistency of the latter modulation while IVSC may supra-modulate QT not-necessarily in an RR-coherent manner. Using mean squared coherence (MSC) one could split IVSC fraction from QT-LF.

To prove this hypothesis, in a study [9] 12 male subjects (ss) aged 19-20 entered a 2 day trial including baseline (10 min) and interventions (7 min): 1) relaxation; 2) mental stress (MS) using a Kraepelin arithmetic test; 3) i.v. propranolol 0.4 mg/kg body in 15 min (1^{st} day) or right atrial pacing (RAP) just above sinus-rhythm, in 9 out of 12 ss (2^{nd} day).

MSC used a 9-line moving-triangle smoothing of its cross- and quadrature- spectral terms. As before, to get the IVSC fraction of QT-LF each QT-LF power "line" was corrected by multiplying with {1-MCS} at that frequency.

Results in table 4 (mean ± SD) showed that MSC is instrumental in subtracting QT modulation by RR from QT-LF: its IVSC fraction is consistently higher during MS versus situations when sympathetic profile is supposed to be low, if any.

Table 4 (see the text). RR in ms; spectral powers in ms^2.

	Baseline	Stress	Propranolol	Baseline	Stress	RAP
Mean RR	837±139	783±128	972±156	915±138	805±150	797±94
RR-LF	605±396	623±605	854±425	640±391	940±1297	3.52±4.4
QT-LF	1.17±0.80	2.36±1.99	0.94±0.51	1.23±0.84	1.41±0.65	0.40±0.29
MSC-LF	0.61±0.21	0.58±0.26	0.63±0.20	0.66±0.16	0.59±0.19	0.19±0.08
IV QT-LF	**0.49±0.68**	**1.06±1.62**	**0.32±0.30**	**0.28±0.20**	**0.64±0.45**	**0.33±0.26**
Wilcoxon p	**0.012**		**0.032**	**0.009**		**0.033**

In the latter situations, neither mean RR-dependent increase of RR-LF by propranolol, nor RAP-dependent fading of RR-LF versus baseline misled the IVSC part of QT-LF, thus named IV QT-LF.

Study concluded that joining RR*QT coherence to QT spectra, stress-dependent IVSC can be non-invasively objectified and monitored free of confusion caused by concurrent alteration in autonomic balance at the sino-atrial node piloting RR intervals. Ambulatory (Holter) high resolution ECG is then in a better position to ascertain the risk of life-threatening arrhythmias associated with chronic exacerbation of IVSC.

Putting the IV QT-LF to work, an other study [10] addressed the question how QT-LF or its IV fraction, that do respond to mental stress (MS), react to the main elements of MS known as having different effects on RR-LF. To respond, 17 male subjects, aged 19-20, went through relaxed rest in supine (10 min), and MS by a Kraepelin test (5 min), as part of a 2-day larger study. Within a polygraphic set-up 23 baseline/stress episodes were assigned to 3 classes according to known cardiotacho-, plethysmo-, and pneumo- graphic marks of "concentrated attention mainly" or "emotion" (e.g. mild mean RR ↓, while RR-LF ↓ or ↑, respectively), or still "high emotion" (mean RR ↓ > 250 ms).

As shown in the table 5 (averages ± SD) using 2-tailed Wilcoxon test (1-tailed for stress IV QT-LF), emotion elicits clear-cut responses in QT-LF, following RR-LF; when RR effect is subtracted, IV QT-LF still remains higher. During attention, QT-LF reaction is blurred but not that of IV QT-LF.

Thus, IV QT-LF appeared tracking myocardial "absolute" strain by cortical activation, irrespective of its psychological color. As strain index, it is robust against various RR-LF and mean-RR correlates of MS, but its lower sensitivity and higher noise contents vis-à-vis of QT-LF could mask subtle reactions.

THE NONLINEAR DYNAMICS HINTS FOR RR AND QT BEAT-BY-BEAT VARIABILITY

In last decade non-linear dynamics methods were used to study RR time-series as output of a chaotic generator.

First application of chaos mathematics to QT interval series [11] collected data from 11 subjects, 31 to 79 years old, healthy volunteers or miscellaneous patients referred for neuro-cardiologic evaluation. Conventional cardiologic examination certified competent myocardium in each of them. An one hour protocol included several tests, typically 5 min long, mimicking by nature and intensity the ordinary daily activities: posture changes, mental concentration, vigorous exercise (bicycle), as well as emotional stress through an interview done during 10-15 min by an investigator fully aware of patient's history (Wolf's semi-structured stress interview).

Table 5 (see the text).

Setting / Variable	Mean RR [ms]	RR-LF [ms^2]	QT-LF [ms^2]	IV QT-LF [ms^2]
Baseline	797 ± 92	715 ± 547	1.11 ± 0.77	± 0.79
Wilcoxon p (N=8)	0.0143	0.0209	NS	0.0391
ATTENTION mainly	698 ± 89	463 ± 370	± 0.99	0.80 ± 0.82
Baseline	909 ± 155	399 ± 377	0.68 ± 0.60	0.15 ± 0.10
Wilcoxon p (N=12)	0.0054	0.0025	0.0033	0.0010
EMOTION	853 ± 153	893 ± 764	1.59 ± 1.50	0.39 ± 0.26
Baseline (N=3)	1001 ± 115	681 ± 454	1.09 ± 0.71	0.48 ± 0.36
HIGH EMOTION	707 ± 119	454 ± 127	1.55 ± 0.55	0.55 ± 0.50
Baseline	881 ± 145	546 ± 458	0.88 ± 0.68	0.33 ± 0.50
Wilcoxon p (N=23)	0.0001	NS	0.0005	0.0002
STRESS (all data)	780 ± 147	686 ± 621	1.54 ± 1.21	0.55 ± 0.56

Table 6. Mean/SD of percent changes in variables with significant response cf. to the sign test (NS = nonsignificant , included to show the trend).

Comparison	# of sessions	Mean RR	RR-HF	RR-LF	RR-PD2	Mean QT	QT-LF	QT-PD2
Standing vs Sitting	12	**-13.7**/5.4 p<0.01	**-66.2**/25.5 p=0.01		**-24.5**/16.4 p=0.05	**-4.6**/2.1 p=0.01		
Stress vs Control	8	**-7.5**/4.0 p=0.01		**+153**/135 p=0.01		**-2.1**/1.1 p=0.05	**+397**/534 p=0.05	**+45.5**/49.3 (NS)
Recovery vs Post-Exercise	7	**+23.8**/17.2 p=0.05				**+12.5**/9.1 p=0.05		

Table 7. Basal QT-LF [ms^2] / Bazett corrected QT [ms] in a 12 subject group including the 11 in the study [11].

AA-36m	A-45m	A-46m	N-65m	NS-36f	NP-45f	IS-72m	WM-70f	AL-81m	T-50f	D-60m	AN-62m
0.96/408	**1.3**/385	**2.5**/406	**3.1**/394	**3.3**/396	**4.8**/401	**6.7**/459*	**7.8**/447	**8.6**/412	**9.1**/457*	**13.0**/437*	**18.7**/400

Legend. AA: moderate aortic regurgitation, hypertrophy; A: athlete; N: normal; NS: normal heart, rare pressure drops; NP; normal pressure, arterial premature beats; IS: moderate ischemia; WM: weak myocardium; AL: Alzheimer; T: tachycardia; D: diabetes; AN: anxiety. 36m= 36 years old male. *= borderline; **= long QT according to Moss & Robinson.

Besides spectral variables, point correlation dimension PD_2 over selected RR and QT epochs were computed using a Skinner's PD_2 published algorithm.

In this larger age-spreading group, standing decreased RR-PD_2, consistent with a loss of complexity in brainstem control sliding from respiration and forebrain influences to single baroreflex dominance (Table 6). LF power in both RR and QT is highly sensitive to emotional stress, while QT-PD_2 nonconclusively responded with 5 +, 2 -, and 1 no-change; the two decreases in QT-D_2 opposing to the expected parallelism to QT-LF were associated with dejection during the stress episode rather then with more general resentment. In 3 subjects with sufficiently stable ECG traces on exercise we got large QT-LF; however there was little group alignment on recovery; in healthy fitted QT-LF gradually decreased, in a case of small-reserves myocardium (moderate aortic regurgitation) QT-LF fell briskly at the very end of exercise, while in aged-myocardia that fall was so severe that later in recovery when approaching the baseline.

QT duration has a double determination: from RR length (classical view, according to Bazett's rule) and from force of ventricular contraction as previously reported. Taken together these data and present results suggest that QT-LF could sensitively monitor the sympathetic drive to ventricles while mean QT shortening would rather reflect the effectual force of contraction. During exercise QT-LF and mean QT go together; however during emotions their splitting in clear enough: mean QT doesn't follow a not-needed

command (see percent changes in Table 6); here the vagal innervations of ventricles, if competent, could play a salutary part.

As table 7 suggests, a chronically enhanced sympathetic drive to an intrinsically weakened myocardium stands for a regulatory adjustment to maintain the cardiac output. However, since sustained sympathetic drive to myocardium is largely viewed as one major factor of risk of sudden death of arrhythmic cause, the QT-LF sensitivity to cognition we now report, could have a clinical relevance related to the behavioral containment of that risk.

SCD RISK DETECTION WITH SHORT TERM RR AND QT SPECTRAL MONITORING

A direct means to ascertain the indexation quality for the IVSC of spectral QT statistics collected in stressful settings is comparison with settings in which a non-controversial higher sympathetic drive to the heart is established, that is with exercise performing.

In such a study 15 subjects with normal myocardia, 47.8 years as average age, were monitored during an interview evoking stressful events in the recent life, and during sub-maximal bicycle exercise lasting 3 to 8 minutes [12].

Results (table 8) proved that mental stress is statistically equivalent from QT-LF standpoint with sub-maximal exercise that cannot be sustained more than a couple of minutes.

Table 8. Mental stress compared with submaximal exercise: RR/QT spectral variables in 15 healthy subjects. Group averages separated by bold lines present significant differences cf. to bilateral Wilcoxon, $p<0.01$.

Variables / **Intervention**	**Mean HR [beat/min]**	**RR-LF [ms^2]**	**QT-LF [ms^2]**
Control	73.7	300.5	2.5
Stress	80.1	894.9	6.7
Exercise (n=8)	131.9	113.3	8.6
Recovery	84.4	242.1	2.4

Suggestion arises that chronic in mature adults psycho-social stress (evocable by interviews cf. studies [11], [12]) may put the myocardium under a undue sympathetic pressure (perceptible using non-invasive QT methods cf. studies [7] to [10] in young) well known to jeopardize electrical robustness of the myocardium in a term depending on heart condition, other life style risk factors, heredity, and ultimately elicit arrhythmic incidents or the fatal accident – sudden death, documented as the first, and the last sign of heart disease in about 25 percent of casualties {see e.g. [3]).

Based upon the above studies, SCD risk can be assessed using a short protocol (about 30 minutes) centered on a stress interview (Wolf method) aiming at detection of an overdue QT-LF or IV QT-LF response in non-cardiac subjects. *Mens Cordis neuro-ECG procedure* [12] used by the CVD Prevention Unit of the Institute of Public Health encompasses: sitting relaxation (5 min), standing relaxation (5 min), and stress interview (neutral conversation for 5 min; stress induced by a pre-informed investigator evoking recent psycho-trauma – 15 min, reassurance – 5 min). Warning criteria for QT-LF or IV QT-LF are: I. Basal > 5 ms^2 ; II. Stress > 10 ms^2; III. Stress > 5 by basal.

Warning severity is proportional with number of over-threshold criteria. ”Treatment” of people at risk comprises anti-stress psychological & physiological conditioning based upon psychological consultance, psychotherapy or exercise complemented with biofeedback techniques directed to increasing the vagal control of heart. As for patients, spectral methods are recently reported as documenting that sequence of pathological heart denervation in diabetes mellitus type I is headed by the vagi [13].

SCD RISK DETECTION WITH LONG TERM SPECTRAL RR MONITORING USING ARTIFICIAL NEURAL NETWORKS

A factor seriously opposing to clinical acceptance of the RR-variability tool is the common undiscriminate consideration of spectra irrespective of their specific psycho-physiological and patho-physiological underlying state. Or, spectrum's alteration in the same individual induced by brainstem "re-

wiring" when posture, mental loading status, or sleep stage is changed fairly competes or overpasses inter-individual differences referred to the same state.

An initial project [14] aiming at state-recognition of Holter ECG-derived RR spectra has been developed using software written in the-latter-includes-the former style, which preserves the independent use of the early modules, for processing 24 hours RR files derived from Holter tapes.

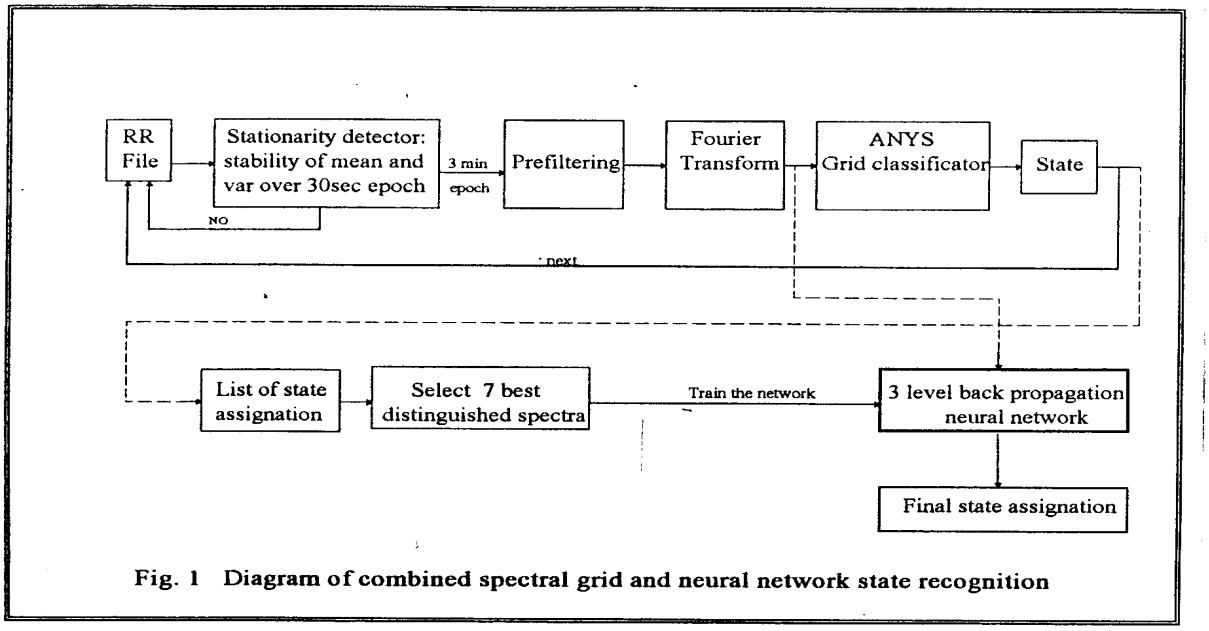

Fig. 1 Diagram of combined spectral grid and neural network state recognition

Fig. 1. The overall diagram of the combined ANYS – neural network procedures.

With reference to fig. 1, the program performed search of every 3-4 minute RR episode complying with quasi-stationarity conditions required by spectral analysis. A conventional Fourier transform was used to derive spectra from the above episodes.

Module ANYS added an expert-system module to recognize the underlying state of a spectrum in terms of probability and, once a validation examination passed, to assign a reference state to certain spectra

Classification used a grid of spectral parameters as follows: RR mean and variance, ratio of THM (0.05-0.15 Hz) and RESP (0.2-0.4 Hz) spectral powers, central THM frequency, THM clustering score, central respiratory frequency.

Reference states were: sitting or standing relaxation, concentrated attention loading, emotional stress, exercise, slow sleep, and rapid (REM) sleep.

Finally, averaging the-same-state group gets a reference template and lastly "judging" the various templates with reference to age-amended normality criteria gave a tentative autonomic diagnosis.

As a step towards automation of state classification, 6 spectral parameters were input to a three level back propagation neural network, featured by seven hidden neurons, outputting probabilities of each of the seven reference states assigned to an incoming spectrum [15].

The neural network written in C used an activation function of sigmoid type: $f(x) = 1/(1+ e^{x})$ and was trained with a spectral values set according to ANYS classification. The training parameters were: $\eta = 0.75$, $\alpha = 0.85$; maximum number of iterations was 500 while minimum error was set to 0.06.

After being trained using parameters of the seven best distinguished spectra assigned by ANYS to each reference state, the neural network proved to be more effective than the ANYS itself in assigning towering probabilities to the rest of spectra. However it needs some initial training using the knowledge-base stored into the grid classifier.

CONCLUSIONS

Clinical studies based upon the armamentarium of information science and technology can offer unique insights toward the states of the mind, even if, for now, within the limits of structural science only. On medium term the above alliance can detect sudden cardiac risk in vague-symptomatic non-cardiac subjects and devise timely countermeasures to save valuable lives at acceptable costs even for today Romania.

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Receiving date : July 3, 2002