

**A CHRONIC DECREASE OF HEART RATE VARIABILITY CAN PRECEDE
SOME CASES OF CANCER**

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S U M M A R Y

The paper brings experimental evidence about the existence of relationship between the chronic decrease of heart rate variability (HRV) and malignancy. It is supposed that this phenomenon can be used for early prediction of health risk towards cancer. In accordance with a long-term lasting prophylactic program HRV measures were obtained in 2147 practically healthy workers from both sexes (712 men and 1435 women) in working age. The epidemiological case control (first part of the study) provided 4 years later proved that the workers with a chronic drift in sympathetical - to - parasympathetic balance towards a sympathetical prevalence are exposed to a higher health risk for carcinomathosis ($p < 0.01$). In the second part of the study the HRV measures were collected in 247 cancer patients (154 men and 93 women, mean age 38 years from Bulgarian Oncological Center) and in a control group being representative for country population (3852 men and 4254 women, mean age 39.5 years). Mean values of both groups were compared statistically. The comparison reveal that the autonomic balance in cancer patients is much more sympathetically oriented ($p < 0.001$).

A short description of the created HRV-based method for prediction of health risk (HR) is presented. Theoretical concept explaining the possible biomedical mechanism underlying the development of cancer as well as the effect of some anticancer intervention procedures are discussed.

Key words: Heart Rate Variability, Cancer, Health Risk.

I N T R O D U C T I O N

Recently the existence of relationship between stress and the development of life threatening diseases (including cancer) become a question, attracting increased scientific interest (15). The terms: stress, eustress, distress, overstress or burnout are well known, but it was not clear how to assess them quantitatively and which are their exact psychophysiological correlates as well as their exact impact on health welfare. On the basis of thousands of investigated persons, followed up by a large scale of psychophysiological, clinical and paraclinical methods, we found, that 9 - 10 % of the population are in distress (overstress). The physiological basis of this phenomenon is a decrease of Heart Rate Variability (HRV) as a result of the increased autonomic sympathetic tone. Stress can be measured quantitatively by the amount of the HRV-based sympathetic drift in autonomic balance. Our more than 25 years of practical experience in the area of work- related stress (1,2) allowed us to create an easy and reliable method for assessment of autonomic balance (respectively of stress level), based on computer analysis of heart rate variability (3). This method proved to allow a better insight in the practical operationalisation of the term stress in different medical areas, where it was used (prophylactic health care, pediatric, surgery, cardiology, sport and transport medicine etc.)

Heart rate variability (HRV) is the amount of heart beats fluctuations around the mean value. The suppression of HRV (a predominance of sympathetic activity) has been found to occur as a result of mental and physical load, the increase of gestational age, acute myocardial infarction, patients with an increased risk for ventricular fibrillation and sudden cardiac death, coronary artery disease, essential hypertension, after spinocerebellar degeneration, Shy-Drager syndrome, polyneuropathy due to diabetes mellitus, chronic alcoholism, Guillain Barre syndrome, in persons exposed to environmental neurotoxic agents as organic solvents or lead, workers executing vibratory tool operations, autonomic neuropathy as a complication of diabetes, renal failure, medication with Atropine, Benzodiazepines, and in the persons influenced by different kinds of long-term lasting stress factors. Contrary, sympathetic activity decrease as a result of beta-adrenergic blockers or calcium channel antagonists (blockers) as *Diltiazem* (it reduce predominantly low-frequency modulated spectral power of heart rate (4,5,6,7,8).

HRV analysis is used by us for assessment of the autonomic balance (respectively the level of **health risk**) in patients as well as in practically healthy persons, namely workers as a part of different prophylactic programs. Some of the elicited by HRV measures have a high predictive value towards development and progressing of clinical symptoms (diabetic autonomic neuropathy, congestive heart failure, allograft reinervation, thyreotoxicosis etc.).

When revealing the relationship between stress and HRV chronic decrease we observed, that some of our close relatives being in chronic stress or burnout (according to the HRV analysis and psychosocial questionnaires) developed after some months or years different kinds of cancer (brain, ovarian, leukemia, cancer of gl. mammae and So.). This turn our attention to the question: are the persons with long-term lasting increased sympathetic tone exposed to a higher health risk for malignancy than "normal" persons, and if it is so, is it possible to use HRV analysis as a predictor of health risk for developing cancer.

METHOD

There exists many different mathematical algorithms for computing the time and the frequency-based HRV measures. The main periodic fluctuations of cardiac activity are connected with breathing (respiratory sinus arrhythmia - 0.2-0.4 Hz). There exists also some additional fluctuations connected with the activity of the thermoregulation (0.02-0.05 Hz) and blood pressure (0.06-0.15 Hz). Many others internal or external factors can influence in a specific way the HRV depending on their force and frequency. The amount of HRV can be presented by calculation of standard deviation (SD) of all R-R intervals, amplitude of Mode (%), total spectral power (TP), SD of beat-to-beat R-R interval differences and So. (Fig.1.). By including them in mathematical expressions it is possible to obtain the best approach to the phenomenon being studied . We have observed that the augmented sympathetic activity caused by physical or mental stress is decreasing HRV as a whole as well as the spectral power in the spectral area between 0.01-0.06 Hz .

The created by us HRV based method for HRV analysis includes a mathematical algorithm computing physical and mental stress in arbitrary units (fig. 2), pulse, the number of ventricular extrasystoles (Fig.3.), the fitness level (Fig. 4.) and the value (in percents) of the estimated health risk (HR %), which is computed as a sum of the all health risk contributing influences, which physical stress, mental stress, extrasystoles and fitness level are possessing (Fig. 5.). The hardware of the method, named *Danev Tests (DANEVTEST)* is a modular (pocket format) converting ECG signal to rectangular beats, working with IBM compatible PC (9V battery supply) (Fig. 6.).

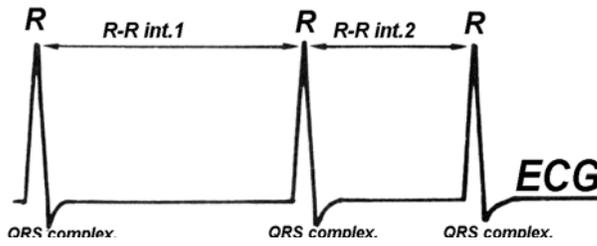


Fig.1 In this figure ECG is electrocardiogram. QRS complexes correspond to heart beats. R-R 1 and R-R .2 are cardiointervals, which *DANEVTEST* are submitting to mathematical assessment.

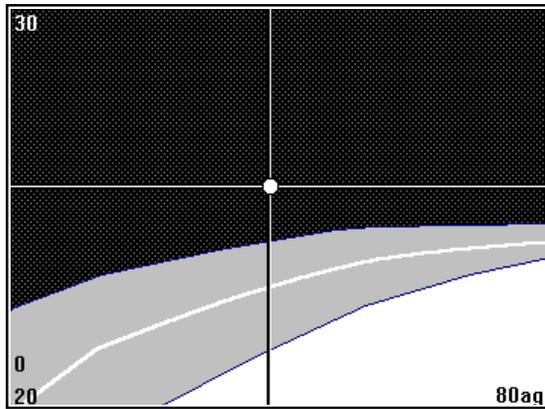


Fig. 2. Assessment of physical stress by *DANEVTEST*.

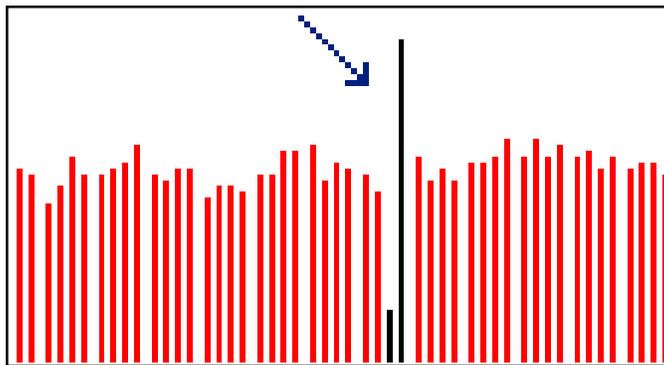


Fig. 3. Graphical presentation of ventricular extrasystole.

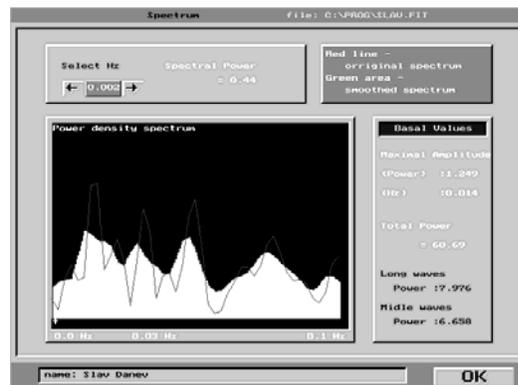
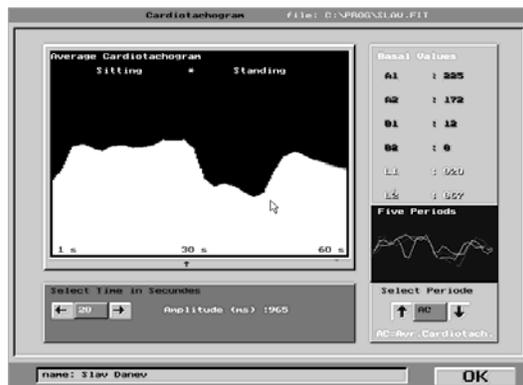


Fig. 4 Assessment of Fitness level by *DANEVTEST*.
 A Average Tachogram , B Spectrum

Physical Stress

Mental Stress
Extrasystoles
Fitness Level

Fig. 5. Components of Health Risk, according to *DANEVTEST*.

Total Health Risk (%)



Fig. 6. *DANEVTEST* hardware.

SUBJECTS

In the first (epidemiological) part of the study took part 2147 practically healthy persons from both sexes (712 men and 1435 women) aged from 36 to 52 years. All of them were workers (operators, mechanics, maintaining personnel, administration and So.) from the biggest Bulgarian steel or cooper producing plants, chemical industry and cotton or wool manufacturing industry. From all population 250 persons with a long-term lasting increased sympathetic tone (high level of health risk), and 250 persons, with it's normal values (low level of health risk) were selected. Further the information concerning the development of different kinds of cancer in the end of the 4 years period was obtained from the individual histories of diseases (data from regional oncological centers).

In the second (clinical) part of the study took part 247 patients from Bulgarian Oncological Center (154 men and 95 women, mean age 38 years) with different kinds of cancer (*carcinoma gl. mammae* , *carcinoma pulmonum*, *carcinoma ventriculi*, *carcinoma colli uteri*, *carcinoma corporis uteri*, *carcinoma ovarii*, *carcinoma tubae*, *carcinoma basocellulare*,

melanoma malignum, mycosis finqoides, meduloblastom, sarcoma maxillaris, leucosis, leucosis blastica, myeloma multiplex, lymphoma malignum, carcinoma gl. prostatae, seminoma testis, carcinoma papil. v. urinariae etc.). The biggest part of the patients had not intoxication.

The mean values of HR were compared with the corresponding age-related bioconstant values of HR, obtained in country population as a result of a long term lasting investigation program including 8106 practically healthy persons (3852 men and 4254 women) aged from 20 to 70. These data were used as a control group.

PROCEDURE

In order to exclude circadian biorhythm the HRV measures were obtained between 9-12 a.m. in three consecutive days. The measuring time was 10 min. in reclining position without movements or talks for obtaining the stress levels and the number of extrasystoles. The measuring time was 5 min. (modified orthostatic test) for obtaining the fitness level. The mean individual values of HR from the three measurements was calculated.

Every subject fulfilled a computerized test for psychosomatic complaints in order to exclude already ill persons. Persons with alcohol dependence or frequently using tranquilisators or other medicaments influencing autonomic balance (beta-blockers f.e.) were also excluded.

RESULTS

a) First part

The first and second groups were named HR-high and HR-low. The comparison between the values of HR obtained in both groups is statistically significant: HR-high = 72.6 ± 23.7 ; HR-low = 44.7 ± 21.1 ; $p < 0.01$. The cohort study (also known as longitudinal or prospective) which was employed, compare two subsets (groups) .

The estimation of the relative risk was done by comparing the sum of the persons in both groups developing cancer in four years period of observation. This procedure reveal the relationship between the value of HR (risk factor) and the examined disease (malignancy).

Some of the persons dropped out from the assessment (12 for the first group and 8 for the second group).Reasons for dropout were : 7 cases death (not from cancer); 4 cases -gone abroad; 9 cases -lost to follow up

Table 1. Assessment of Relative Risk for Developing Malignancy

Groups	Nb. of cases, developing cancer within 4 years	Nb. of cases, not developing cancer within 4 years	total
HR - high	16(a)	222(b)	238
HR - low	1(c)	241(d)	242

The relative risk is the probability for progressing malignancy in a period of 4 years. It is : a/ for "exposed" population (first group) = $16:(16 \pm 222) = 0.067$; b/ for "unexposed" population (second group) = $1:(1 \pm 241) = 0.004$.

The resultative risk is: = $\{a.(c + d)\} : \{c.(a + b)\} = 16.27$. This value can be assessed as very high.

Thus, the persons from group HR-high are 16 times more likely to progress cancer but only in the case that their HR value was oscillating around 72.6 (or change to higher) in the period of following-up.

The attributable risk can be computed in two ways:

$AR = (I_p - I_{ne}) : I_p$, or $AR = \{(I_e - I_{ne}) : I_{ne}\}$. In these two ratios - I_p , I_e and I_{ne} are the incidences of carcinomathosis in all country population; in "exposed" and in "not exposed" groups. As I_p can't be well defined it is better to use the second ratio. In this case it is = $(0.067 - 0.004) : 0.004 = 0.063 : 0.004 = 15.75$

The exponential endpoints for 95% confidence intervals for Relative Risk are:

$\log \{a.(c + d) : c.(a + b)\} + 1.96. 1/a - 1/(a + c) + 1/b - 1/(b + d) = \log 16 + 1.96. 1/16 - 1/17 + 1/234 - 1/483 = \log 16 + 1.96.(0.073) = 1.34.$

The confidence interval is presenting the probability that HR around 72.6 is a significant risk for developing malignancy.

These results suggest that the long-term lasting sympathetically oriented drift in autonomic balance (pointing overstress) is a risk factor for developing cancer. According to our experience such a state, which we named *Dysadaptemia* is a rather common phenomenon.

b) Second part

The second part of the study was carried out in Bulgarian Oncological Center. The HR values of investigated patients were compared with age-related bioconstant values of a control group, being representative for country population. The mean group value of HR for patients was 74.2 ± 37 (%), whereas the bioconstant value is 44 ± 26 (%). This difference was found to be statistically highly significant ($p < 0.001$, Student "t"-test), which indicates more chronic sympathetic tone in cancer patients as compared with healthy population. It is difficult to draw a clear cut decision whether the patients were in this state before to become ill, or not. The multiple step-regression analysis as well as the discriminative analysis reveal that HR have higher predictive force towards malignancy as compared with depression, lack of social support, age and neurosis, which scores were elected by specialized questionnaires. The bigger part of the patients had sleep disturbances.

DISCUSSION

The presented here scientific evidence about the positive relationship between chronic distress (accumulated stress) and malignancy is possible to be explained by the proposed "**Stress-based malignancy model**". According to this model, the development of malignancy is passing over the following steps:

1. Accumulated (chronic) stress (which we are quantitatively assessing by *DANEVTEST* and presenting as **health risk**) is decreasing the effectiveness of the negative feed-backs of the biological system. As a result the system becomes more and more ergotropic than trophotropic oriented, even in the night time when sleeping, what is not biologically necessary. This reaction can be regarded as a kind of hypersensibilisation.

2. All that is unfavorably influencing the exchange of biological information between separate cells, the whole organism and surrounding nature. The quality of the controlled cells regeneration is reduced. The cells overgrowth becomes a fact. That can be regarded as an atavistic reaction aimed to assure cells surviving in changed bioinformational conditions (fig. 7).

As can be seen, the model supposes (not obligatory) the existence of the phenomenon "exchange of biological information" which is thought to be optimal in deep rest (in "A" i.e. in deep sleep, what is explaining the biological role of sleeping). Group HR-high had a

higher rate of sleep disturbances, according to the questionnaires for psychosomatic complaints. Accumulated stress is deteriorating this optimality.

The proposed recently "Bioinformational exchange theory" (9) is postulating that DNA of the chromosomes is containing only a part of the cells genom. 95-97% of the genes are "silent" or "egoistic". It is speculated that they are connected in some way with the field-based part of the genom. It is thought that chromosomes contain information regulating the topological organization of the body (cells), but this information is not sufficient to learn the biological structure how to be alive. Field-based genom, which is a space - organized holographic matrix is transmitting the life important biological information from the external bioinformational bank to the DNA based genom (12).

Although there is not clear cut scientific evidence about the existence of the field-based part of the genom, that proposition is very probable, because the chromosomes are transferring only linear-chapped information, whereas the field-based part (holographic matrix) is possessing a higher possibilities to contain biological information. Without it the living process is difficult to be explained. The external bioimformational bank is probably objectively and permanently existing in the nature (10,11).

CONCLUSION

This study brings evidence that chronically increased sympathetic tone (distress) can facilitate cancer development. This finding is similar to the discovered by us positive relationship between chronic sympathetic tone and other life threatening diseases (16). All that gives right to conclude, that the optimal equilibrium of the autonomic balance can play an extremely important role, so why it should be quantitatively controlled when providing cancer management. It seems that most of the complementary medical approaches for cancer treatment are based on parasympathetic facilitation. *DANEVTEST* revealed that chemotherapy, operations or radiotherapy are additionally increasing the sympathetic activity, which can contribute to the insufficient efficacy they are demonstrating. The management of malignancy is seeking for new methods decreasing cancer recurrence, relapses and assuring a metastasis-free survival (13,14). Those methods should provide (according to the proposed model) as stronger as it is possible periods of deep relaxation (vago-tonia), because it is facilitating the work of the sc. "intern health promoting mechanism". So why the global antimalignancy management(or strategy) should be directed not only towards "killing cells", but also towards improvement of their informational government. Cells are not "ill" from biological point of view, but the whole organism. Unfortunately, the humans are learning more on how to work and less on how to assure themselves a really complete rest.

Fig.7 Graphical presentation of Stress-based malignancy model.

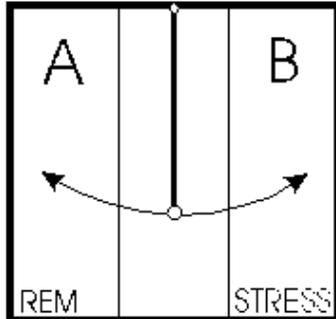
(The quality "health" needs a regular oscillation of biological activity between A and B.As higher is the sympathetic prevalence in the day time (B), as higher is the parasympathetic prevalence in the night time (A)).

A stands for: Night (rest); Increased parasympathetic (vagal) tone; Information exchanging (receiving); Deep relaxation in sleep; Paradox sleep - REM; Trophotropic orientation of the system (open system).

B stands for: Day (action); Increased sympathetic tone; Information processing (loosing); High activation in wakefulness; Ergotropic orientation of the system (closed system).

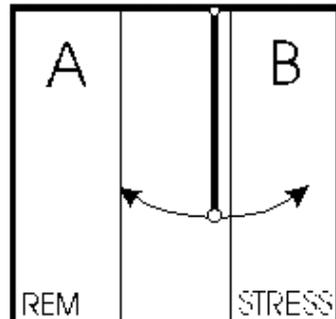
There are mainly three types of oscillations:

Autonomic balance



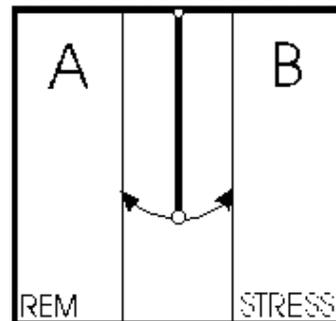
1. Normal. It was observed in yang, absolutely healthy persons and in sportsmen (not overtrained). There exists an optimal “exchange” (receiving) of information in the night time (parasympathetical (vagal) autonomic prevalence-REM) and it’s “processing” in the day time (sympathetic autonomic prevalence). System does not need intervention.

Autonomic balance



2. Highly pathogenic. It was observed in persons with overstress and in ill persons, including cancer patients. The biological activity is more “B” oriented. The possibility to “exchange” life important biological information in rest is restricted. System needs more “A” activity.

Autonomic balance



3. Pathogenic. It was observed in aged persons as well as in persons from younger age groups, not willing to spent “effort”. The biological activity is less in “A”, due to decreased “B” activity. The possibility to “exchange” life important biological information in rest is decreased. System needs more “B” activity.

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