

REDUCED VAGAL CARDIAC CONTROL VARIANCE IN EXHAUSTED AND HIGH STRAIN JOB SUBJECTS

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Abstract

Objectives: This paper has two primary objectives. First, the paper proposes methodological strategies for analyzing multiscale vagal cardiac control based on the Stress Disequilibrium Theory (SDT) using high frequency power of heart rate variability (HFP) and short term variance of HFP. Second, the paper provides evidence of reduced vagal cardiac control range and variability in high strain job and exhausted subjects. **Materials and Methods:** Job Strain was measured using the Job Content Questionnaire, 8/day diary reports, and a nationally standardized occupational code linkage in 36 healthy mid-aged males with varying strain jobs. Subjects were Holter-monitored for 48 hours, including a work and rest day. Subjects responded to questions on a daily diary as well as on the Job Content Questionnaire to test for exhaustion as a dichotomous state variable. Vagal cardiac control was measured by components of electrocardiograph: heart rate variability based measures of high frequency power (HFP). We assessed range of vagal cardiac control using extreme value analysis (data in upper tail); and short term vagal variability using Poincaré plots of HFP. Comparisons were made between high (N = 10) and low job strain (N = 22) jobs. Furthermore, subjects categorized as exhausted (N = 4) were separately analyzed. **Results:** Exhausted subjects displayed a reduced range of vagal cardiac control on the workday; and both high strain and exhausted subjects displayed reduced short-term variance in vagal cardiac control. A repeated measures ANOVA controlling for age confirms reductions in variance of cardiac vagal activity in high job strain subjects (0.01), with further reductions in subjects reporting exhaustion ($p = 0.001$). **Conclusion:** This analysis supports the hypothesis that (a) job strain is associated with reductions in cardiac vagal — or system level — variance; and (b) that reduced system variability may be a characteristic of exhaustion.

Key words:

Job strain, Exhaustion, Heart rate variability, Cardiac regulation, Vagal cardiac control

INTRODUCTION

This paper presents a method to test Karasek's Stress Disequilibrium Theory using data obtained through ambulatory electrocardiograph monitoring. The Stress Disequilibrium Theory links job strain with physiological system deregulation with systems-theoretic principles, implicating, amongst other hypotheses, limitations in a subject's job control as a cause of his/her restricted internal possibilities for physiological control and physiological deregulation [1].

We hypothesize that deregulation of physiological control increases the risk of exhaustion and disease from stress exposure. The demand control model (or demand/control/support model) is perhaps the most commonly utilized hypothesis associating psychosocial stress at work with cardiovascular outcomes [2]. The demand control model classifies jobs based on psychological demands (such as work deadline pressure) and decision latitude (control over the work situation), and identifies a risk-exposed group consistent with SDT. The primary hypothesis involves high psychological demands coupled with low decision latitude

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(defined as “job strain”), proposed to increase the risk of cardiovascular disease [3], a finding confirmed by a large number of CVD epidemiological studies [3–5]. The specific physiological pathway of disease development from this social environmental risk, however, is not well documented. A benefit of ambulatory electrocardiograph monitoring is the ease of obtaining indicators of vagal cardiac control over extended periods to assess a pathway based on autonomic deregulation. In this paper we have measured vagal cardiac control using components of the electrocardiograph: the heart rate variability measures of high frequency power (HFP) [6]. This paper takes an additional step, based on the Stress Disequilibrium Theory (SDT), by incorporating a two-step multi-scale (or multi level) analysis of vagal cardiac regulation, each analysis representing a different level of emergent physiological complexity. At one level there is information about the electrophysiological potentials that results in the ECG tracing, from the ECG tracing there is physiological significance in the interpretation of the heart rate (such as information about the vagal cardiac control), finally there is information in the interpretation in the dynamic cycles of the vagal cardiac control. The first two levels of inquiry are well-accepted approaches in job stress research [6]. At the first scale electrocardiograph data is obtained, the second scale involves determination of the HFP as an estimate of vagal cardiac control. The third scale involves the additional step of two analyses of the vagal cardiac control (as measured by HFP). A Poincaré plot analysis of vagal cardiac regulation was used to assess the short-term (epoch to epoch) variability of vagal control; and an extreme values analysis was used to assess the amount of vagal cardiac control in the high range of possible values. The paper provides a theoretical introduction to these methods, and then applies them in an analysis of existing data of subjects with high and low job strain, and an additionally stratified sample of exhausted subjects.

The HRV measures that form the majority of the dependent variables in published studies are based on the RR interval time series [6,7], using time and frequency domain analyses (HR, SDANN, HFP, Low/High Ratio, etc.). The RR interval time series represents the most

fundamental level of complexity when analyzing cardiac temporal regulation and this analysis of variation yields information related to the autonomic nervous system. The RR series analyzed within each time period epoch (i.e. 5 minutes, 2 minutes, etc.) provides data about the state of the subject’s physiological system. The statistical analyses performed on aggregated data across epochs (usually as a mean of the above variables) attempt to make use of this information to investigate the differences regarding physiological system status between groups, during work, rest, sleep, and when subjected to demands (position, exertion, strain) [8,9]. However, to restrict these analyses to the mean values across time periods, the applied procedure ignores the next level of within-subject variation that occurs in the subjects physiological state. While the analysis of RR interval variation yields information that represents the physiological state (vagal cardiac regulation), the variation in physiological states of an individual may provide additional valuable information regarding a subject’s adaptive or control capacity to situational environmental demands [10,11].

We expect that general assessment of response variability — within the context of understandable environmental exposure demands — can be an important technique to assess physiological exhaustion. Lack of ability to respond effectively to environmental demands is a definition of system exhaustion. However, complete monitoring of all environmental demands — including all external demands and many internally interpreted demands — is beyond practical feasibility, and so we cannot structure perfect experimental tests of the exposure/response linkage. However, this paper does indeed control for the largest environmental variations in demands using sociological periods (work, rest, sleep, intermediate periods, etc), and does test for variability in response between such periods. (Furthermore, in analyses not reported in this paper, we match detailed diary assessment of environmental demands eight times a day with time-proximate HRV epochs, for even more detailed testing). Nevertheless, given these important and measurable exceptions, many environmental demands would, in general, appear as unpredictable, random challenges — to be met

with healthy response of adaptive physiological change (such as increase of HR), followed by efficient return to baseline. These challenges should manifest themselves then in provoked, random variability of the physiological response — in this case HFP assessing vagal control of the heart. This form of variability is then also assessed in this paper using two methods common in systems dynamics research: investigation of extreme values of response distribution, and Poincaré analysis of interval-to-interval signal variability over time. This attempt to interpret variability “directly” in terms of physiological response effectiveness — via SDT below — also differs significantly from some current research approaches: the new field of “chaos theory”-related physiological variability assessment. This rapidly expanding field does indeed provide us with new metrics for variability phenomena (and has affected our analyses) [12]. However, this research area almost never relates the physiological response variability to the subject’s requirements for environmental response (i.e. environmental stressors and activity period differences are not jointly investigated with the physiological variability). Thus, this approach does not really test for specific physiological explanations of exhaustion of individual response capability, but attempts only to find new identifiers for individuals at risk relating to non-linear systemic behavior arising in unspecified manners.

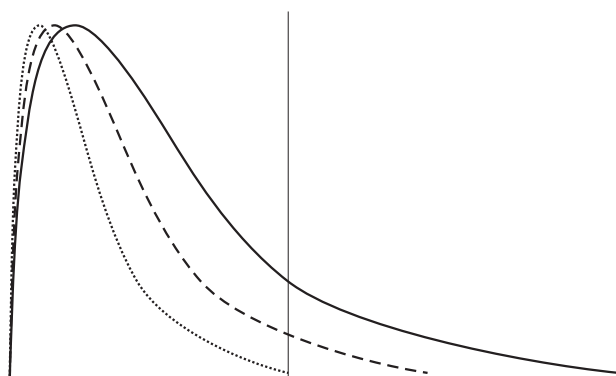
Control capacity, as elucidated in the SDT, refers to the high level of organization throughout the central nervous system required to maintain effective integrated physiological coordination in the context of facing environmental demands. Control capacity is hypothesized to emerge from lower level outputs, which are configured — at the next higher level — into a constraint structure. This constraint structure then can restrict the plentiful, but disorganized energy that is available at this higher level, forming it into a limited set of very organized and precise responses — which now also are of higher energy and able to affect a wider range of systems and scales, spatial and temporal. Thus, the limitation in response created by these constraint structures at each lower level, allows the organism precise control of its actions at the next higher level of organization. And this happens at successively higher and

higher organizational levels, building control capacity up to the highest levels of CNS organization.

Control capacity implies the organism will have several control options at each level — to provide a robust platform or state space for physiological response [1,13]. However, this small number of precise control possibilities at each level represent a very dramatic reduction from the astronomically high number of true alternatives for all the components which are to be coordinated at each level, and thus represents a dramatic reduction in entropy of the response compared to the entropy of the input disorganized energy at each level. Thus, creating control capacity is “costly” and is strictly limited by the Second Law of Thermodynamics. Control capacity is then constantly “used up” in daily life activity, as the organism precisely specifies the states of its subsystems when taking its adaptive actions in the environment (further reducing entropy). Actual development of control capacity, and using it up, typically occurs in cycles (like a steam engine cycles): many cycles are required to achieve major action in the environment. This cyclical nature of “adaptive action/restoration of control capacity” could occur at many time cycles — each characteristic of a particular subsystem, among many such systems in the organism — resulting in the response pattern of complex variability in healthy systems.

Vagal (parasympathetic) control in general, and vagal cardiac control in particular, are identified in much CVD epidemiology and CVD physiology as critical elements on the etiologic pathways between social/environmental exposures and cardiovascular disease [14]. The SDT would hypothesize that it is not just the overall “level” of vagal activity that is important — but the system’s ability to precisely control and coordinate vagal cardiac control. Coordination of vagal cardiac control requires an appropriate range and variability of vagal response capacities as a necessary condition for coordination.

Two methods are used to assess variability of vagal response in this study. The range of vagal response capacity is assessed in this paper using the extreme values of HFP achieved during ambulatory monitoring. Vagal cardiac control (measured by HFP) is routinely demonstrated to possess a log normal distribution. The right skewed



This figure depicts three theoretical distributions, all with a right skew, but with different amounts of data in the right tail. During the extreme value analysis we identified a cut point (vertical line) at a particular value of the high frequency power of HRV and determined the percentage of data falling in the upper tail.

Fig. 1. Extreme value analysis: reduced data in upper tail.

distribution is common in systems bound at one end — zero binds vagal activity; you cannot have less than zero vagal control. A decrease in overall vagal cardiac control can decrease the standard deviation by bringing the mean closer to the bound value of zero. This is not the sort of range reduction we would propose to be associated with reduced control capacity. We would hypothesize that reductions in extreme values demonstrated by less data in the skewed tail demonstrate limitations in the range of the vagal control capacity (Figure 1). For the second method, short-term variability of vagal cardiac control is assessed using a Poincaré plot of HFP with a residual analysis of simple linear regression based on the Poincaré plot.

We hypothesized that subjects with low job strain (low demands, high control) would have greater short-term vagal cardiac control variability and range than subjects with high job strain. High job strain subjects will have greater short-term vagal cardiac control variability and range than subjects reporting symptoms of significant exhaustion.

MATERIALS AND METHODS

Data Collection

Details of the subject population, recruitment and methods is presented elsewhere [8]. In summary, a sample of healthy employed men (N = 26) between 35–59 years of

Table 1. Sociological periods

Day	Recording	Diary social activity and time of recording
Work	1	Morning at Work
	2	Lunch
	3	Afternoon at Work
	4	After Work before Dinner
	5	Dinner until Sleep
	6	Sleep
Rest	7	Awake on Rest Day
	8	Time that corresponds to Morning at Work
	9	Time that corresponds to Lunch at Work
	10	Time that corresponds to Afternoon at Work
	11	After 10 until Dinner
	12	Dinner until Sleep
	13	Sleep
	14	Awake on Second Rest Day — remove monitor

age, members of a community based health maintenance organization, were recruited from an ongoing investigation of seasonal variance in cholesterol (Seasons) [15]. An additional sample (N = 10) of healthy employed men (35–59 years of age) was recruited from the University of Massachusetts Worcester Medical Center’s stress reduction clinic. The monitoring protocol utilized Holter monitors (Marquette 8500) worn in the workplace and at home to collect 48 hours of continuous ECG recordings beginning in the morning of (prior to) a workday.

Table 2. Analysis Time Periods that the data is aggregated into for the Poincaré plots

Day	Poincaré Plot	Time Period of Recording
Work	1	Work Day
	2	Work Day Evening
	3	Work Day Sleep
Rest	4	Rest Day
	5	Rest Day Evening
	6	Rest Day Sleep

Subjects were required to note the time indicating changes in the social situation, such as start work, start lunch, return to work, end work, eat dinner, etc during the monitoring period on a diary. These times were utilized to construct Sociological Periods and Poincaré plot analysis time periods (Table 1 and 2). Subjects removed the Holter monitor in the morning 48 hours after having had the monitor applied and were provided with a pre-paid envelope to mail the Holter monitor and the diary to the study team.

Sociological Periods

During the monitoring period subjects were asked to complete a diary to allow linkage of ECG data to daily events. Sociological periods (Table 2) of the day allow control for potential diurnal rhythm variations (circadian rhythm) that may be related to cardiovascular function. They allow for a more precise understanding of the social determinants of daily activity effects based on the subject's actual daily life schedule, which may be the most salient component. Thus, periods will reflect wake/sleep boundaries, meal breaks (evening after dinner, lunch), and social activity boundaries (morning at work), etc.

Job Strain

Assessment of job strain was conducted using three tools, the Job Content Questionnaire, Diary questions on the Workday, and imputed demand and control data from each subjects' three digit occupational code and is described in a previous publication's appendix [8]. High strain jobs were classified using tertiles from the U.S. national sample with subjects in the three tertiles associated with the lowest weighted decision latitude and highest weighted psychological demands categorized as high strain. This method of classification yielded 13 high strain subjects, 23 low strain subjects.

Exhaustion

To categorize subjects as exhausted, two questions from the Job Content Questionnaire were utilized ("At the end of the day, I am completely exhausted mentally and physically" and "I am unusually tired in the

morning"). Responses were scored as, 1 = hardly ever, never; 2 = sometimes; 3 = most of the time. To consider the most extreme cases of exhaustion, only subjects responding "most of the time" to both questions were categorized as being exhausted ($N = 4$). Of the four subjects categorized, three are also high strain. The exhausted subjects (mean age (SD) = 39(3)) are significantly younger than the non-exhausted subjects (48 (5)).

Data Processing

Holter data tapes were analyzed for ventricular arrhythmias and RR-interval variability at the Research Holter Laboratory at Columbia University by published methods [16]. In summary, the dependent variables of this study were computed from 5-minute epochs throughout the 48-hour period. The 48-hour records were digitized using a Marquette 8000 scanner, submitted to Marquette algorithms for QRS identification and editing, and then downloaded to a Sun workstation for further editing using algorithms developed at Columbia University. The power spectrum was computed as previously described [17]. A fast Fourier algorithm was utilized to compute the power spectrum in the high frequency (HF = 0.15–0.40 Hz) spectra.

High Frequency Power

Frequency domain analysis (spectral analysis) of HRV decomposes the time series into sinusoidal components. Power (variance) is plotted as a function of frequency and the analysis computes power in defined frequency regions. The spectral analysis reveals the frequency of variations in the time series, and also the amount of power (variance) within certain frequency ranges. The high frequency power (HFP) spectrum (0.15–0.4 Hz) is highly related to vagal cardiac control [17].

Vagal Control Range & Variance

Two methods were utilized to analyze the variation and range in vagal cardiac activity in an attempt to identify differences in control capacity. The extreme value analysis calculated the percentage of data in the upper tail (> 1 SD) of the high frequency power distribution for

each subject within each sociological period as an assessment of range. For each subject the mean and standard deviation of HFP was computed for the entire monitoring period. Then for each subject within each sociological period, the percentage of data in the upper tail (> 1 SD) of the sociological period distribution was calculated. This extreme value analysis allows us to consider whether the reduction of variation of the vagal system is due to approaching the lower boundary by specifically testing the amount of data falling into the upper tail of the distribution.

The second method utilized Poincaré plots for each subject to calculate the short-term variations in vagal cardiac control (HFP) during each of four approximately spaced periods. Poincaré (or recurrence) plots provide a two-dimensional analysis of one variable as a function of itself from some lagged earlier value [18]. They allow quantification of short-term variability in the time series. The residuals vary perpendicular to the linear fit and reflect short-term variations. If all period-to-period differences are zero, then all points fall on the linear fit, and if not: higher and lower subsequent values can occur in large steps, many small regular steps, small irregular steps, etc., as revealed by the data points falling off of the linear fit. The residuals display a Gaussian distribution with a mean of zero. The horizontal and vertical axes of the plot are scaled from 0–9 representing the natural log of high frequency power. The R^2 from the linear regression is provided.

The first step to creating the Poincaré plots for this analysis involved creating a lagged time series of HFP data for each subject. To test epoch-to-epoch variations we lagged the data by one 5-minute epoch. Then a linear regression was performed between the lagged and the original time series for each subject in each time period. The residuals from this linear regression represent the variation of the lagged data point and the data point to follow (from the original time series) and provided a measure of the short-term or epoch-to-epoch variations. Poincaré plots were created for each subject for each of six time periods during the 48 hour monitoring which represent relative homogeneity with respect to environmental demands

(Table 2) allowing roughly 100 data points in each time series. The residuals were saved for each epoch of each subject within each period. The standard deviations of the epochs for each subject were calculated during each period that a plot was constructed.

Ethics

Subjects agreeing to participate in the study provided informed consent prior to being asked to complete questionnaires or being connected to the Holter monitor that was approved by the Fallon Community Health Plan and the University of Massachusetts Medical Center Institutional Review Board for Human Subjects. The procedures followed were in accordance with the ethical standards of the Fallon Community Health Plan and the University of Massachusetts Medical Center Institutional Review Board for Human Subjects and with the Helsinki Declaration of 1975, as revised in 1983.

Statistical Analysis

Graphical analysis was performed on all data. A repeated measures ANOVA controlling for age was performed to test for significant differences between short term vagal variance as assessed by Poincaré plot analysis in the low strain, high strain and exhausted groups. All analyses were performed with SPSS 11.1.

RESULTS

Extreme Value Analysis:

Percentage of Data in Upper Tail

Figure 2 displays the percentage of data greater than one standard deviation during each sociological period. The high and low strain subjects have similar percentages of data in the upper tail; however, the exhausted group has no data in the upper tail of their distribution during the workday until sleep. Their vagal cardiac control displays less range in the upper tail of their own distribution on the workday. Physiologically this finding may indicate that they demonstrate less control capacity (assessed as variation) during the workday, and in the hours following the workday. They do not display an increase in variation in

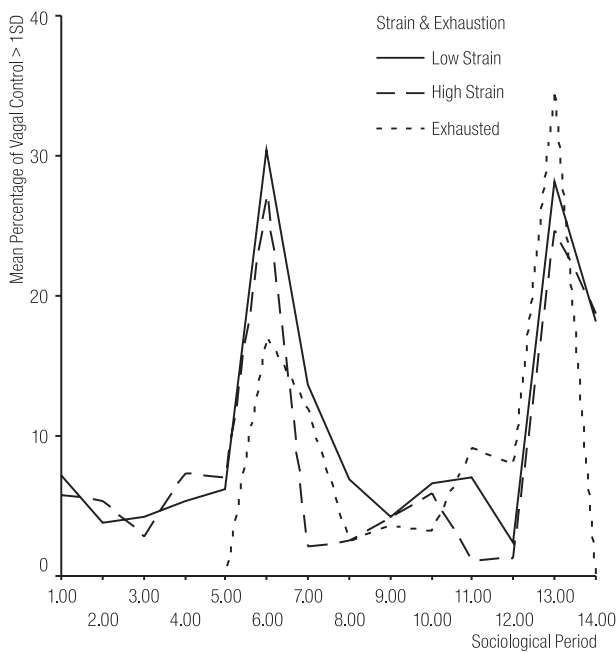


Fig. 2. Extreme value analysis: percentage of vagal control in the upper tail (> 1 SD).

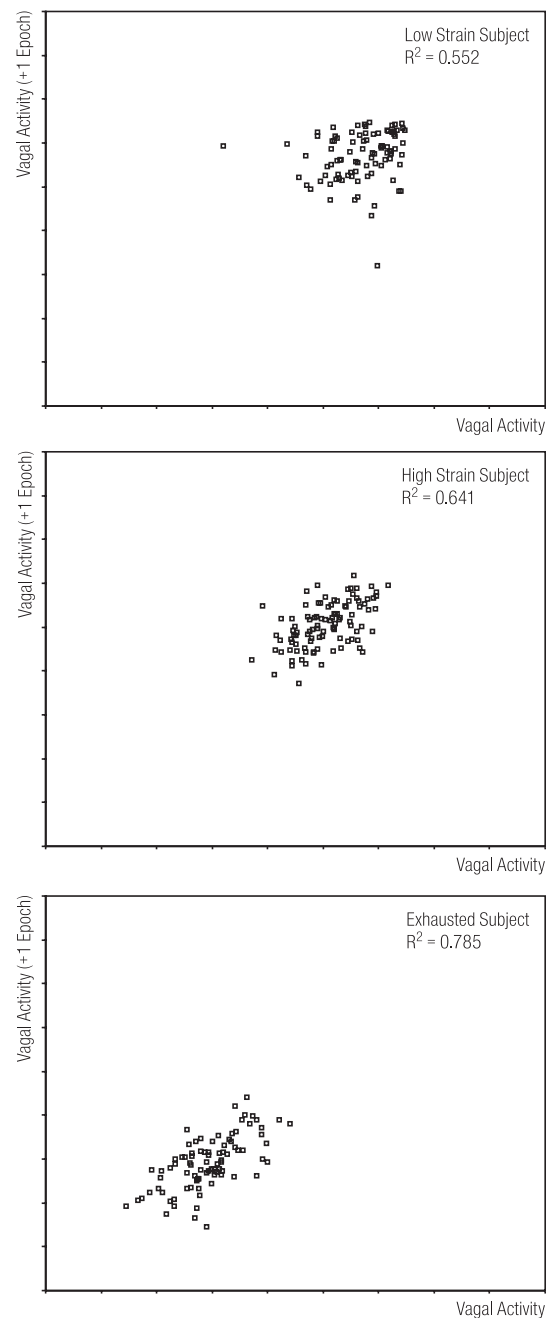
the upper tail until sleep. Even with sleep, it takes an additional 24 hours of rest before values reach levels that are comparable to the non-exhausted subjects during sleep of the rest day.

Poincaré Plot Analysis

Poincaré plots of vagal cardiac control as a function of its previous value from the time series allowed determination of the residual variance. Plots typical for subjects in each category for a low strain, high strain and exhausted subject are presented on the same scale in Figure 3 (x & y axes are Log Transformed HFP from 0–9). It is evident in comparing these three subjects that there are reductions in the mean high frequency power, in addition to reductions in short-term variation — going from low to high strain and then to exhaustion — with a tighter fit in the exhausted subject.

To compare groups of subjects quantitatively, residuals were saved and the standard deviation of the residuals was determined for each subject in each of six time periods during the 48-hour monitoring.

Figure 4 demonstrates the predicted reductions in short-term variation in the high strain group, and more significantly in the exhausted group. Very strong decreases in



Note: the x and y axes of all plots are from 0 to 9 Log transformed HFP.

Fig. 3. Sample Poincaré plot for work day.

short term variations of vagal activity in the exhausted subjects are found during the workday, with slight increases for this group on the rest day. There is a slight reduction in the high strain group on the workday, with greater decreases in this group on the rest day.

Table 3 provides the repeated measures ANOVA results, controlling for age, which confirms reductions in variance

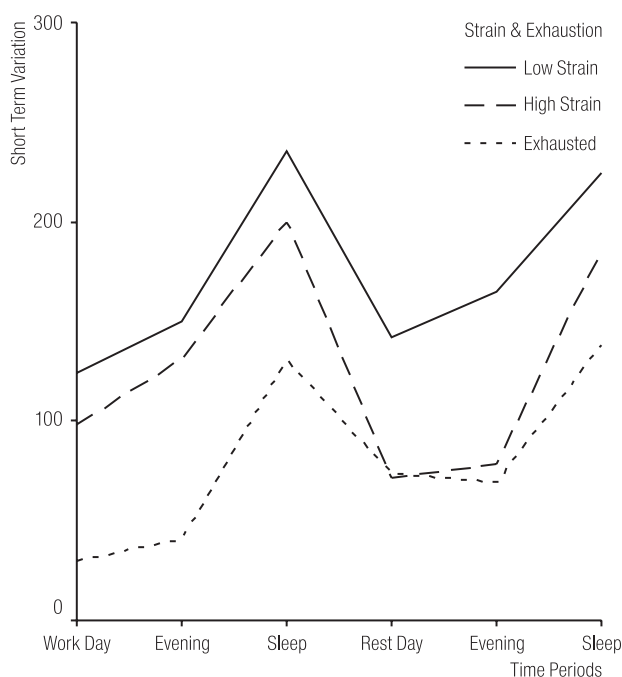


Fig. 4. Short term variance of vagal cardiac control.

of cardiac vagal activity in high job strain subjects (0.01), with further reductions in subjects reporting exhaustion ($p = 0.001$).

Table 3. Repeated Measures ANOVA including coefficients

Parameter	Estimate	SE	Significant
Low Strain	103.82	36.23	–
High Strain	61.65	32.89	0.010
Exhausted	48.77	37.61	0.001

SE — Standard error.

DISCUSSION

The goal of the paper is to demonstrate the utility of an analytic approach to the study of physiological regulation based on response variation analysis, and to suggest how the results may be interpreted within the framework of the Stress Disequilibrium Theory (SDT). This is tested by observation of reductions in HRV-related cardiac vagal control range and variance in subjects with high strain jobs and in exhausted subjects. Significant findings are indeed found in the predicted direction both for high strain jobs, and for subject exhaustion.

High strain subjects demonstrate potentially compromised cardiac control response compared to the low strain subjects: they have significantly lower levels of vagal activity which may imply a deregulation in the direction of exhaustion, although they do not show as severe a degree of this deregulation as the exhausted subjects. Collins et al. [8], using the same data set, shows this deficit for low control job holders persists after this “work” stress exposure: starting from the work day throughout the 48 monitoring period including sleep on that rest day following work. This paper shows, in addition, that high strain subjects also had a reduction in the short-term variability of their vagal cardiac control. Furthermore, subjects with symptoms of exhaustion have even further, significant, reductions in short-term vagal cardiac control, and in fact display zero vagal cardiac control in the extreme high values (upper tail beyond one standard deviation) while at work. We propose that this lack of vagal response variability (supplementing reduced levels of vagal response) represent measurable signs of deregulation of vagal cardiac control related to exhausted control capacity. It could be a useful biomarker of chronic disease risk.

The proposed methods and results are consistent with hypotheses of the Stress Disequilibrium Theory and its predictions relating to reduction of cardiac control capacity in low control, high demand jobs. The demand/control model and its physiological regulatory explanation in terms of the Stress Disequilibrium Theory [1,2], is based on the concept that stress is most relevant when viewed using systems principles. As such, stress is viewed as a systemic problem where disruptions in one part of the system can affect other parts of the system. This paper has utilized two analytic strategies to assess response variability. The trend of increasing dysfunction in the predicted direction of reduced variability, with the exhausted subjects presenting with what might represent some form of system deregulation and work related reductions in adaptive capacity, and the high strain subjects representing some intermediate point between “normal” and exhausted is an interesting set of findings.

Since these are theoretically explainable findings and consistent with current analytic techniques used in systems

analysis, we anticipate they should be reproducible in further research. But we expect that we are observing still pre-clinical physiological states, given our certified heart-healthy base population. Thus, these are bio-monitoring strategies potentially relevant for early risk monitoring and disease prevention.

While this approach indeed provides a clear, statistically significant support for the analytic strategy of using ambulatory HRV–HFP data for job strain based on the Stress Disequilibrium Theory (SDT), caution must be observed in interpretation the findings. The subject pool was limited in size and demographic range and the cross-sectional design limits causal interpretation of adaptive changes.

Demitrack et al have demonstrated impairments in cortisol function similar to the changes we have identified in chronic fatigue patients (CFS). CFS patients had reduced overall cortisol secretion and reduced variation in cortisol values over a 24-hour period. The authors attributed this to an inability of the hypothalamic-pituitary-adrenal axis to respond to environmental challenges due to being exhausted [19].

The methods described have been tested on data obtained from ambulatory electrocardiograph recordings. While several previous job stress studies have employed ambulatory ECG monitoring they have tended to utilize traditional analytic approaches [6]. As Karasek points out, the rationality of stress theories pose a problem to science with a different form of cause and effect, one that includes complex multiple interacting subsystems [2]. “Stress is a systemic concept referring to disequilibrium of the system as a whole, in particular a system’s control capabilities” [2]. Analyzing the physiological effect, therefore, must extend beyond simple approaches of determining whether homeostasis has been altered.

Static measures may not be the first indication of increased risk. Rather, altered range and/or variance of control systems may represent a change from normal that is the beginning of alteration — these may represent the pathological mechanisms between strain (high demand, low control) and disease.

Significant theory has been developed and backed by empirical evidence pointing to a role for exhaustion in the

development of stress related disease. Existing stress theories usually include some linkage between stress and exhaustion states. The General Adaptation Syndrome has the potential to culminate in limitations of the organism leading to adaptation breakdown referred to by Selye as exhaustion [20]. Additional concepts that overlap include burn-out, vital exhaustion and chronic fatigue syndrome [10,21,22]. Vital exhaustion represents the second of a two-phase process leading to disease. The first phase includes exposure to long lasting stressful conditions and overexertion leading to a breakdown in adaptation to stressors ultimately leading to vital exhaustion. At this point systemic changes are thought to be part of the disease process [23]. However, the term exhaustion remains vaguely defined as a break down in the system leading to a loss of adaptive capacity. Despite the need to consider complex systems dynamics in the determination of what exhaustion might represent, most attempts have focused on determination of the existence of homeostasis [24]. This may be the result of restrictions imposed by previous research reflecting the difficulty collecting real time physiological data using blood, urine or even saliva samples of hormone-based systems. Ambulatory ECG monitoring provides a clear benefit in allowing much easier collection of continuous real time data. Despite this benefit, job stress studies utilizing ambulatory ECG monitoring have nevertheless adhered to traditional statistical analysis methods [6,7].

This paper has attempted to remedy two problems we see with the above approach. First, according to Karasek’s Stress Disequilibrium Theory [1] we are considering the step that precedes exhaustion as more than an onslaught of excessive demands with consequential breakdown and loss of adaptive capacity. We consider the step preceding exhaustion as long-term adaptations of an individual to an environment that has reduced the subjects control capacity. Environments with a lot of control are enriched, and as such promote highly adaptive individual behavior, while environments that limit personal control and flexibility are restricted, in many ways impoverished, leading to limited adaptive capacity. (Internal restrictions in restoration cycles, from many sources, could also contribute to loss of

control capacity). In the concept of biological adaptability, reduced adaptive capacity is associated with reductions in variation [25]. Reductions in variation can exist on multiple scales, such as reductions in HRV at one level, and reductions in variations of vagal cardiac activity at the next level. The reductions in variation may either precede or be the result of altered coordination patterns. It is biologically plausible that a robust range and variation of physiological capacity of interacting regulatory sub-systems is a necessary (but not sufficient) condition of coordinated control. In addition, it is plausible that a reduction in range/variation is a consequence of reduced environmental control. A simplified version of this hypothesis is that with reduced environmental control physiological systems are never utilized in particular ranges which leads to loss of range, loss of variance, and subsequent loss of control capacity/coordination. These are high-level phenomenon that occurs prior to alterations in homeostasis and structural damage. Identifying a connection between such high-level pre-clinical states would offer a major step forward in job strain research for identifying causal associations.

The second problem we have attempted to remedy is the limited use of ambulatory ECG data in studies investigating job stress. This paper acknowledges value in the traditional (aggregation of the mean HRV and/or HFP) approaches. However, there is a loss of information when the multi-level data available from a source as rich as that obtained by ambulatory ECG is not explored. It is important to point out that interpretation of the physiological meaning of such variability data requires information about the social & environmental situation during the monitoring period.

In a possible extension of Karasek's Stress Disequilibrium Theory, the reduction of control capacity may be viewed as adaptive neural networks evolving as part of phenotype plasticity. The terminology "phenotype" can be utilized to allow a linkage to biological adaptability theory. Phenotype refers to the biological and physiological internally interacting sub-systems that emerge to create an organism's traits. The phenotype represents the complex combinations of physicochemical integration within the system and a phenotype possesses a range of capabilities for

response to the environment. The ability of the phenotype to adapt to its environment can be referred to as its adaptive capacity.

We hypothesize that an environment that restricts control, leads to the development of a phenotype that is fixed, rigid, and not adaptable. During the life of an individual, variation in phenotype is a function of the environment in which the individual exists. Impoverished, restricted, non-variable environments lead to phenotypes that are less adaptive, and to an organism that is less capable to change in its phenotype. Some phenotypes may evolve to present a lack of response from the vagal system, and an inability to switch to relaxation modes after work, or during a rest day, eventually leading to fatigue or exhaustion due to these inabilities to provide optimal physiological coordination for each and every environmental situation. The neural networks forming the basic control mechanisms of the stress response with coordinated patterns integrating visceral function and behavior may have evolved to become separated structurally and/or functionally from networks capable of allowing relaxation, ultimately leading to the finding of an inability to return to a relaxation state as evidenced by the perpetual reductions in short term vagal variation until the second night of sleep in the exhausted subjects.

It is important to note that we cannot demonstrate causality of the environmental adaptation processes we have hypothesized — because of our cross-sectional study design. On the other hand, it can be noted that the ECG measurements of response are potentially causally related to the environmental situations as discussed, since most of the job measures assess long-term aspects of the environmental setting that necessarily precede the monitoring sequences (with exposures that are often rather constant over work career periods of years), and we also observe plausible time-variations relating to exhausted response after the job assessments are recorded. Furthermore, we cannot exclude the possibility that the exhausted subjects and high strain subjects may have always been different from the low strain group in terms of physiological responses we demonstrate. However, there is no literature we know of that describes how individuals systematically

select into their environments on the bases of the sub-clinical response variations we observe. Instead, it is more likely that subjects feeling exhaustion would select away of demanding work situations.

It is important to remind the reader that this investigation did not recruit “exhausted” subjects. The study utilized a population-based sample to identify low and high strain subject pools from which to sample for a pilot study on job strain and heart rate variability. Once collected, a small sub-sample of subjects ($N = 4$) was self identified via questionnaire as having exhaustion symptoms. We recognize that our findings and significance test parameters may vary substantially from those that would be identified from a sample recruited specifically for detection of exhaustion/non-exhaustion differentials (exhaustion prevalence in this sample is not markedly different from what would be expected in random full population samples).

In previous investigations, the independent variables shown to influence high frequency power between subjects have been age, sex, and physical fitness [26]. Study selection criteria assured that study subjects were male, between the ages of 35 and 59, generally healthy and not using medications known to affect HRV. Although level of obesity, cholesterol profiles, and smoking status information was not collected for subjects, the literature does not suggest a relationship between these factors and atypical HRV [26]. There is no evidence in the literature to suggest a relationship between decision latitude and physical fitness. It may be hypothesized that greater decision latitude is conducive to a lifestyle with greater potential for the pursuit of personal fitness. If so, this suggests that high decision latitude individuals might self-select toward better physical fitness. Validation of this possible association should be considered in future investigations.

It is also possible that other work environment exposures influence heart rate variability measures through their influence on autonomic nervous system function. Two possibilities include noise and air particulate exposure [6]. Future studies should control for the effects of these additional environmental exposures. The possibility that autonomic nervous system alterations occur due to a multitude of environmental demands adds to the importance

for methodologies for the assessment of ECG data in an attempt to determine system-based adaptations that lead to disease. Additionally, with an implication of reduced adaptive capacity due to reduced environmental control there could be an exacerbation of the physiological response to these physical and/or chemical exposures as is hypothesized in the case of multiple chemical sensitivities.

In conclusion, we have explained two approaches to analysis of ambulatory ECG and HRV data in job strain research that test control capacity hypotheses of the Stress Disequilibrium Theory. We provide preliminary evidence that high strain subjects have reduced vagal cardiac control capacity, and exhausted subjects have additional reductions in such capacity. The methods described require additional validation, also across physiological levels. We would hope to assess, for example, whether the variability of control response at one physiological level could indeed be found to insure stability at a higher level (for example: the variability of heart rate supporting the stability of the blood pressure levels). More validation of the implications is required: including investigations of how the measures relate to risk for pathological end points; and a generalized interpretation of results requires further study in additional age and gender populations. It is quite feasible that both of these steps can be, at least initially, achieved with secondary analysis of available data.

REFERENCES

1. Karasek R. *Low social control and physiological deregulation — the stress–disequilibrium theory, towards a new demand–control model*. SJWEH 2008;6:117–35.
2. Karasek R, Theorell T. *Healthy work: stress productivity, and the reconstruction of working life*. New York: Basic Books; 1990.
3. Schnall PL, Belkic K, Landsbergis P, Baker D, editors. *The Workplace and Cardiovascular Disease*. Occupational Medicine: State of the Art Reviews no. 15. Philadelphia: Hanley & Belfus, INC.; 2000.
4. Belkic KL, Landsbergis PA, Schnall PL, Baker D. *Is job strain a major source of cardiovascular disease risk?* Scand J Work Environ Health 2004;30(2):85–128.

5. Landsbergis PA, Schnall PL, Pickering TG, Warren K, Schwartz JE. *Life-course exposure to job strain and ambulatory blood pressure in men*. Am J Epidemiol 2003;157(11):998–1006.
6. Togo F, Takahashi M. *Heart rate variability in occupational health — A systematic review*. Ind Health 2009;47(6):589–602.
7. Collins S. *Emerging methods for the physiological assessment of occupational stress*. Work 2001;17:209–19.
8. Collins SM, Karasek RA, Costas K. *Job strain and autonomic indices of cardiovascular disease risk*. Am J Ind Med 2005;48(3):182–93.
9. Hanson EKS, Godaert GLR, Maas CJM, Meijman TF. *Vagal cardiac control throughout the day: the relative importance of effort-reward imbalance and within-day measurements of mood, demand and satisfaction*. Biol Psych 2001;56(1):23–44.
10. Appels A. *Exhausted subjects, exhausted systems*. Physiol Scand 1997;161:153–4.
11. Collins SM. *Job strain and electrocardiographically assessed pathophysiological mechanisms*. Lowell: Department of Work Environment, University of Massachusetts Lowell; 2003.
12. Glass L. *Introduction to controversial topics in nonlinear science: Is the Normal Heart Rate Chaotic?* Chaos 2009;19:028501. DOI 10.1063/1.3156832.
13. Ashby WR. *Introduction to Cybernetics*. London: Chapman & Hall Ltd.; 1957.
14. Thayer JF, Lane RD. *The role of vagal function in the risk for cardiovascular disease and mortality*. Biol Psych 2007;74(2): 224–42.
15. Merriam PA, Ockene IS, Hebert JR, Rosal MC, Matthews CE. *Seasonal variations of blood cholesterol levels study: study methodology*. J Biol Rhythms 1999;14(4):330–339.
16. Bigger JT Jr. *Spectral analysis of RR variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans*. In: Zipes DP, editor. *Cardiac Arrhythmias: From Cell to Bedside*. Philadelphia: WB Saunders; 1995. p. 1151–70.
17. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Heart rate variability standards of measurement, physiological interpretation, and clinical use*. Eur Heart J 1996;17:354–81.
18. Contreras P, Canetti R, Migliaro ER. *Correlations between frequency-domain HRV indices and lagged Poincaré plot width in healthy and diabetic subjects*. Physiol Meas 2007;28(1): 85–94.
19. Demitrack MA, Dale JK, Straus SE. *Evidence of impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome*. J Clin Endocrinol Metab 1991;73:1224–34.
20. Selye H. *The stress of life*. New York: McGraw Hill; 1976.
21. Appels A, Mulder P. *Fatigue and heart disease. The association between 'vital exhaustion' and past, present and future coronary heart disease*. J Psychosom Res 1989;33(6):727.
22. Leone SS, Huibers MJH, Knottnerus JA, Kant IJ. *The temporal relationship between burnout and prolonged fatigue: a 4-year prospective cohort study*. Stress Health 2009;25(4):365–74.
23. Prescott E, Holst C, Gronbaek M, Schnohr P, Jensen G, Barefoot J. *Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study*. IEA 2003;32:990–7.
24. Wantanabe T, Sugiyama Y, Sumi Y, Watanabe M, Takeuchi K, Kobayashi F, et al. *Effects of vital exhaustion on cardiac autonomic nervous functions assessed by heart rate variability at rest in middle-aged male workers*. Int J Behav Med 2002;9(1): 68–75.
25. Hallgrímsson B, Hall BK, editors. *Variation: a central concept in biology*. Burlington, San Diego, London: Elsevier Academic Press; 2005.
26. Kleiger RE, Stein PK, Bigger JT Jr. *Heart rate variability: measurement and clinical utility*. Ann Noninvasive Electrocardiol 2005;10(1):88–101.