

## INVITED REVIEW ARTICLE

# A long-term perspective on cardiovascular job stress research

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**Abstract**

This review provides perspectives on cardiovascular occupational stress research since the 1960s until now. The author argues for closer links between basic science and clinical follow-up examinations of patients. In an excellent way urinary excretion of adrenaline and noradrenaline during wake hours mirrors day to day or week to week variations in sympathomedullary activity which could be related to variations in the patient's and cardiovascular and psychosocial situation. Modern methods for following variations over time in heart contractility should also be related to the patients' psychosocial situation. In addition the author argues for more extensive use of the increasing knowledge regarding regeneration and vagal activity in relation to variations in job conditions and development or prevention of cardiovascular disease.

**KEYWORDS**

critical life change, DHEA-s, heart contractility, ischemic heart disease, job strain, myocardial infarction, testosterone, urinary excretion of adrenaline

## 1 | ON CRITICAL LIFE CHANGES AND HEART BEAT FORCE

The aim of this review is to relate cardiological clinical and basic research in the 1960s to 1990s to the scientific discussion today. Cardiological research at the Medicine Department at the Seraphimer Hospital, which was part of the Karolinska Institute, is the point of departure. This department belonged to the most progressive cardiology departments at the time. Pacemakers with intracardiac electrodes as a clinical routine as well as intensive coronary care had their world start there, and both epidemiological and basic metabolic research was extensive. A review of these 50 years of research shows that the basic research ideas were good but, not unexpectedly, the research tools were less advanced than they are today. Examples from representative research areas during the 1960s to 1990s are used. These examples are focused on research relevant to the understanding of occupational stress cardiology.

During the 1960s and 1970s the role of significant life changes preceding illness onset was an important theme. Life change research is difficult firstly because the definition of a significant life change is vague and secondly because the time course of a life change may be difficult to characterize. For these and other reasons very few prospective studies of stress related outcomes in relation to the onset of significant life changes have been published. However, in a study of patients who had attended a cardiological out-patient clinic at regular intervals for several years after having suffered a myocardial infarction the individuals were systematically interviewed about ongoing life changes. The cardiologists made notes about significant life changes that the patients had gone through since the preceding visit. Using a standardized schedule all the life changes were assigned a score and for each half-year a total life change score was calculated from the sum of these scores. The 18 patients who died a cardiac death (from re-infarction) and who had complete life change data for a two-year period preceding death were individually

matched with regard to age and sex with 18 patients who did not die and had complete life change data for the same period. Events related to the coronary artery disease itself were not included. The results showed<sup>1</sup> that the life change score showed a statistically significant peak during the period 7-12 months before the cardiac death. There was no such accumulation in the survivor group. However, in addition the cardiologists had recorded ballistocardiography for assessing the heart's contractile pattern on all the clinic visit occasions. From those recordings a score indicating the force of the heart beat (the IJ amplitude) could be calculated. The analyses showed that the mean force of the heart beat increased in a pronounced way during the months (0-6) preceding cardiac death while no similar increase was observed in the survivor group. Accordingly this longitudinal study showed that there was a life change accumulation preceding increased force of the heart beat—which then preceded cardiac death in a vulnerable group with manifest ischemic heart disease (IHD).

The ballistocardiograph is an accelerometer which records the vertical movement in the body triggered by the contraction of the heart muscle. This recording technique was introduced by Starr in the 1960s.<sup>2</sup> It was one of the most reliable methods available at the time for assessment of contractile patterns in the heart muscle. It was used in Stockholm for studies<sup>3</sup> of pacemaker patients but also (while concomitantly recording blood pressure, finger plethysmography and ECG) for exploring cardiovascular reactions while discussing life problems in patients with coronary heart disease.<sup>4</sup> The argument here is not to recommend the use of ballistocardiography (there are more direct ways of measuring cardiac contractility today) again but rather to make it clear that merely talking about significant life changes is useful for the patients, in particular when cardiovascular parameters are recorded online. This could be very useful in a deeper examination of the working conditions for a patient. Individual examples of widely differing cardiovascular reactions during talk about work stress<sup>5</sup> were published. Among patients in working ages talk about significant job-related life changes often evoked strong cardiovascular reactions, for example arrhythmias, or combined peripheral vasoconstriction, tachycardia and increased force of the heart beat resulting in marked elevation of diastolic and systolic blood pressure. This served as proof that the psychosocial work situation is of great importance for the patients but also that the cardiovascular reactions to adverse conditions were highly individualized.

From the 1950s to the 1970s the most frequent measure of sympathoadrenomedullary activation ("stress") was the excretion of catecholamines in urine. In studies of working conditions, a frequent design was to collect urine during working hours and to compare the catecholamine excretion during these hours to the excretion during the same hours on a work-free day. In one of the few longitudinal studies<sup>6</sup> individual variations in work-hour catecholamine excretion

were examined in relation to the life change score during the preceding work. The life change score for the past week was based upon an interview with a social worker who used the standard list of life changes described above. The 21 (male) participants had all suffered a myocardial infarction and were back to their normal lives in work and leisure. They were accordingly a group with enhanced sensitivity to stress. They were followed during on average of 7 weeks providing 149 observations. The adrenaline excretion was shown to be sensitive to life changes. On average a doubling of the life change score compared to the subject's own mean life change level corresponded to a 50% increase in urinary excretion of adrenaline compared to the subject's own mean excretion. Although diet, drinking, and smoking were kept constant there are many other factors that may contribute to variations in adrenaline excretion and thus the observed correlation ( $r = 0.33$ ) only explained 10% of the variation. There was a striking difference between individuals. About one third of the subjects showed strong associations between life change score and adrenaline excretion while one third showed no such association. On the other hand, the variations due to these real-life variations were often more pronounced than those usually observed in laboratory experiments. The assessment of urinary excretion of adrenaline during working hours is still an interesting and valuable tool both in research and practice.

There is growing consensus today that job stress may be of particular importance for vulnerable subjects who have IHD or risk factors for IHD.<sup>7,8</sup> While the odds ratio for developing cardiovascular disease for subjects with job strain in the general population is in the order of 1.3 (see more details below), the odds ratio for having a re-infarction is in the order of 1.6 for subjects with manifest cardiovascular disease when they are exposed to job strain. Similarly, the hazard ratio for death related to exposure to job strain is in the order of 1.7 in subjects with cardiometabolic disease. Accordingly, cardiologists have a duty to examine their patients' working conditions before sending them back to work.

Most of the job stress epidemiology during the 1960 to 1990s was focused on myocardial infarction as an outcome variable. One of the few prospective studies of the predictive value of significant life changes was published by our group.<sup>9</sup> Eight thousand middle-aged male building-construction workers filled out a standardized life change questionnaire. Subjects with known IHD were excluded in a one-year follow-up. The total life change score (using the standard score technique) for the year preceding the questionnaire was not significantly predictive of risk of suffering a myocardial infarction during a year of follow-up. However, one individual item related to the job situation, namely increased responsibility at work, was a significant predictor of increased myocardial infarction risk. The take-home message from the few case-control and prospective studies that have been published

on critical life changes is that the general level of life change during a given year is not related to near-future myocardial infarction risk. What seems to be more important is the dynamic picture; is there an unusual amount of critical life change for the individual given what he/she is accustomed to? For logistic reasons this is a difficult scientific question in relation to an outcome that is relatively infrequent in the population—we would need multiple sequential assessments in large numbers of subjects. However, certain kinds of life changes such as increased job responsibility, rather than changes in general, may indeed be predictive. Furthermore, in the building construction worker study a psychosocial index of work load including conflicts at work was significantly predictive of increased myocardial infarction risk during a two-year follow-up.<sup>10</sup> In a large case-control study published in 2005<sup>11</sup> similar findings were made: Increased responsibility and conflicts at work with clear negative implications were reported significantly more often for the year preceding myocardial infarction group than during the corresponding year in controls, both among men and among women.

## 2 | PSYCHOLOGICAL DEMANDS AND CONTROL AT WORK

After Karasek had introduced the demand control model—later supplemented with the social support dimension resulting in the demand-control-support model<sup>12,13</sup>—most of the attention in job stress research moved away from life changes and focused on work organization. Although discussions about individual reactions to working conditions enforced by cardiovascular recordings may still be important in cardiological practice (and deserves to be further developed), examination of the work organization has a solid basis of rationality since improvement of work organization should be the basis for the occupational health care units. The development of the demand-control-support model is well-known to the readers of this journal. There have been extensive debates about the model and the assessment of its dimensions. However, three recent developments are of particular importance.

First of all, with the use of a combined median split for demands (high) and median split for control (low) as the operational definition of job strain, both prospective and case-control studies seem to show an odds ratio for myocardial infarction of approximately 1.3. This is both for men and women and after adjustment for other risk factors.<sup>15</sup> Due to measurement errors and vague differentiation between risk and non-risk job strain measures (due to the median split) the number 1.3 could be an underestimation of the true association, however.

Secondly,<sup>16</sup> if the job strain assessment is combined with an assessment of effort reward imbalance the combined odds ratio improves. This shows that—although there is overlap

between the models—the combination of them may be helpful. This may be applicable to a number of specified job conditions including chemical and physical exposures. It is the total risk exposure that is relevant, not parts of it.

Thirdly, in a study published recently,<sup>17</sup> job strain has been shown to be related to a shortened “healthy life expectancy” in a recent population study (on average 2.0 years in men and 1.5 years in women). This type of observation may be a highly relevant step in epidemiology since health impairment in general may be the outcome of long-lasting exposure to a bad work environment. The limitation of calculations of the excess risk associated with poor working conditions with specified illnesses without reference to the fact that these illnesses often arise partly due to general stress mechanisms provides society with spuriously weak arguments for improvement of working conditions.

There have been extensive discussions regarding the assessment of demand and control and the empirical support for the idea that there is a true interaction between high demands and low control (job strain) in generating illness risk. I will not go into that discussion here. At present most researchers emphasize that lack of decision latitude (control) at work is more important than psychological demands and some researchers even argue that the demand dimension has little value. This, however, seems to differ between time periods and between countries. In most studies both demands and control seem to add value to predictions, and although true multiplicative interaction between demand and control has not been proven most researchers would agree that there is additive value in using both dimensions.

During an earlier phase of research on the relationship between exposure to job strain and risk of developing a myocardial infarction a *job exposure matrix* (JEM) was developed.<sup>18</sup> This Swedish JEM was one of the first JEMs in the world and we decided to test it in the large case-control study of myocardial infarction in Stockholm (SHEEP). The JEM builds upon the idea that subjects representing the whole labor market respond to questions about work (in this case psychological demands and decision latitude/control). Subjects with the same job title (eg, carpenters, nurse aids) are assumed to have the same decision latitude in subsequent steps. This means that the average decision latitude score among carpenters is used as the value for decision latitude among carpenters in other studies where individual assessments are not available. Further distinctions can be made, however, for gender and for age so that male carpenters aged above 45 will not necessarily have the same score as female carpenters of younger age. The JEM provided a possibility to compare the more “objective” JEM decision latitude and demand rating with the corresponding self-reported scores. Unfortunately, the questions were not identical in the two sets of score constructions—with more difference for the demand than for the control measures. With the use of JEM scores in the decision latitude

analysis as “golden standard” a sensitivity (true positive rate) of 53.0% for the cases and 46.0% for the referents was shown for self-reports in relation to JEM. The specificity (true negative rate) was almost identical for cases and referents (83.6% and 84.0%, respectively). The corresponding sensitivity for psychological demands was, respectively, 27.5% and 31.0% and the specificity was 83.1% and 81.9%. Thus, although the JEM measure of demands was inadequate the general impression was that the subjective ratings of demand and control in those patients who had suffered a recent myocardial infarction did not deviate more from the more objective measures than did those of the healthy referents. The reason why this is important is that it speaks in favor of using case control studies instead of expensive prospective studies when the relationship between job strain and risk of myocardial infarction is studied. In fact, a recent review<sup>19</sup> showed very similar odds ratios for job strain in relation to myocardial infarction risk in case control studies and prospective studies.

### 3 | LINKING LIFE EVENTS AND WORK ENVIRONMENT STUDIES

Another potentially important observation in the SHEEP case control study of myocardial infarction was that the variable “negative change in inferred decision latitude” significantly discriminated patients from controls, also after adjustment for other risk factors. This was calculated from subtraction of the JEM based decision latitude score 10 years before the myocardial infarction from the corresponding score during the year when the myocardial infarction occurred. According to our data subjects with unfavorable development of decision latitude at work were more likely to be patients than referents, even after adjustment for other risk factors (OR 1.4, 1.0-2.0). This illustrates, like the observations on critical life changes, that the dynamics of psychosocial development may be important. The difference between patients and referents was particularly visible during five years preceding the infarction and was confined entirely to subjects below age 55 (when the subjects were still in their “careers”). This study only included men. Accordingly, we do not know whether this phenomenon applies to women as well.

### 4 | ABILITY TO HANDLE EMOTIONS AND BLOOD PRESSURE REGULATION AT WORK

To interpret and differentiate, as well as to describe and communicate emotions, is of great importance for social interactions and for well-being, and consequently also for health, not the least at work. In psychosomatic medicine difficulty in such abilities is labelled alexithymia. It has been shown that

alexithymia is associated with early development of hypertension and that ability to handle emotions can be improved in cultural programs.<sup>20</sup> In one study<sup>21</sup> handling of emotions in employees was studied by means of a standardized “emotion protocol.” The 58 participants were asked to fill out this protocol once every hour during the wake hours of four different working days dispersed during a whole working year. The adjective list contained a number of negative and positive adjectives (for instance joyful, angry, irritated, sad, anxious). Each adjective had a four-graded scale ranging from *not at all* to *very much*. On each occasion the participant also recorded his/her own blood pressure. In addition, for each one of the four working days the participant filled out the Swedish version of the demand control questionnaire. This enabled us to group the four working days into those two for which the participant reported the most and those two for which the least job strain (ratio between demand and control score) was reported. All the graded adjective reports were plotted against the individual’s blood pressure recording on each occasion. For every individual it was possible to calculate a correlation between position with regard to a defined adjective on the four-grade scale and systolic blood pressure on that occasion. In some subjects many adjectives were correlated with systolic blood pressure variations whereas in others no adjective showed any blood pressure correlation. The analyses showed that the number of *blood pressure correlated* adjectives was associated with the rise of mean systolic blood pressure during the job strain days compared to the days with little job strain. However, the association was strongly U-shaped. Those who had 0 blood pressure correlated adjectives had a mean job strain related systolic blood pressure elevation of 6 mm Hg. Those with six or more adjectives had a systolic blood pressure elevation of on average 9 mm Hg during job strain days, but those with the least elevation were those in the intermediate position with two or three adjectives—1 mm Hg. The association was perfectly described as a quadratic equation. The most likely interpretation of this finding is that there is a common denominator. Both those who do not report any connection between blood pressure and emotion and those who describe excessively many such relationships may suffer from alexithymia. This relation should be reexamined. During increasing job strain, alexithymia could cause worsened tensions resulting in rising blood pressure. It has been shown that alexithymia can be affected beneficially for instance by an art experience intervention (the Culture Palette)—as was recently shown in a randomized trial comprising women with burnout syndrome.<sup>22</sup>

### 5 | POSITIVE HORMONES

In most textbooks and handbooks on stress, considerable attention is given to the mechanisms of energy mobilization and the dangers associated with long-lasting energy



mobilization without periods of recuperation. There is less emphasis on how regenerative forces in the body may stimulate repair and replacement of worn-out cells. In interventions, a distinction should always be made between improvement of “good” forces and reduction of “evil” forces. Two steroids have been examined in relation to working conditions in our research, testosterone and DHEA-s. The first study was performed on male subjects<sup>23</sup> who were followed during spontaneous variations in job strain during a working year. The findings showed that the plasma concentration of testosterone increased when job strain decreased and vice versa. Akishita et al<sup>24</sup> have shown that low testosterone levels are associated with increased myocardial infarction risk in men. As long as the discussion is about normal regulation of testosterone (and not externally added anabolic steroids or tumours producing anabolic steroids), good psychosocial conditions are associated with high testosterone levels and vice versa.

Although the total testosterone concentration in plasma markedly differentiates women and men (with ten- to twenty-fold differences) the differences are not as pronounced in saliva (which mirrors the concentration of free testosterone in plasma). Most of the difference between men and women with regard to the total plasma concentration of testosterone is due to the fraction of testosterone that is bound to globulin and accordingly is not reflected in daily variations in saliva testosterone concentration. Furthermore, the regulation of saliva testosterone seems to follow the same pattern in men and women, with increasing saliva testosterone when life conditions improve. An illustration of this was seen in a longitudinal study of musicians in two different symphony orchestras<sup>25</sup> followed every 6 months for 2 years. In one of the orchestras the solo oboist fainted in front of the audience during two different concerts. This resulted in markedly deteriorated work environment in the orchestra, both in female and male participants. The situation improved after half a year when the oboe player had had a cardiac pacemaker implanted and group discussions had taken place in the orchestra. Our observations showed that saliva testosterone (six assessments from awakening to bedtime once every 6 months) was substantially lower than in the other orchestra in the first observation but then did not differ from the other groups. A similar significant pattern was observed in the 24-hour continuous recordings of ECG on the same occasions: The “very low frequency power” (VLFP) in the heart rate variability was weakened in the affected orchestra during the crisis period but not in the other orchestra. Since VLFP has been assumed to reflect baroreceptor regulation and vagal activity, the likely interpretation is that the vagal activity may have been down-regulated during the crisis period. In the same vein the lowered saliva testosterone level may reflect lowered regenerative activity in the body. In future research we should pay attention both to the general level of vagal activity which probably protects the

arteries from atherosclerosis development<sup>26</sup> and to regenerative hormones.

A steroid precursor of both male and female sex hormones is DHEA-s which exhibits high concentrations in plasma both in men and women (with slightly higher levels in men). DHEA-s is the sulphated water-soluble form of DHEA (dehydro-epiandrosterone). DHEA-s is strongly correlated with age, particularly in men. It has anabolic effects in itself. Low levels of DHEAs are associated with a high degree of carotid artery atherosclerosis<sup>27</sup> and with an elevated likelihood of developing atrial fibrillation.<sup>28</sup> Long-term stress<sup>29</sup> seems to attenuate the normal DHEA-s response to acute stress, and in addition subjects who report chronic stress have lower DHEA-s levels than others.<sup>30</sup> Savineau et al<sup>31</sup> have summarized the protective role of DHEA in cardiovascular health.

It is possible to stimulate DHEA-s by means of psychosocial intervention. This can be done individually, for instance by means of yoga and meditation-based life-style change.<sup>32</sup> We have also shown that DHEA-s levels in employees can be improved by means of a leadership intervention using strong cultural experiences (ethically provoking poetry interfoliated by specially selected music and followed up by discussions in groups as well as later discussions based upon diaries.<sup>33</sup> This study was performed as a controlled trial with managers randomly allocated to art intervention or more regular psychosocial stress-focused education, in both groups with meetings once every month during a 9-month period. Of particular importance was the finding that the employees who worked for the corresponding “art-exposed” and “lecture-exposed” managers respectively differed significantly in development with regard to a number of psychological and health-related variables. Willingness to discuss problems actively (rather than avoid or cover them up), mental health (sum of standard scores for sleep problems, emotional exhaustion and depressive symptoms) and plasma concentration of DHEA-s in morning blood were the variables that showed significantly better development in the employees with art-exposed managers than in the other group—with benefit for the employees in this group versus the other group. The findings were more evident after 18 months post start than immediately after the end of the interventions in the employees, when the attitudes and behaviors in the managers had had time to influence the employees. With regard to DHEA-s it should be mentioned that both groups of employees had slightly lower DHEA-s levels than at start but the control group’s employees had significantly more pronounced decrease than the intervention group’s employees. This probably reflects the same phenomenon that we observed among symphony musicians (see above) whose saliva testosterone levels were followed in six-month intervals. In the leadership study the first two blood samples were drawn with a 12-month interval during the late spring whereas the follow-up sample was drawn during early winter when regenerative activity is normally lower

than during the brighter and warmer periods in Sweden's relatively cold climate. It could be summarized as meaning that the art experiences made the managers more empathic and engaged (significantly increased agreeableness scores according to Big Five) after the art intervention and that this may have prevented some of the expected winter regeneration decrease in their employees.<sup>34</sup>

## 6 | GENERAL CONCLUSIONS

The first conclusion from bringing up the older scientific ideas is that cardiovascular occupational stress needs to return to combined clinical and epidemiological approaches. There may be a danger as we approach larger and larger sizes in our epidemiological studies that we lose track of the delicate interplay between individual endocrine, behavioral and cardiovascular responses to psychosocial stressors. Urinary excretion of catecholamines during wake hours is still an interesting parameter the individual variations of which could be followed clinically and discussed in relation to ongoing life changes with an understanding clinician. Similarly, variations in cardiac contractile patterns could be followed and related to ongoing life problems.

A second conclusion: Our observations regarding ability to handle emotions point to the importance of that variable when we try to relate the effect of environmentally caused problems in modern working conditions on cardiovascular regulation. Blood pressure variations in relation to individual emotional regulation patterns should be explored further.

A third conclusion is that we should become more interested in regeneration and parasympathetic activity. These correspond to strong protective mechanisms and seem to be quite sensitive to variations in psychosocial conditions.

## DISCLOSURE

Approval of the research protocol: NA. Informed consent: NA. Registry and the registration no. of the study/trial: NA. Animal studies: NA.

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