Bial

University of BRISTOL
Henry Wellcome Laboratories for Integrative Neuroscience & Endocrinology

MRC Medical Research Council

HSRC Health Services Research Collaboration

Bursary Number: 36/04

IDENTIFYING THE DETERMINANTS OF STRESS AND STRESS-RELATED ILLNESSES IN NEWLY QUALIFIED DOCTORS

Lightman, S.L., Wetherell, M.A., Crown, A.L., Vedhara, K.

BACKGROUND

Psychological stress is known to alter the functioning of several physiological systems, including the nervous, endocrine, and immune systems. These stress-related alterations have been shown to result in increased vulnerability to new diseases and more rapid progression in existing conditions. It is, however, unclear why some individuals are more vulnerable to the effects of stressful encounters than others, and whether this may be related to dysregulation in the responses of these systems. Indeed, very little is known about what factors (e.g., state, trait, and situational factors) determine individual differences in response to stress and what consequences they have for the individual.

One group for which this is a pertinent issue is newly qualified doctors (Pre-Registration House officers. This group is of interest for two reasons. Firstly, Pre-registration House Officers (PRHOs) are a group, for whom, stress and stress-related illness can result in negative consequences for the individual as well as consequences for those in their care. Secondly, in their first year, PRHOs experience discreet periods of low and high stress as they spend 3 or 4-month periods in different clinical settings (rotations). Consequently, the start of each post is associated with increased novelty, high demand and low control over the environment, all of which contribute to increases in perceived stress. In contrast, the end of each post is associated less uncertainty and greater control and thus, less stress. The structure of the first PRHO year, therefore, provides an opportunity to simultaneously assess the effects of situational factors (e.g., changes in levels of background stress) and individual factors (psychological and behavioural factors) on the responses of key physiological systems involved in the stress response.

In order to assess the responses of these systems it is logical to stimulate them in a controlled research setting. This, therefore, provides a snapshot of these system responses, which should be representative of how that individual would respond to a stressful encounter in everyday life. Several techniques are currently used to assess reactivity to stressful situations in the laboratory, however, these methods are often limited in terms of the responses they elicit and their ability to represent the stressors encountered in everyday life. In this study we utilised two laboratory stressors that address these issues. Firstly, we have developed a novel acute stressor involving the inhalation of a single vital capacity breath of a mixture of 35% carbon dioxide (CO_2) and 65% oxygen (The 35% CO_2 Stress Test). Our development work demonstrates that the test reliably activates the sympathetic nervous system and elicits psychological responses associated with increased perception of stress (Kaye et al., 2004). The test also elicits stable individual differences in endocrine (cortisol) responses and these responses are related to psychological perceptions of the test (Wetherell et al., 2006). Furthermore, unlike other acute stressors that elicit these responses, the 35% CO_2 Stress Test also elicits a parasympathetic response (Kaye et al., 2005). The test, therefore, provides a safe and reliable method of assessing all of the mechanisms involved in the human stress responses and can, therefore, be used to assess the factors that contribute to individual variation in these responses. Secondly, we used a performance based stressor (the Multi-tasking Framework, Wetherell et al., 2004). The Framework comprises a battery of individual tasks or modules, specifically designed to represent the range of tasks encountered by the study population in their working environment (i.e., monitoring heart rate, entering blood test results, monitoring patient status and calculating drug dosages). It, therefore, allows for assessment of stress-related performance on job-specific tasks. When used in combination, the 35% CO_2 Stress Test and the Multi-tasking Framework, therefore, provide a comprehensive snapshot of how an individual would respond to acutely stressful events encountered in everyday life.

PROGRESS

As the testing periods for the study are dictated by the PRHO first year rotations the number of testing sessions in a given time period is limited. The BIAL bursary has, therefore, provided funding for the first year of testing. A total of 22 PRHOs have, therefore, been recruited and tested from four hospitals in the region. Subsequent funding is currently providing support for the second and final year of recruitment and testing.

METHODS

Design (see Figure 1 for study design overview)

All PRHOs attended a baseline / familiarisation session. This session comprised a physical assessment (height, weight, body mass index, blood pressure, heart rate, general health status), individual factors (personality, mood, coping style, perceived stress, burnout, job content, social support) and an assessment of work-related performance using the Multi-tasking Framework. PRHOs then attended a further two sessions; at the beginning of a rotation (high stress) and at the end of a rotation (low stress) in a counterbalanced order. At each session, PRHOs completed questionnaires related to background levels of perceived stress and mood. They then provided baseline saliva and blood samples for analysis of cortisol and noradrenaline and completed a questionnaire of psychosomatic symptoms. The 35% CO_2 Stress Test was then administered and further saliva and blood samples were taken at 2, 10, 20 and 30 minutes post-CO_2 inhalation. Psychosomatic symptoms were assessed at 2 minutes (peak effect) post-CO_2 inhalation. Following the 30-minute sampling period, PRHOs were administered the Multi-tasking framework for a period of 10 minutes and completed questionnaires regarding mood and perceived workload immediately prior to and following performance on the framework. Finally, at the end of each session, PRHOs completed further questionnaires for mood and psychosomatic symptoms. Heart rate and blood pressure was assessed throughout.

INTERIM RESULTS (YEAR 1)

Repeated measures ANOVAs were used to assess time (sampling time, e.g., pre Vs post Vs recovery) and session (e.g., low Vs high stress).

Psychosomatic reactivity

Figure 2 shows psychosomatic symptom reports at pre, post and recovery at both low and high stress sessions. The inhalation of 35% CO_2 resulted in significant time effects. That is, inhalation elicited significant post-CO_2 increases in reports of negative symptoms (e.g., stressed and anxious) and reductions in positive symptoms (e.g., happy). Significant session effects were also observed. That is, reports of negative symptoms were greater at all time points at high stress compared to low stress. In contrast, reports of positive symptoms were reduced.

Physiological reactivity

A significant effect of time ($P < 0.01$) but no differences between low and high stress were observed for heart rate. Significant interactions ($P < 0.05$) were observed for systolic blood pressure, noradrenaline and salivary cortisol characterised by normal reactivity during low stress (i.e., a post-CO_2 increase in all parameters) but elevated pre-CO_2 levels and reduced reactivity at high stress. These results are shown in Figure 3.

Figure 4 shows physiological reactivity to the Multi-tasking Framework (baseline, task and recovery) at the familiarisation session and low and high stress. Significant increases and return to recovery were observed for both heart rate and systolic blood pressure at the familiarisation session but not at either high or low stress.

Perceived work demand, mood and performance

Figure 5 shows perceived workload and mood effects following the Multi-tasking Framework at low and high stress. At high stress PRHOs reported the task to be significantly more frustrating ($P < 0.05$) and perceived their performance to be reduced compared with low stress ($P < 0.05$). Furthermore, significant reductions in feelings of 'alertness' and 'calm' were reported at high stress compared with low stress. With regards to performance, at high stress PRHOs had significantly degraded total performance ($P < 0.01$) and missed more responses (errors) on the individual tasks ($P < 0.05$) when compared with low stress. These results are shown in Figure 6.

DISCUSSION

Reports from participating PRHOs, indicate that the combination of the current assessment techniques (e.g., the CO_2 Stress Test and the Multi-tasking Framework) provide a thorough representation of how individuals respond to acute physiological stress and workload stress. That is, PRHOs have reported that the effects of the CO_2 Stress Test are similar (although of greater intensity and shorter duration) to the feelings they experience when there is a critical emergency in the hospital. Similarly, they report that the tasks presented in the Multi-tasking Framework are representative of many of the routine tasks that they must undertake on the wards. These tests, can, therefore, be usefully employed in future research studies to assess psychophysiological stress responses in the laboratory, thus providing an indication of how individuals respond to stressors encountered in everyday life.

The interim results indicate significant differences in physiological stress reactivity, performance and mood at high stress. In response to the 35% CO_2 Stress Test, normal patterns of physiological and psychological stress reactivity were observed at low stress. That is, increases in reports of negative symptoms and reductions in positive symptoms and increases in blood pressure, noradrenaline and cortisol. However, at high stress psychological reactivity was increased for negative symptoms and reduced for positive symptoms at all time points indicating that PRHOs had greater negative mood at baseline and were more affected by CO_2 inhalation than at low stress. With regards to physiological reactivity, PRHOs demonstrated greater baseline levels and attenuated reactivity at high stress. A similar pattern of results were observed in relation to the Multi-tasking Framework. That is, heart rate and blood pressure responses were attenuated at both low and high stress when compared to reactivity at the familiarisation session. In addition, PRHOs had degraded performance and greater error rates and also reported greater negative mood change in response to the Framework at high stress compared with low stress.

Attenuated reactivity in response to stress has previously been associated with a variety of deleterious health outcomes. For example, blunted HPA and sympathetic responses are associated with increased incidence of autoimmune disorders and inflammatory diseases (Masi et al., 1996, Buske-Kirschbaum et al., 2002), depressive disorders (Burke et al., 2005), metabolic syndrome (Brunner et al., 2002) and hypertension (Gerrin et al., 1995).

With regards to differences in performance and missed responses at high stress, these differences are not necessarily indicative of an increased likelihood of making clinical errors. The tasks, although representative of the everyday tasks encountered by the PRHOs are presented in controlled laboratory conditions and as such lack the perceived importance and urgency related to these tasks in real life. However, the consistent reduction in performance, coupled with negative changes in mood reported during the tasks at high stress indicate that performance on some everyday tasks may be compromised whilst experiencing higher levels of background stress.

Overall, the beginning of a clinical rotation, characterised by reduced control over the environment and increased novelty resulted in dysregulated physiological stress reactivity and reductions in performance and mood. This pattern of results was consistent across two stressors which, when used in combination can provide a comprehensive snapshot of how an individual responds to stressful situations. Further data will be collected over the next year.

REFERENCES

Buske-Kirschbaum, A., Geiben, A., Hollig, H., Morschhauser, E., Hellhammer, D. 2002. Altered responsiveness of the hypothalamus-pituitary-adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. J. Clin. Endocrinol. Metab. 87, 4245-4251.

Brunner, E., Hemingway, H., Walker, B., Page, M., Clarke, P., Juneja, M., Shipley, M., Kumari, M., Andrew, R., Seckl, J., Papadopoulos, A., Checkley, S., Rumley, A., Lowe, G., Stansfeld, S., Marmot, M. 2002. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. Circulation 106, 2659-2665.

Gerin, W., Pickering, T.G. 1995. Association between delayed recovery of blood pressure after acute mental stress and parental history of hypertension. J. Hypertens. 13, 603-610.

Kaye, J., Buchanan, F., Kendrick, A., Johnson, P., Lowry, C., Bailey, J., Nutt, D., Lightman, S. 2004. Acute carbon dioxide exposure in healthy adults: Evaluation of a novel means of investigating the stress response. J. Neuroendocrinol. 16, 256-264.

Kaye, J.M., Corrall, R.J., Lightman, S.L. 2005. A new test for autonomic cardiovascular and neuroendocrine responses in diabetes mellitus: evidence for early vagal dysfunction. Diabetologia 48, 180-186.

Masi, A.T., Chrousos, G.P. 1996. Hypothalamic-pituitary-adrenal-glucocorticoid axis function in rheumatoid arthritis. J. Rheumatol. 23, 577-581.

Wetherell, M.A. & Sidgreaves, M.C. (2005). Secretory Immunoglobulin A Reactivity Following Increases in Workload Intensity Using the Defined Intensity Stressor Simulation (DISS). Stress and Health, 21, 99-106.

Figure 1. ***Study design overview***

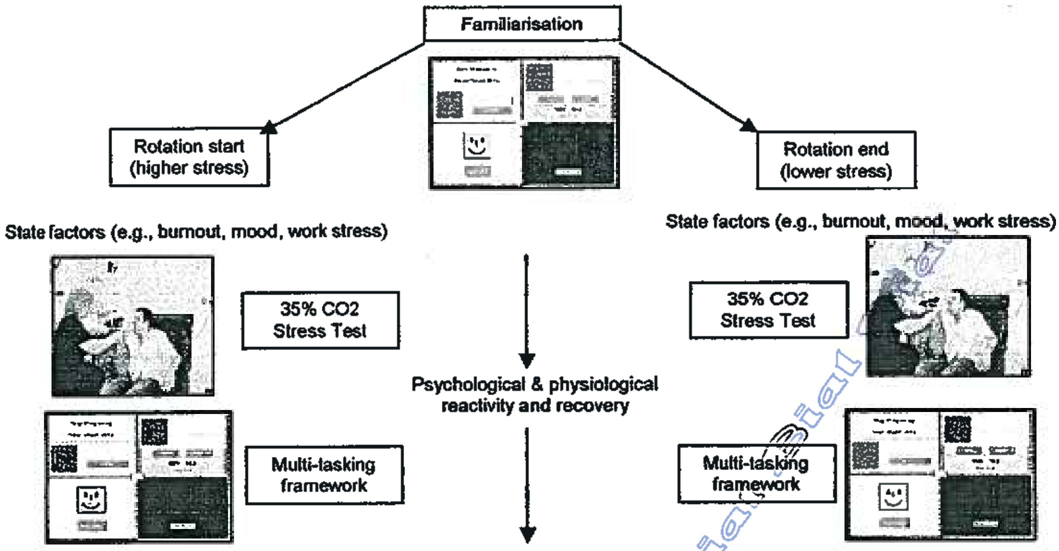
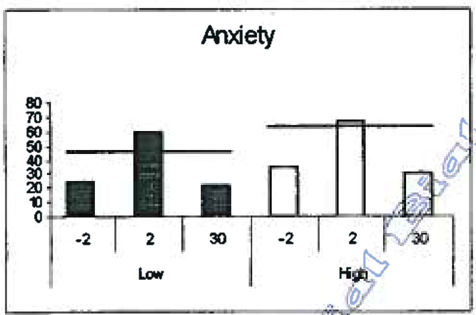
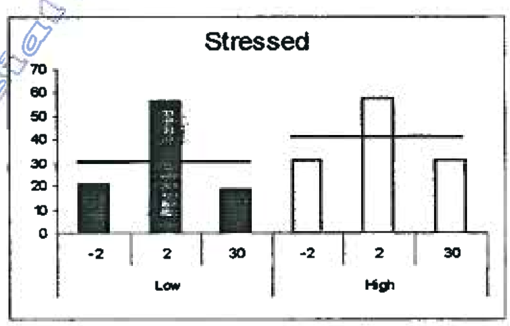


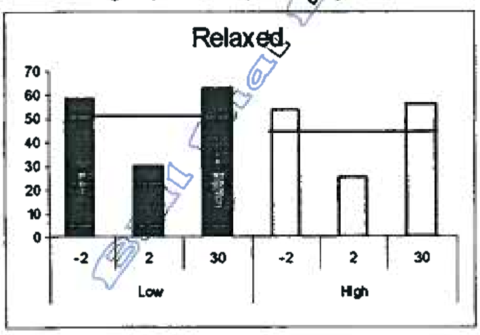
Figure 2. ***Psychosomatic symptoms reports at low and high stress***



Low Vs High (P< 0.05) Time (P<0.01)

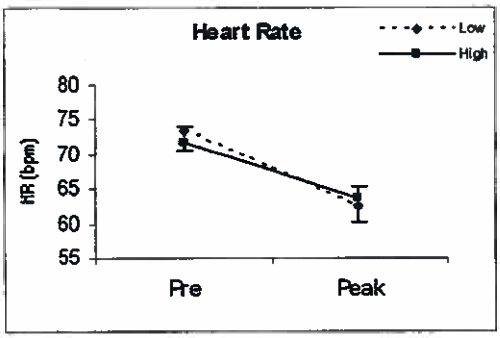


Low Vs High (P< 0.01) Time (P<0.01)

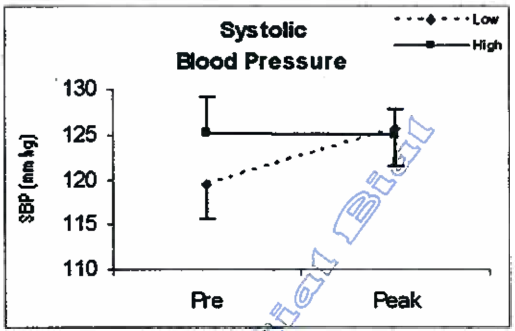


Low Vs High (P< 0.01) Time (P<0.01)

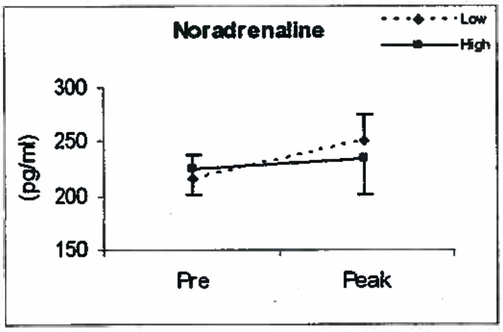
Figure 3. ***Physiological reactivity to the 35% CO_2 Stress test at low and high stress***



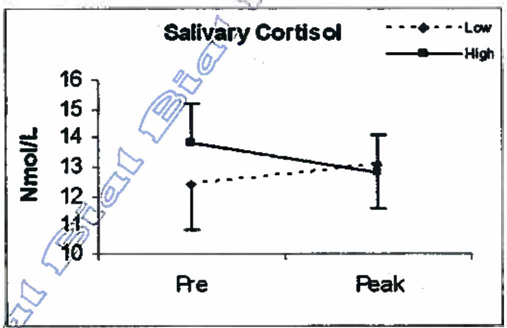
Low Vs High (NS) Time (P< 0.01))



Low Vs High (NS) Time (NS) interaction (P< 0.05)

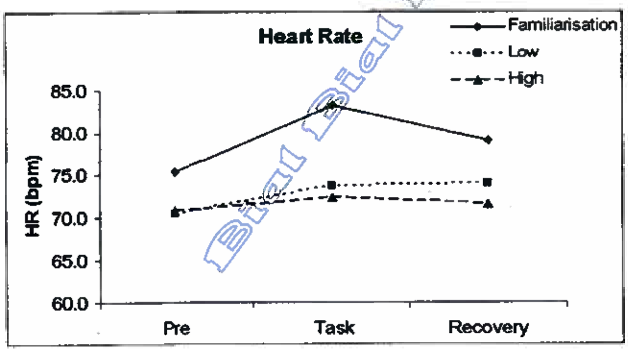


Low Vs High (NS) Time (NS) interaction (P< 0.05)



Low Vs High (NS) Time (NS) interaction (P< 0.05)

Figure 4. ***Physiological reactivity to the Multi-tasking Framework at low and high stress***



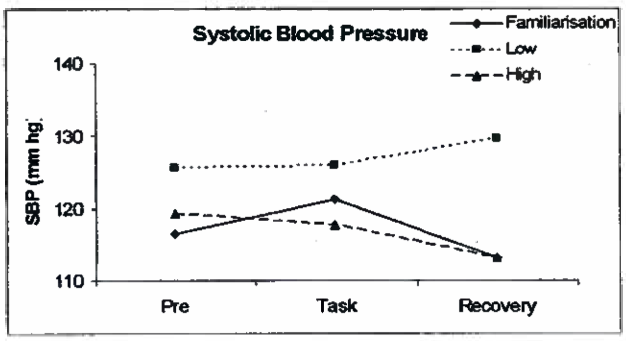


Figure 5. ***Perceived workload and mood following the Multi-tasking Framework at low and high stress***

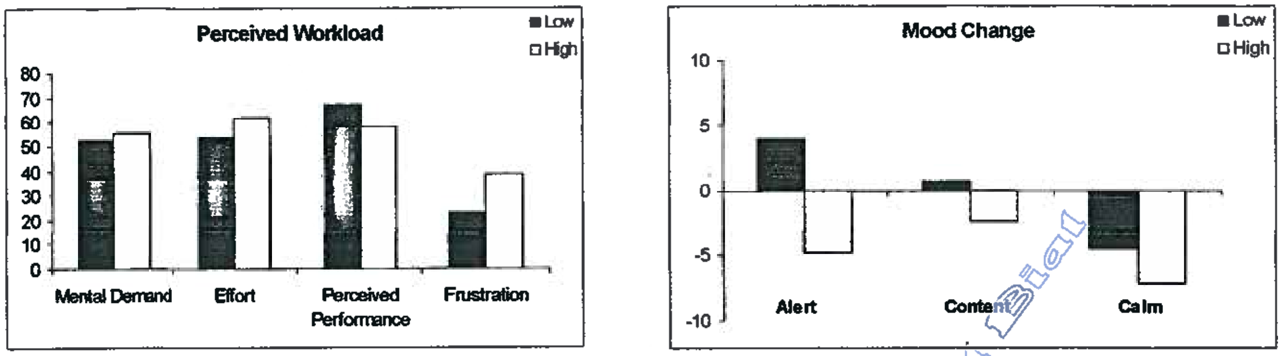


Figure 6. ***Performance and error rates on the Multi-tasking Framework at high and low stress***