The Psychological and Physiological Effects of Acute Occupational Stress in New Anesthesiology Residents: A Pilot Trial

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Abstract

Background—Occupational stress in resident physicians has profound implications for wellness, professionalism, and patient care. This observational pilot trial measured psychological and physiological stress biomarkers before, during, and after the start of anesthesia residency.

Methods—Eighteen physician interns scheduled to begin anesthesia residency were recruited for evaluation at three time points: baseline (collected remotely before residency in June 2013); first month visit 1 (July); and follow-up visit 2 (residency month 3–5, Sept–Nov). Validated scales

were used to measure stress, anxiety, resilience, and wellness at all 3 time points. During visits 1 and 2, we measured resting heart rate variability, responses to laboratory mental stress (hemodynamic, catecholamine, cortisol, and interleukin-6) and chronic stress indices (C-reactive protein, 24 h ambulatory heart rate and blood pressure, 24 h urinary cortisol and catecholamines, overnight heart rate variability).

Results—Thirteen interns agreed to participate (72% enrollment). There were seven men and six women, ages 27–33 years. The mean ± SD of all study variables are reported.

Conclusion—The novelty of our report is the prospective design in a defined cohort of residents newly exposed to the similar occupational stress of the operating environment. Because of the paucity of literature specific to the measures and stress conditions in this investigation, no data were available to generate *a priori* definition of primary outcomes and a data analytic plan. These findings will allow power analysis for future design of trials examining occupational stress and stress-reducing interventions. Given the importance of physician burnout in our country, the impact of chronic stress on resident wellness requires further study.

BACKGROUND

The health and well-being of physicians and other health care providers is critical to our nation's healthcare system. Unfortunately, increasing evidence suggests that the nation's physicians and nurses are experiencing epidemic levels of burnout, dissatisfaction, and work-related stress.[1–3] These factors appear to be a particular concern for resident physicians where burnout and distress have been shown to impact patient safety[4,5] and be related to medical knowledge as assessed by standardized tests.[6] Stress encompasses a wide range of psychological and physical perturbations that negatively affect health, relationships, quality of life and well-being. Recent surveys have shown increasing levels of stress and burnout in physicians[3] and also a connection between burnout and patient outcomes.[1] Given this association, an intense area of new empirical interest is occupational stress in the context of professionalism among healthcare workers. This is particularly important in perioperative resident physicians who have the least experience in the operating room organizational hierarchy. Furthermore, compared to other healthcare providers, residents are most affected in health, personal support, professional support, and outside activities.[7]

To identify the impact of stress on well-being, one strategy is to select a cohort of residents who will encounter an anticipated training stressor. The first month of anesthesiology residency represents an extreme degree of psychological, intellectual, procedural, technical, managerial, and logistical stress. In addition to the factors just described, the start of anesthesiology residency may also impact health behaviors, including a stress component that can be considered "deprivation stress," which may involve less sleep, an irregular sleeping schedule, a reduction in physical activity level, a reduction in pleasurable activities or hobbies, poor nutrition, and a reduction in personal or family time.[8]

The emotional stress and burnout risk in residency training has been well documented, but the method of data collection has primarily been through psychological surveys that evaluate stress level, burnout or mood. Similarly, for physiological measures, while some variables have been recorded in simulator training modules,[9] nothing has been collected during real-

time "in the field" patient care activities. Thus, there is a major knowledge gap in the quantifiable psychological and physiological effects of the profound occupational stress associated with novice medical residents transitioning to residency training. Reliable markers of stress would be considered essential repeated measures in interventional trials aimed at reducing stress and optimizing the training experience, with implications for resident wellness, professionalism, and patient care.

With this information as background, the purpose of this pilot and feasibility trial was to prospectively collect high-resolution psychological and physiological data in new clinical anesthesia year-one trainees. Therefore, the study goals were to 1) quantify the acute psychological stress of starting anesthesia residency by measuring physical activity level, perceived stress, state anxiety, resilience, and perceptions of well-being; 2) record heart rate variability (HRV) as a marker of cardiac autonomic modulation; 3) measure chronic markers of stress including 24 h urinary catecholamines (epinephrine and norepinephrine), 24 h urinary cortisol, and C-reactive protein (CRP); and 4) administer an acute mental stress protocol in our laboratory to generate a data base of acute cardiovascular and biomarker responses during the first month of anesthesiology residency and a follow-up visit.

MATERIALS AND METHODS

Subjects

This study received approval from the Department of Anesthesiology and the Mayo Clinic Institutional Review Board, Rochester, MN. Eighteen incoming clinical anesthesia year-one residents scheduled to begin anesthesia training on July 1, 2013, were recruited in June 2013. All individuals were completing postgraduate year-1 (PGY-1) at the time of recruitment. An Institutional Review Board-approved written informed consent form and health screening questionnaire was sent to each incoming resident by mail. Upon return of the signed consent form, the health screen was reviewed by the research nurses to ensure that no medical, psychiatric, or physical conditions would preclude participation in this study. Personal details such as marital status, children, or personal conflicts were not obtained. To ensure confidentiality, no investigator had access to the participants' health screen or medical records. Even though this was considered a minimal risk protocol, pregnant women were excluded. Under the principles of protection of human subjects, no information was gathered on individuals who declined participation.

Preanesthesia residency "baseline" condition

As shown in figure 1, participants were evaluated during three time conditions: pre-stress baseline (collected remotely pre-residency in June 2013); first month visit 1, between five and 14 working days after starting residency (July 8–19, 2013); and follow-up visit 2 (any working day during an operating room or pain service rotation 3–5 months after starting residency between September 18 and November 21, 2013). During the pre-stress baseline, subjects completed the following survey instruments, which are provided in appendices 1–4:

Appendix 1: Minnesota Leisure-Time Physical Activity Questionnaire (MLTPAQ), to determine the amount of energy expended over the previous 12 months. The questionnaire recorded information on frequency and duration of activities, providing

an estimate of the amount of energy expended per activity, averaged per day in metabolic equivalents (METs).[10]

Appendix 2: Cohen's Perceived Stress Scale (PSS), a 14-item scale designed to measure the degree to which situations in one's life are appraised as stressful.[11] The PSS has been shown to be a predictor of psychological symptoms, physical symptoms, and utilization of health services. The mean Cohen's PSS score for working adult men and women ages 26–35 years is 25.0 ± 8.2.[12] The mean Cohen's PSS scores for college-age men is 22.4 ± 6.8, and for college-age women is 23.6 ± 7.6.[13] Cronbach's alpha coefficient for the internal reliability of the scale is 0.78.[14]

Appendix 3: Spielberger State Anxiety Index, a scale for measuring anxiety and has been used in simulated trauma scenarios for resident trainees.[15] It includes 20 questions with a scale (20 to 80 points, higher score indicates higher anxiety) to describe how the respondent feels at a particular moment in time (state anxiety) using subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system.[16] In a population of working adults (n = 1,387/451 Men/Women), the mean Spielberger State Anxiety Index is 35.7 ± 10.4, and in college students (n = 296/481 M/W) the mean is 38.8 ± 12.[17] The internal consistency of the state anxiety scale has an alpha of 0.92.[15]

Appendix 4: Resiliency and Daily Well-being Surveys. Two questions provided an abbreviated index of the Connor-Davidson Resilience Scale.[18] The mean Connor-Davidson Resilience Scale score is 6.91 ± 1.5 in a general adult population.[18] Four questions provided a fast and simple assessment of daily well-being as used in employee wellness trials at our institution.[19] For the stress level (scale 0–10), a report at our institution on a cohort of 104 employees undergoing a stress reduction program found a mean stress level of 4.2 ± 2.25 at baseline, and 5.6 ± 2.07 after the 12-week program.[19]

First month visit 1

Three days before this visit, subjects were fitted with a Body Media Sensewear (BodyMedia, Inc., Pittsburgh, PA) physical activity monitor.[20] This is an elastic band worn on the upper arm that measures activity, energy expenditure, sleep, and sleep efficiency. Subjects wore the band for three days and nights until arriving for their study visit. The Daily Well-being and Resiliency Surveys were also completed at this time. To control for daytime variations, all study visits were conducted between noon and 4 pm in the Clinical Research Unit (CRU). Upon arrival, vital signs were obtained; the Daily Well-being and Resiliency Surveys were completed by the subjects. To measure dietary habits, an Automated Self-Administered 24-Hour Dietary Recall was administered.[21] Subjects were placed supine in a quiet room. An 18–20 gauge intravenous catheter was placed in the antecubital fossa for blood draws. Heart rate (HR) was measured by 3-lead electrocardiogram and recorded at 1000 Hz on LabChart (AD Instruments, Colorado Springs, CO). Respiratory rate was measured by capnography with a nasal cannula, and blood pressure was measured continuously by finger plethysmography (Nexfin, Edwards Lifesciences, Irvine, CA) and confirmed periodically with an automated brachial oscillometric cuff. Stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) were derived from pulse

contour analysis of the finger plethysmography waveform according to Nexfin algorithms.[22] A Polar chest belt was fitted that transmits HR to a proprietary HRV application on a smart phone (@-life, Mikropis Holding, Inc. Zalec, Slovenia).[23]

After resting in the supine position for 20 minutes, HR was recorded for HRV analysis. The electrocardiogram signal was imported into the Nevrokard Advanced HRV Analyses software (version 13.2.1, Nevrokard Kiauta k.d., Slovenia) for time and frequency domain analyses as described recently.[24] Following this, venous blood draws were collected for the following assays. Serum CRP was determined as a generalized measure of systemic inflammation, elevated in chronic job strain and caregiver strain.[25,26] Serum cortisol, serum epinephrine, and serum norepinephrine were determined to measure the degree of sympathoexcitation at rest and during mental stress.[27] Salivary cortisol was also collected for comparison with serum cortisol. Serum interleukin-6 was collected as a biomarker shown to respond to mental stress to a greater extent than CRP.[28] Inter-assay variability and coefficients of variation are described in detail in appendix 5.

Once resting blood samples were drawn, subjects were moved to a semi-recumbent chair for a computerized mental stress protocol, described in detail in appendix 5.[29] Following 2 min of baseline HR and blood pressure recording and 30 s of instructions, a mathematical subtraction test commenced for 5 min, followed by the Stroop colored word conflict test for 5 min, and concluding with 4.5 min of a second mathematical subtraction test, for a total stress duration of 15 min. At the end of the 15 min, blood sampling was repeated for serum cortisol, serum epinephrine and norepinephrine, and serum interleukin-6. Saliva was collected for salivary cortisol. Following a 5 min recovery period, subjects were de-instrumented and completed a psychological distress survey modified from a mental arithmetic stress survey by Reims and colleagues.[30]

As detailed in the appendix 5, prior to discharge, subjects were fitted with a 24 h ambulatory blood pressure monitor. Blood pressure and HR were measured using the Spacelabs 90202 recorder (Spacelabs Inc., Snoqualmie, WA) as described by our lab.[31] Subjects were also instructed to wear the Polar chest belt from bedtime to awakening the next morning, and HR was recorded by the proprietary application on a mobile smartphone (@-life, Mikropis Holding, Inc.). Finally, subjects received containers for 24 h urine collection and were instructed to return all devices 24 h later. Urine was analyzed for cortisol, epinephrine, and norepinephrine as indicators of stress over 24 h and controls for circadian variability.[32–34]

Follow-up visit 2

Subjects were not scheduled following a call night or during a critical care rotation. All procedures were identical to first month visit 1 as described above (last paragraph of page 8).

Measurements and statistical analysis

Data are summarized using mean ± SD for continuous variables. Daily Well-being and Resiliency scores were averaged for the three preceding days and the visit day, on the day of study visits 1 and 2.

RESULTS

Demographics

Thirteen of 18 (72%) incoming anesthesia residents were consented and enrolled. Enrolled subjects consisted of seven men and six women. No health issues or medications were detected by the screen nurses that precluded participation. The mean age of enrollees was 29.2 ± 1.9 years and the mean body mass index was 22.6 ± 2.8 kg/m^2. All thirteen subjects completed the screen questionnaires and the first month visit 1, while one subject was automatically excluded from follow-up visit 2 because of pregnancy.

Psychological variables

Table 1 displays the psychological and estimated daily physical activity variables that were collected at all three time points. Reference values are listed for each survey where applicable.

Measured health behaviors and chronic stress biomarkers during first-month visit 1 and follow-up visit 2

Table 2 displays energy expenditure, physical activity, sleep, and sleep efficiency measured by the arm accelerometer band. Dietary caloric intake and caloric components from the Automated Self-Administered 24-Hour Dietary Recall online service are shown. Finally, the 24 h urinary cortisol, catecholamines, and CRP are also depicted.

Cardiac autonomic modulation at rest and during acute mental stress

Table 3 lists the HRV measures during 10 min supine rest and 15 min mental stress, and the Reims perceived stress scores that were collected immediately after completion of the mental stressor.

Cardiovascular hemodynamics and acute stress biomarkers at rest, during, and after acute mental stress

Hemodynamic variables in the mental stress trials are listed for both visits in table 4. The acute stress biomarkers collected at the conclusion of the resting HRV and immediately following mental stress are displayed in table 5. To compare the two methods of obtaining cortisol (serum and saliva), a linear regression was performed on the absolute values of serum *versus* salivary cortisol at rest and during mental stress in both visits. The serum and saliva samples were collected in separate tubes and processed in different labs (serum cortisol: Immunochemical lab in the Mayo CRU; salivary cortisol: Endocrinology lab at Mayo). As shown in figure 2, the correlation coefficients in all four conditions were significant ($P < 0.01$ for all).

Ambulatory hemodynamics and nighttime cardiac autonomic modulation

Table 6 displays the 24 h ambulatory blood pressure monitor variables from the ambulatory cuff and nighttime HRV from the chest belt.

DISCUSSION

The overall goal of this pilot study was to determine the feasibility of enrolling and collecting high-resolution psychological and physiological variables in incoming resident physicians. The exploratory study objective was to measure stress variables and related health behaviors that have direct implications for professionalism, quality of healthcare, and well-being of residents. The novel nature of our report is the prospective design in a defined cohort of new residents newly exposed to the similar occupational stress of the operating environment. Because of the paucity of literature specific to the repeated measures and stress conditions in this investigation, no data were available to generate *a priori* definition of primary outcomes and a data analytic plan. The sample size was dependent on the number of incoming residents that were available, with a 72% enrollment rate. While the sample size was underpowered to make statistical inferences from our findings, the findings instead will allow power analysis for future study design of trials examining occupational stress and stress-reducing interventions.

Well-being in residents is associated with their capacity for empathy and patient care,[35,36] and it has been postulated that the stressors of residency may counter the goals of training to promote professionalism and high-quality patient care.[37,38] Scores indicative of burnout have been associated with lower medical student empathy scores and with lower professionalism climate scores observed in medical students, residents, and faculty.[39,40] Specific to anesthesiology, perioperative patient safety and efficiency requires high performance by a health care team that absolutely depends on professionalism among anesthesia providers.[7] Early in training, anesthesia residents are likely to perceive a low degree of latitude in the setting of high expectations or demand.

Additional measures of well-being such as health behaviors were gathered to gain insight into factors that would potentially influence perceived stress. Resilience is a measure of coping ability, hardiness, and the ability to thrive in the face of adversity.[18] Based on the resiliency scores, our subjects appeared to adapt their schedules and health behaviors to combat the sudden disruption in work-life balance, an idea that has been described as a "time for temporary imbalance," when professional effort gives way to other life domains.[8] It is cautionary that residents may have already become accustomed to intermittent work-life imbalances, as a variety of internship rotations were likely filled with novel professional and personal challenges. Residents may also be particularly optimistic about the onset of training in their field of choice, and welcomed the onset of anesthesiology as a stressful yet engaging stressor.

Decreased HRV indicates a sympathetic dominance and/or reduced vagal activity which occurs in normal aging and many pathological conditions including hypertension, diabetes, and heart failure.[41] Detrimental effects of job strain are partly mediated through increased HR reactivity to a stressful workday, increased systolic blood pressure, and lower vagal tone.[42] A recent study using 24 h Holter monitors on 54 residents in multiple specialties found that those who reported high job strain (high-demand, low-latitude) had decreased HRV compared to low strain residents.[43] This is consistent with an earlier study in non-physician middle-age males that showed job strain and low decision latitude were associated

with a reduction in cardiac vagal control (HF) and elevations in sympathetic control (LF).[44] Thus, we measured both daytime resting and nighttime HRV in the first month and follow-up visit. We were also interested in the HRV response to laboratory mental stress during the stress encountered in starting residency, as we have previously shown that dietary sodium affects HRV at rest and during mental stress in healthy non-physician men and women.[24] One drawback of this methodology is the detection of HRV alterations in subjects who are healthy, physically fit trainees with little change in their lifestyle habits (including sleep). Additionally, while some authors have reported that vagal control (HF) is reduced with stress[42,45,46] other studies have shown no relationship,[47,48] and the overall utility of HRV in sleep deprivation is mixed.[49] Finally, perceived control is highly predictive of stress, and because residents select their training site, they may have a high level of perceived control over the challenges they encounter as new residents.[50]

Two endocrine response systems are particularly reactive to psychological stress: the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathoadrenal system.[51] Cortisol, the primary effector of HPA activation in humans, is a common biomarker in stress research. Catecholamines, which are released in response to sympathoadrenal activation, work in concert with the autonomic nervous system to exert regulatory effects on the cardiovascular and immune system among others. Prolonged or repeated activation of the HPA axis and sympathoadrenal systems can interfere with their control of other physiological systems, resulting in increased risk for physical and psychiatric disorders.[11,52] It is noteworthy that in healthy volunteers, the search for a consistent and reliable chronic stress biomarker remains a major challenge as recently reviewed in a meta-analysis of 31 studies on 38 biomarkers.[53]

A limitation of measuring serum and salivary cortisol levels is the wide range of inter-individual variance. The kinetics of cortisol production and metabolism is dependent on circadian rhythm, menstrual cycle, oral contraceptives, and cortisol binding globulin which, aside from circadian rhythm, were not controlled for in this study cohort.[32,54] Additionally, an interpretive challenge arises when the change in cortisol values from rest to stress falls within the assay's coefficient of variation, as it did for several of our subjects. For example, the finding that cortisol values decreased in response to mental stress during the follow-up visit seemed counterintuitive. To address this, we found that serum cortisol strongly correlated with salivary cortisol, which re-enforced the integrity of the cortisol values.

Additional limitations of this report deserve mention. Despite the strength that every participant in this cohort was subjected to a similar occupational stressor (the operating room environment at one institution as opposed to a multitude of rotations), the delicate nature of studying new resident trainees within the ethical boundaries of confidentiality and coercion limited the number of participants. We acknowledge the potential for selection bias, as the degree of resiliency in our participants may be such that many of the psychological and physiological variables explored were not affected by the stress of starting residency, but might be affected in a broader population of trainees. Finally, protocols of this nature are limited by the logistical challenge of prospective data collection in resident volunteers across convenient time points.

Preservation of health behaviors with respect to diet, physical activity level, and quality of sleep confer resiliency during periods of acute stress. Strategies to preserve or enhance these health behaviors merit further evaluation. The overall implication for resident education and occupational wellness is that subjective surveys quantifying psychological stress remain an important tool for prospective, longitudinal cohort studies. The development of objective, high-resolution physiological variables remains a significant challenge in identifying useful variables in a cohort of physician trainees. Given the importance of physician burnout in our country, the impact of chronic stress on resident wellness requires further study. Future protocols with larger samples capable of detecting psychological and physiological effects of occupational stress will require multiple time points to appreciate the full nature of chronic job strain and its relevance to interventions designed to optimize the training experience. This report demonstrates the feasibility of studies of this nature, and provides the preliminary data necessary to generate *a priori* definition of primary outcomes and a data analytic plan.

Acknowledgments

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Appendix 1: Minnesota Leisure Time Activity Questionnaire

To be completed by participant Activity	Did you perform the activity?	Do not write in this space	Number of times since July 1	Time per occasion	
				Hour	Min

Section A: Walking and misc.   N   Y

		N	Y				
010	Walking for pleasure						
020	Walking to work						
030	Using stairs when elevator is available						
040	Cross country hiking						
050	Back packing						
060	Mountain climbing						
115	Bicycling to work and/or for pleasure						
125	Dancing ballroom, square and/or disco						
135	Dancing, aerobic, ballet						
140	Horseback riding						

Section B: Conditioning Exercise

150	Home Exercise						
160	Health Club Exercise						
180	Jog/walk combination						
200	Running						
210	Weight lifting						

Section C: Water Activities

220	Water Skiing						
235	Sailing in Competition						
250	Canoeing or Rowing for Pleasure						
260	Canoeing or Rowing in Competition						
270	Canoeing on a Camping Trip						
280	Swimmin (at least 50ft) at a pool						
295	Swimming at the Beach						
310	Scuba Diving						
320	Snorkeling						

To be completed by participant **Activity**	Did you perform the activity?		Do not write in this space	Ave. Number of times per month	Time per occasion	
					Hour	Min

Section E.
Sports   N   Y

		N	Y			
390	Bowling					
400	Volley Ball					
410	Table Tennis					
420	Tennis, Singles					
430	Tennis, Doubles					
440	Softball					
450	Badminton					
460	Paddle Ball					
470	Racket Ball					
480	Basketball: non-game					
490	Basketball: game play					
500	Basketball: officiating					
510	Touch Football					
520	Handball					
530	Squash					
540	Soccer					
	Golf					
070	Riding a Power Cart					
080	Walking, Pulling Clubs on Cart					
090	Walking and Carrying Clubs					

Section F.
Lawn and Garden Activities

550	Mowing Lawn with Riding Mower					
560	Mowing Lawn Walking behind a Power Mower					
570	Mowing Lawn Pushing Hand Mower					
580	Weeding and Cultivating Garden					
590	Spading, Digging, Filling in Garden					
600	Raking Lawn					

Section G.
Home Repair Activities

620	Carpentry in Workshop					
630	Painting Inside of House includes Paper Hanging					
640	Carpentry Outside					
650	Painting Outside of House					

Section H.
Fishing and Hunting   N   Y

		N	Y			
660	Fishing from River Bank					
670	Fishing in Stream with Wading boots					
680	Hunting Pheasant or Grouse					
690	Hunting Rabbits, Prairie Chickens, Squirrels, Racoon					
710	Hunting Large Game: Deer, Elk, Bear					

Section I.
Other Activities

Appendix 2: Cohen's Perceived Stress Scale-14

INSTRUCTIONS:

The questions in this scale ask you about your feelings and thoughts during THE LAST WEEK. In each case, you will be asked to indicate your response by placing an "X" over the circle representing HOW OFTEN you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer fairly quickly. That is, don't try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

	Never 0	Almost Never 1	Sometimes 2	Fairly Often 3	Very Often 4
1. In the last week, how often have you been upset because of something that happened unexpectedly?	○	○	○	○	○
2. In the last week, how often have you felt that you were unable to control the important things in your life?	○	○	○	○	○
3. In the last week, how often have you felt nervous and "stressed"?	○	○	○	○	○
4. In the last week, how often have you dealt successfully with day to day problems and annoyances?	○	○	○	○	○
5. In the last week, how often have you felt that you were effectively coping with important changes that were occurring in your life?	○	○	○	○	○
6. In the last week, how often have you felt confident about your ability to handle your personal problems?	○	○	○	○	○
7. In the last week, how often have you felt that things were going your way?	○	○	○	○	○
8. In the last week, how often have you found that you could not cope with all the things that you had to do?	○	○	○	○	○
9. In the last week, how often have you been able to control irritations in your life?	○	○	○	○	○
10. In the last week, how often have you felt that you were on top of things?	○	○	○	○	○

PSS-14

	Never 0	Almost Never 1	Sometimes 2	Fairly Often 3	Very Often 4
11. In the last week, how often have you been angered because of things that happened that were outside of your control?	○	○	○	○	○
12. In the last week, how often have you found yourself thinking about things that you have to accomplish?	○	○	○	○	○
13. In the last week, how often have you been able to control the way you spend your time?	○	○	○	○	○
14. In the last week, how often have you felt difficulties were piling up so high that you could not overcome them?	○	○	○	○	○

Appendix 3. Spielberger State Anxiety Index

Please answer the following questions for how you feel now.

1. I feel calm.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

2. I feel secure.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

3. I am tense.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

4. I feel strained.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

5. I feel at ease.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

6. I feel upset.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

7. I am presently worrying over possible misfortunes.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

8. I feel satisfied.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

9. I feel frightened.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

10. I feel comfortable.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

11. I feel self-confident.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

12. I feel nervous.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

13. I feel jittery.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

14. I feel indecisive.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

15. I feel relaxed.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

16. I feel content.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

17. I feel worried.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

18. I feel confused.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

19. I feel steady.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

20. I feel pleasant.

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

Appendix 4: Resiliency and Daily Well-being Surveys

1. I am able to adapt to change.

0	Not true at all
1	Rarely true
2	Sometimes true
3	Often true
4	True nearly all of the time

2. I tend to bounce back after illness or hardship.

0	Not true at all
1	Rarely true
2	Sometimes true
3	Often true
4	True nearly all of the time

3. My current stress level:

As good as it can be. ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ As bad as it can be.
0 1 2 3 4 5 6 7 8 9 10

4. My current energy level:

As bad as it can be. ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ As good as it can be.
0 1 2 3 4 5 6 7 8 9 10

5. My concentration:

As bad as it can be. ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ As good as it can be.
0 1 2 3 4 5 6 7 8 9 10

6. How well I slept last night:

As bad as it can be. ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ As good as it can be.
0 1 2 3 4 5 6 7 8 9 10

Appendix 5. Supplemental methods

Heart rate variability

Components of HRV included mean HR, mean NN interval, standard deviation of normalized RR intervals (SDNN), square root of the mean squared difference of successive normalized RR intervals (RMSSD), low frequency (LF), high frequency (HF), low frequency normalized units (LFnu), high frequency normalized units (HFnu), and LF/HF ratio.

Mental stress

The computerized mental stress protocol was conducted in a semi-recumbent study chair with the legs elevated to the approximate level of the heart. Headphones were placed for automated audio input. Following 2 min of baseline HR and BP recording, a voiced recording of the printed instructions were played for each subject lasting 30 seconds. The instructions reminded subjects that their best effort was required and that their performance on the test would be compared to the other subjects. A computerized mathematical subtraction test for 4.5 minutes, was administered as described in detail elsewhere.[24] To maximize the stress induced, the standard recording (via headphones) used vocally consistent monologue urging each subject to respond faster and to concentrate fully throughout the test. This was followed by 30 second instructions for a Stroop colored word test, then a 4.5 min computerized version of the Stroop colored word conflict test used previously in our laboratory was given.[29] When this portion was completed, a second 5 min mental stress test immediately commenced, for a total stress duration of 15 minutes.

Following a 5 min recovery period, subjects were de-instrumented and completed a psychological distress survey modified from a mental arithmetic stress survey by Reims and colleagues, consisting of three questions: (1) Did you feel stressed while performing the color word task? (i.e., "perceived stress"); (2) Was it important for you to obtain a good result on the color word task? (3) How did you experience the task altogether? In response to each question, subjects marked one of ten unnumbered boxes between extremes of least to highest degrees of perceived stress, effort, and overall discomfort, respectively.

Ambulatory blood pressure monitoring

Following discharge from our laboratory, subjects were outfitted with an ambulatory blood pressure monitor (ABPM) Spacelabs 90202 recorder (Spacelabs Inc., Issaquah, WA, USA) as described by our lab.[31] The participants were asked to continue their regular activities and to go to bed no later than 11 PM, but were not allowed to exercise during the 24-hr recording period. Systolic BP (SBP), diastolic BP (DBP) and heart rate were measured every 15 min from 6 AM to 10 PM, and every 20 min from 10PM to 6 AM. The daytime period was defined as the interval from 8 AM to 10 PM; nighttime, from midnight to 6 AM (40,41). The standard deviation (SD) and coefficient of variation (CV) of the 24-h recordings were used as an index of HR, systolic blood pressure (SBP) and mean arterial pressure (MAP) variability. Nocturnal dipping was expressed as the nocturnal fall in BP calculated as the

difference between daytime and nighttime BP adjusted for the daytime BP level and expressed in percentages.

Overnight heart rate variability

Subjects were also instructed to wear the Polar chest belt from bedtime to awakening the next morning, and HR was recorded by the proprietary application on a mobile smartphone (@-life, Mikropis Holding, Inc. Zalec, Slovenia).

Biomarker measurements and assays

Serum cortisol was measured by a competitive binding immunoenzymatic assay on the DxI automated immunoassay system (Beckman Instruments, Chaska, MN 55318). Intra-assay CV's are 13.1%, 9.4%, and 6.6% at 1.56, 2.85 and 30.2 ug/dL respectively. Inter-assay CV's are 9.0%, 8.1%, and 9.3% at 2.47, 17.3, and 27.5 ug/dL respectively. (12-22-09). The lower limit of the CRR is 0.4 μg/dL.

Salivary cortisol was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Thermo Fisher Scientific, Franklin, Massachusetts 02038 and Applied Biosystems-MDS Sciex, Foster City, CA 94404). Saliva intra-assay C.V.'s are 5.6%, 4.5%, and 2.6% at 53.5, 292.5, and 1611.5 ng/dl, resp.; Inter-assay C.V.'s are 15.2%, 7.5%, and 8.1% at 49.6, 293.3, and 1560.5 ng/dl, resp.

Urinary cortisol was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Thermo Fisher Scientific, Franklin, Massachusetts 02038 and Applied Biosystems-MDS Sciex, Foster City, CA 94404). Intra-assay C.V.'s are 6.8%, 6.9%, and 5.0% at 0.84, 4.88, and 13.57 mcg/dl, resp. Urine inter-assay C.V.'s are 10.3%, 6.7%, 6.8% at 0.88, 4.6, and 13.0 mcg/dl, resp.

Serum catecholamines were measured by reversed phase HPLC with electrochemical detection after extraction with activated alumina. Serum intra-assay C.V.'s are: Norepinephrine 4.5% and 3.3% at 224 and 429 pg/mL; Epinephrine 12.2% and 3.6% at 13.8 and 242 pg/mL; Inter-assay C.V.'s are: Norepinephrine 4.6% and 8.6% at 235 and 1096 pg/mL; Epinephrine 6.4% and 8.2% at 61and 917 pg/mL.

Urine catecholamines were measured by reversed phase HPLC with electrochemical detection after extraction with activated alumina. Urine intra-assay C.V.'s are: Norepinephrine 2.1% at 6.0 ng/ml; Epinephrine 3.9% at 2.3 ng/ml; Urine inter-assay C.V.'s are: Norepinephrine 13.8%, 9.0% and 11.9% at 1.3, 22, and 156 ng/ml, resp; Epinephrine 11.0%, 7.3%, and 8.7% at 0.96, 8.9, and 34 ng/ml, resp.

Serum C-Reactive Protein, High Sensitivity was measured on the Roche Cobas c311 chemistry analyzer (Roche Diagnostics, Indianapolis, IN 46250) by a latex particle enhanced immunoturbidimetric assay from Roche Diagnostics. Intra-assay CV's are 1.9%, 1.0%, and 0.2% at 0.107, 0.179, and 1.227 mg/dL respectively. Inter-assay CV's are 2.4%, 1.7%, and 3.4% at 0.107, 0.171, and 1.226 mg/dL respectively.

Interleukin 6, high sensitivity was measured by a quantitative two-site enzyme immunoassay from R & D Systems (Minneapolis, MN 55413). Intra-assay C.V.'s are 8.4%, 3.6% and 4.0% at 0.42, 3.88, and 9.77 pg/mL respectively. Inter-assay C.V.'s are 9.7%, 7.6%, and 7.7% at 0.52, 2.91, and 5.53 pg/mL respectively.
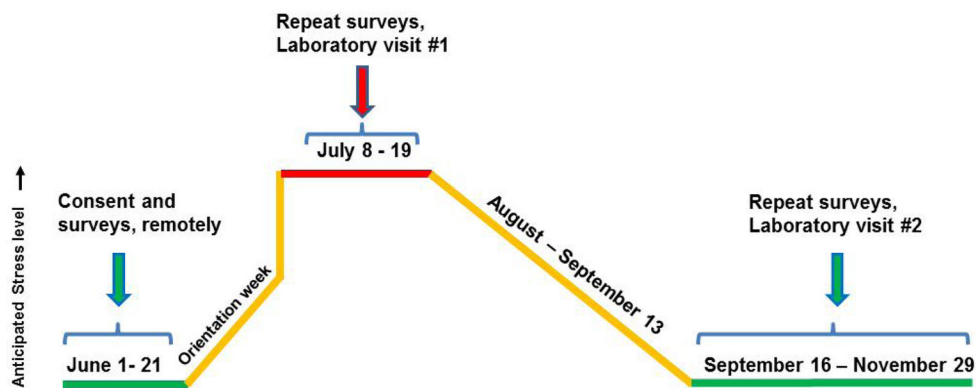
Figure 1. Study timeline

Incoming clinical anesthesia year-one (CA-1) trainees were evaluated in 2013 during three conditions. The month prior to starting anesthesia was considered baseline and psychological data were collected remotely. In-person visit 1 occurred in weeks 2 and 3 of the first month of CA-1 training. Follow-up visit 2 was identical to visit 1 and occurred during an operating room or pain rotation in the fall.
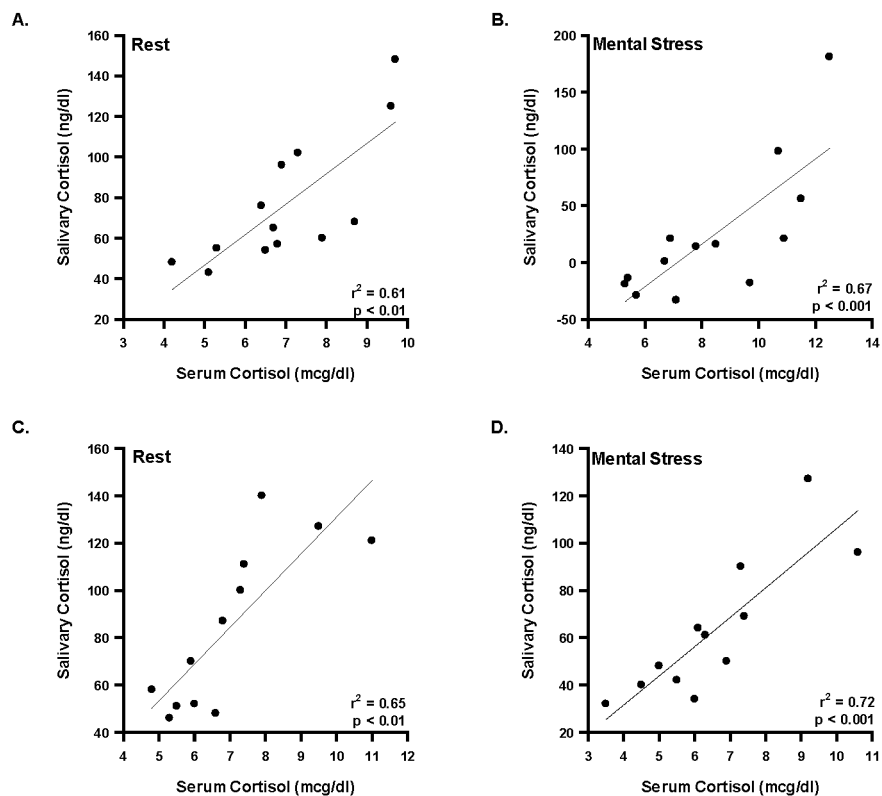
Figure 2. Linear regression analysis of serum versus salivary cortisol
A) displays the correlation between serum and salivary cortisol at rest during visit 1; B) displays the correlation between serum and salivary cortisol during mental stress in visit 1. C) displays the correlation between serum and salivary cortisol at rest during visit 2; D) displays the correlation between serum and salivary cortisol during mental stress in visit 2.

Table 1

Psychological variables and activity at screen, first month, and follow-up visit.

Variable	Screen	First month visit 1	Follow-up visit 2	Reference values
Cohen's PSS (0–56: low–high)	17.8 ± 6.5	23.6 ± 5.3	19.1 ± 6.1	25.0 ± 8.2[12]
Spielberger SAI (20–80: low–high)	34.5 ± 9.4	38.7 ± 10.7	32.7 ± 6.3	35.7 ± 10.4[17]
CD-RISC2 (0–8: low–high)	6.9 ± 1.0	6.6 ± 0.8	6.5 ± 0.9	6.9 ± 1.5[18]
Stress Level (0–10: low–high)	3.5 ± 1.8	5.9 ± 2.0	4.4 ± 1.7	4.2 ± 2.25[19]
Energy Level (0–10: low–high)	6.8 ± 2.2	5.4 ± 2.1	6.2 ± 1.5	
Concentration (0–10: poor–good)	7.1 ± 2.1	6.2 ± 1.2	6.5 ± 1.4	
Quality of Sleep (0–10: poor–good)	7.2 ± 2.5	5.8 ± 2.4	6.8 ± 1.5	
Est. Daily Physical Activity (METS)	7.3 ± 4.9	7.2 ± 4.2	6.3 ± 6.7	

Data are presented as mean ± SD. Data for the screen condition was collected by mail-in questionnaires prior to the start of residency, including estimated daily physical activity that was determined by the Minnesota Leisure-Time Physical Activity Questionnaire. PSS, perceived stress scale; SAI, state anxiety index; CD-RISC, Connor-Davidson Resiliency Scale abbreviated; METS, metabolic equivalents. As described in the Methods, reference values are published means from similar populations where available.

Table 2

Measured health behaviors and chronic stress biomarkers during study visits.

Variable	First month visit 1	Follow-up visit 2
Daily Energy Expenditure (Cal)	3021 ± 691	3111 ± 663
Daily Physical Activity > 3 METS (hr)	3.8 ± 1.4	4.1 ± 1.2
Daily Sleep (hrs)	6.5 ± 1.1	6.7 ± 1.2
Daily Sleep Efficiency (%)	83.8 ± 4.7	85.4 ± 5.4
Caloric Intake, 24-hr (Cal)	2349 ± 1282	2189 ± 871
• Fat Intake, 24-hr (g)	97.7 ± 57.9	81.5 ± 41.9
• Saturated Fat Intake, 24-hr (g)	36.7 ± 23.4	30.8 ± 21.3
• Carbohydrate Intake, 24-hr (g)	244.2 ± 148.5	244.7 ± 116.1
• Sodium Intake, 24-hr (mg)	4088 ± 1953	4287 ± 1523
Urine Cortisol, 24-hr (mcg/dl)	30.23 ± 14.02	29.42 ± 9.20
Urine Epinephrine, 24-hr (mcg/dl)	8.85 ± 6.01	8.46 ± 5.11
Urine Norepinephrine, 24-hr (mcg/dl)	36.62 ± 16.23	35.67 ± 10.04
Serum C-Reactive Protein (mg/dl)	0.066 ± 0.086	0.074 ± 0.077

Data are presented as mean ± SD. Data for the screen condition was collected by mail-in questionnaires prior to the start of residency, including estimated daily physical activity that was determined by the Minnesota Leisure-Time Physical Activity Questionnaire. PSS, perceived stress scale; SAI, state anxiety index; CD-RISC, Connor-Davidson Resiliency Scale abbreviated; METS, metabolic equivalents.

Table 3

Heart rate variability during supine rest and during mental stress

Variable	First month visit 1		Follow-up visit 2	
	Rest	**Mental stress**	**Rest**	**Mental stress**
Mean NN	1044.5 ± 177.1	811.1 ± 180.2	1062.9 ± 209.9	825.0 ± 151.1
SDNN (ms)	71.1 ± 38.9	77.0 ± 27.2	66.9 ± 27.7	75.6 ± 24.4
RMSSD (ms)	68.0 ± 56.9	42.1 ± 25.2	57.5 ± 27.2	42.1 ± 19.9
LF (ms^2)	750.1 ± 1212.6	330.1 ± 272.0	574.3 ± 881.6	329.0 ± 224.6
HF (ms^2)	567.1 ± 917.7	164.8 ± 127.2	455.1 ± 507.8	152.7 ± 80.6
LFnu	51.3 ± 14.1	62.3 ± 12.4	47.8 ± 16.4	60.9 ± 12.6
HFnu	44.8 ± 12.9	30.1 ± 12.4	48.3 ± 16.1	30.1 ± 10.3
LF/HF	1.37 ± 0.9	2.6 ± 1.6	1.3 ± 1.0	2.5 ± 1.7
Perceived Stress Score	24.1 ± 4.3		22.9 ± 3.4	

Data presented as mean ± SD. Perceived stress scores acquired immediately after stress trial as described in text. Mean NN, mean normal-to-normal interval; SDNN, standard deviation of the N-N intervals; RMSSD, square root of the mean squared differences of successive N-N intervals; LF, low frequency; HF, high frequency; LFnu, low frequency normalized units; HFnu, high frequency normalized units; LF/HF, LF-to-HF ratio; MAP, mean arterial pressure.

Table 4

Hemodynamics before, during, and recovery from mental stress

Variable	First month visit 1			Follow-up visit 2		
	Rest	**Mental stress**	**Recovery**	**Rest**	**Mental stress**	**Recovery**
HR (bpm)	64.0 ± 12.4	78.2 ± 16.1	63.6 ± 12.9	58.4 ± 21.1	69.9 ± 24.9	57.0 ± 19.8
SBP (mmHg)	129.9 ± 9.1	143.3 ± 12.4	136.9 ± 14.1	117.6 ± 36.8	132.1 ± 40.9	124.0 ± 38.8
DBP (mmHg)	75.0 ± 5.7	83.2 ± 7.8	77.8 ± 8.4	68.0 ± 21.2	75.6 ± 24.1	69.4 ± 21.8
MAP (mmHg)	95.5 ± 5.4	107.2 ± 9.3	100.2 ± 9.1	87.0 ± 27.0	97.9 ± 30.9	89.9 ± 28.1
Cardiac Output (L/min)	6.8 ± 1.4	8.3 ± 1.7	7.0 ± 1.4	6.3 ± 2.1	7.6 ± 2.5	6.5 ± 2.2
Stroke Volume (ml)	108.7 ± 21.3	108.3 ± 19.7	111.9 ± 21.0	102.6 ± 36.6	104.0 ± 36.4	107.5 ± 37.5
SVR (dyn·s/cm^5)	1172.8 ± 268.3	1079.6 ± 241.2	1180.5 ± 226.6	1122.2 ± 158.2	1036.5 ± 141.8	1126.3 ± 154.5

Data presented as mean ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic BP; MAP, mean arterial pressure; SVR, systemic vascular resistance.

Table 5

Stress biomarkers before and after mental stress

Variable	First month visit 1		Follow-up visit 2	
	Rest	**Mental stress**	**Rest**	**Mental stress**
Serum cortisol (mcg/dl)	7.01 ± 1.66	8.36 ± 2.46	7.0 ± 1.80	6.53 ± 1.96
Salivary cortisol (ng/dl)	76.7 ± 31.9	99.4 ± 63.5	84.3 ± 34.5	62.8 ± 28.8
Serum Epi (pg/ml)	13.7 ± 9.4	25.4 ± 16.1	17.3 ± 11.7	27.8 ± 12.3
Serum NE (pg/ml)	155.4 ± 53.0	203.7 ± 58.9	171.2 ± 52.4	212.1 ± 62.5
Serum IL-6 (pg/ml)	0.81 ± 0.69	0.83 ± 0.69	0.84 ± 0.71	0.85 ± 0.70

Data are presented as mean ± SD. Epi, epinephrine; NE, norepinephrine; IL-6, interleukin-6. Due to the counter-intuitive nature of cortisol decreasing in response to mental stress during visit 2, a linear regression analysis was highly significant for serum vs. salivary cortisol in all four conditions (rest, mental stress, visit 1, visit 2) as described in the text.

Table 6

Twenty-four hour ambulatory hemodynamics and night-time heart rate variability

Variable	First month visit 1	Follow-up visit 2
HR (bpm)		
24-hr	67.3 ± 10.6	70.1 ± 10.3
Day	70.6 ± 11.7	73.3 ± 10.5
Night	58.6 ± 8.8	60.3 ± 9.8
SBP (mmHg)		
24-hr	118.8 ± 11.7	119.4 ± 8.7
Day	121.7 ± 11.3	121.2 ± 7.6
Night	110.0 ± 13.5	109.4 ± 12.3
DBP (mmHg)		
24-hr	71.3 ± 8.6	71.3 ± 8.0
Day	75.1 ± 8.9	75.6 ± 8.4
Night	60.4 ± 8.9	59.1 ± 6.8
MAP (mmHg)		
24-hr	86.7 ± 8.7	86.4 ± 7.0
Day	90.1 ± 8.5	91.1 ± 8.1
Night	76.8 ± 9.3	75.4 ± 7.4
Night-time HRV		
Mean NN	1114.3 ± 179.8	1009.1 ± 158.5
SDNN (ms)	131.0 ± 24.8	150.0 ± 85.5
RMSSD (ms)	66.6 ± 22.8	70.3 ± 59.6
LF (ms^2)	869.5 ± 695.2	906.3 ± 972.4
HF (ms^2)	721.0 ± 585.9	976.4 ± 1705.3
LFnu%	54.4 ± 10.1	58.2 ± 10.5
HFnu%	45.6 ± 10.1	41.8 ± 10.5
LF:HF ratio	1.31 ± 0.62	1.53 ± 0.59

Data are presented as mean ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HRV, heart rate variability. LFnu% is derived from LF/LF+HF and HFnu% is derived from HF/LF+HF as described in the text.