Defence Research and Development Canada | Recherche et développement pour la défense Canada

CAN UNCLASSIFIED

Biological Response to Stress During Battlefield Trauma Training:Live Tissue Versus High-Fidelity Patient Simulator

Henry Peng, PhD
Oshin Vartanian, PhD
Shawn G. Rhind, PhD
Jerzy Jarmasz, PhD
DRDC – Toronto Research Centre

Catherine Tenn, PhD
DRDC – Suffield Research Centre

COL (Ret.) Homer Tien, MD
Sunnybrook Health Sciences Centre, Toronto

LTC Andrew Beckett, MD
McGill University, Montreal
Royal Canadian Medical Services, Ottawa

Name of Journal: Military Medicine
Volume number: Vol. 00, 0/0 2018

Date of Publication from Ext Publisher: June 2018

Defence Research and Development Canada
External Literature (P)
DRDC-RDDC-2018-P088
June 2018

Canada

IMPORTANT INFORMATIVE STATEMENTS

This document was reviewed for Controlled Goods by Defence Research and Development Canada (DRDC) using the Schedule to the *Defence Production Act*.

Biological Response to Stress During Battlefield Trauma Training: Live Tissue Versus High-Fidelity Patient Simulator

Henry T. Peng, PhD; Catherine Tenn, PhD†; Oshin Vartanian, PhD*; Shawn G. Rhind, PhD*; Jerzy Jarmasz, PhD*; COL (Ret.) Homer Tien, MD‡; LTC Andrew Beckett, MD§‖; For the LT-SIM study group*

ABSTRACT Introduction: Tactical Combat Casualty Care (TCCC) training imposes psychophysiological stress on medics. It is unclear whether these stress levels vary with the training modalities selected. It is also unclear how stress levels could have an impact on medical performance and skill uptake. Materials and Methods: We conducted a pilot study to compare the effects of live tissue (LT) with a high-fidelity patient simulator (SIM) on the level of stress elicited, performance, and skill uptake during battlefield trauma training course in an operating room (OR) and in a simulated battlefield scenario (field). In the report, we studied the effects of training modalities and their changes on stress levels by measuring different biomarkers (salivary amylase, plasma catecholamines, and neuropeptide Y) at various time points during the trauma training course. Results: We found that the training resulted in significant psychophysiological stress as indicated by elevated levels of various biomarkers relative to baseline immediately after both OR and field assessment ($p < 0.05$). Compared with pre-OR levels, the LT training in the OR resulted in significant increases in the plasma levels of epinephrine, norepinephrine, and neuropeptide ($p = 0.013$, 0.023, 0.004, respectively), whereas the SIM training in the OR resulted in significant increases in the plasma levels of norepinephrine and neuropeptide ($p = 0.003$ and 0.008). Compared with pre-field levels, we found significant increases in plasma epinephrine concentration in the SIM group ($p = 0.016$), plasma norepinephrine concentration in the LT group ($p = 0.015$), and plasma neuropeptide Y concentration in both LT ($p = 0.006$) and SIM groups ($p = 0.029$). No differences in the changes of biomarker levels were found between LT and SIM groups in the OR and field. Compared with pre-field levels, the testing on the same modality as that in the OR in the simulated battlefield resulted in significant increases in norepinephrine and neuropeptide levels ($p = 0.013$ and 0.015), whereas the testing on different modalities resulted in significant increases in amylase, epinephrine, and neuropeptide levels ($p = 0.016$, 0.05, 0.018, respectively). There was a significantly larger increase in plasma norepinephrine concentration ($p = 0.031$) and a trend toward a greater increase in the salivary amylase level ($p = 0.052$) when the field testing involved a different modality than the OR compared with when OR and field testing involved the same modality. Although most of the biomarkers returned to baseline levels after 24 h, plasma norepinephrine levels remained significantly higher regardless of whether field testing occurred on the same or different modality compared with OR ($p = 0.040$ and 0.002). Conclusion: TCCC training led to significant increase in psychophysiological stress, as indicated by elevated levels of various biomarkers. The training modalities did not result in any differences in stress levels, whereas the switch in training modalities appeared to elicit greater stress as evidenced by changes in specific biomarkers (amylase and norepinephrine). A comparative study with a larger sample size is warranted.

INTRODUCTION

Both live tissue and simulator have been used for medical training including trauma skills acquisition.[1–3] However, the use of live animals in medical education has been controversial for more than a decade.[4] Although ethical issues and advances in simulator technologies have led to a decline in the use of live animals, there is currently insufficient evidence for its replacement. A recent study suggested combined live tissue and simulation training for emergency procedures[5] given that the replacement of live tissue with simulation remains in debate.[6,7] This ongoing debate also attributes to the lack of studies on the differences in stress response and its relationship with skill uptake between the two methods for trauma training. On the other hand, the medical training may impose a broad spectrum of stressors

*Defence Research and Development Canada, Toronto Research Centre, Toronto, ON M3K 2C9, Canada.
†Defence Research and Development Canada, Suffield Research Centre, Medicine Hat, AB T1A 8K6, Canada.
‡Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada.
§McGill University, Montreal, QC H3Z 2G5, Canada.
‖Royal Canadian Medical Services, Ottawa, ON K1A 0K2, Canada.
doi: 10.1093/milmed/usx236

on health care personnel;[8] however, it is unclear if there are any differences in the stress response to medical training using different methods and how the stress response may be associated with medical performance and skills uptake. Daglius et al reported that psychological stress was increased as measured by the changes in salivary amylase levels during emergency care training in a real medical situation, but not in a simulated scenario.[9] Ingacio et al found no significant differences in acute stress and performance between high-fidelity simulators and standardized patient modality for preparing students for managing deteriorating patients.[10] Generally, studies have shown that stress could enhance performance and retention of skills in medical training,[11,12] but excessive stress may impair performance and learning outcomes.[13] This is in agreement with the inverted U-shape theory for stress–performance relationship.[14] On the other hand, the learners' perception of their competence and performance during training may modify their stress.[13] For example, novices may be unaware of their skills or performance gaps and thus may show a different stress response from learners with prior knowledge. There may exist a personal task-dependent threshold above which stress becomes detrimental to medical performance.[15] As a result, combined LT and SIM training was warranted to utilize the best aspects of each training model in a procedure-specific approach.

Tactical Combat Casualty Care (TCCC) training provides trainees with the particular stress of performing lifesaving operations on a patient under battlefield conditions. There could be technically two stressors in one: battlefield conditions and the emotional strain of potentially losing or being unable to help a patient. It is generally believed that the above stressors are desirable and should be experienced by trainees during training and that live tissue training delivers this stress better than simulator. A subjective assessment of medical students during their surgical clerkship showed that students perceived increased stress levels in a live tissue animal laboratory compared with a trainer-based simulation workshop.[16] It is thus important to confirm using objective assessment if the TCCC training actually induces stress as it is intended to do and if there is a difference in stress levels between LT and SIM training, and how the training-induced stress affects medical performance and learning.

Biomarkers have been used to measure stress levels during medical training. For example, salivary cortisol and amylase were used as stress markers during pre-hospital emergency medicine training using either high-fidelity simulation or standardized patients[17] and different simulators.[18] Furthermore, higher cortisol levels were associated with greater knowledge acquisition in a birthing simulation training model,[19] whereas blood cortisol levels showed no association with performance during simulated cardiopulmonary resuscitation.[20] In addition, salivary amylase was not associated with performance levels during human-based anesthesia simulator training.[21]

Recently, we conducted a pilot study comparing live tissue (LT) model with a high-fidelity patient simulator (SIM) for battlefield trauma training of Canadian Armed Forces (CAF) medics. In a previous paper, we reported that there was no difference in performance between medics trained on LT and SIM, even though medics preferred the LT model over SIM as indicated in their exit surveys and interviews.[22] We also studied hypothalamic–pituitary–adrenal (HPA) responses as measured by salivary cortisol and dehydroepiandrosterone and found a positive correlation between stress and cognitive function during training, but no associations of training modalities with stress levels or cognitive function in the study participants.[23] In addition to the activation of HPA axis, training-induced acute stress may activate the sympathetic nervous system. Therefore, this article extends our investigation of the psychophysiological stress response as measured by changes in sympathetic biomarker levels of salivary amylase, circulating catecholamines, and neuropeptide Y during the battlefield trauma training. The main objective of this article was to elucidate various sympathetic components of stress response during a combat casualty care training course on two different training modalities in the OR and in a simulated battlefield scenario and determine if stress levels would be affected by training modalities and modality changes.

MATERIALS AND METHODS

Participants

Twenty healthy CAF Medical Technicians (medics) were recruited from military bases across Canada for a combat casualty lifesaving training course. The participants were all naïve to this training course and were screened to ensure that they were free from psychotropic medication, steroids or drug abuse, and any transitory or chronic conditions (e.g., Addison and Cushing syndrome). A written informed consent was obtained from all the participants. The study was approved by the Human Research Ethics Committee at Defence Research and Development Canada. In addition, while conducting this research, the authors adhered to the "Guide to the care and use of experimental animals" and "The Ethics of Animal Experimentation" published by the Canadian Council of Animal Care.

Procedures

The study participants were instructed to refrain from eating or drinking 1 hr before the study starting so as not to interfere with biomarker evaluation. The study details have been described in our previous papers.[22,23] Briefly, the study began with a single day of classroom pedagogical instruction and collection of demographics. Baseline biological samples (i.e., saliva and blood) were collected on Day 2 in the morning before the commencement of didactic training. Additional salivary samples were collected in the afternoon in order to calibrate for circadian variation of salivary amylase levels. After completing baseline sample collection, participants were randomly assigned to one of the two training

modalities: anesthetized porcine model (Live Tissue; LT) or a high-fidelity patient simulator (CAESAR; CAE Healthcare, Saint-Laurent, Quebec, Canada; SIM). The participants had never been exposed to these modalities before this study. They were initially trained on five different TCCC lifesaving procedures, that is, open cricothyrotomy, needle decompression of a tension pneumothorax, packing of a junctional, exsanguinating wound, tourniquet application on an injured extremity, sternal intraosseous insertion, using either the LT (designated as LT group) or the SIM model (designated as SIM group), and then evaluated on that modality in a controlled operating room (OR) environment. Both saliva and blood were collected immediately before and after the OR assessment. The next day, the study participants were tested in a simulated combat field environment involving simulated gun fire, explosion, and smoke. The participants were again tested on the same five lifesaving skills, but using either the same (designated as the same modality group) or different modalities (designated as the different modality group) as they were tested in the OR. As a result, half of the participants ended up being tested in the field on the same modality as they were tested on in the OR (static model) and the other half switched to the other modality (dynamic model). All groups were exposed to the same training environment not specific to an individual procedure. Both saliva and blood were collected immediately before and after the field assessment. The study ended 24 hr after the field testing with recovery sample collections of saliva and blood. Each sample was analyzed in duplicate and the difference between duplicate results of a sample was less than the coefficient of variation of each biomarker assay as detailed below.

Measurement of Salivary Amylase

Saliva was collected using Salivette (SARSTEDT Inc., Montreal, Quebec, Canada). The participants were instructed to chew on a synthetic swab gently for 45 s and then to allow the swab to soak in their mouths for another 45 s. The swab was spat into a Salivette and was immediately centrifuged at 2700 × *g* at 4°C for 5 min to yield clear saliva. The saliva samples were frozen and stored at −70°C until analyses were conducted.

The frozen saliva samples collected using Salivette were thawed at room temperature, vortexed, and centrifuged at 1500 × *g* for 15 min. The saliva sample was analyzed for amylase activity using a standard laboratory kinetic enzyme assay kit (Salimetrics, LLC, State College, PA, USA) as per manufacturer's instructions. The assay possesses intra- and inter-assay coefficients of variation of ≤7.2% and ≤5.8%, respectively, and analytical sensitivity of 3.28 U/mL, according to the manufacturer's technical note.

Measurement of Plasma Catecholamines and Neuropeptide Y

Blood was drawn via phlebotomy from each participant into BD vacutainers containing EDTA (Fisher Scientific, Nepean, Ontario, Canada). The blood sample was centrifuged at 1300 × *g* for 10 min at 4°C and plasma was aliquoted into Eppendorf tubes and kept frozen at −70°C until analyses were conducted.

Plasma catecholamines (epinephrine and norepinephrine) were analyzed using an enzyme immunoassay kit (ALPCO Diagnostics, Salem, NH, USA) as per manufacturer's instructions. The assay possesses intra- and inter-assay coefficients of variation of 15.0% and 13.2% for epinephrine and 16.1% and 8.5% for norepinephrine, respectively, in the low concentration range and analytical sensitivity of 10 pg/mL for epinephrine and 50 pg/mL for norepinephrine, according to the manufacturer's technical note.

Plasma neuropeptide Y was analyzed using an enzyme immunoassay kit (EMD Millipore, St. Charles, MO, USA) as per manufacturer's instructions. The assay possesses intra- and inter-assay coefficients of variation of ≤4.3% and ≤4.5%, respectively, and analytical sensitivity of 2 pg/mL, according to the manufacturer's technical note.

Data Analysis

Changes in biomarker levels were calculated by subtracting baseline or pre-testing values from values at other time points (post-OR, post-field, and recovery), respectively, for each biomarker for the same participant.[24,25] For salivary amylase, the baseline values at either the morning or afternoon were used in correspondence to the time (morning or afternoon) when salivary samples were collected in the OR and field to account for circadian variations. In such a way, each participant acted as their own control. One-sample *t*-test was used against a value of zero (0) to determine if any changes in biomarker levels relative to baseline were significant.[8] Independent *t*-test was performed to compare the changes between the two groups at the same time points.

All data were presented as mean ± standard deviation (SD) and were analyzed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA). For all statistical analyses, $p \leq 0.05$ was considered significant.

RESULTS

Significant increases (above 0) were observed in all biomarker levels relative to baseline after the testing in the OR and field, as shown in Figures 1 and 2. Specifically, there were significant increases in salivary amylase activity ($p = 0.003$ and 0.001), plasma epinephrine concentration ($p = 0.014$ and 0.002), plasma norepinephrine concentration ($p = 0.001$ and < 0.001), and plasma neuropeptide Y concentration ($p = 0.004$ and 0.015) in both LT and SIM groups in the OR (Fig. 1). There were no significant differences in the changes of salivary amylase level ($p = 0.42$), plasma epinephrine concentration ($p = 0.93$), plasma norepinephrine concentration ($p = 0.47$), and plasma neuropeptide Y concentration ($p = 0.58$) between the LT and SIM groups in the OR.

Similarly, in the field, there were significant increases (larger than 0) in salivary amylase level ($p = 0.010$ and 0.008), plasma

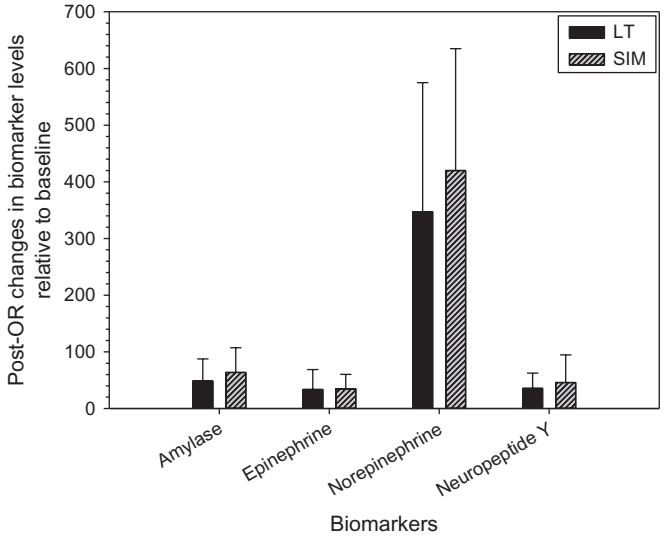

FIGURE 1. Post-OR changes in biomarker levels relative to baselines in the live tissue (LT) and simulator (SIM) groups. Data represent mean ± SD ($n = 10$). Significant increases in all biomarker levels relative to baselines were observed after the testing in the operating room (OR) ($p < 0.05$).

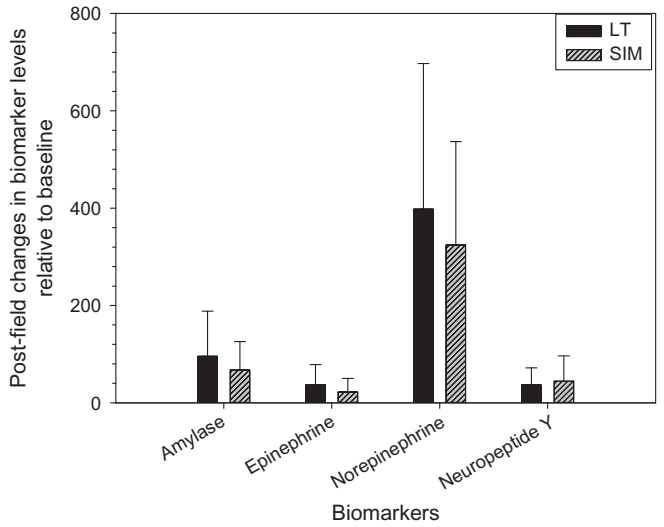

FIGURE 2. Post-field changes in biomarker levels relative to baselines in the live tissue (LT) and simulator (SIM) groups. Data represent mean ± SD ($n = 10$). Significant increases in all biomarker levels relative to baselines were observed after the testing in the battlefield scenario (field) ($p < 0.05$).

epinephrine concentration ($p = 0.021$ and 0.033), plasma norepinephrine concentration ($p = 0.002$ and 0.001), and plasma neuropeptide Y concentration ($p = 0.013$ and 0.025) in both LT and SIM groups. There were no significant differences in the changes of salivary amylase level ($p = 0.45$), plasma epinephrine concentration ($p = 0.37$), plasma norepinephrine concentration ($p = 0.53$), and plasma neuropeptide Y concentration ($p = 0.72$) between the LT and SIM groups.

Furthermore, significant increases in post-field biomarker levels relative to baseline were observed in the same and different modality groups for salivary amylase ($p = 0.037$ and 0.002), plasma epinephrine ($p = 0.030$ and 0.016), plasma

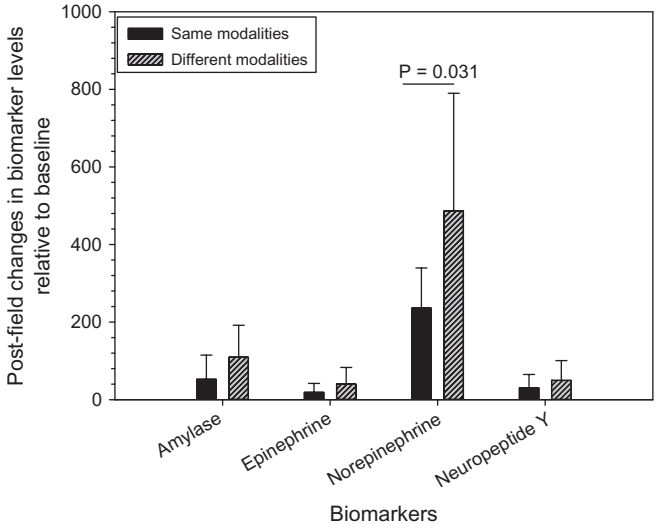

FIGURE 3. Post-field changes in biomarker levels relative to baselines in the same and different modality groups. Data represent mean ± SD ($n = 10$). Significant increases in all biomarker levels relative to baselines were observed after the testing in the battlefield scenario (field) ($p < 0.05$). A significant difference was observed in the levels of plasma norepinephrine ($p = 0.031$) between the same and different modality group.

norepinephrine ($p < 0.001$ and $= 0.001$), and plasma neuropeptide Y ($p = 0.025$ and 0.014), respectively (Fig. 3). There were no significant differences in the changes of salivary amylase level ($p = 0.11$), plasma epinephrine concentration ($p = 0.18$), and plasma neuropeptide Y concentration ($p = 0.37$) between the same and different modality groups in the field. However, there was a significant difference in plasma norepinephrine ($p = 0.031$) between the same and different modality groups in the field.

Further analyses indicated no significant differences in the biomarker changes relative to baseline between OR and field for amylase ($p = 0.059$), epinephrine ($p = 0.52$), norepinephrine ($p = 0.66$), and neuropeptide Y ($p = 0.97$).

Figures 4 and 5 depict changes in biomarker levels relative to pre-testing levels in the OR and the field, respectively. Compared with pre-OR testing, we found significant increases in epinephrine, norepinephrine, and neuropeptide levels in the LT group ($p = 0.013$, 0.023, and 0.004) and in norepinephrine and neuropeptide levels in the SIM group ($p = 0.003$ and 0.008) (Fig. 4). There were no significant differences in the changes of amylase ($p = 0.98$), epinephrine ($p = 0.66$), norepinephrine ($p = 0.40$), and neuropeptide ($p = 0.40$) between the LT and SIM groups.

Compared with pre-field testing, we found significant increases (larger than 0) in plasma epinephrine concentration in the SIM group ($p = 0.016$), plasma norepinephrine concentration in the LT group ($p = 0.015$), and plasma neuropeptide Y concentration in both LT ($p = 0.006$) and SIM groups ($p = 0.029$), but no significant changes in salivary amylase level in the LT group ($p = 0.055$) and SIM group ($p = 0.14$), plasma epinephrine concentration in the LT group ($p = 0.153$), and plasma norepinephrine concentration in the SIM group

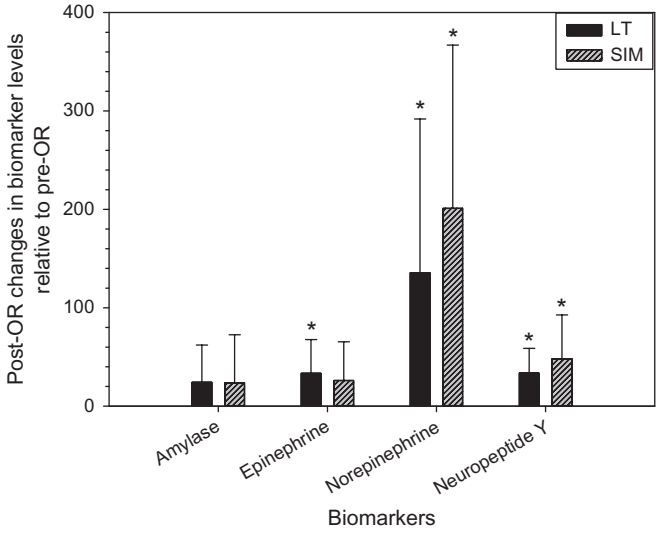

FIGURE 4. Changes in biomarker levels relative to pre-testing in the operating room (OR). Data represent mean ± SD ($n = 10$). *Significant increases in epinephrine, norepinephrine, and neuropeptide levels in the live tissue (LT) group ($p = 0.013$, 0.023, and 0.004) and in norepinephrine and neuropeptide levels in the simulator (SIM) group ($p = 0.003$ and 0.008).

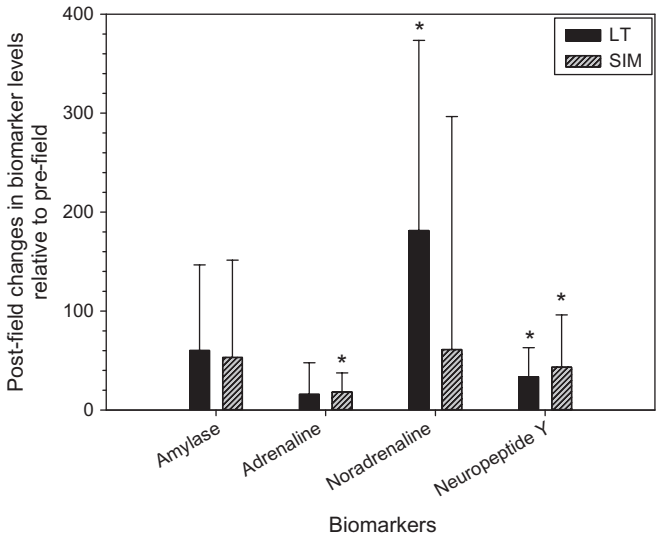

FIGURE 5. Post-field changes in biomarker levels relative to pre-field in the live tissue (LT) and simulator (SIM) groups. Data represent mean ± SD ($n = 10$). *Significant increases (larger than 0) in plasma adrenaline concentration in the SIM group ($p = 0.016$), plasma noradrenaline concentration in the LT group ($p = 0.015$), and plasma neuropeptide Y concentration in both LT ($p = 0.006$) and SIM groups ($p = 0.029$).

($p = 0.43$). In addition, a comparison between the LT and SIM groups found no significant differences in the changes of salivary amylase level ($p = 0.87$), plasma epinephrine concentration ($p = 0.84$), plasma norepinephrine concentration ($p = 0.23$), and plasma neuropeptide Y concentration ($p = 0.62$).

Comparing changes in the biomarker levels relative to pre-testing levels indicated no significant differences between OR and field for amylase ($p = 0.13$), epinephrine ($p = 0.16$), norepinephrine ($p = 0.46$), and neuropeptide Y ($p = 0.87$).

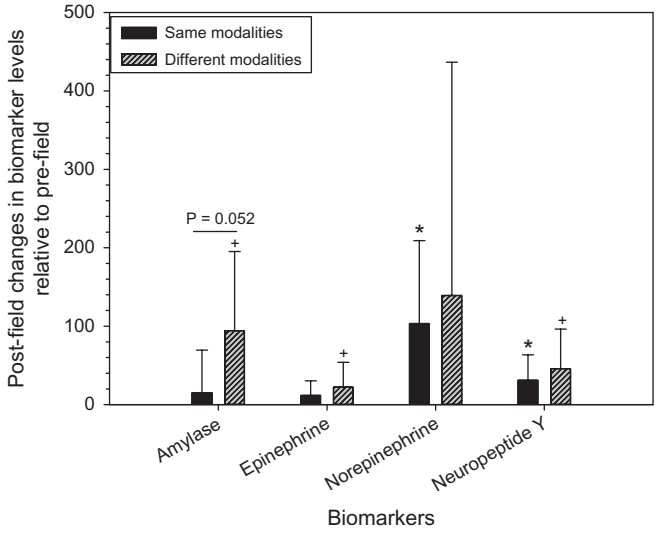

FIGURE 6. Changes in biomarker levels relative to pre-testing in the battlefield scenario (field). Data represent mean ± SD ($n = 10$). *Significant increases in norepinephrine and neuropeptide levels in the same modality group ($p = 0.013$ and 0.015); +significant increases in amylase, epinephrine, and neuropeptide levels in the different modality group ($p = 0.016$, 0.05, and 0.018). There was a close to significant difference in the changes of salivary amylase levels ($p = 0.052$) between the same and different modality groups.

Furthermore, we found significant increases in norepinephrine and neuropeptide levels in the same modality group ($p = 0.013$ and 0.015) and in amylase, epinephrine, and neuropeptide levels in the different modality group ($p = 0.016$, 0.05, and 0.018) (Fig. 6). There was no significant difference in plasma epinephrine ($p = 0.38$), norepinephrine ($p = 0.73$), and neuropeptide Y concentration ($p = 0.45$) between the same and different modality groups.

Figure 7 shows significantly higher levels of plasma norepinephrine ($p = 0.001$ and < 0.001) in both same and different modality groups and lower plasma neuropeptide Y ($p = 0.006$) in the same modality group. There were no significant differences between recovery and baseline levels of amylase ($p = 0.16$, 0.87) and epinephrine ($p = 0.30$, 0.68) in both same and different modality groups and neuropeptide ($p = 0.84$) in the different modality group. Comparing the same and different modality groups indicates no significant differences in the changes of recovery levels of salivary amylase ($p = 0.34$), plasma epinephrine ($p = 0.49$), and plasma norepinephrine concentration ($p = 0.36$), but a significant difference in plasma neuropeptide Y ($p = 0.037$).

DISCUSSION

As expected, the data clearly showed that regardless of the training modality (LT and SIM) or the settings (OR and field), medics experienced significant acute stress immediately after the OR and field testing and recovered well at the end of the training course (next day after the field testing). The sympathetic stress response as indicated by elevated

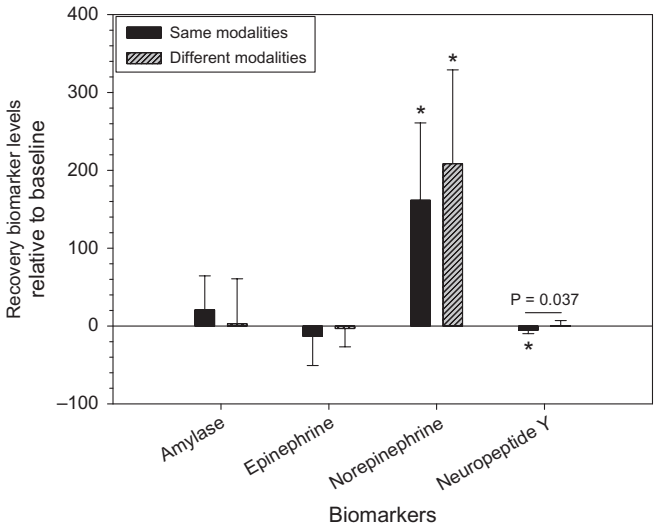

FIGURE 7. Recovery biomarker levels relative to baselines 24 h after the testing in the field. Data represent mean ± SD ($n = 10$). *Significantly higher levels of plasma norepinephrine ($p = 0.001$ and < 0.001) were seen in both same and different modality groups. In addition, a lower plasma neuropeptide Y level ($p = 0.006$) was observed in the same modality group. There was a significant difference in the plasma neuropeptide Y levels ($p = 0.037$) between the same and different modality groups.

salivary and plasma biomarker levels was consistent with other studies investigating stress response in army nurses during combat casualty simulation[25] and human-based anesthesia simulator training,[21] where the salivary amylase activity was shown to increase. Our study demonstrated that plasma neuropeptide Y levels increased in medics after the trauma training, which is consistent with the increased neuropeptide Y concentrations observed in humans exposed to military survival training.[26] Second, the medics might have experienced anticipatory stress immediately before the OR and field testing, leading to increased levels of certain biomarkers. Such anticipatory stress has been reported by others who studied the impact of acute stress on medical residents' performance during simulated resuscitation.[27] Therefore, we also evaluated the stress response based on the changes in biomarker levels relative to pre-OR and pre-field and further confirmed the elevated stress levels by the training. However, unlike the changes relative to baselines, not all biomarker levels significantly changed relative to pre-OR and field. This may be due to increased stress level before the testing from anxiety. The training modality in the OR and field had no further impact on the changes in stress levels relative to either baseline or pre-testing. This finding is consistent with our previous report from the same study where the stress responses were measured by salivary cortisol, dehydroepiandrosterone, and self-report.[23] Although higher levels of stress were expected in the field than in the OR due to the inclusion of external stressors such as fear, loud, and noises, the comparable changes in the biomarker levels between the OR and field imply that acclimatization in the OR may have occurred resulting in the attenuation of stress response in the field.

Importantly, it appears that the switch of training modalities in the field could lead to more stress, which was elucidated by the increase in plasma norepinephrine and salivary amylase levels. The lack of compatibility between LT and SIM had the effect of making the task more difficult for trainees whose training modalities were switched. Thus, it could be reasonably expected that this switch could also induce more stress. This is consistent with our previous findings that the modality changes led to a higher fail rate for some of individual TCCC skills/steps.[22] These results suggest that the skills learned in one modality did not transfer well to the other modality, likely because of the wide difference in respective perceptual cues and behaviors provided by each model. However, it is unclear whether the drop in performance was because of more stress or mainly incompatibility between the two modalities. In addition, it is difficult to elucidate the exact source of stress. It may be not only from the scenario difficulty but also from emotions, noises, fear of the simulated combat environment, the subjective perception of being appraised, or anxiety due to the presence of the evaluators. It should be noted that acclimatization in the OR might influence the stress response in the field. To our knowledge, we are the first to investigate the effects of training modalities on specific adrenergic stress biomarkers and to demonstrate increased stress levels when changing training modalities.

In our previous paper, stress levels were measured by cortisol and dehydroepiandrosterone levels based on the activation of the HPA axis.[23] In this article, amylase and catecholamines (epinephrine and norepinephrine) were used as biomarkers for objective measures of stress that activates the sympathetic nervous system.[28,29] Compared with cortisol, amylase reacts more rapidly to a psychological stressor with no carryover effect.[30] Furthermore, amylase provided a more sensitive measure of the stress response than cortisol during pre-hospital emergency medicine training.[17] In contrast, catecholamines have not been widely used for stress measures in medical training, whereas neuropeptide Y is relatively unknown for its role in stress response. These findings support the use of sympathetic biomarkers as objective measures of stress response to TCCC training in future studies.

Although both biomarkers decreased significantly at recovery, plasma norepinephrine concentration remained higher than baseline values, suggesting sustained stress afterward, whereas plasma neuropeptide Y concentration was below baseline value in the same modality group. These findings are consistent with those reported by Morgan III et al who showed that plasma norepinephrine concentration remained significantly higher at recovery than at baseline while plasma neuropeptide Y was below baseline.[24]

Although not always statistically significant, the increases in biomarker levels in the different modality group were generally larger than in the same modality counterpart following the battlefield scenario. This consistent trend suggests that switching of modalities could contribute to a larger stress response in trainees – an important finding particularly in

light of our low sample size (and associated statistical power). In addition, the sensitivity and specificity of each biomarker in response to stress may be different. As a result, the increased stress resulting from the modality changes in the field did not reach significance as measured by all biomarkers. A larger sample size is required to further confirm the finding.

Out study has a number of limitations. First, the sample size is relatively small. Larger sample size would have given us more statistical power to probe biomarker responses and explore their relationships with performance in the combat trauma training on different modalities. With larger sample size, we may have also been able to compare the stress response to the medical training among the four conditions in the study (OR training modality field testing modality: LT-LT, LT-SIM, SIM-LT, and SIM-SIM) to show the effects of OR modality and its transition in the simulated battlefield. Second, stress was not measured by biomarkers during the training course to avoid interning with the medics' activities while they were being evaluated on their performance. Physiological measures with minimal interference with the training (e.g., heart rate) could provide more information about the relationship between real-time stress and each specific skill during the training. Furthermore, the influence of other stressors such as fear due to the simulated combat environment or intimidation by the evaluators could be explored.

CONCLUSION

This study provides new information to support previous findings that medical training including battlefield trauma training on either living tissue or simulator models imposes stress and activates the sympathetic nervous system as evidenced by the elevation of multiple sympathetic biomarkers, both in saliva and plasma. The training modality might not make any difference in the effect on the degree of stress, but changing modalities could lead to more stress and increases in biomarker levels. Integrating the biomarker measures of stress in combat trauma training may help to understand an individual's stress management and help optimize training programs for medical care providers. Future studies with a larger sample size and real-time stress measures are warranted.

ACKNOWLEDGMENTS

The LT-SIM study group consisted of Kristen Blackler, Ann-Renee Blais, Fethi Bouak, Norleen Caddy, Capt Dylan Pannell, Doug Saunders, Ingrid Smith, and Wendy Sullivan-Kwantes. This manuscript is dedicated to the memory of LCol Erin Savage. We would like to acknowledge the following personnel from Defence Research and Development Canada: Stephen Bjarnason, Michelle Garrett, Corry Byrne, Cory Vair, Danielle Poissant, Kendal Weatherby, Ira Hill, Capt Russell McAllister, Aidan Thompson and Blake Martin, as well as Matthew Jubelius from Medicine Hat College, Alberta, Canada. The authors also wish to thank The Technical Cooperative Panel HUM TP12 for their valuable comments and insights on the topic of medical modeling and simulation versus live tissue training.

REFERENCES

1. da Luz LT, Nascimento B, Tien CH, et al: Current use of live tissue training in trauma: a descriptive systematic review. Can J Surg 2015; 58 (3 Suppl 3): S125–S34.
2. Lineberry M, Walwanis M, Reni J, et al: Comparative research on training simulators in emergency medicine: a methodological review. Simul Healthc 2013; 8(4): 253–61.
3. Gala SG, Goodman JR, Murph MP, et al: Use of animals by NATO countries in military medical training exercises: an international survey. Mil Med 2012; 177(8): 907–09.
4. Hansen LA, Boss GR: Use of live animals in the curricula of U.S. Medical schools: survey results from 2001. Acad Med 2002; 77(11): 1147–49.
5. Barnes SL, Bukoski A, Kerby JD, et al: Live tissue versus simulation training for emergency procedures: is simulation ready to replace live tissue? Surgery 2016; 160(4): 997–1007.
6. Barnes SL, Kerby J, Armstrong J, et al: Response to: comment on: live tissue versus simulation training for emergency procedures: is simulation ready to replace live tissue? Surgery 2017; 161(5): 1464–1465.
7. Hart D, McNeil MA, Hegarty C, et al: Literature evidence on live animal versus synthetic models for training and assessing trauma resuscitation procedures. Journal of Special Operations Medicine 2016; 16(2): 44–51.
8. Arora S, Russ S, Petrides KV, et al: Emotional intelligence and stress in medical students performing surgical tasks. Acad Med 2011; 86(10): 1311–17.
9. Daglius Dias R, Scalabrini Neto A: Stress levels during emergency care: a comparison between reality and simulated scenarios. J Crit Care 2016; 33: 8–13.
10. Ignacio J, Dolmans D, Scherpbier A, et al: Comparison of standardized patients with high-fidelity simulators for managing stress and improving performance in clinical deterioration: a mixed methods study. Nurse Educ Today 2015; 35(12): 1161–68.
11. DeMaria S Jr, Bryson EO, Mooney TJ, et al: Adding emotional stressors to training in simulated cardiopulmonary arrest enhances participant performance. Med Educ 2010; 44(10): 1006–15.
12. DeMaria S Jr, Levine A: The use of stress to enrich the simulated environment. In: The Comprehensive Textbook of Healthcare Simulation, pp 65–72. Edited by Levine A, DeMaria S Jr, Schwartz A, Sim A New York, NY, Springer, 2013.
13. Bong CL, Fraser K, Oriot D: Cognitive load and stress in simulation. In: Comprehensive Healthcare Simulation: Pediatrics, pp 3–17. Edited by Grant VJ, Cheng A. Cham, Switzerland, Springer International Publishing, 2016.
14. Hancock PA, Warm JS: A dynamic model of stress and sustained attention. Human Factors 2003; 31: 519–37.
15. LeBlanc VR: The effects of acute stress on performance: implications for health professions education. Acad Med 2009; 84(10): S25–33.
16. Daly SC, Wilson NA, Rinewalt DE, et al: A subjective assessment of medical student perceptions on animal models in medical education. J Surg Educ 2014; 71(1): 61–4.
17. Valentin B, Grottke O, Skorning M, et al: Cortisol and alpha-amylase as stress response indicators during pre-hospital emergency medicine training with repetitive high-fidelity simulation and scenarios with standardized patients. Scand J Trauma Resusc Emerg Med 2015; 23(1): 31.
18. Müller MP, Hänsel M, Fichtner A, et al: Excellence in performance and stress reduction during two different full scale simulator training courses: a pilot study. Resuscitation 2009; 80(8): 919–24.
19. Lee H, Park J, Kim S, et al: Cortisol as a predictor of simulation-based educational outcomes in senior nursing students: a pilot study. Clin Simul Nurs 2016; 12(2): 44–8.
20. Hunziker S, Semmer NK, Tschan F, et al: Dynamics and association of different acute stress markers with performance during a simulated resuscitation. Resuscitation 2012; 83(5): 572–78.
21. McKay KAC, Buen JE, Bohan KJ, et al: Determining the relationship of acute stress, anxiety, and salivary α-amylase level with performance of student nurse anesthetists during human-based anesthesia simulator training. AANA J 2010; 78(4): 301–09.

22. Savage EC, Tenn C, Vartanian O, et al: A comparison of live tissue training and high-fidelity patient simulator: a pilot study in battlefield trauma training. J Trauma Acute Care Surg 2015; 79(4): S157–S63.
23. Vartanian O, Tenn C, Sullivan-Kwantes W, et al: Battlefield trauma training: a pilot study comparing the effects of live tissue vs. high-fidelity patient simulator on stress, cognitive function and performance. Mil Psychol 2017; 29(4): 345–54.
24. Morgan CA III, Wang S, Rasmusson A, et al: Relationship among plasma cortisol, catecholamines, neuropeptide y, and human performance during exposure to uncontrollable stress. Psychosom Med 2001; 63(3): 412–22.
25. McGraw LK, Out D, Hammermeister JJ, et al: Nature, correlates, and consequences of stress-related biological reactivity and regulation in army nurses during combat casualty simulation. Psychoneuroendocrinology 2013; 38(1): 135–44.
26. Morgan Iii CA, Wang S, Southwick SM, et al: Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biol Psychiatry 2000; 47(10): 902–09.
27. Piquette D, Tarshis J, Sinuff T, et al: Impact of acute stress on resident performance during simulated resuscitation episodes: a prospective randomized cross-over study. Teach Learn Med 2014; 26(1): 9–16.
28. Nater UM, Rohleder N: Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. Psychoneuroendocrinology 2009; 34: 486–96.
29. James GD, Brown DE: The biological stress response and lifestyle: catecholamines and blood pressure. Annu Rev Anthropol 1997; 26: 313–35.
30. Takai N, Yamaguchi M, Aragaki T, et al: Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults. Arch Oral Biol 2004; 49(12): 963–68.

DOCUMENT CONTROL DATA

*Security markings for the title, authors, abstract and keywords must be entered when the document is sensitive

1. ORIGINATOR (Name and address of the organization preparing the document. A DRDC Centre sponsoring a contractor's report, or tasking agency, is entered in Section 8.)

DRDC – Toronto Research Centre
Defence Research and Development Canada
1133 Sheppard Avenue West
Toronto, Ontario M3K 2C9
Canada

2a. SECURITY MARKING (Overall security marking of the document including special supplemental markings if applicable.)

CAN UNCLASSIFIED

2b. CONTROLLED GOODS

NON-CONTROLLED GOODS
DMC A

3. TITLE (The document title and sub-title as indicated on the title page.)

Biological Response to Stress During Battlefield Trauma Training: Live Tissue Versus High-Fidelity Patient Simulator

4. AUTHORS (Last name, followed by initials – ranks, titles, etc., not to be used)

Peng, H. T.; Tenn, C.; Vartanian, O.; Rhind, S. G.; Jarmasz, J.; Tien, H.; Beckett, A.

5. DATE OF PUBLICATION (Month and year of publication of document.)	6a. NO. OF PAGES (Total pages, including Annexes, excluding DCD, covering and verso pages.)	6b. NO. OF REFS (Total references cited.)
June 2018	8	30

7. DOCUMENT CATEGORY (e.g., Scientific Report, Contract Report, Scientific Letter.)

External Literature (P)

8. SPONSORING CENTRE (The name and address of the department project office or laboratory sponsoring the research and development.)

DRDC – Toronto Research Centre
Defence Research and Development Canada
1133 Sheppard Avenue West
Toronto, Ontario M3K 2C9
Canada

9a. PROJECT OR GRANT NO. (If appropriate, the applicable research and development project or grant number under which the document was written. Please specify whether project or grant.)	9b. CONTRACT NO. (If appropriate, the applicable number under which the document was written.)

10a. DRDC PUBLICATION NUMBER (The official document number by which the document is identified by the originating activity. This number must be unique to this document.)	10b. OTHER DOCUMENT NO(s). (Any other numbers which may be assigned this document either by the originator or by the sponsor.)
DRDC-RDDC-2018-P088	

11a. FUTURE DISTRIBUTION WITHIN CANADA (Approval for further dissemination of the document. Security classification must also be considered.)

Public release

11b. FUTURE DISTRIBUTION OUTSIDE CANADA (Approval for further dissemination of the document. Security classification must also be considered.)

12. KEYWORDS, DESCRIPTORS or IDENTIFIERS (Use semi-colon as a delimiter.)

stress; biomarkers; medical training; trauma care

13. ABSTRACT/RÉSUMÉ (When available in the document, the French version of the abstract must be included here.)

Introduction: Tactical Combat Casualty Care (TCCC) training imposes psychophysiological stress on medics. It is unclear whether these stress levels vary with the training modalities selected. It is also unclear how stress levels could have an impact on medical performance and skill uptake. Materials and Methods: We conducted a pilot study to compare the effects of live tissue (LT) with a high-fidelity patient simulator (SIM) on the level of stress elicited, performance, and skill uptake during battlefield trauma training course in an operating room (OR) and in a simulated battlefield scenario (field). In the report, we studied the effects of training modalities and their changes on stress levels by measuring different biomarkers (salivary amylase, plasma catecholamines, and neuropeptide Y) at various time points during the trauma training course. Results: We found that the training resulted in significant psychophysiological stress as indicated by elevated levels of various biomarkers relative to baseline immediately after both OR and field assessment ($p < 0.05$). Compared with pre-OR levels, the LT training in the OR resulted in significant increases in the plasma levels of epinephrine, norepinephrine, and neuropeptide ($p = 0.013$, 0.023, 0.004, respectively), whereas the SIM training in the OR resulted in significant increases in the plasma levels of norepinephrine and neuropeptide ($p = 0.003$ and 0.008). Compared with pre-field levels, we found significant increases in plasma epinephrine concentration in the SIM group ($p = 0.016$), plasma norepinephrine concentration in the LT group ($p = 0.015$), and plasma neuropeptide Y concentration in both LT ($p = 0.006$) and SIM groups ($p = 0.029$). No differences in the changes of biomarker levels were found between LT and SIM groups in the OR and field. Compared with pre-field levels, the testing on the same modality as that in the OR in the simulated battlefield resulted in significant increases in norepinephrine and neuropeptide levels ($p = 0.013$ and 0.015), whereas the testing on different modalities resulted in significant increases in amylase, epinephrine, and neuropeptide levels ($p = 0.016$, 0.05, 0.018, respectively). There was a significantly larger increase in plasma norepinephrine concentration ($p = 0.031$) and a trend toward a greater increase in the salivary amylase level ($p = 0.052$) when the field testing involved a different modality than the OR compared with when OR and field testing involved the same modality. Although most of the biomarkers returned to baseline levels after 24 h, plasma norepinephrine levels remained significantly higher regardless of whether field testing occurred on the same or different modality compared with OR ($p = 0.040$ and 0.002). Conclusion: TCCC training led to significant increase in psychophysiological stress, as indicated by elevated levels of various biomarkers. The training modalities did not result in any differences in stress levels, whereas the switch in training modalities appeared to elicit greater stress as evidenced by changes in specific biomarkers (amylase and norepinephrine). A comparative study with a larger sample size is warranted.