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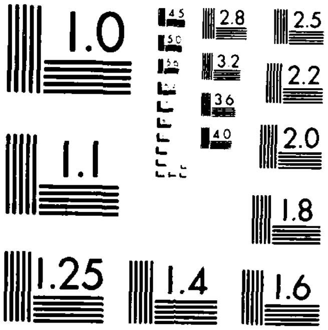
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ALTERATIONS IN CUTANEOUS VASOMOTOR REGULATION DURING ACUTE AND CHRONIC HYPOXIA

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Running title: Cutaneous Vasomotor Regulation During Hypoxia

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Abstract

The effects of acute and chronic hypoxic exposure on peripheral skin blood flow were examined in six naive subjects by measuring skin blood flow in the right index finger with a laser doppler velocimeter. After baseline skin blood flows were determined, measurements of the vasoconstrictor responses to breath holding (BH), Valsalva maneuver (VM), and cold pressor test (CPT) employing ice water immersion of the contralateral hand were made. Subjects were first tested at sea level (SL), after two-hour exposure to a simulated altitude (SA) of 4300 meters (445 torr), and then tested on days 2, 3, 5, and 8 during chronic exposure at Pikes Peak, Colorado (4300 meters). Baseline and vasoconstrictor responses were not significantly altered by acute hypobaric exposure. However, during days 2-5 of chronic exposure there were significant falls in baseline peripheral skin blood flow ($p<0.05$). Similar reductions were also found in vasomotor responsiveness on days 2-5 but had recovered by day 8. The results suggest that there is a significant increase in resting vasomotor tone probably mediated by adrenergic sympathetic input which may lead to diminished baseline peripheral skin blood flows and a reduced ability to respond to vasoconstrictor stimuli during the first few days of altitude but not seen during 2 hrs of simulated altitude. Symptoms of acute moutain sickness (AMS) as determined by an environmental symptoms questionnaire had returned to baseline long before alterations in peripheral blood flow resolved. The lack of temporal changes does not support the hypothesis that shunting of blood volume from the periphery into the central compartment is one of the underlying causes of AMS.

KEYWORDS: altitude, hypoxia, skin blood flow, laser Doppler velocimetry, Acute Mountain Sickness

It is well known that exposure to hypoxia is associated with profound alterations in blood flow and volume. Animal studies have suggested that acute hypoxia is accompanied by an increase in skin blood flow due to vasodilation (3,8). On the other hand, human studies employing water plethysmography have shown that venous compliance is diminished during the early phases of high altitude exposure (5,19,21). The present study was designed to employ a newer methodology of laser doppler velocimetry to determine peripheral skin blood flow changes during acute and chronic hypoxic exposure in man. This new technology offers the advantage of sampling skin blood flow directly without having to sample volumetric changes in an entire forelimb. In addition, several simple, non-invasive provocative maneuvers can be employed to directly assess skin vasomotor responsiveness (9). It has been demonstrated that increases in central blood volume occur during early acclimation. These changes have been hypothesized to play a role in the pathophysiology of acute mountain sickness (AMS) and high altitude pulmonary edema (HAPE) (12,17,21). Since peripheral vasoconstriction has been hypothesized to play a significant role in shunting blood into the central compartment during acclimatization (21), an effort was made to determine whether alterations in peripheral skin blood flow temporally coincided with symptoms of AMS.

Methods

Six young, healthy men served as test sbjects after giving their informed consent. A seventh subject was excluded from this study because of a history of cold-induced urticaria which suggested that his cutaneous reactivity might have been abnormal. All the subjects were life-long residents at low altitude, and none had experienced any prolonged exposure to altitudes greater than 2500 meters in the six months immediately preceeding the study. Each subject's medical history was reviewed and a physical examination and laboratory screening performed prior to inclusion in the study. The mean (± S.E.) age, height and weight of the subjects were 22 (± 1) years of age, 176 (± 2cm) in height, and 75.3 (± 1.8) kg, respectively.

The study employed a repeated measures design to determine changes occurring during hypoxic exposure. Subjects were first tested at sea level, and again after two-hours exposure to a simulated exposure of 4300 meters (P_b = 445 torr) in the hypobaric chamber facility at USARIEM, Natick, MA. They were then transported to the USARIEM Pikes Peak Laboratory Facility on the summit of of Pikes Peak (4300m) in Colorado Springs, CO. within 6 hours and tested on days 2, 3, 5, and 8 of residence.

An LDV 5000 laser Doppler velocimeter (Med Pacific Corp., Seattle, WA) with a low-power (5 mW) helium-neon laser source was used to measure finger blood flow. Laser light, delivered to the skin by means of flexible graded-index fiberoptic light guides, is reflected by both fixed andmoving anatomical structures after penetrating the skin to only a depth of 1 mm. Reflected light from non-moving structures does not undergo a Doppler frequency shift while the fraction of light which strikes moving red blood cells is reflected with a frequency shift. All the reflected light is guided from the skin surface through a second fiberoptic light channel, mixed (heterodyned), and analyzed in real time by an analog processor to provide a continuous output of the instantaneous blood flow. Reflected light is assume to be derived from a 1 mm^3 tissue volume (9,18). The optics and analog processor have been optimized for clinical determinations of tissue blood flow with high temporal resolution and linearity for the two orders of magnitude seen in normal and diseased tissues (9,18). A Heater Probe Controller Model TC 1000 (Med Pacific Corp., Seattle, WA) was also used in conjunction with the velocimeter. This device heats the probe and maintains a uniform skin temperature of 35° C to open skin capilllary beds and ensure that ambient temperature variations are minimized during the recordings.

Calibration for zero flow preceded any recording. The laser probe was placed in a calibration clamp against a surface containing no moving structures. The instrument was then rendered null for a condition of no flow by subtracting for any extraneous electrical noise. The voltage output is displayed digitally and the analog output recorded on chart paper in millivolts (mV). The skin of the right index finger was first cleaned and a double-sided adhesive disc attached first to the outer circumference of the laser probe. The probe was then applied to the palmar surface of the distal phalanx of the finger. A gain of 1X was used throughtout the study for the paper chart recording. An event marker was employed to record onset and end of vasoconstrictor maneuvers.

Subjects received a full orientation to the equipment and were instructed how to perform the various maneuvers. They were asked to recline in a lounge-chair and relax for 10 minutes. Once the subjects had become comfortable, they were asked to avoid extraneous movements and to refrain from moving the right arm so as to prevent momentary fluctuations in blood flow associated with movement. After a stable baseline was achieved (usually within 1 to 5 mins), testing was started. The same sequence of vasomotor testing was employed during each trial so that comparisons between baseline data obtained during each phase of the study (SL, SA, and CA) could be made and still take into account any changes in resting skin blood flow which might have occurred during the testing sequence and to avoid any interactions between maneuvers.

For breath holding (BH) subjects were asked "to take a deep breath in and hold it" for 30 seconds and then release it. The onset and end of IG were recorded on the chart record for later measurement. The reduction in skin blood flow was expressed as a percentage of resting skin blood flow: (RSBF-MSBF)/(RSBF) where RSBF is the mean resting skin blood flow and MSBF is the minimal value for skin blood flow obtained during or immediately after the maneuver. Because it was often found that baseline blood flow was slightly altered throughput the prolonged sequence of serial vasomotor response testing, baseline blood flow data were determined before each maneuver. Each vasoconstrictor maneuver was conducted three times and the results meaned to yield an individual mean value for each maneuver at each sampling interval.

For the Valsalva manuever (VM), subjects were asked to maintain a forced expiratory pressure of 20cm H_2O for ten seconds. One subject was eventually excluded from the VM because he developed syncopal symptoms during the procedure. Therefore, for VM statistical analyses the number of subjects was effectively reduced to 5. The cold-pressor test (CPT) involved placing the left hand into ice water to the wrist 30 seconds. The data were analyzed in the same fashion for each of the three maneuvers.

The Environmental Symptoms Questionnaire (ESQ) is a 67-question inventory of symptoms which can occur in stressful environments including heat, cold, and high altitude (14). It was administered to subjects individually using an interactive computer software package (7). The program queries each subject about specific symptoms which he then rates based on six phrases ranging from "not at all" to "extreme". The responses were assigned numbers from 0 (not at all) to 5 (extreme), and a weighted average of cerebral symptoms termed "AMS-C" and respiratory symptoms termed "AMS-R" were derived from the scores. These measures have been shown in previous studies to accurately and reliably identify individuals suffering from AMS (15).

Values are represented as group mean values ± S.E. unless otherwise noted. A one-way analysis of variance for repeated measures was performed separately on the data for baseline blood flow, vasoconstrictor responses to each of the manuevers, and AMS-C and AMS-R scores using BSDM software on a HP Series 2000-9836 (Hewlett Packard; Fort Collins, CO). Post hoc significant differences were identified using the Tukey's Test (2).

Results

1. Baseline skin blood flow measurements

A typical skin blood flow recording from subject 3 is shown in Figure 1. Event markers indicate the onset and end of each vasoconstrictor maneuver in each frame. No significant differences were found between different sea level trials so these data were averaged to yield a mean baseline value for later comparison.

Group mean baseline skin blood flow data are summarized in Figure 2. There were no significant differences between mean baseline skin blood flow measurements during at SL or during SA. The mean baseline skin blood flow did, however, change during the early days of acclimatization. Unless otherwise indicated, differences between blood flow determinations were not significantly different when compared with SL and SA values. As is shown in Figure 2, mean baseline flows between BH trials dropped significantly ($p < 0.02$) from SL and SA values of 803 (± 166) mV and 708 (± 178) mV, respectively to a value of 523 (±169) mV on day 3 of altitude exposure. Similarly, there was a significant (p

<0.01) reduction from mean SL and SA baseline values between VM trials of 793 (±220) mV and 728 (±/151) mV respectively to 479 (±202) mV on day 3 and 370 (±148) mV on day 5 of altitude exposure (see Figure 2). Mean baseline blood flow between CPT trials also dropped significantly (p <0.01) from SL and SA values of 650 (+/- 171) mV and 614 (+/- 171) mV respectively to a low on day 5 of 372 (+/- 222).

2. Vasoconstrictor Responses

Group mean reductions in blood flow from baseline *in response to all three* of the vasoconstrictor maneuvers are shown in Figures 3. Reductions are expressed as percent change from baseline in order to normalize responses and allow comparisons. As with the mean baseline blood flow data, vasoconstrictive manuevers evoked the same degree of blood flow reduction at sea level as they did after two hours of simulated altitude. As can be seen in Figures 3 both BH and VM showed a decisive trend towards reduced vasoconstriction in response to the manuevers when compared with testing carried out at SL and SA but not reach statistical significance. However, in the case of CPT, there was a significant (p <0.003) *reduction in* the group's ability to reduce peripheral skin blood flow in response to 15 seconds of *immersion* of the left hand in ice water on days 2,3 and 5 but not on day 8 of acclimatization (Figure 3).

3. Environmental Symptoms

Group mean AMS-C and AMS-R scores from ESQ-III are listed in Table I. The mean AMS-C and AMS-R scores were only statistically ($p < 0.01$ and $p < 0.03$, respectively) different from the mean values obtained at sea level on day 2 of altitude exposure.

Discussion

The main findings of this study are that resting baseline skin blood flow is dramatically reduced during the first five days of acclimatization and returns towards sea-level values by the eighth day at high altitude. In addition, the ability to reduce to peripheral cutaneous blood flow in response to a vasoconstrive stimulus such as immersion of the hand in ice water is dramatically diminished during the same interval. Finally, while there was a significant elevation of the group's AMS-related symptoms only on day 2 of altitude exposure, the diminished baseline skin blood flow and peripheral venoconstrictive responsiveness were still demonstrable long after the subjects' symptoms of altitude sickness had abated.

Laser Doppler velocimetry has been show both _in vitro_ and _in vivo_ to be linearly related to blood flow (2,10,16,18). Clinical studies have shown that the index finger is an optimal site for placement of laser probe as it contains only vasoconstrictor fibers (11) and therefore produces less ambiguous cutaneous reactivity to temperature and vasoconstrictive maneuvers (9). At the Mayo Clinic, Low _et al._ (9) examined the vasoconstrictor responses to BH, VM and CPT in 63 healthy male and female subjects ranging in age from 10 to 70 years old. They found that median reduction in blood flow in this group varied from 44% for BH, 46% for VM and 51% for CPT. The data obtained in this study show a more dramatic reduction in cutaneous blood flow with these three maneuvers which were carried out in virtually identical fashion but our group was substantially younger and the data collected by the Mayo Clinic. Since Low et al. (9) showed a trend towards attenuated skin blood responses with increasing age and our group was comprised of relatively fit military male enlisted personnel, this difference may be in large part be age-related.

The wide variability of skin blood flow measurements seen amongst our group of test subjects has been reported in previous studies using both water-filled plethysmography (19) and laser Doppler velocimetry (9). The variability can be attributed to a wide variety of factors such as individual differences in skin vasoconstrictor reactivity, fluctuations in room temperature, degree of relaxation, ambient noise and other extraneous stimuli. We attempted to control these external factors as much as possible to reduce environmental pertubations. Nonetheless, significant trends were identified despite the relatively small size of this group.

Our results support the previously reported findings (10) that under normal sea-level conditions skin vasomotor reflex tests produce consistent results on serial examinations. Cutaneous blood flow measurements during high-altitude exposure have traditionally relied upon plethysmographic recordings

(4,5,19,21). Water-filled plethysmography has the advantage of permitting measurements to be performed in a well-controlled thermal medium but has a distinct limitation in that it is only capable of summing up volume changes in the entire forearm or hand in relation to changes in venous pressure. Laser Doppler velocimetry, on the other hand, allows a virtually instantaneous record of alterations in skin blood and provides an accurate record of cutaneous blood flow without contamination from alterations in deeper tissues in the hand or the rest of the forearm.

Distensibility of the forearm and hand capicitance vessels has been shown to diminish during prolonged altitude exposure (5,19,21). Weil et al. (19) demonstrated that venous compliance was diminished in man throughout the first week of residence at 4300 meters. Studies with moderate hypoxia (PaO_2 50 mmHg) and severe hypoxia (PaO_2 37mmHg) in man showed that venous compliance was only acutely altered with severe hypoxia and did not occur with moderate hypoxia unless hypocapnia was allowed to occur (19). These findings are at odds with a later chronic study (4) during which CO2 supplementation during 4 days of hypobaric hypoxic exposure failed to alter forearm blood flow as determined by plethysmography. This suggested that acute responses to hypoxia might be different from those witnessed during chronic exposure. A similar lack of effect of CO_2 on venous compliance was demonstrated amongst residents and newly arrived lowlanders at an altitude of 3750 meters (6). Our findings showed that acute hypobaric hypoxia was not associated with any significant alterations in cutaneous skin blood flow but that chronic exposure was accompanied by dramatic alterations in both resting skin blood and reflex vasoconstrictive reactivity.

Earlier studies have demonstrated alterations in venous compliance during acute hypoxic exposure. Cruz et al. (4) showed a significant fall in venous compliance occuring within 2 hours after exposure to a simulated exposure of 4300 meters. While Weil et al. (19) also showed a fall in venous compliance occuring almost immediately after exposure to hypobaric hypoxia, this study failed to show a statistically significant fall until subjects had undergone at least 10 hours of sustained hypoxia. Both studies employed water-filled plethysmography and altitudes identical to the one employed in our studies. Using laser Dopler velocimetry we did not see any significant alteration in either baseline skin blood velocities or venomotor reactivity after 2 hours of simulated exposure, although by 48 hours significant changes were demonstrated. This discrepancy may be explained by the fact that our methodology solely addressed cutaneous digital blood flow and not employ volumetric changes to infer venomotor alterations. The fact that neither the resting flow rates nor the reactivity of the digital vasomotor tone to provocative maneuvers was altered acutely suggests that this was a reliable finding since alterations in venous compliance should have had a direct effect on both of these measures.

There is disagreement over the time course over which changes in cutaneous blood flow occur during acclimation. Weil et al. (19) reported a significant fall in venous compliance as measured with plethysmography which was sustained throughout a week's residence at Pikes Peak. Durand et al. (5) examined alterations in venous distensibility in lowlander transplanted to 3,750 meters and found that while it fell dramatically during the first four days after arrival at altitude, it had returned towards sea-level values by the end of one month's stay. Data from a later study (4) showed a fall in venous compliance during the first two days which then reversed back towards sea-level control values but this trend did not reach significance. Wood and Roy (21), on the other hand, employed plethysmography to demonstrate that mean venous distensibility in a group of soldiers transported to 11,800 feet was only significantly reduced during days 2 through 4 of altitude exposure after which it returned back towards the sea-level baseline. While it is hard to directly compare results of forearm venous compliance as measured with plethymography with results of digital skin blood flow obtained by means of a Doppler velocimetry, our results indicate that cutaneous flow is diminished only for the first five days of acclimatization and that reduction is no longer significant by the end of eight days' residence at high altitude.

Symapthetic adrenergic input has been shown to play an important role in regulating cutaneous vasomotor tone (8,11,20) and in mediating reflex vasomotor responsiveness to such manuevers as IG, VM and CPT (9). As early as 1957, Roddie et al. (11) demonstrated that nerve blockade with lidocaine released vasoconstrictor tone to permit increased digital blood flow during hyperthermia, a well-documented vasodilatory stimulus to permit increased heat elimination. A more recent study (13) described acute cutaneous vascular responses in man to heat load at sea level and at a simulated altitude of 5600 meters and demonstrated that hypoxia interfered with thermally induced digital venodilation. Alterations in sympathetic activity have been hypothesized to mediate the changes in cutaneous blood flow during acclimation (21). Our studies demonstrated that cutaneous vasomotor reactivity was reduced with CPT. This study suggested but failed to demonstrate a statistically significant fall with VM nd BH. VM and BH are both largely dependent upon the individual subject's volition and ability to cooperate in carrying out a maximally effective manuever. This may in part explain why we failed to see a significant fall with BH and VM during the first few days at altitude when many of the subjects were the most ill with symptoms of AMS. CPT, on the other hand, is a much more reliable test since voluntary input has little effect on the efficacy on the manuever. It is therefore noteworthy that CPT responses were dramatically diminished on days 2 through 5 at altitude. The mechanism for this reduction would appear to be an increase in resting baseline vasomotor tone (as shown by the reductions in baseline velocities) that inhibited the same degree of maximal vasoconstriction as was seen at sea level. In essence, the subjects were unable to recruit the same degree of vasoconstrictive response because their cutaneous vasomotor tone was already at a higher resting state. How hypoxia brings about an alteration in vasomotor tone is unclear. Cruz _et al._ (4) have suggested that hypoxia has a direct venoconstrictive effect while hypocapnia does not. These investigators failed to demonstrate any systemic rise in catecholamine levels as reflected in urinary catecholamine output during hypobaric hypoxia unless supplemental CO_2 was administered.

However, urinary catecholamine output serves only as a very distant reflection of changes in adrenergic tone and it is possible that hypoxia had a direct, local effect on vasomotor smooth muscle.

Studies (21) on venomotor responses to an acute 10,000 ft and chronic 11,800 ft altiude exposure in man suggested a shift of blood from the periphery towards the central compartment as a possible etiology for symptoms at high altitude. While the altitudes are not directly comparable, our subjects exhibited the expected time course of respiratory and neurological symptoms at high altitude, reaching maximal symptomatic illness on the second day of their altitude exposure. Our finding that the symptoms of AMS resolve more quickly than does peripheral vasoconstriction does not support the hypothesis that a shift of blood volume from the peripheral comparment to the central compartment is an underlying mechanism for AMS. However, compensatory redistribution from the central compartment to other splanchnic beds or other fluid compartments cannot be excluded.

In summary, this study employed recently developed laser Doppler velocimetry technology to obtain an accurate reflection of cutaneous blood flow changes during acclimatization. The results demonstrate that neither resting skin blood or vasomotor responsiveness to BH, VM or CPT are altered by an acute simulated altitude exposure of two hours' duration but that both of these functions are significantly affected during the first days of acclimation. The results suggest that resting vasomotor tone is elevated by chronic hypoxic exposure and that this rise prevents a full response to provocative tests. While the findings of this study are often at odds with previously reported studies employing plethysmography, it is felt that laser Doppler technology provides a more accurate picture of how cutaneous vasomotor regulation is altered during hypoxic exposure.

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LEGENDS

Figure 1: Depicts a laser Doppler velocimeter tracing of the voltage output display over time obtained at sea level from Subject 3 during breath holding (BH). Arrows indicate the onset and end of the manuever; two separate trials 5 min apart are displayed. The second and third panels demonstrate similar tracings obtained during a Valsalva maneuver (VM) and a cold pressor test (CPT), respectively. Time and voltage scales are the same for all three panels.

Figure 2: Depression of mean baseline digital skin blood flow (DSBF) during breath holding (BH), Valsalva manuever (VM) and cold pressor test (CPT) maneuvers at sea level, after 2 hrs of simulated altituded (Chamber), and on days 2, 3, 5, and 8 of residence at Pikes Peak (4300m). * indicates measures which are significantly different compared to sea-level measures ($p \leq 0.05$).

Figure 3: Mean percent reduction in digital skin blood flow (DSBF) from baseline in response to breath holding (BH), Valsalva maneuver (VM) and cold pressor test (CPT) maneuvers at sea level, after 2 hrs of simulated altituded (Chamber), and on days 2, 3, 5, and 8 of residence at Pikes Peak (4300m). An asterix indicates measures which are significantly different compared to sea-level measures ($p \leq 0.05$).

TABLE I: ACUTE MOUNTAIN SICKNESS (AMS) SYMPTOMS AT PIKES PEAK

AMS-C SCORES

	MEAN	S.E
SEA LEVEL	0.07	0.05
ALTITUDE DAY 2	1.13*	0.51
ALTITUDE DAY 3	0.55	0.31
ALTITUDE DAY 5	0.19	0.09
ALTITUDE DAY 8	0.17	0.14

AMS-R SCORES

	MEAN	S.E.
SEA LEVEL	0.10	0.03
ALTITUDE DAY 2	0.63*	0.23
ALTITUDE DAY 3	0.44	0.13
ALTITUDE DAY 5	0.38	0.15
ALTITUDE DAY 8	0.51	0.15

Asterix signifies a significant difference ($p < 0.05$) compared to sea-level scores

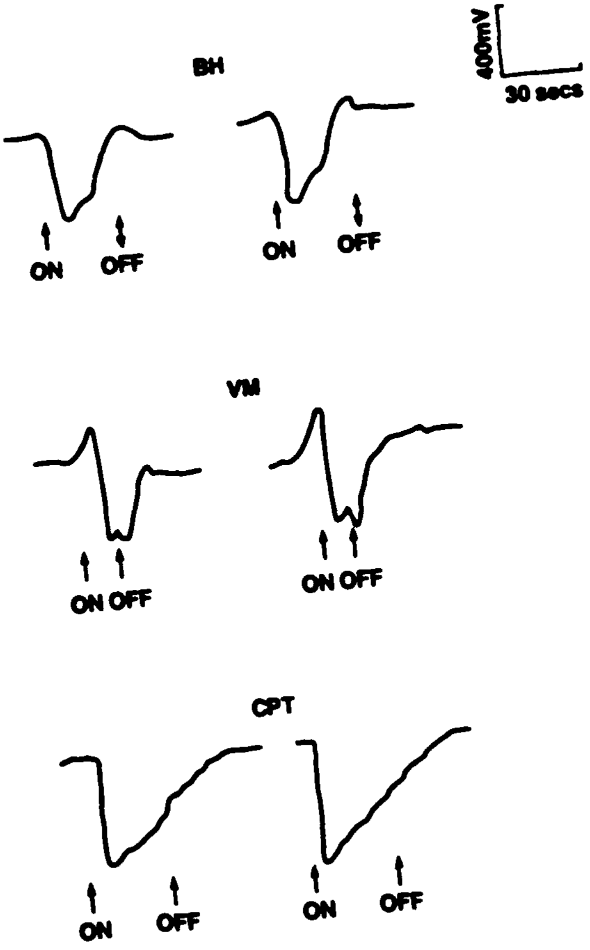
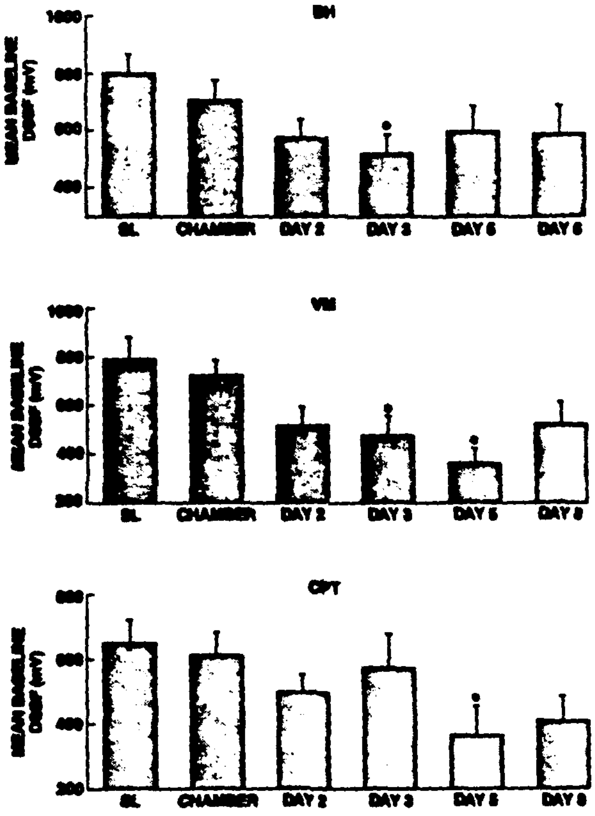


figure 1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*

figure 2

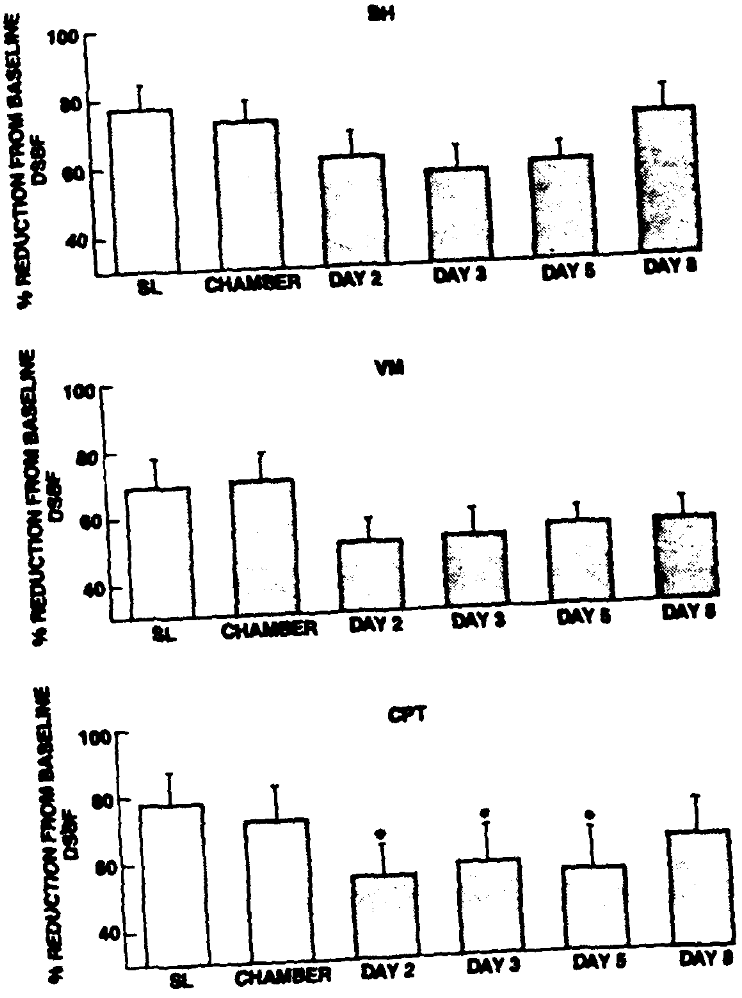
SH
% REDUCTION FROM BASELINE DSBF
100
80
60
40
SL
CHAMBER
DAY 2
DAY 3
DAY 5
DAY 8
VM
% REDUCTION FROM BASELINE DSBF
100
80
60
40
SL
CHAMBER
DAY 2
DAY 3
DAY 5
DAY 8
CPT
% REDUCTION FROM BASELINE DSBF
100
80
60
40
SL
CHAMBER
DAY 2
DAY 3
DAY 5
DAY 8

figure 3

END
DATE
FILMED
6-88
DTIC