The Metabolic and Ventilatory Response to the Infusion of Stress Hormones

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Sepsis and trauma result in increases in epinephrine, glucagon, and cortisol secretion as well as alterations in respiratory pattern that is characterized by increased minute ventilation, decreased tidal volume, and increased frequency. Six male subjects were infused for 5.5 hours with cortisol, epinephrine, and glucagon in amounts designed to simulate plasma levels seen in patients following trauma. During the initial 20 minutes of the hormone infusion, minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production ($\dot{V}_{CO_2}$) increased above preinfusion values. $\dot{V}_{CO_2}$ increased more than $\dot{V}_{O_2}$ resulting in an increase in respiratory quotient (RQ) from 0.93 to 1.14. The increase in $\dot{V}_E$ was due to increased tidal volume and not frequency (f). After 4.5 hours, the $\dot{V}_E$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ were still above preinfusion levels but the RQ had decreased to 0.98 because of a decrease in $\dot{V}_{CO_2}$. Frequency had increased from 19 ± 4.8 breaths/min preinfusion to 22 ± 4.7 after 4.5 hours. After 4.5 hours, V_T was still above preinfusion levels while pH and $PaCO_2$ had decreased below them. The latter was associated with an increase in serum lactate. At no time was a decrease in tidal volume observed. Therefore, the infusion of these hormones does not simulate all the alterations observed during trauma and sepsis.

PATIENTS UNDERGOING physiologic stress, *e.g.*, sepsis and trauma, typically have increases in circulating levels of epinephrine, glucagon, and cortisol[1] as well as respiratory patterns characterized by increased breathing frequency, decreased tidal volume, and elevated minute ventilation.[2] Shamoon et al.[3] have demonstrated that in normal subjects many of the metabolic and biochemical changes that occur during stress can be reproduced by infusing these three "counterregulatory" hormones in amounts designed to simulate the plasma levels seen in patients following trauma. They have observed that these hormones act synergistically in altering biochemical and metabolic parameters; *i.e.*, the response to the simultaneous infusion of all three is greater than the algebraic sum of the responses to each infused individually.[4] The present study examines the effects of stress hormone infusion on metabolic rate and respiratory pattern. Specifically, it attempts to determine whether the rapid respiratory rates and small tidal volumes seen in stressed patients[2] can be reproduced by the infusion of hormone. Measurements of respiration and metabolic rate were made prior to, during the first 30 minutes of, and after 4.5 hours of the infusion.

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Methods

Six healthy male subjects aged 22 to 30 years participated in a study designed to assess the metabolic and biochemical effects of infusing the stress hormones into normal subjects receiving a high carbohydrate diet. Each subject was admitted to the Surgical Metabolism Unit (SMU) of the Columbia-Presbyterian Medical Center (CPMC) for 3 days on two separate occasions. On each occasion they were placed on a high carbohydrate diet for the first 2 days. This was provided as 2880 kcal/day of Sustacal (Mead Johnson, Evansville, IN). The diet was 55% carbohydrate, 24% protein, and 21% fat. On the third day, an intravenous infusion of 15.4 g/h of dextrose was started at 7:30 AM. On one occasion saline was infused intravenously starting at 11:30 AM, while on the other, cortisol (5 mg/m^2/h) was started at 9 AM and epinephrine (1.2 μg/m^2/min) and glucagon (3 mg/kg/min) added at 11:30 AM according to the protocol of Shamoon et al.[3] The infusions were continued until 5 PM. Measurements of oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), and respiration were made using a canopy-spi-

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rometer-computer system at 8 AM, between 11 AM–12 noon, and at 4 PM. The 11 AM–12 noon segment was divided into 10 minute periods to allow for examination of the initial hormonal effects. At 8 AM and 4 PM, respiratory measurements were made during room air breathing and during the administration of 2% and 4% CO_2.

The canopy-computer-spirometry system used in the present study has been described in detail previously[5]; it is composed of a head canopy connected to a spirometer (Med-Science model 470, St. Louis, MO) and a Prime 300 computer (Prime Computer Co., Natick, MA). The canopy is a rigid transparent head chamber with a neck seal, ventilated by a continuous airstream. The spirometer connected to the canopy provides a breath-by-breath record of changes in lung volume. Gas composition in the canopy is continuously sampled and analyzed by means of a LIRA CO_2 analyzer (model 200 FP, Mine Safety Appliance Co., Pittsburgh, PA) and a Servomex O_2 analyzer (model OA 250, Servomex Controls Ltd., London, England). Spirometry and gas exchange data are acquired and processed by the digital computer. Airflow to the canopy is set at 40 l/min and is controlled to provide a stable spirometer baseline position. Computer-executed algorithms quantify each breath and determine tidal volume (V_T), frequency (f), CO_2 production ($\dot{V}_{CO_2}$), O_2 consumption ($\dot{V}_{O_2}$), peak inspiratory and expiratory flows, and inspiratory (T_I) and expiratory (T_E) time. T_I is taken from the start of inspiration to the start of expiration. Mean inspiratory and expiratory flows (V_T/T_I, V_T/T_E) and the ventilatory equivalents for O_2 and CO_2 ($\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$) at room air were calculated. An accuracy of ±10 ml in V_T measurements is achieved for breathing frequencies in the range of 5–40 breaths/min. The program excludes all V_T less than 40 ml, as these have been considered too small to represent a breath.

All metabolic and respiratory measurements were made in the supine position. The response to CO_2 was assessed by allowing the patient to breathe room air and then 2% and 4% CO_2. At each condition, measurements were made for 10 minute periods once stable levels of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ had been achieved. Arterial blood was sampled from an indwelling radial artery catheter at the end of each measurement period and analyzed using an IL 1303 blood gas analyzer (Instrumentation Laboratories, Lexington, MA) for pH, PO_2, and PCO_2.

Statistical analysis was performed using a repeated measures analysis of variance.

Written informed consents were obtained from all subjects. This study was approved by the Institutional Review Board of Columbia University, Health Sciences Center.

Results

Figure 1 displays the changes in $\dot{V}_E$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, V_T, and f during the infusions of saline and hormones. Saline

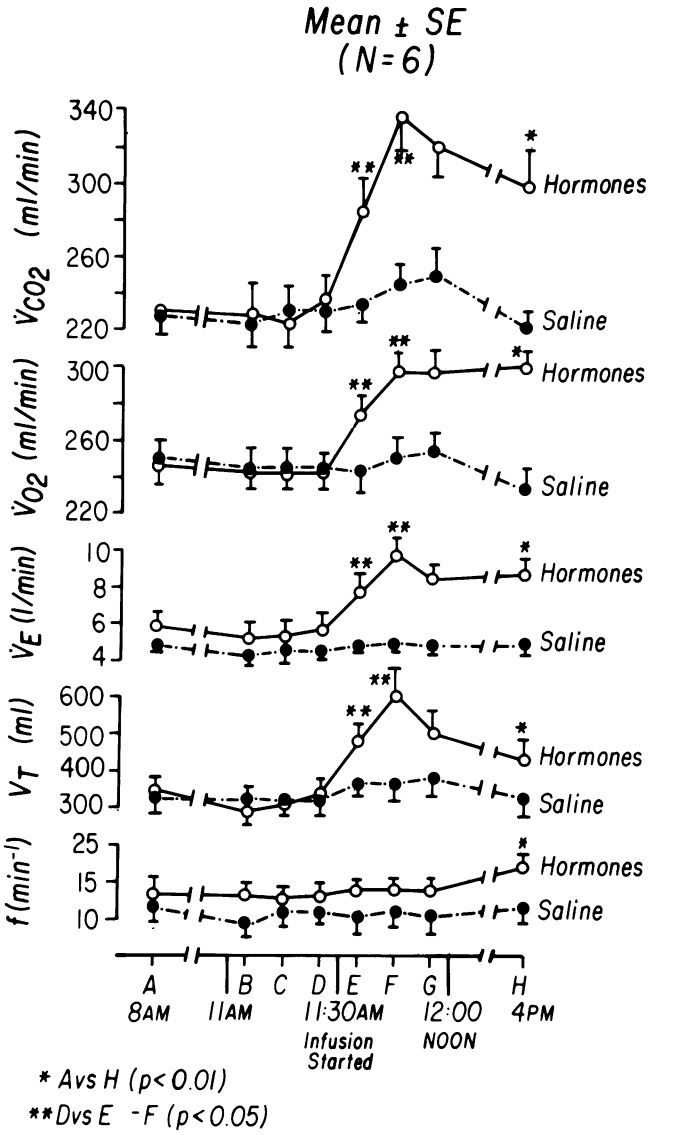

FIG. 1. Carbon dioxide production ($\dot{V}_{CO_2}$), oxygen consumption ($\dot{V}_{O_2}$), minute ventilation ($\dot{V}_E$), tidal volume (V_T), and frequency (f) are plotted *vs.* time. Mean ± SE for six subjects.

resulted in no change in either metabolic or respiratory patterns. With the hormone infusions, two patterns of respiration were observed. During the initial 20 minutes of the hormone infusion, there was a greater increase in $\dot{V}_{CO_2}$ than $\dot{V}_{O_2}$, resulting in an RQ as high as 1.14 (preinfusion RQ was 0.93). Minute ventilation increased, as did V_t, while f changed little. Compared to the measurements made 10–20 minutes after the start of the infusion, those made after 4½ hours revealed that $\dot{V}_{O_2}$ was unchanged, while $\dot{V}_E$ ($p < 0.02$) and $\dot{V}_{CO_2}$ ($p < 0.03$) had decreased; thus the RQ decreased to 0.98. Frequency increased from a mean of 19 ± 5 to 22 ± 5 breaths/min ($p < 0.002$) while V_T decreased ($p < 0.02$).

Further analysis of the respiratory patterns revealed that during the initial 30 minutes of the hormone infusion, T_I

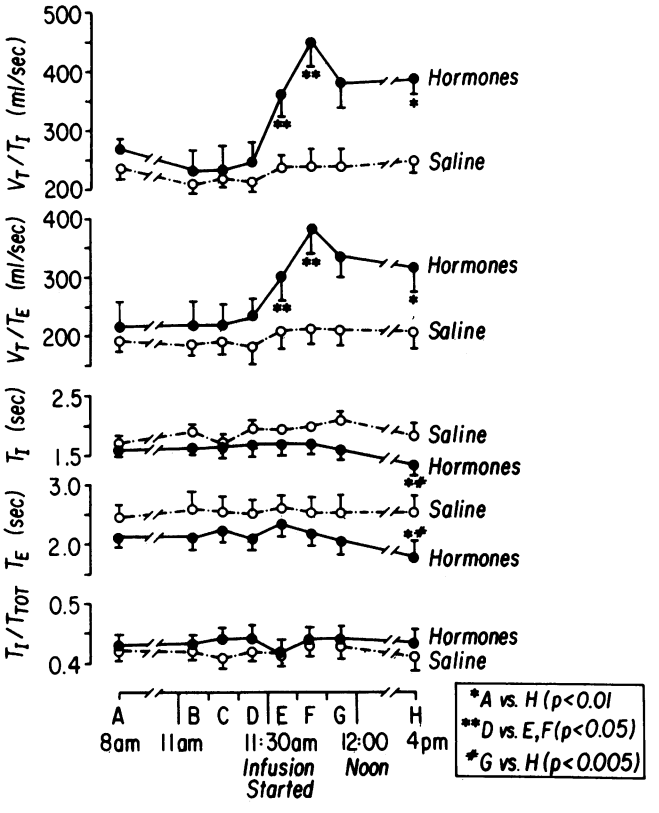

FIG. 2. Mean inspiratory flow (V_T/T_I), mean expiratory flow (V_T/T_E), inspiratory and expiratory times (T_I/T_E), and inspiratory duty cycle (T_I/T_{TOT}) are plotted *vs.* time. Mean ± SE for six subjects.

and T_E did not change significantly, while V_T/T_I and V_T/T_E both increased significantly. Four and a half hours after the start of the infusion, V_T/T_I and V_T/T_E had decreased significantly from the levels observed 10 to 20 minutes after the start of the infusion. Also, T_I and T_E were decreased ($p < 0.005$, Fig. 2), while T_I/T_{TOT} was unchanged.

The ventilatory equivalents for O_2 and CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$) were unchanged during the saline infusion, but increased significantly (Fig. 3) during the infusion of hormones.

During the saline infusions, no changes in serum lactate, pH or $PaCO_2$ were observed. During the hormone infusions, however, both pH and $PaCO_2$ decreased significantly, while serum lactate increased (Table 1).

Inspection of the $\dot{V}_E$-$PaCO_2$ relationship revealed a significant shift to the left during the hormone infusion. No shift was seen with saline (Fig. 4).

Discussion

The present study demonstrates that the simultaneous infusion of the three counterregulatory hormones into normal subjects increases minute ventilation and alters the respiratory pattern. The initial 30 minutes of the infusion was marked by rapid changes in both ventilatory and metabolic parameters. Minute ventilation and carbon dioxide production were highest 10–20 minutes after the start of the infusion. Carbon dioxide production increased more than oxygen consumption; the RQ thus increased from a preinfusion value of 0.94 to 1.14 and 1.08, 10–20 and 20–30 minutes, respectively, after the start of infusion. This is consistent with the observations of Fellows et al.,[6] who noted increases in RQ during the first 15 minutes of the infusion of 50 ng/min/kg and 10 ng/min/kg of epinephrine. Lundholm et al.[7] also observed a greater increase in $\dot{V}_{CO_2}$ than $\dot{V}_{O_2}$ 3 and 8 minutes following the start of an intravenous infusion of 0.15 μg/kg/min of epinephrine. In that study[7] arterial $PaCO_2$ was slightly increased from preinfusion levels at 3 minutes and unchanged at 8 and 30 minutes after the initiation of the infusion; pH decreased only slightly. Sjostrom et al.[8] also did not observe any changes in $PaCO_2$ during the initial period of infusion. These results are in contradistinction to those of Bradley et al.,[9] who found that an infusion of 0.20 μg/kg/min of epinephrine stimulated respiration and decreased $PaCO_2$. In the latter study,[9] arterial blood samples were placed on ice and analyzed some hours later, a method that appears to result in lower PCO_2 than when samples are analyzed immediately.[7] Review of the data

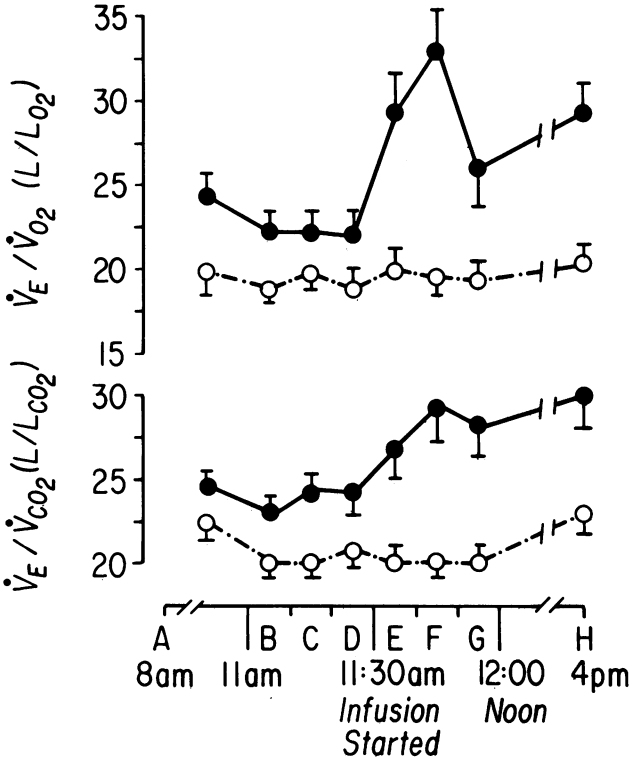

FIG. 3. The ventilatory equivalents for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) and O_2 ($\dot{V}_E/\dot{V}_{O_2}$) are plotted *vs.* time. Mean ± SE for six subjects.

of Lundholm et al.[7] reveals no change in the ventilatory equivalent to CO_2 3, 8, and 30 minutes after the initiation of the infusion. This, coupled with no change in $PaCO_2$, would indicate that there is no change in V_D/V_T; this is interesting, since epinephrine is a bronchial dilator.[10] This is in contradistinction to our data, in which there was a significant increase in the ventilatory equivalent to CO_2 during the period immediately following the start of the infusions. In the current study, an infusion of three hormones that act synergistically was used, and it is possible that this resulted in a situation where the respiratory increases were greater and were well out of proportion to $\dot{V}_{CO_2}$. If the $PaCO_2$ does not change and $V_E/\dot{V}_{CO_2}$ increases, V_D/V_T must have increased, while, if $PaCO_2$ decreases, there may not be major changes in V_D/v_T. If $PaCO_2$ does decrease, then the greater increase in $\dot{V}_{CO_2}$ than $\dot{V}_{O_2}$ is most likely due to hyperventilation, *i.e.*, a primary respiratory event. This may be caused directly by a hormone-induced increase in respiratory drive or indirectly by a feeling of anxiety. If $PaCO_2$ does not change and there is no increase in V_D/V_T, then the CO_2 eliminated must be produced by some metabolic process.[7] Therefore, more detailed investigation of this dynamic initial infusion period is necessary, with frequent measurements of arterial $PaCO_2$ to make these distinctions.

The increase in V_T, but not f, during the initial period of hormone infusion is consistent with the results of other investigators.[11] The increase in mean inspiratory flow (V_T/T_I) with no change in inspiratory duty cycle (T_I/T_{TOT}) implies an increase in ventilatory drive but not timing.[12] The increase in respiratory drive caused by the infusion of hormones may be due to different mechanisms, depending on the specific catecholamine used. Both epinephrine and norepinephrine stimulate respiration to a comparable degree in man, in spite of the lack of any consistent increase in oxygen consumption after norepinephrine administration.[7] Epinephrine has been thought by some to stimulate respiration by increasing CO_2 production and lactate production.[7] Norepinephrine, as well as epinephrine, may increase respiration at least in part by a different mechanism, an increase in the sensitivity of the peripheral arterial chemoreceptors.[11,13] This is evidenced by the observation that the increased minute ventilation seen after the infusion of norepinephrine can be abolished by the simultaneous inhalation of 100% oxygen[11] and can be enhanced by hypoxia.[13] Section of a cat's carotid sinus and aortic nerve prevented both epinephrine and norepinephrine from increasing minute ventilation,[14] thus lending additional evidence to the importance of arterial chemoreceptors in catecholamine-induced hyperpena.

Four and a half hours after the start of the infusion, both $\dot{V}_{O_2}$ and minute ventilation were unchanged from values 20–30 minutes after its inception. Whelan and

TABLE 1. *Arterial Blood Gases and Serum Lactate*

	pH	$PaCO_2$ (torr)	PaO_2 (torr)	Lactate (μmol/ml)
Saline				
8:00 AM	7.39 ± 0.02	41.4 ± 4.0	92.1 ± 7.5	0.71 ± 0.15
4:30 PM	7.40 ± 0.01	40.4 ± 2.8	98.0 ± 8.2	0.63 ± 0.12
Hormone				
8:00 AM	7.41 ± 0.02	41.9 ± 3.8	92.2 ± 9.9	0.65 ± 0.38
4:30 PM	7.38 ± 0.02*	38.1 ± 2.9*	102. ± 7.9*	3.32 ± 1.05*

N = 6.
* Significantly different than 8 AM value ($p < 0.05$).
Values are means ± SD.

Young[15] observed that the effects of a continuous infusion of epinephrine on minute ventilation was short lived. Others have observed similar tachyphylaxis with the biochemical response[3] when epinephrine, but not all three counterregulatory hormones, was infused. This, along with the observations made in this study, demonstrate that the synergism between these hormones appears to prevent tachyphylaxis from occurring.

The respiratory pattern after 4.5 hours differed from that during the first 30 minutes. Thus, the ventilatory pattern observed when a more steady state had been achieved differs from that seen during the first 30 minutes of the infusion. The difference may be due to the fact that after 4.5 hours not only is metabolic rate elevated but

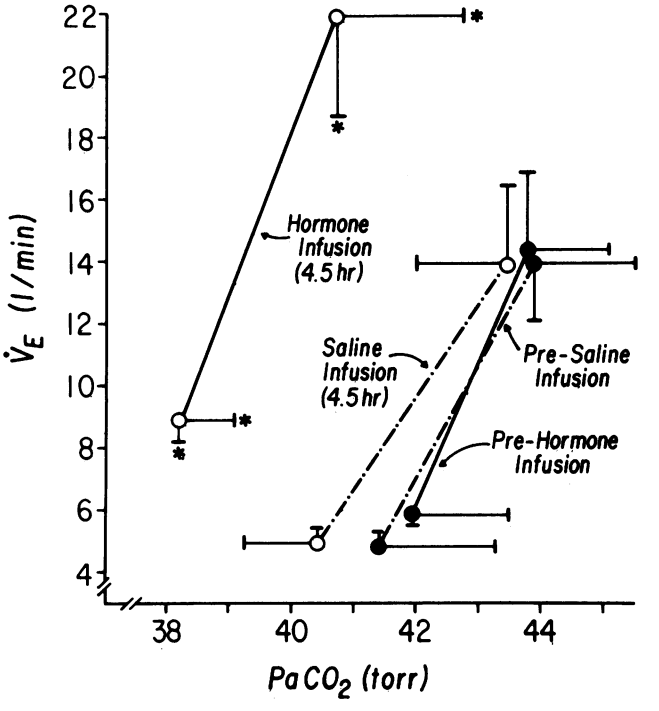

FIG. 4. $PaCO_2$ is plotted *vs.* minute ventilation ($\dot{V}_E$). Points are room air and 4% CO_2. Mean ± SD for six subjects. *Significantly different ($p < 0.025$) from prehormone infusion values.

there is also respiratory compensation for a mild metabolic (lactic) acidosis (Table 1). The latter is evidenced by significant decreases in both pH and $PaCO_2$ as compared to preinfusion values. The increases in $\dot{V}_E$ at this time continue to be associated with an increase in V_T/T_I rather than T_I/T_{TOT}, indicating an increase in drive but not timing. Further investigation of respiratory drive using the ventilatory response to CO_2 demonstrates that infusion of hormones causes no change in the slope of the $\dot{V}_E$-$PaCO_2$ relationship but a significant shift to the left. This shift is most likely due to a small increase in ventilatory drive caused by mild metabolic acidosis and possibly also by the increase in metabolic rate.[16]

These results indicate that the combined infusion of epinephrine, glucagon, and cortisol in amounts designed to produce plasma levels similar to those seen in stressed patients results in a dynamic sequence of respiratory and metabolic changes. Presumably, the increase in ventilation observed is due mainly to the epinephrine. Epinephrine-induced increases in ventilation are thought to be mediated at least partly by beta adrenergic stimulation,[11,17] since selective alpha adrenergic stimulation reduced the degree of increase in minute ventilation[11] produced by norepinephrine infusion. If beta receptor activity is the primary mediator involved in the increase in $\dot{V}_E$, the synergistic effects of epinephrine and glucagon may be explained by the fact that glucagon also increases intracellular cyclic-AMP, but *via* a non-beta receptor mechanism.[17] Similarly, cortisol has been reported to act synergistically with epinephrine.[19,20] The mechanisms proposed include cortisol-induced inhibition of catechol-O-methyl transferase[19] and blockade of catecholamine reuptake.[20]

The effects of a high carbohydrate diet on these observations must also be considered. Increasing carbohydrate intake results in parallel rises in carbon dioxide production and minute ventilation.[21] It is possible that the additional metabolic stimulation may result in some differences in the metabolic and respiratory responses when compared to those of subjects on different diets or in the postabsorptive and starved state.

In conclusion, the combined infusion of the three counterregulatory hormones into normal subjects reproduces many of the biochemical changes seen in stressed patients.[3] However, it fails to reproduce completely the respiratory pattern of stressed patients. It does result in increased frequency and elevated minute ventilation but does not cause the decrease in tidal volume (shallow rapid pattern) so often seen in postoperative patients.[2] Therefore, although the increase in ventilation seen during the stressed state may be partly due to the effects of these three hormones, the specific respiratory pattern must be influenced by other considerations. These include changes in respiratory mechanics such as decreased compliance secondary to increased interstitial lung water.

In summary, this study examines the metabolic and ventilatory effects of the simultaneous infusion of cortisol, glucagon, and epinephrine and demonstrates the dynamic nature of the response.

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