Cardiorespiratory, Metabolic and Endocrine Changes after Hemorrhage in Man

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EXPERIMENTAL design has an important influence on the body's response to induced hemorrhage.[6] Species differences are especially important in the activation of the sympathetic nervous system and the influence of sympathetic activity on the cardiovascular system.[48] Most studies of acute hemorrhage in animals have been performed by various modifications of technics which aimed to keep arterial pressure constant.[46, 47] Withdrawal of a known percentage of the blood volume has been suggested as an appropriate way to assess the role of the sympathetic nervous system in hemorrhage.[6] Anesthesia has profound effects on the cardiovascular and respiratory systems.[17, 34, 35, 47]

The present study is the first to investigate interrelationships among the cardiovascular, respiratory, metabolic, and endocrine systems after acute hemorrhage in unanesthetized fasting resting healthy man. The experimental design required that a constant fraction of the blood volume be withdrawn, and is similar to that used to investigate other effects of acute blood loss in normal man.[7, 24, 27, 39-41]

Methods

Sixteen normal healthy men (ages 19 to 28 years) were admitted to the hospital for a 3-day period. Each was informed completely of the protocol details before selection. Each had a routine history, physical examination, blood count, urinalysis, chest film, and electrocardiogram on the day of admission. The blood volume was measured on the day of admission by Cr^{51} tagged autologous red cells and Evans blue dye.[28] All subjects were kept supine at bed rest until noon on the day before the study in order to simulate the next day's physical activity, when they were also supine until the completion of the protocol. At all other times they were allowed limited ambulation and standard hospital diet.

Free norepinephrine (NE) and epinephrine (E) in specimens of urine collected at 4-hr. intervals one day before and on the day of bleeding were measured by the spectrophotofluorometric method of Anton and Sayre.[2] Recoveries of norepinephrine and epinephrine in urine were $69 \pm 4\%$ (SEM) and $77 \pm 6\%$, respectively. Corrections for recovery were omitted from the tabulated results.

Serum free fatty acids (FFA) were measured by the method of Dole and Meinertz.[9] Serum glucose was measured by an automated modification of the method of Hoffman.[21] Serum insulin (IRI) and serum growth hormone (HGH) were measured by double antibody radioimmunoassay technics.[4, 42] Measurements of FFA, serum glucose, IRI and HGH were made before hemorrhage and at increments of 250 ml. of blood loss and at 15 min., 45 min., 90 min., 3 hr. and 24 hr. after blood loss. All

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TABLE 1. *Cardiovascular Changes after Acute Blood Loss or Exchange Transfusion in Man*

Measurement	No. Subjects	Control	1 Min.*	*p*	90 Min.*	*p*
1. Cardiac index (l./m.²/min.)						
Hem.	11	3.13 ± 0.14	2.67 ± 0.18	<0.01	2.66 ± 0.22	<0.01
Ex. Trans.	5	2.73 ± 0.05	3.01 ± 0.07	<0.05	2.92 ± 0.13	—
2. Stroke volume (ml./beat)						
Hem.	11	89 ± 5	74 ± 7	<0.01	70 ± 6	<0.001
Ex. Trans.	5	94 ± 13	89 ± 9	—	94 ± 8	—
3. Left ventricular work (Kg. m./min.)						
Hem.	11	7.9 ± 0.4	5.6 ± 0.6	<0.005	5.8 ± 0.4	<0.001
Ex. Trans.	5	6.8 ± 0.4	7.8 ± 0.5	<0.025	7.7 ± 0.6	<0.05
4. Total peripheral resistance (dynes sec. cm.$^{-5}$)						
Hem.	11	1150 ± 61	1659 ± 438	—	1310 ± 108	—
Ex. Trans.	5	1234 ± 94	1134 ± 82	—	1205 ± 74	—
5. Pulse rate (beats/min.)						
Hem.	11	68 ± 3	73 ± 4	—	74 ± 4	<0.01
Ex. Trans.	5	65 ± 6	70 ± 7	—	64 ± 6	—
6. Mean arterial blood pressure (mm. Hg)						
Hem.	11	92 ± 2	76 ± 4	<0.025	82 ± 1	<0.001
Ex. Trans.	5	90 ± 4	92 ± 5	—	93 ± 4	—
7. Central venous pressure (mm. Hg)						
Hem.	11	6.9 ± 0.8	4.2 ± 0.7	<0.001	4.5 ± 0.7	<0.001
Ex. Trans.	5	7.7 ± 1.2	7.7 ± 1.2	—	7.6 ± 1.2	—

* After hemorrhage (Hem.) or exchange transfusion (Ex. Trans.). *p* = Significance level of paired comparison with control; — means $p > 0.05$. All values ± SEM.

measurements were made with subjects in the unanesthetized, fasting, resting state.

Cardiac output was determined by dye-dilution (indocyanine green) with a Gilson densitometer and Lexington analog cardiac output computer (time constant = 0.245). Densitometer and computer curves were simultaneously recorded on a Brush 4-channel rectilinear writer (model 240). Cardiac outputs were computed from the step function of the computer curves. An analysis of cardiac output values obtained from computer-analyzed curves and those obtained from direct readout of the densitometer showed no significant differences.[38] Each cardiac output value was the mean of at least three separate dye-dilution curves. For measurement of central venous pressure (CVP), blood withdrawal, and indocyanine green injections, a polyethylene catheter (Clay Adams PE205, length 36″) was inserted into a brachial vein and passed into the right atrium or superior vena cava. For measurement of arterial pressure and sampling of arterial blood for cardiac output measurements and blood gases, an 18-gauge Cournand needle was inserted percutaneously into the common femoral artery. Arterial pressure and central venous pressure were measured with Statham pressure transducers (P23Dd and P23BB).

Minute ventilation ($\dot{V}E$) was determined by collecting a 3-min. sample of expired gas in a meteorological balloon. Expired oxygen concentration ($F\bar{E}\ O_2$) was measured with a Beckman oxygen analyzer (model E2), and expired carbon dioxide concentration ($F\bar{E}\ CO_2$) was measured with an infrared carbon dioxide analyzer (Beckman model LB-1). All values were corrected to BTPS. Physiologic dead space to tidal volume (V_D/V_T) ratio was calculated from the Enghoff modification of the Bohr equation (12):

$$V_D/V_T = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}},$$

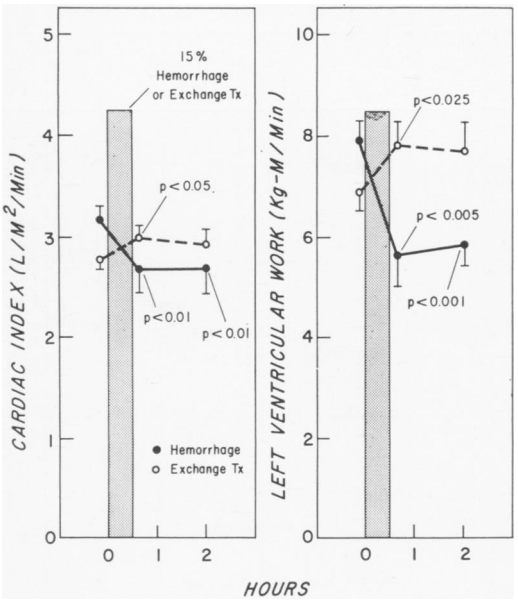

FIG. 1. Cardiac index and left ventricular work after 15% blood loss or exchange transfusion. The significant changes are in opposite directions in the two groups. Closed dots are hemorrhage; open dots are exchange transfusion. All values are mean ± SEM.

where Pa_{CO_2} is arterial carbon dioxide tension and $P\bar{E}\ CO_2$ is mixed expired carbon dioxide tension. Arterial carbon dioxide tension (Pa_{CO_2}) and arterial pH (pHa) were measured on Radiometer blood gas equipment. Respiratory quotients (R.Q.) were measured from simultaneous measurements of oxygen uptake and carbon dioxide excretion.

Cardiovascular and ventilatory measurements were made before, one min. after and 90 min. after blood loss or exchange transfusion. Subjects were randomly selected for the bleeding or exchange transfusion protocol and were not blindfolded during the procedure. Acute venous hemorrhage was performed by the rapid removal of 15% of the measured blood volume (mean hemorrhage volume = 800 ml. removed in 15.5 min.). Exchange transfusion in control subjects was performed by the simultaneous removal from one central venous catheter and replacement through another venous catheter of 15% of the measured blood volume. The replaced blood was autologous blood drawn 7–10 days previously. Previous studies of hemorrhage in normal subjects have shown that 100% transcapillary refilling occurs by 48 hours after blood loss.[39] The result was no net blood volume change (mean exchange transfusion volume = 822 ml. exchanged in 20 min.). Statistical analyses were performed by computer programs of paired and unpaired t tests.

Results

Cardiovascular. Cardiovascular changes produced by 15% acute blood loss or exchange transfusion (controls) are shown in Table 1 and Figures 1 and 2. Hemorrhage was associated with a significant decrease in cardiac index, stroke volume, left ventricular work, mean arterial pressure and central venous pressure at 1 min., a trend which was sustained during the subsequent 90-min. observation period. A sig-

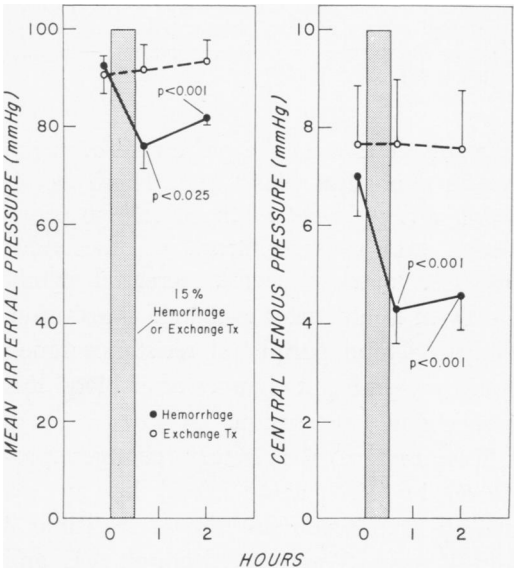

FIG. 2. Mean arterial pressure and central venous pressure changes after 15% blood loss or exchange transfusion. A significant decrease of mean arterial and central venous pressure occurred after blood loss, changes which were not observed in the exchange transfusion group.

TABLE 2. *Respiratory Changes after Acute Blood Loss or Exchange Transfusion in Man*

Measurement	No. Subjects	Control	1 Min.*	p	90 Min.*	p
1. VE (l./min.)						
Hem.	11	7.7 ± 0.7	12.1 ± 1.4	<0.005	11.2 ± 1.6	<0.025
Ex. Trans.	5	8.6 ± 1.6	10.3 ± 3.0	—	9.7 ± 2.3	—
2. V_T (ml.)						
Hem.	11	597 ± 54	870 ± 98	<0.025	833 ± 102	<0.05
Ex. Trans.	5	812 ± 129	870 ± 204	—	860 ± 142	—
3. $\dot{V}O_2$ (ml./min.)						
Hem.	11	280 ± 27	338 ± 30	—	335 ± 23	<0.05
Ex. Trans.	5	296 ± 15	320 ± 13	—	314 ± 12	—
4. $\dot{V}CO_2$ (ml./min.)						
Hem.	11	244 ± 27	325 ± 39	<0.005	320 ± 34	<0.025
Ex. Trans.	5	253 ± 17	275 ± 24	—	268 ± 20	—
5. R.Q.						
Hem.	11	0.87 ± 0.04	0.95 ± 0.04	<0.05	0.93 ± 0.05	—
Ex. Trans.	5	0.86 ± 0.04	0.86 ± 0.06	—	0.85 ± 0.06	—
6. $PaCO_2$ (mm. Hg)						
Hem.	11	42 ± 1	35 ± 2	<0.005	38 ± 2	<0.005
Ex. Trans.	5	41 ± 2	41 ± 3	—	40 ± 2	—
7. pHa						
Hem.	11	7.41 ± 0.01	7.45 ± 0.02	<0.025	7.44 ± 0.02	<0.05
Ex. Trans.	5	7.41 ± 0.01	7.44 ± 0.02	—	7.42 ± 0.01	<0.01
8. V_D/V_T						
Hem.	11	0.24 ± 0.01	0.26 ± 0.02	—	0.27 ± 0.02	—
Ex. Trans.	5	0.23 ± 0.02	0.26 ± 0.02	—	0.25 ± 0.02	—

* After hemorrhage (Hem.) or exchange transfusion (Ex. Trans.). $\dot{V}E$ = minute ventilation; V_T = tidal volume; $\dot{V}O_2$ = oxygen consumption; $\dot{V}CO_2$ = carbon dioxide production; R.Q. = respiratory quotient; $PaCO_2$ = arterial carbon dioxide tension; pHa = arterial pH; V_D/V_T = dead space to tidal volume ratio; p = significance level of paired comparison to control; — means $p > 0.05$. All values ± SEM. $\dot{V}O_2$, VE, V_T, $\dot{V}CO_2$ were corrected to BTPS.

nificant increase in the pulse rate occurred by 90 min. after blood loss. These trends were never present in the exchange transfusion group. By contrast, cardiac index and left ventricular work increased significantly at 1 min. after exchange transfusion. Only the total peripheral resistance failed to show significant changes after blood loss or exchange transfusion.

Respiratory. Respiratory changes produced by 15% acute blood loss or exchange transfusion are shown in Table 2 and Figures 3 and 4. Although $\dot{V}E$ and V_T were stimulated in both the hemorrhage and exchange transfusion group, the increase was statistically significant only in those subjects who were bled (Fig. 3). These same trends were also observed for $\dot{V}O_2$ and $\dot{V}CO_2$ (Fig. 4). Significant alveolar hyperventilation occurred after blood loss and was responsible for a significant rise in arterial blood pH (Table 2). Significant alveolar hyperventilation did not occur in the exchange transfusion group. The respiratory stimulation induced by bleeding was maximal at 1 min. after bleeding when compared to the 90-min. observation period. A significant increase in respiratory quotient (R.Q.) occurred 1 min. after acute blood loss (Table 2). There were no comparable changes in R.Q. in the exchange transfusion group. Changes in V_D/V_T were not statistically significant in either the hemorrhage or exchange transfusion group.

Metabolic. Serial blood glucose and FFA changes after 15% acute blood loss or exchange transfusion are shown in Table 3 and Figures 5 and 6. The blood glucose increased significantly after blood loss; the peak rise occurred at 15 min., with a significant rise being maintained at the 45-min. observation period (Fig. 5). Blood glucose levels in all subsequent periods were not significantly different from control. A significant rise in blood glucose occurred after 500 ml. of exchange transfusion, but all subsequent values were not different from control.

Free fatty acid values were significantly lower at 24 hours after hemorrhage in comparison to the control value on the day of study (Fig. 6). The peak FFA levels after bleeding occurred at 3 hr. with a significant increase being observed also at 90 min. The 24-hour value was in the normal control range,[9] and was significantly lower than the control value on the day of hemorrhage. Although the pattern of FFA changes in the exchange transfusion group showed a similar trend to those of the hemorrhage group, these fluctuations were not significantly different from control.

Hormonal. Urinary norepinephrine (NE) and epinephrine (E) excretion values are shown in Table 4 and Figures 7–9. A significant increase in 24-hr. urinary NE excretion occurred in both the hemorrhage ($p < 0.01$) and exchange transfusion group ($p < 0.05$). The change in NE excretion was almost identical in both groups (ΔNE excretion $= 6.9 \pm 2.1$ μg./24 hr. in the hemorrhage group versus 6.9 ± 2.5 μg./24 hr. in the exchange transfusion group) (Fig. 7). The release of NE produced by the control study is identical therefore to that produced by hemorrhage. In contrast to NE excretion, the adrenal release of E is significantly greater in the hemorrage group in comparison to exchange transfusion controls (ΔE excretion $= 5 \pm 1$ μg./24 hr. in hemorrhage group; $\Delta E = -1 \pm 2$ μg./24 hr. in exchange transfusion group,

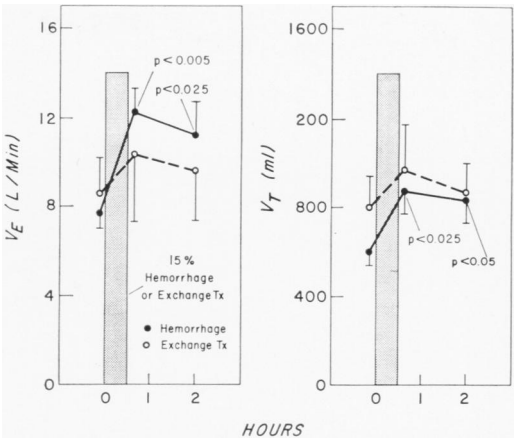

FIG. 3. Minute ventilation ($\dot{V}E$) and tidal volume (V_T) changes after 15% loss or exchange transfusion. A significant stimulation of ventilation ($\dot{V}E$ and V_T) occurred with hemorrhage. Insignificant stimulation of ventilation occurred in the exchange transfusion group.

$p < 0.05$). Exchange transfusion was associated with less adrenal release of E than was seen in the day preceding the study. The diurnal changes in NE and E excretion are reflected by the 4-hr. urinary excretion values plotted in Figures 8 and 9. On the day before hemorrhage the peak E excretion occurred in the 2 p.m. to 6 p.m. sample in the hemorrhage group and 6

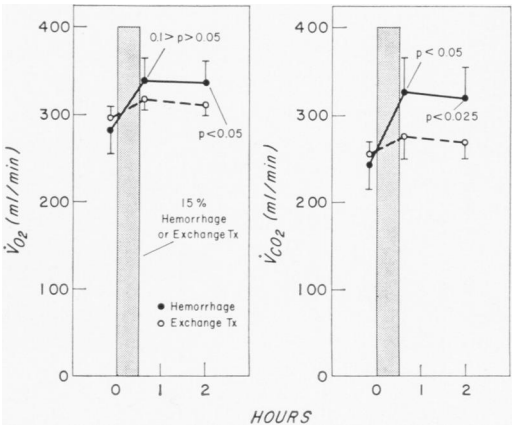

FIG. 4. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) changes after 15% blood loss or exchange transfusion. $\dot{V}O_2$ and $\dot{V}CO_2$ were both stimulated after blood loss. These changes were not observed with exchange transfusion.

TABLE 3. *Serum Growth Hormone, Insulin, Free Fatty Acid and Glucose after Blood Loss or Exchange Transfusion in Man*

Measurement	No. Subj.	Control	Values at Intervals during Hemorrhage or Ex. Trans.*			Time after Hem. or Ex. Trans. (Min.)++				
			1*	2*	3*	15	45	90	180	24 Hr.
1. HGH (mμg./ml.)										
Hem.	11	2.8 ± 0.7	3.4 ± 0.3	3.5 ± 0.8	2.8 ± 1.0	7.0 ± 2.1	9.7 ± 2.5‡	6.2 ± 2.6	6.9 ± 2.4	2.1 ± 0.9
Ex. Trans.	4	4.6 ± 1.1	8.2 ± 1.1	7.3 ± 4.4	7.4 ± 4.4	7.2 ± 3.1	6.3 ± 1.6	5.9 ± 1.6	7.1 ± 1.6	5.3 ± 2.7
2. IRI (μU./ml.)										
Hem.	4	14.5 ± 2.5	14 ± 0.8	16 ± 2.0	21.5 ± 4.9	20 ± 3.7	26 ± 7.3	37 ± 21.1	19 ± 5.4	22 ± 7.4
3. FFA (μEq./l.)										
Hem.	11	1361 ± 205	1377 ± 232	1306 ± 255	1275 ± 233	1478 ± 307	1391 ± 295	1757 ± 246‡	1782 ± 192‡	624 ± 101‡
Ex. Trans.	5	1121 ± 478	1077 ± 388	1177 ± 423	1080 ± 351	1076 ± 377	1143 ± 430	1354 ± 551	1318 ± 510	509 ± 116
4. Blood glucose (mg./100 ml.)										
Hem.	11	87 ± 4	96 ± 3	91 ± 4	87 ± 4	103 ± 5‡	98 ± 5	93 ± 4	89 ± 3	95 ± 3
Ex. Trans.	5	84 ± 9	89 ± 4	95 ± 7	92 ± 8	87 ± 6	85 ± 5	86 ± 3	83 ± 4	89 ± 5

* Values at 250 ml. increments during Hem. or Ex. Trans.; 1 = 250, 2 = 500, 3 = 750 ml. increment. ++ Hem. = hemorrhage; Ex. Trans. = exchange transfusion; HGH = serum growth hormone; IRI = serum insulin; FFA = serum free fatty acid. All values are ± SEM. ‡ Significance level of $p < 0.025$ or greater compared to control (see Figs.).

p.m. to 10 p.m. sample in the exchange transfusion group. The lowest E excretion values were seen in the 2–6 a.m. samples for both groups. Paired *t* tests of identical 4-hr. urine pools on the day before compared to the day of hemorrhage showed a significant rise of E excretion only in the 10 a.m.–2 p.m. sample (10 a.m.–2 p.m. E excretion day before bleeding = 0.8 ± 0.2 μg.; 10 a.m.–2 p.m. E excretion day of bleeding = 3.4 ± 0.6 μg., $p < 0.001$).

The peak 4-hr. urine excretion of NE occurred in the 2 p.m.–6 p.m. sample in the hemorrhage group and in the 10 a.m.–2 p.m. sample in the exchange transfusion group. The lowest NE excretion occurred in the 6–10 a.m. sample in the hemorrhage group and in the 10 p.m.–2 a.m. sample in the exchange transfusion group. No significant differences were observed in NE excretion over identical 4-hr. periods on the day before compared to the day of bleeding.

HGH levels rose rapidly after hemorrhage to their peak value at 45 min. (control HGH = 2.8 ± 0.7 mμg./ml.; 45 min. after bleeding HGH = 9.7 ± 2.5 mμg./ml., $p < 0.025$) (Fig. 10). The 90 min.- and 3 hr.-HGH values, though still elevated, were not statistically different from control. No significant changes in HGH occurred in the exchange transfusion study in comparison to the control levels.

IRI values increased in the hemorrhage group after bleeding; because of the small number of subjects tested (n = 4) and the wide scatter, there were no significant changes from the control value (Fig. 11). A comparison of the mean IRI value at 250 ml. of blood loss with the 45-min. value indicates a change which approaches significance, $0.1 > p > 0.05$ (Fig. 11). No IRI measurements were performed in the exchange transfusion group, and it is not possible to state whether these changes were related to blood loss or the procedure itself.

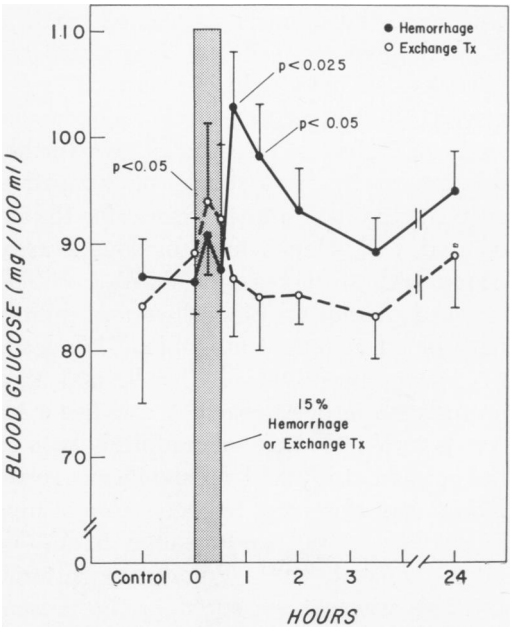

FIG. 5. Blood glucose changes after 15% hemorrhage or exchange transfusion. The peak glucose rise occurred 15 min. after acute blood loss and then declined rapidly. The only significant rise of glucose after exchange transfusion occurred at the 500 ml. exchange transfusion mark.

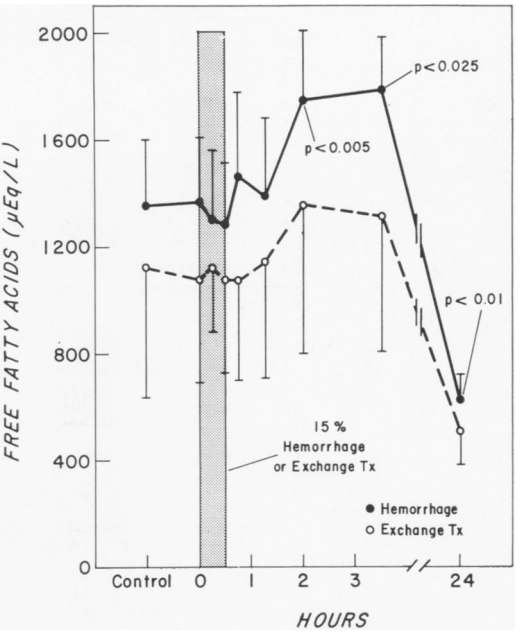

FIG. 6. Serum free fatty acid (FFA) changes after 15% hemorrhage or exchange transfusion. The peak FFA rise occurred 3 hr. after hemorrhage. By 24 hr. after hemorrhage the mean FFA value fell within the normal range. No significant changes in FFA levels occurred in the exchange transfusion group.

Discussion

A significant decrease of cardiac index, stroke volume, left ventricular work, mean arterial pressure, and central venous pressure was observed in the subjects who were acutely bled. Some of these changes were observed in a previous study of acute blood loss in man.[41] The absence of these changes in the exchange transfusion group suggests that although stimulation of the sympathetic nervous system was equivalent (as indicated by a similar increase in urinary norepinephrine excretion) in both bled and control subjects, the increased adrenal release of epinephrine in the bled group was not sufficient to maintain cardiovascular compensation for the loss of circulating blood volume. Even at 90 min. after blood loss the cardiac index was still significantly lower than in the control group. All sub-

TABLE 4. *Urinary Catecholamine Changes after Acute Blood Loss or Exchange Transfusion in Normal Man*

Measurement	No. Subjects	Day Prior to Bleed	Day of Bleed	p
1. Norepinephrine (μg./24 hr.)				
Hem.	11	21.5 ± 5.2	28.3 ± 6.0	<0.01
Ex. Trans.	5	14.9 ± 2.5	21.8 ± 3.0	<0.05
2. Epinephrine (μg./24 hr.)				
Hem.	11	5.6 ± 1.8	8.5 ± 1.8	—
Ex. Trans.	5	8.2 ± 1.0	6.9 ± 2.0	—

p values = significance level of paired comparison to control day. Values are ± SEM.

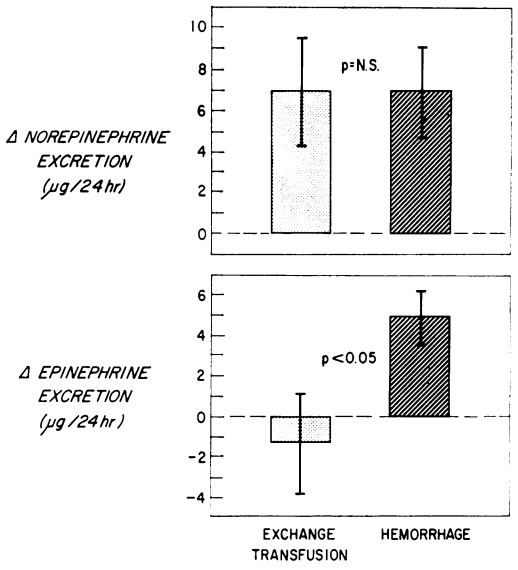

FIG. 7. Changes in 24 hr. excretion of norepinephrine (NE) and epinephrine (E) after hemorrhage and exchange transfusion. Although NE excretion was significantly elevated after blood loss and exchange transfusion, there was no difference in the change of NE excretion in the two groups (p = NS). Epinephrine excretion was significantly elevated in the hemorrhage group compared to exchange transfusion controls ($p < 0.05$).

jects became aware of the bleeding or exchange transfusion procedure during the study period. It is conceivable that the difference between the cardiac indices in the control period of the hemorrhage versus the exchange transfusion group represents the experience of the group that underwent exchange transfusion with phlebotomy 7–10 days earlier.

Acute hemorrhage in man, as in the cat[8, 10] and dog,[36] stimulates alveolar ventilation. In the cat at low blood pressures it appears that these acid-base changes are controlled mainly by carotid body chemoreceptors.[10] Significant increases of $\dot{V}O_2$ and $\dot{V}CO_2$ were observed after acute blood loss in man, changes which have also been observed during graded hemorrhage in the dog.[22] As in the present study, Nahas and associates found that when arterial pH was maintained during experimental hypovolemic shock $\dot{V}O_2$ is increased.[31] Stimulation of the sympathoadrenal system or catecholamine infusion is associated with a marked increase in $\dot{V}O_2$.[18] The significant increases of blood glucose and FFA observed in the present study and in the study of Nahas and associates give further support to the importance of sympathoadrenal stimulation as the cause for the increased $\dot{V}O_2$. Hemorrhage in dogs is associated with an increase of V_D/V_T.[13, 14] The reduced pulmonary blood flow and pulmonary blood volume [23] after blood loss leads to uneven perfusion of alveoli, and thus an increase in dead space. A significant increase in V_D/V_T was not uniformly seen in the present study and no significant correlation was observed between the change in cardiac output and change in V_D/V_T after hemorrhage.[44] Pulmonary arterial pressure was not measured in the present study and it may be that epinephrine release caused an acute increase in pulmo-

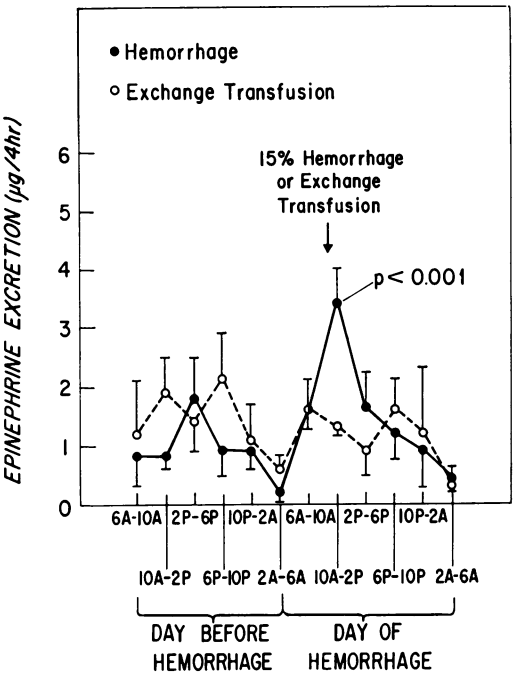

FIG. 8. Diurnal 4-hourly urinary excretion of epinephrine (E) on the day before and day of hemorrhage. Only in the 10 a.m. to 2 p.m. sample on the day of hemorrhage was there significant additional excretion of E in comparison to the day before hemorrhage.

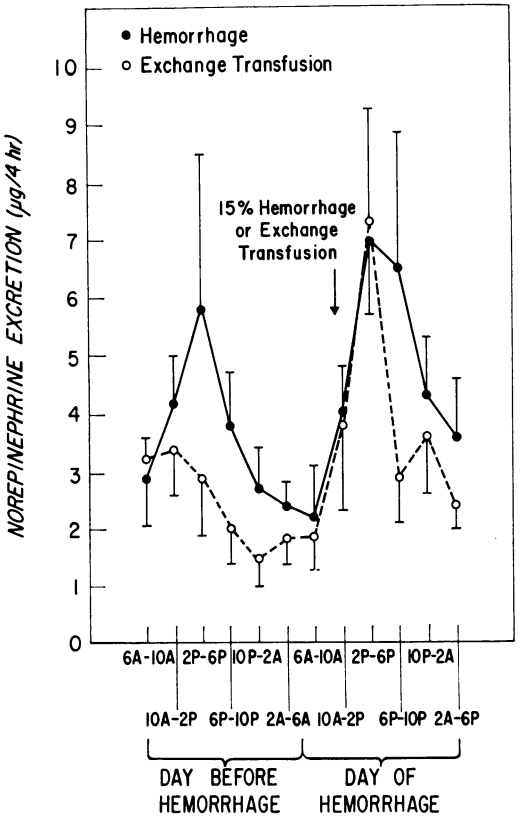

FIG. 9. Diurnal 4-hourly excretion of norepinephrine (NE) on the day before and day of hemorrhage. Similar stimulation of NE excretion is seen in both the hemorrhage and exchange transfusion studies.

nary arterial pressure[5] which maintained a more even distribution of pulmonary blood flow or, alternatively, that the magnitude of hemorrhage was not sufficient to consistently cause an acute increase of V_D/V_T.

Significant stimulation of norepinephrine was observed in bled and control subjects. The 4-hr urinary excretion of norepinephrine and epinephrine shows the diurnal fluctuations which appear to be related largely to assumption of the upright posture. Adrenal release of epinephrine was significantly greater, however, in the bled subjects compared to exchange transfusion controls. Norepinephrine increases VO_2 in the guinea pig,[25] rabbit,[26] cat,[29] dog,[16] and man,[48] but it is generally considered that this action is small in comparison to epinephrine.[20] The R.Q. during prolonged infusions of norepinephrine which increase VO_2 in dogs is about 0.70, whereas the R.Q. produced by similar infusions of epinephrine is about 0.85.[19] An R.Q. of 0.87 was seen in the bled subjects and 0.87 in the exchange transfusion study during the prehemorrhage period, when FFA levels were already 1361 ± 205 μEq./l. and 1,121 ± 479 μEq./l., respectively. This suggests that FFA was the major source of fuel even in the control period when sympathoadrenal stimulation was already apparent. Control levels of FFA on the day of study are greatly elevated above normal fasting FFA values.[9] The greater rise in blood glucose after hemorrhage in comparison to exchange transfusion is consistent with the hypothesis that epinephrine release was responsible for this rise, since epinephrine infusion causes a greater rise in blood sugar levels than norepinephrine.[19] The delayed peak of FFA seen in the bled group was probably secondary to insulin release (Fig. 11) in response to the rising blood

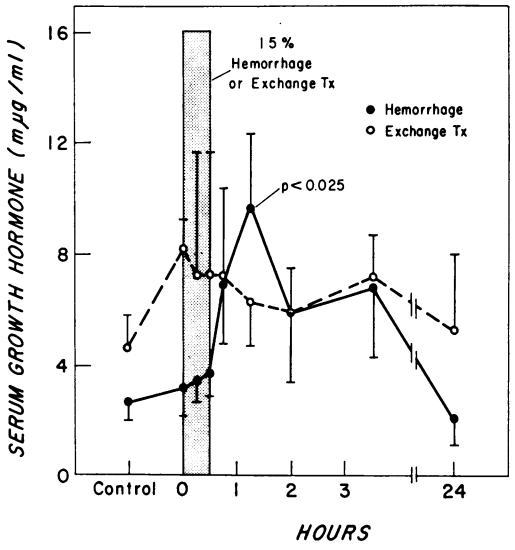

FIG. 10. Serum growth hormone (HGH) changes after hemorrhage and exchange transfusion. A significant increase of mean HGH occurred at 45 min. after blood loss. Similar changes were not observed after exchange transfusion.

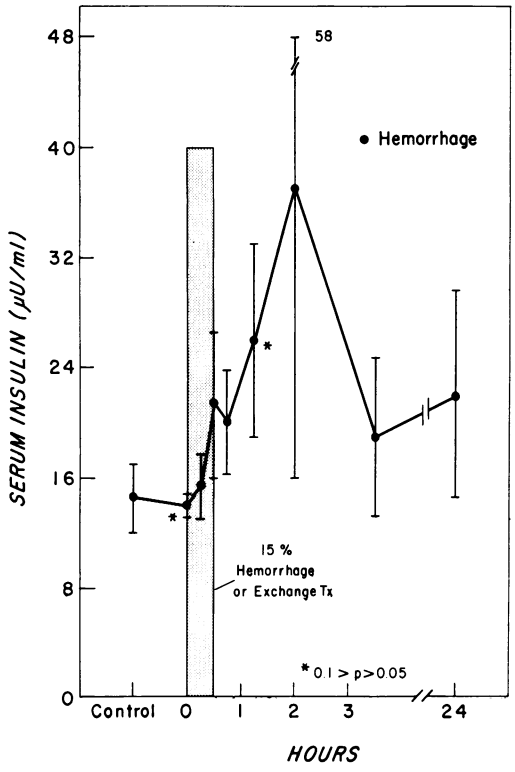

FIG. 11. Serum insulin (IRI) changes after hemorrhage. An increase of IRI which approaches statistical significance was observed at 45 min. after blood loss. No comparable data for exchange transfusion are available. (* refers to comparison of IRI values at 250 ml. of blood loss with value at 45 min—see text.)

sugar, since insulin is an inhibitor of the hydrolysis of neutral fat into FFA and glycerol.[11] Although IRI levels have been found to be reduced in hemorrhagic shock in anesthetized baboons [80] and in the acute phase of myocardial infarction in man,[1] it is apparent that the inhibitory effect of epinephrine on serum insulin release [82] was not sufficient to prevent a rise in insulin levels after hemorrhage.

The potential of FFA to uncouple oxidative phosphorylation may explain the calorigenic effect of FFA mobilization.[83] The present experiments do not preclude the possibility that glucagon may also participate in the release of FFA from adipose tissue.[45] Growth hormone levels were at peak concentration 45 min. after hemorrhage. It appears unlikely that HGH plays a significant role in the increased rate of lipolysis after hemorrhage.[3, 45] Although a rise in blood sugar decreases HGH levels,[87] various psychological and physical stresses such as fear, major surgery, and trauma stimulate HGH secretion, despite a rise in blood sugar.[15] It is apparent that the acute stress of bleeding also stimulates HGH levels in the presence of increased blood sugar levels.

Summary

The effect of acute rapid venous hemorrhage or isovolumetric exchange transfusion (15% of the measured blood volume in 15.5 min.) on cardiorespiratory, metabolic and endocrine interrelationships was studied in 16 normal male subjects. Hemorrhage was associated with a significant decrease in cardiac index, stroke volume, left ventricular work, arterial pressure and central venous pressure, changes which were not observed in the exchange transfusion control study. Significant alveolar hyperventilation and alkalemia were observed after hemorrhage, but no systematic change in dead space to tidal volume ratio was observed in these experiments. It would appear that the increased minute ventilation, oxygen consumption, and carbon dioxide production seen after hemorrhage are most likely related to the stimulation of epinephrine release from the adrenal gland. This calorigenic effect is not caused by increased circulatory requirements, but seems primarily related to the mobilization and oxidation of free fatty acids as the major fuel substrate. The early peak rise of blood sugar and delayed peak rise of free fatty acids suggest that insulin release may inhibit lipolysis after hemorrhage. Growth hormone release was also stimulated.

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