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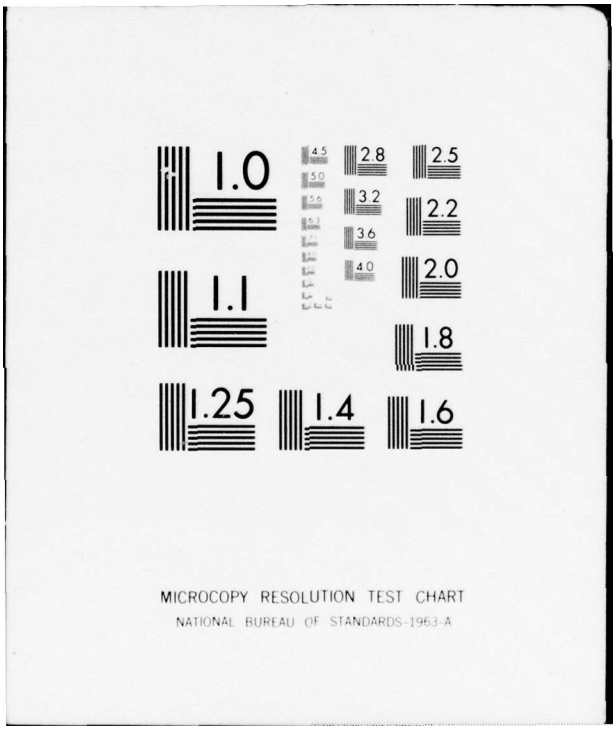
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THE ROLE OF INORGANIC PHOSPHATE IN OXYGEN TRANSPORT.

ANNUAL PROGRESS REPORT. 1976-1977

George F. Sheldon, M.D.

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Oxyhemoglobin dissociation curve; P50; 2,3 diphosphoglycerate; adenosine triphosphate; inorganic phosphate; cardiac output; blood transfusion; erythropoietin.

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

The studies examine the mechanisms causing anemia associated with massive transfusion, injury, and protein depletion. Following injury protein depletion occurs, with loss of inorganic phosphate. As inorganic phosphate modulates red cell glycolysis, it is basic to oxygen transport.

The study suggests that during anemia, oxygen unloading is over

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increased as 2,3 DPG levels increase.

By assessing erythropoietin in conjunction with red cell oxygen unloading.capabilities, we have presumptive evidence that the hypoxic stimulus which results in erythropoietin elevation which causes red cell production, is compensated for by 2,3 DPG elevation. The persistent reticulopenic anemia which follows injury and results in the need for blood transfusion, may be due to DPG compensation for hypoxia failure of erythropoietin production and persistent anemia.

ARMY CONTRACT ANNUAL PROGRESS REPORT

Contract #DADA 17-72-C2030

Introduction

Moderate reticulocytopenic anemia commonly persists through convalescence following major injury. Aregenerative anemia is particularly common after thermal injury and massive transfusion. The etiology and clinical significance of this anemia and the degree to which it merits correction by transfusion have not been defined. Reports concerning the etiology of the aregenerative anemia following injury regarding hormonal or bone marrow components have been scanty and their verdicts mixed (Cartwright & Wintrobe 1952; Andes & Rogers 1975). No previous studies have examined the interaction among erythrocyte metabolism, oxygen transport, and erythropoiesis following injury.

This report describes the relationship between oxygen transport, red cell metabolism, and erythropoiesis with reference to the metabolic profile of patients recovering from massive trauma and blood replacement. Specific questions addressed are: 1) What combination of factors can account for the persistant anemia which accompanies injury? and 2) what therapeutic intervention is warranted?

Methods

1) Seven patients with thermal injury receiving transfusion during the initial course of treatment (debridement and grafting) were studied. The magnitude of injury ranged from 50% burns with relatively minimal (20% or less) injury to the extremities (Table I). All patients with >30% burns received total parenteral nutrition during the course of their treatment. Two additional patients received parenteral nutrition for chronic inflammatory disease of the gastrointestinal tract were studied as a control group.

Serum levels of erythropoietin (ESF) were measured by the plethoric mouse bioassay (Fogh) and by radioimmunoassay (RIA). The RIA which seemed to more sensitively detect moderate anemia (<20mU/ml) than the bioassay (Garcia 1974) (see Abstract-Table II). Serum assays of erythropoietin were considered preferable to urinary assays because levels of the hormone change rapidly and show a circadian variation. RIA is expressed as mU/ml; and the bioassay as $\%^{59}Fe$ uptake following administration of test serum to a plethoric mouse.

The P_{50} of the oxy-hemoglobin dissociation curve, red cell 2-3 diphosphoglycerate and ATP, red cell morphology and serum chemistries were all measured on the same aliquot of venous blood used in the ESF assays. P_{50} was derived from the triple-tonometer system previously described (Sheldon 1976) and is expressed as mmHg standarized to 37°C., pH = 7.4 PCO_2 = 40. Red cell glycolytic intermediates and whole blood lactate were measured using Calbiochem kits and are expressed respectively as μM/g Hgb and mM/ml whole blood. Osmotic fragility was measured using standard saline dilution

without incubation. Urinary cyclic AMP (cAMP) was measured by competitive protein-binding assay (Amersham-Searle kit).

Serum phosphate ($P_I$mg/100), Iron (Fe mg/100), and iron-binding capacity (TIBC mg/100) were measured by the hospital central laboratories on the autoanalyzer. Red cell morphology and reticulocyte count, hematocrit, hemoglobin, mean corpuscular hemoglobin content were measured on the Coulter computer.

Nitrogen and non-protein caloric intake were calculated from parenteral and tube feeding data. Parenteral feeding employed hypertonic dextrose-Freamine II mixture. Vivonex-HiN was used for tube feeding. When patients were allowed oral intake, protein and caloric consumption was estimated by the hospital dietary department. Glycosuria and elevated blood sugar were corrected with supplementary insulin, standard practice in our institution. Nitrogen excretion was estimated from the nitrogenous content of the urine collected under toluene with HCl preservative. Change in body nonprotein nitrogen pool was estimated by the change in calculated body water (0.6 x body weight) times the change in serum nonprotein nitrogen. Nitrogen balance (Nbal) was calculated as (nitrogen intake) - (nitrogen excretion). Patients were given supplemental vitamins (MVI) with folate while on parenteral nutrition.

Results were analyzed using multiple linear regression and non-parametric ranking techniques (Kendall's rank correlation statistic, Mann-Whitney Test for population differences). The more powerful nonparametric tests were used when applicable. Test of association individual values were standarized to the patient mean value (Conover, Draper and Smith). Statistical tests were performed on all complete sets of data with the exclusion noted in Table III. The dataset with the largest value of "n" was considered the best sample for testing correlations.

RESULTS

Data on individual patients are summarized in Table I.

Increased osmotic fragility was not observed in the patient studies. Weak but significant ($p<.05$) inverse correlations were observed between the red cell glycolytic intermediate DPG (not ATP) and the saline concentrations at which 10, 50 and 90 percent hemolysis occurred. With this exception, ATP was not a statistically significant element in any correlation analyzed in this study. One patient had microcytic normochromic anemia with low (<60) serum iron levels unresponsive to oral iron supplements. With the exception of this patient red cell morphology was normal in all patients. Reticulocyte production indices were all within normal limits (normal = 1.0-2.0) (<1.5) despite the moderate anemia (<10 gm%) observed in burns exceeding twenty percent.

No significant correlation (Abstract-Table 2) was found between the two assays for erythropoietin (Bio-Assay, Radioimmunology). In five of the seven patients, however, a reciprocal relationship be-

tween the bioassay and RIA with respect to time (Fig. I) was present. Pronounced increases in bioassay ESF occurred in the acute phase (<7 days post injury) and were associated with relatively depressed levels of RIS-ESF, though the latter are minimally elevated above normal. Following the first seven post injury days, bioassay levels for ESF fell and RIA levels increased without consistent alteration in the level of anemia. Overall, the bioassay for erythropoietin correlated negatively with hemoglobin and positively with percent reticulocytes (Table III).

Red cell 2,3 DPG varied as a function of nitrogen balances, serum inorganic phosphate levels, caloric intake, hemoglobin level, and time elapsed from injury. These variables accounted for 65 to 82 percent of the DPG variation observed in our sample (Table IV). The half saturation point (P_{50}) of the oxy-hemoglobin dissociation curve correlated with DPG ($p<.001$ level $r = .631$), and accurately reflect intra-erythrocytic regulation of oxygen transport.

Cyclic AMP (cAMP) correlated negatively with nitrogen balance.

When differentiated with respect to hemoglobin, the bioassay and 2,3 DPG showed a highly significant negative correlation ($r = -.43$, $p<.005$; Table IV). DPG in patients with thermal injury was elevated more than patients with GI disease ($p<.001$); nitrogen balance ($p<.025$) and caloric intake ($p<.05$) were lowered to the burn patients and rectal temperature was higher ($p<.001$).

Both RIA and DPG were higher in the convalescent period (>7 days after injury) when the hemoglobin values were lower than the immediate post-injury phase. Nitrogen balance, caloric intake and DPG increased significantly as functions of time (Table IV). Most DPG values (65%) obtained during the convalescent period fell more than four standard deviations above normal (11.9 ± 1.2).

Discussion

A shift to the right of the oxy-hemoglobin dissociation curve (lowered hemoglobin affinity for oxygen) is commonly associated with hypoxia or anemia. The shift is felt to be an intra-erythrocytic adaptation to lowered red cell mass or hypoxia. The lowering of the affinity of hemoglobin for oxygen is modulated by erythrocyte glycolysis, with the formation of 2,3 DPG and ATP. With increasing quantities of 2,3 DPG, dissociation of oxygen from the hemoglobin molecule is enhanced and the hypoxic state presumably ameliorated.

Conditions that increase red cell glycolysis are frequently associated with an increase in erythropoietin. By stimulating bone marrow production of the erythrocytes, red cell mass is normalized. ESF levels declined in time, suggesting that a new hemeostatic set-point had been reached (Schooley and Malmann; Miller, et al.), suggesting that DPG elevation removes the stimulus to erythropoietin synthesis with consequent persistence of anemia.

Although the main determinants of 2,3 DPG production (pH, Inorganic phosphate) have been defined, other metabolic influences on 2,3 DPG synthesis are less well described. Valeri has suggested that the red cell and its metabolic state may well serve as a

"metabolic biopsy."

The data reported in this study allow us to correlate 85% of red cell 2,3 DPG elevation to metabolic and nutritional factors, such as nitrogen balance, caloric intake, the presence of sufficient inorganic phosphate and time elapsed after injury (Table IV).

Nitrogen balance and caloric intake increased with time. Another mechanism through which elapsed time may influence DPG levels is suggested by the work of Wilmore (1976), who notes a persistent increased basal metabolic rate in thermally injured patients which peaks at about ten days post burn, then returns to normal as wound closure occurs. An early perios (<6 days post burn) of catabolism is followed by a lengthy period of anabolism. Our data are consistent with the hypothesis that increased DPG may reflect this state of hypermetabolism. DPG levels in the burn patients are considerably higher than in the patient with gastrointestinal disease and are considerably higher than normal.

Inverse relationships between DPG and hormonal mediators of erythropoiesis have been reported in experimental hemorrhage (Miller, 1976) and exposure to low ambient oxygen tensions for various periods of time (Schooley & Mahlmann; Miller 1973). Following a step change in oxygen delivery a sharp increase in ESF occurs. Within 24° after the initiation of hypoxia DPG rises and ESF levels fall. DPG remains elevated throughout the hypoxic period, while ESF levels rapidly return to normal. Within 72 hours reticulocytes appear and the red cell mass increases.

Although our data demonstrate a correlation between ESF elevation and reticulocyte values, ESF is only minimally elevated, and reticulocyte values are within normal limits. Moreover, no increase in hemoglobin or hematocrit is observed even when patients are followed as long as 72 days postburn. During the time when ESF is elevated, serum lactate is elevated (>2.0), suggesting the presence of a hypoxic stimulus.

Erythropoietin (radioimmunoassay) is elevated throughout the convalescent phase, and shows a negative correlation with DPG, suggesting that complete compensation for the red cell mass deficit has not occurred.

Elevations of the radioimmunoassayable erythropoietin without corresponding elevated bioassayable ESF have been noted in uremia, suggesting a "block" in the elaboration of bioactive ESF by the kidneys (Garcia, 1975). Our patients, however, had no evidence of renal dysfunction to explain this finding.

CONCLUSIONS

This study gives indirect support to the hypothesis that the hypermetabolic state following massive trauma is associated with a rise in 2,3 DPG sufficient to normalise oxygen transport despite moderate anemia, which presumably compensates for the hypoxia which

results in elaboration of erythropoietin with consequent erythropoiesis. The patients with burns had considerably higher DPG values than the patients with GI disease, reflecting the hypermetabolic state of the burns.

The fact that elevation in ESF as measured by both methods could occur during the convalescent period (Fig. 1, Table II) indicates that this type of anemia is not secondary to an inability to produce erythropoietin. If ESF production is stimulated in response to oxygen deficit, then these patients were not hypoxic during their convalescence. Probably this degree of anemia does not merit transfusion.

TABLE I

Patient Data Relating to ESF

Patient	Variable Expression	Study Period Days $\bar{p}$ Injury	ESF: Bioassay % ^{59}Fe Uptake	ESF: RIA mU	P_{50} mmHg	DPG µM/gm Hgb	Lactate mM/f.	Hgb g/boml	Nbal mg/kg mlda	Caloric Intake KCal Kg/da	PO_4 mg%	Comp µM/24°	Retic %
Normal		NA	<2.0	<20.0	26.5	11.9	2.0	>12$_1$0	-	30-40	>3.0	-	0.5-1.5
A. BURN													
22 year old male	mean	NA	1.30	20.3	24.3	18.0	2.23	9.4	44.	35.8	3.53	-	-
45% burn	low	1	0.17	8.0	23.2	12.5	1.50	6.5	-180	0	2.1	-	-
6 units blood	high	72	4.34	52.0	26.2	22.0	3.54	13.6	170.	65.4	4.7	-	-
22 year old male	mean	NA	4.16	22.2	24.0	17.2	2.07	9.9	-16	21.0	3.12	-	1.1
30% burn	low	10	1.03	11.2	23.9	15.5	1.23	8.1	-48	9.4	2.3	-	0.7
11 units blood	high	43	10.70	38.0	24.1	18.6	2.65	10.8	16	32.5	3.8	-	1.5
63 year old male +	mean	NA	2.54	27.8	24.8	17.4	3.17	13.2	-38	16.2	-	-	-
30% burn, inhalation	low	5	0.97	24.0	24.5	15.8	2.55	12.0	-	-	-	-	-
	high	7	4.16	32.5	25.2	19.0	2.70	13.5	-	-	-	-	-
75 year old male +	mean	NA	0.92	27.6	23.7	16.8	2.51	9.0	-26	26.9	2.7	-	-
50% burn	low	3	0.35	14.5	21.5	10.9	1.71	6.6	-150.0	0	1.1	-	-
7 units blood	high	72	1.81	72.0	24.8	20.0	4.23	12.3	118	64.1	4.2	-	-

+ = expired

(continued)

TABLE I (continued)

Patient	Variable	Study Period	(ESF) Bioassay	(ESF) RIA	P_{50}	DPG	Lactate	Hgb	Nbal	Caloric Intake	PO_4	Comp	Retic
	Expression	Days $\bar{p}$ Injury	% ^{59}Fe Uptake	mU	mmHg	μM/gm Hgb	mM/f.	g/boml	mg/kg mlda	KCal Kg/da	mg%	μM/24°	%
Normal		NA	<2.0	<20.0	26.5	11.9	2.0	>12$_1$0	-	30-40	>3.0	-	0.5-1.5
A. BURN (continued)													
67 year old male +	mean	NA	0.57	92.0	24.1	15.4	2.20	8.9	41	12.1	2.8	-	0.9
35% burn, inhalation	low	8	0.41	88.0	22.7	13.8	1.69	7.5	-76	4.7	1.4	-	0.3
13 units blood	high	24	0.73	1000	25.2	16.9	2.70	10.5	266	24.0	3.6	-	1.6
20 year old male	mean	NA	0.74	16.7	23.3	16.1	1.61	11.8	62	33.3	4.7	-	-
20% burn	low	5	0.21	2.0	23.0	14.0	1.07	11.2	11	33.1	3.0	-	-
	high	31	1.63	38.0	23.6	17.1	2.16	12.1	99	33.7	5.7	-	-
22 year old male	mean	NA	1.14	14.5	24.0	18.4	2.33	11.2	-90	25.5	3.8	-	-
15% burn	low	14	0.88	5.2	23.7	16.9	1.96	10.2	-122	13.5	3.2	-	-
	high	42	1.52	34.0	24.3	19.5	2.79	12.0	23	27.0	4.3	-	-
+ = expired													
B. G-I DISEASE (Central)													
67 year old female	mean	NA	0.65	-	25.5	14.6	2.95	9.5	149.	80.0	2.9	2.45	1.5
Short bowel	low	NA	0.34	-	22.8	9.6	0.98	8.8	-57	26.0	1.9	1.3	0.3
No blood Bizarre DPG values	high	NA	0.98	-	28.3	24.4	4.40	10.6	313	109.9	3.8	4.5	2.8

(continued)

TABLE I (continued)

Patient	Variable	Study Period	(ESF) Bioassay	(ESF) RIA	P_{50}	DPG	Lactate	Hgb	Nbal	Caloric Intake	PO_4	Comp	Retic
	Expression	Days $\bar{p}$ Injury	% ^{59}Fe Uptake	mU	mmHg	μM/gm Hgb	mM/f.	g/boml	mg/kg mlda	KCal Kg/da	mg%	μM/24°	%
Normal		NA	<2.0	<20.0	26.5	11.9	2.0	>$12_1$0	-	30-40	>3.0	-	0.5-1.5
B. GI DISEASE (Central) (continued)													
Gastric outlet	mean	NA	1.63	-	25.9	14.6	1.75	9.4	137	51.3	3.6	3.5	0.9
Obstruction (??)	low	NA	0.39	-	23.8	11.6	1.30	8.6	69	29.5	2.5	1.8	0.3
Iron deficient	high	NA	3.04	-	27.7	16.3	2.30	11.0	213	65.9	4.4	6.7	1.4

1 unit blood

TABLE II

ERYTHROPOIETIN ELEVATION IN ANEMIA OF THERMAL INJURY

RICHARD SANDERS, MD, JOSEPH GARCIA, PHD,
GEORGE F. SHELDON, MD, FACS, JOHN SCHOOLEY, PHD,
RICHARD FUCHS, AND GARY CARPENTER, MS

AREGENERATIVE ANEMIA of thermal injury has been attributed to failure to produce erythropoietin or unresponsive bone marrow. Conflicting reports of both high and low levels of erythropoietin in burn anemia fail to clarify the pathophysiological mechanisms involved (1-3).

MATERIAL AND METHODS

Seven thermally injured patients were studied for 8 to 50 days. Burns were greater than 30% in three patients and less than 30% in four. Daily samples were obtained during the first postburn week, and then weekly. Serum erythropoietin was measured by both hypoxic mouse bioassay and radioimmunoassay (RIA). In addition, hemoglobin, hematocrit, and lactate were measured.

RESULTS

Serum erythropoietin values, as percent ^{59}Fe incorporation in the mouse bioassay, were minimally elevated for the first seven days in three patients. After seven days, however, the bioassay failed to detect erythropoietin ($< 2\%$ ^{59}Fe incorporation). Erythropoietin values, however, determined by RIA were elevated (> 10 mU/ml) in 33 of 36 samples ($P < .001$). RIA values declined during recovery of three patients with burns $< 30\%$, but were variable in burns $> 30\%$. Mild anemia (mean hematocrit, 30.6 ± 4.6) correlated inversely with lactate levels (mean lactate, 25 ± 12.7; normal, $15 \pm 2 \mu M$/gm hemoglobin) (Fig 1).

CONCLUSION

Erythropoietin is elevated following thermal injury consistent with the degree of anemia. Conflicting reports in the past may be due to failure of the bioassay to detect minimal elevation of erythropoietin, or failure to elaborate biologically active precursors of erythropoietin. Minimal elevations of lactic acid correlate with hematocrit and may stimulate erythropoietin production.

From the Department of Surgery and Trauma Center, University of California, San Francisco General Hospital, San Francisco, and Lawrence-Berkeley Laboratory. *Supported by National Institute of General Medical Sciences grant 18470 and US Army contract DADA 17-72-C2030, GMO7032-02.*

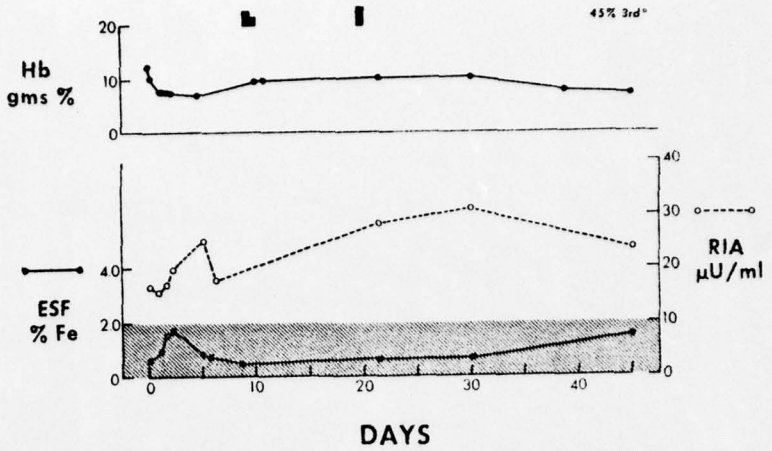

Fig 1. Erythropoietin values measured by bioassay and radioimmunoassay (RIA) in patient with anemia following thermal injury. During resuscitation, both RIA and bioassayable erythropoietin were elevated; during period of stable anemia, only RIA was elevated.

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TABLE III

Significant Correlations

Variables	Group Exclusions	Trans	# Pts	N	Test Statistic	P<
	I Erythropoietin					
Bioassay vs Hemoglobin	All Pts [1]	Z [2]	7 [2]	49 [3]	r = -.54	.001
Bioassay vs DPG	All Pts	Z	7	49	r^{1}(HGB) = -.43 [4]	.005
Bioassay vs Reticulocytes	Gastrointestinal Pts Bioassay (T) vs Retics	Z	3	12	TK = 53	.010
Radioimmuno-assay vs 2,3 DPG	Burn Pts Chron Phase	Z	6	33	TK = 197	.005
	I Red Cell - Metabolic					
2,3 DPG vs Nitrogen Balance	Burn Pts	-	7	35	TK = 214	.005
2,3 DPG vs Nitrogen Balance	All Pts	-	7	40	TK = 193	.05
2,3 DPG vs Caloric Intake	Burn Pts	-	7	35	TK = 282	.001
2,3 DPG vs Caloric Intake	All Pts	-	9	46	TK→ Z = 2.03	.05
2,3 DPG vs Serum PO_4	All Pts	Z	7	47	TK→ Z = 2.80	.005
2,3 DPG vs P_{50}	All Pts	Z	9	43	TK→ Z = 4.25 (r = 1631)	.001
Nitrogen Balance vs cAMP	Gastrointestinal Pts	-	2	9	TK = -28	.05

(continued)

TABLE III (continued)

1) To be included, samples had to show a hematocrit <45.

2) Indicates transformation to standard normal deviate (Z for individual patient. When Z - transformation is used variables must be sampled more than 3 times per patient; hence disparity between # patients.

3) Total number of samples analysed.

4) First-order partial product-moment correlation coefficient (r) differentiated with respect to hemoglobin.

5) Kendall's rank correlation coefficient.

6) "T + 1" denotes next study day following study day "T;" interval = 3-6 days.

7) AG excluded because of questionable DPG values.

TABLE IV

Variables Influencing DPG

1) Determinants of DPG:

Patient Group	R^2	Independent Variables			
Burns	.82	Nbal***	Hgb*	Kcal***	Time*** elapsed
Burns	.65	Nbal***	PO_4	Hgb*	Cal**
Burns + CaR	.76	Hb***	Kcal**	Time*** elapsed	

2) Correlations, Burn Patients:

	PO_4	HGB	Kcal	Elapsed Time	DPG
Nitrogen Balance	.401	-.421*	.537**	.538**	.632***
PO_4		.308	.310	.369	.278
HGB			.085	-.330	-.462*
Kcal				.643***	.645***
Elapsed Time					.865***

* $p<.05$
** $p<.01$
*** $P<.001$

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