Published in final edited form as:
J Surg Res. 2013 January ; 179(1): 132–137. doi:10.1016/j.jss.2012.09.008.

Altered thyroid function in severely injured patients

Elena Grill, BA[a], **Michelle Strong, MD, PhD**[b], **Seema S. Sonnad, PhD**[c], **Babak Sarani, MD**[a], **Jose Pascual, MD, PhD**[a], **Heather Collins, PhD**[d], and **Carrie A. Sims, MD, MS**[e,*]

[a] Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

[b] Tacoma General Hospital, Tacoma, Washington

[c] Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

[d] Institute of Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

[e] Center for Resuscitation Science, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Background—Hemorrhagic shock profoundly affects the neuroendocrine profile of trauma patients, and we hypothesized that massive resuscitation would negatively impact thyroid function.

Methods—A prospective, observational study investigating thyroid function in hypotensive trauma patients (systolic blood pressure <90 mm Hg × 2) who survived >48 h was conducted at a Level I center over a 6-mo period. Blood samples for thyroid function were collected at time of presentation to the trauma bay and serially for 48 h. Collected data included demographics, injury data, vital signs, transfusion needs, crystalloid use, and vasopressor requirements. Patients receiving >5 units packed red blood cells (PRBC) within 12 h were compared with those receiving ≥ 5 units.

Results—Patients who required >5 units of PRBC/12 h had significantly lower total and free T4 levels on initial presentation, and levels remained significantly depressed over the next 48 h when compared with patients who required a less aggressive resuscitative effort. T3 values were markedly suppressed during the initial 48 h post trauma in all patients, but were significantly lower in patients requiring >5 units PRBC. TSH levels remained within the normal range for all time points. Lower trauma admission T4 levels were associated with the need for greater crystalloid resuscitation within the first 24 h.

Conclusion—Measurements of thyroid function are significantly altered in severely injured patients on initial presentation, and low T4 levels predict the need for large resuscitation. Further research investigating the profile and impact of thyroid function in trauma patients during resuscitation and recovery is warranted.

[*]*Corresponding author*. Division of Traumatology, Surgical Critical Care, and Emergency Surgery, 3400 Spruce Street, 5th Floor Maloney Building, Hospital of the University of Pennsylvania, Philadelphia, PA 19104. Tel.: +1 215 588 5154; fax: +1 215 349 5917. carrie.sims@uphs.upenn.edu (C.A. Sims)..

Keywords

Thyroid function; Hemorrhagic shock; Trauma

1. Background

Although not typically considered a “stress hormone,” thyroxine may play a critical role in maintaining vasomotor tone during times of physiologic stress. Abnormalities in thyroid function are known to influence cardiovascular stability and diminished levels of circulating thyroxine are associated with reduced myocardial energy, hemodynamic instability, and increased need for inotropic support [1–4]. Thyroid hormone replacement may reverse these metabolic derangements and dramatically improve myocardial dysfunction [1,5–7]. Intravenous thyroxine has recently been shown to improve the hemodynamic stability in severely brain-injured patients awaiting organ procurement and may be a useful cardiovascular adjunct following cardiac surgery [2,8].

Relative hypothyroidism has been observed following hemorrhagic shock and may contribute to decreased hemodynamic reserve and poor survival. Experimental models of hemorrhagic shock have demonstrated a strong association between degree of blood loss and the development of thyroid dysfunction. Specifically, T3 and T4 plasma concentrations fall drastically within minutes of experimental hemorrhagic shock [9,10]. These levels further decline during resuscitation and remain depressed for several days post hemorrhage. Animal studies also suggest that the magnitude of the T3 and T4 reduction may serve as a useful predictor of survival, with a higher mortality noted when thyroid indices failed to improve following hemorrhage [10]. Supplemental intravenous T3 following experimental hemorrhagic shock, however, appears to improve both cardiac function and survival [6,7,11].

Depressed thyroid function appears to be a harbinger of poor clinical outcome and increased mortality in critically ill patients [12]. To date, however, limited clinical data exist characterizing thyroid function in trauma patients [9,13,14]. Moreover, we hypothesize that alterations in thyroid function may be particularly pronounced in severely injured trauma patients who require massive resuscitation. In order to address this question, we investigated the profile of circulating thyroid hormone levels in severely injured trauma patients during their initial hospitalization and evaluated the potential impact of resuscitation.

2. Methods

A prospective observational study of trauma patients admitted to the Hospital of the University of Pennsylvania was conducted from March 2008 through September 2008. The Institutional Review Board of the University of Pennsylvania approved the study protocol. Initial blood samples were collected under waiver of informed consent and stored until consent and Health Insurance Portability and Accountability Act authorization were obtained from the patient or next of kin. If informed consent or Health Insurance Portability and Accountability Act authorization were not granted, samples were discarded without analysis.

2.1. Patients

All consecutive trauma patients (≥ 18 y old) assessed during the study period were evaluated prospectively. Patients who were hypotensive (systolic blood pressure <90 mm Hg × 2) and/or those who received packed red blood cells (PRBC) during their initial trauma resuscitation were considered for enrollment. The decision to initiate transfusion was made by the attending trauma surgeon. Exclusion criteria were pregnancy, significant intracranial injury requiring neurosurgical intervention, significant neck trauma, dialysis dependence, and thyroid supplementation or corticosteroid use within the prior 3 mo. Because of difficulty in obtaining consent, patients who died within 48 h of admission also were excluded.

2.2. Data collection

Demographic information, past medical history, mechanism of injury, Glasgow coma score, and injury severity score were documented for all patients. Serial blood samples were drawn at the following time points: on presentation to the trauma bay, on admission to the intensive care unit (ICU), and 24 and 48 h post admission. The total amount of PRBC and total crystalloid volume infused were also recorded. A PRBC requirement of >5 units within 12 h was deemed a large-volume resuscitation *a priori*. Vital signs and the use of vasopressors also were documented. The use of medications known to depress hormonal secretion (dopamine, haloperidol, and corticosteroids) was noted.

2.3. Blood sample analysis

Blood samples were collected in the trauma bay prior to the administration of intravenous fluids or blood products. Samples were processed but were discarded if patients did not meet inclusion criteria. Blood samples were collected in serum vacutainers (BD, Franklin Lakes, NJ) and were processed immediately upon collection. Serum samples were stored at −80° C until *post hoc* analysis. Thyroid hormone levels were quantified by the Diabetes and Endocrinology Research Center at the University of Pennsylvania using commercially available radioimmunoassay kits (MP Biomedicals, Solon, OH) to determine free thyroxine (unbound T4), total thyroxine (both bound and unbound T4), total triiodothryonine (total T3), free triiodothryonine (free T3), and thyroid stimulating hormone (TSH).

2.4. Statistical analysis

Mann-Whitney tests allowed comparison of T4, T3, free T3, and TSH in patients receiving >5 units of PRBC and patients receiving ≤5 units within 12 h of admission. *P* values of <0.05 were considered statistically significant.

3. Results

During the 6-mo study period, the trauma service evaluated 936 injured patients, of whom 96 met inclusion criteria of hypotension and/or blood transfusion for presumed hemorrhagic shock. Seventy-five of these patients were excluded due to survival <48 h, family declining consent, age <18 y, recent history of thyroid supplementation or steroid use, or chronic renal failure requiring dialysis. Eighteen patients met the inclusion criteria and all were transported directly from the scene. Patients were predominantly male (89%), between the

ages of 18 and 75 y (mean age 31 ± 15 y), with injury severity scores ranging from 10–50 (mean 27 ± 14). Over 70% of these patients had sustained penetrating injuries (n = 13). Twelve patients received >5 units of PRBC and six patients received 5 or fewer units within 12 h of admission; the two groups had similar demographics, injury severity scores, and injury mechanism (Table 1).

Patients requiring >5 units of PRBC within 12 h of admission had abnormally depressed total T4 concentrations (normal range 5.6–13.7 μg/dL) on initial presentation and throughout the 48-h observational period. When compared with those receiving ≤5 units of PRBC, patients requiring >5 units had significantly lower total T4 values on trauma bay presentation (8.76 ± 5.19 *versus* 3.86 ± 1.97; P = 0.02; Fig. 1). T4 values nadired after admission in both groups, but patients requiring >5 units had significantly lower values when compared with those who required less blood product resuscitation at all time points (Fig. 1).

On average, free T4 levels in all patients were lower than normal values upon admission to the trauma bay and remained depressed during the subsequent 48 h. Patients receiving >5 units of PRBC, however, had significantly lower free T4 concentrations than those receiving ≤5 units at all time points (Fig. 2).

Total and free T3 levels were within the range of normal on initial evaluation in patients requiring ≤5 units of blood (Table 2). In contrast, patients who subsequently required large-volume blood product resuscitation (>5 units/12 h) had significantly depressed free T3 levels on trauma bay admission (1.92 ± 1.01 *versus* 3.88 ± 2.04, P = 0.02, Table 2). Total T3 levels on initial evaluation were also lower in patients receiving >5 units; however, this difference did not achieve statistical significance (55.8 ± 8.95 *versus* 87.44 ± 44.41, P = 0.087). In all patients, both free T3 and total T3 levels fell dramatically at 12 h and remained lower than the assay's limit of sensitivity. As such, further statistical significance could not be determined.

TSH levels were within the normal range for all patients, with no significant difference between the two groups at any time point (data not shown).

Lower trauma bay total and free T4 values were associated with increased crystalloid resuscitation needs during the initial 12 h post admission (Figs. 3 and 4). Higher injury severity scores and the need for vasopressors, however, did not reach statistical significance because of the small sample size.

4. Discussion

Massive hemorrhage leads to marked alterations in critical hormone levels important to the maintenance of vasomotor tone [9,10,13,14]. In this prospective observational study of patients surviving at least 48 h post traumatic injury, we demonstrated that thyroid levels are profoundly altered immediately after injury. Importantly, both T4 and T3 levels declined by as much as 40% within the first 24 h following profound blood loss and remained depressed in the subsequent 48 h following traumatic injury. Specifically, patients requiring >5 units of PRBC within 12 h of admission demonstrated significant reductions in thyroid hormone

levels compared with patients who required less aggressive blood product resuscitation at all time points. Moreover, patients whose thyroid levels were depressed upon presentation to the trauma bay were more likely to require large-volume crystalloid resuscitation during the first 12 h post admission.

The current study represents the largest clinical evaluation to date investigating the profile of thyroid function in trauma patients presenting in shock. Although Vitek and Shatney [14] have previously reported that injury results in a biphasic dysfunctional thyroid response, we did not observe this phenomenon. In the study conducted by Vitek and Shatney, patients with injuries ranging from smoke inhalation to motor vehicle accidents were included. Patients in this study demonstrated a “fight or flight” response immediately following injury that was characterized by decreases in free and total T4 and significant increases in T3, TSH, and cortisol concentrations. However, of the 33 patients initially evaluated, only six patients in their study were followed beyond the initial trauma bay admission. This small cohort of patients demonstrated decreased TSH, T3, and T4 concentrations in conjunction with an increase in reverse triiodothyronine levels [14]. This pattern of “sick euthyroid” following traumatic injury has previously been described in other critically ill patients and may represent an adaptive physiologic response [15]. In contrast, all of the patients included in our analysis were hypotensive on arrival, severely injured (average injury severity score of 27), and primarily victims of penetrating trauma. Given this clinical profile, the failure to observe an increase in either T3 or TSH on initial presentation may suggest that the thyroid surge is more transient than previously reported or that severely injured patients may, in fact, have a blunted thyroid response. A longer observational period would nonetheless be needed to determine if these critically injured patients are at risk for developing a “sick euthyroid syndrome” or if low circulating thyroid hormone levels are associated with a worse prognosis.

Depressed thyroid function following trauma may reflect a maladaptive response to increased physiologic stress or a predictor of poor clinical outcome. In a similar study of injured patients requiring admission to a trauma unit, Phillips *et al*. describe a significant relationship between acute injury and depressed T3 levels that persisted over a 2-wk observation period [13]. Interestingly, in this study, total and free T4 levels were normal on arrival in all patients, but fell dramatically in the four patients who died within the 48 h of admission. In contrast, although only injured patients who survived to discharge were included in our study, we observed that both T4 and T3 concentrations decreased significantly during the first 48 h post injury in all patients. Initial T4 and T3 values, however, were more depressed in patients with higher injury severity scores and in those who required a more aggressive resuscitative effort.

Although our findings suggest that injured patients presenting with decreased thyroid function have increased resuscitative needs in terms of blood products and fluids, the physiologic mechanisms contributing to this observation require further elucidation, and causality remains to be determined. Several factors may contribute to the observed decrease in circulating thyroid hormone levels. In healthy adult humans the biological half-life of TSH is less than 1 h, while T3 is 24 h and T4 is 5–7 d. Although thyroid hormone levels are acutely altered in the setting of surgical and psychological stress, very little is known about

the kinetics of thyroid hormone in acute settings [16–18]. As such, the biological half-life of key thyroid hormones following severe trauma is unknown. Decreased blood flow to the thyroid gland during shock may impede the release of available thyroid hormone. In the setting of significant trauma and blood loss, elevated cortisol levels may decrease the formation and release of T4 and can inhibit the peripheral conversion of free T4 to the physiologically active T3 form [19]. Shock-associated tissue hypoxia can further compromise serum T3 levels by preferentially increasing the conversion of T4 to the inactive reverse T3 isomer (Fig. 5) [20]. Finally, because the blood products and fluids used for resuscitation do not contain thyroid hormones, the subsequent decrease in thyroid levels following resuscitation may be, in part, the result of dilution.

There are several limitations to this study. While this is the largest prospective clinical study investigating thyroid function following hemorrhagic shock and resuscitation, a greater sample size is needed to definitively establish the profile of thyroid indices in all trauma patients, including those who do not present in hemorrhagic shock. Moreover, it would be beneficial to follow patients for a greater length of time as the impact of hemorrhage on thyroid function and recovery may have a slower time course. In addition, patients who died were excluded from this study and, therefore, the impact of thyroid function on survival could not be assessed. Finally, although T3 levels were significantly depressed following ICU admission, limitations in the assay's sensitivity restricted the ability to definitively quantify the impact of hemorrhagic shock.

In conclusion, severely injured trauma patients are at risk for alterations in thyroid function. In particular, trauma patients with suppressed T4 values on arrival tend to require a more aggressive resuscitative effort. Although supplemental T3 administration following hemorrhagic shock may improve cardiovascular parameters and enhance survival in experimental models, further clinical research investigating thyroid function in trauma is needed and may provide the basis for using thyroid supplementation as a targeted adjunct during resuscitation.

Acknowledgments

This work was funded through a grant from the American Association for the Surgery of Trauma. Assays were supported by a NIH grant to the Penn Diabetes and Endocrinology Research Center (P30 DK19525) and performed by Heather Collins, PhD.

REFERENCES

[1]. Strauer BE, Schulze W. Experimental hypothyroidism: depression of myocardial contractile function and hemodynamics and their reversibility by substitution with thyroid hormones. Basic Res Cardiol. 1976; 71:624. [PubMed: 1016193]

[2]. Van Bakel AB, Pitzer S, Drake P, et al. Early hormonal therapy stabilizes hemodynamics during donor procurement. Transplant Proc. 2004; 36:2573. [PubMed: 15621093]

[3]. Davis PJ, Davis FB. Nongenomic actions of thyroid hormone on the heart. Thyroid. 2002; 12:459. [PubMed: 12165107]

[4]. Cini G, Carpi A, Cini L, et al. Thyroid hormones and the cardiovascular system: pathophysiology and interventions. Biomed Pharmacother. 2009; 63:742. [PubMed: 19917524]

[5]. Pantos C, Mourouzis I, Cokkinos DV. Thyroid hormone as a therapeutic option for treating ischaemic heart disease: from early reperfusion to late remodeling. Vascul Pharmacol. 2010; 52:157. [PubMed: 19951746]

[6]. Shigematsu H, Smith RA, Shatney CH. Triiodothyronine increases survival in canine hemorrhagic shock. Resuscitation. 1987; 15:233. [PubMed: 2831596]

[7]. Dulchavsky SA, Lucas CE, Ledgerwood AM, et al. Triiodothyronine (T3) improves cardiovascular function during hemorrhagic shock. Circ Shock. 1993; 39:68. [PubMed: 8481977]

[8]. Kaplan EM, Sanchez A, Beale E, et al. Clinical review: thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review. J Clin Endocrinol Metab. 2010; 95:4526. [PubMed: 20668034]

[9]. Vitek V, Shatney CH, Lang DJ, Cowley RA. Thyroid hormone responses in hemorrhagic shock: study in dogs and preliminary findings in humans. Surgery. 1983; 93:768. [PubMed: 6857495]

[10]. Vitek V, Shatney CH, Lang DJ, Cowley RA. Relationship of thyroid hormone patterns to survival in canine hemorrhagic shock. Eur Surg Res. 1984; 16:89. [PubMed: 6698080]

[11]. Yuan HQ, Shatney CH, Dewitt DS, et al. Triiodothyronine (T3) antagonizes adverse effects of high circulating reverse-T3 (rT3) during hemorrhagic shock. Am Surg. 1988; 54:720. [PubMed: 3195847]

[12]. Peeters RP, Wouters PJ, van Toor H, et al. Serum 3,3′,5′-triiodothyronine (rT3) and 3,5,3′-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. J Clin Endocrinol Metab. 2005; 90:4559. [PubMed: 15886232]

[13]. Phillips RH, Valente WA, Caplan ES, et al. Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome. J Trauma. 1984; 24:116. [PubMed: 6694235]

[14]. Vitek V, Shatney CH. Thyroid hormone alterations in patients with shock and injury. Injury. 1987; 18:336. [PubMed: 3508880]

[15]. Goldberg PA, Inzuchhi SE. Critical issues in endocrinology. Clin Chest Med. 2003; 24:583. [PubMed: 14710692]

[16]. Saranteas T, Tachmintzis A, Kasikeris N, et al. Perioperative thyroid hormone kinetics in patients undergoing major oral and maxillofacial operations. J Oral Maxillofac Surg. 2007; 65:408. [PubMed: 17307585]

[17]. Ilias I, Tzanela M, Mavrou I, et al. Thryoid function changes and cytokine alterations following major surgery. Neuroimmunomodulation. 2007; 14:243. [PubMed: 18073499]

[18]. Morgan CA, Wang S, Mason J, et al. Hormone profiles in humans experiencing military survival training. Biol Psychol. 2000; 47:891.

[19]. De Groot LJ. Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin. 2006; 22:57. [PubMed: 16399020]

[20]. Simonides WS, Mulcahey MA, Redout EM, et al. Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic-ischemic disease in rats. J Clin Invest. 2008; 118:975. [PubMed: 18259611]

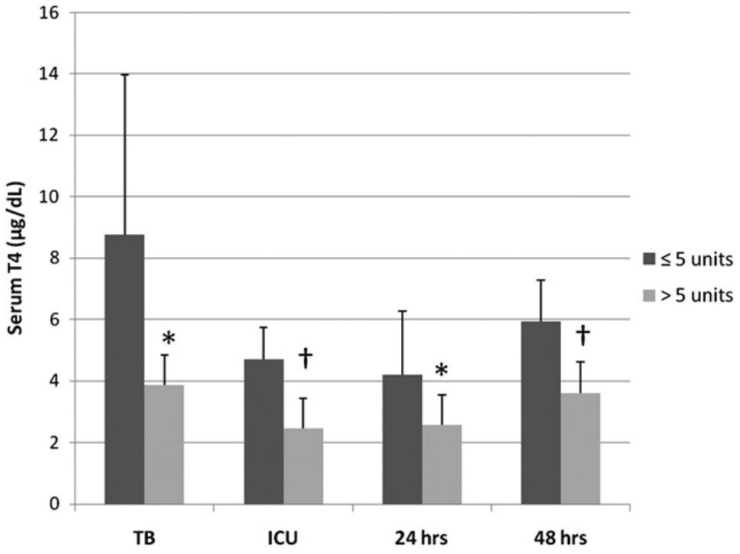

Fig. 1.

– Comparison of the units of PRBC received and total T4 concentrations. Normal range for total T4 in healthy volunteers: 5.6–13 µg/dL. Average serum T4 levels with standard deviation at each time point. ≤5 *versus* >5 units of PRBC transfused within 12 h were compared at each time point. * signifies $P < 0.05$ and † signifies $P < 0.001$.

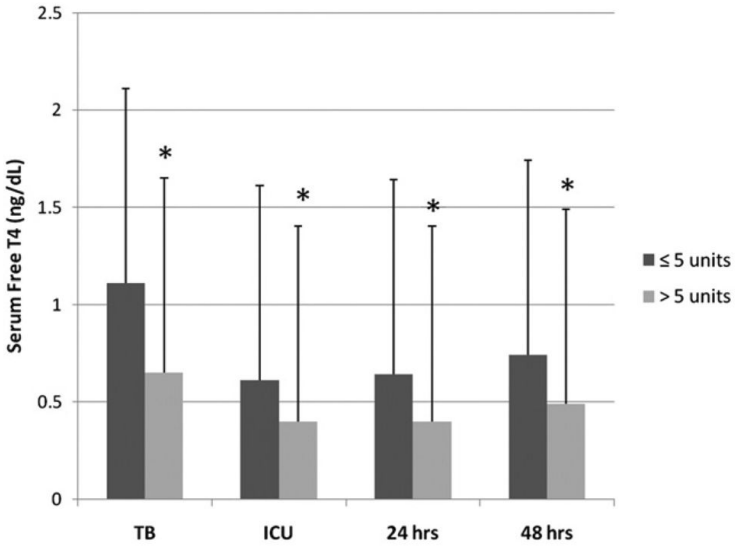

Fig. 2.

– Comparison of the units of PRBC received and free T4 concentrations. Normal range for free T4 in healthy volunteers: 0.8–1.5 ng/dL. Average serum free T4 levels with standard deviation at each time point. ≤5 *versus* >5 units of PRBC transfused within 12 h of admission were compared at each time point. * signifies $P < 0.05$.

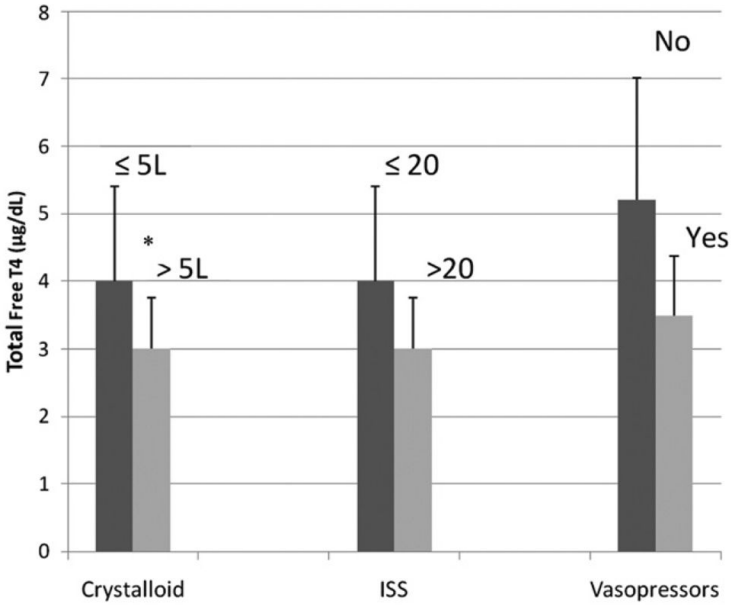

Fig. 3.

– Total T4 concentration on admission to the trauma bay as a function of crystalloid requirement within 12 h post admission, injury severity score, and the need for vasopressor support. The trauma bay total T4 levels (average with standard deviation) were compared according to crystalloid within 12 h of admission (≤5 *versus* >5 L), injury severity score (ISS ≤20 *versus* >20), and need for vasopressors within 48 h of ICU admission (No *versus* Yes). **P* < 0.05 considered statistically significant.

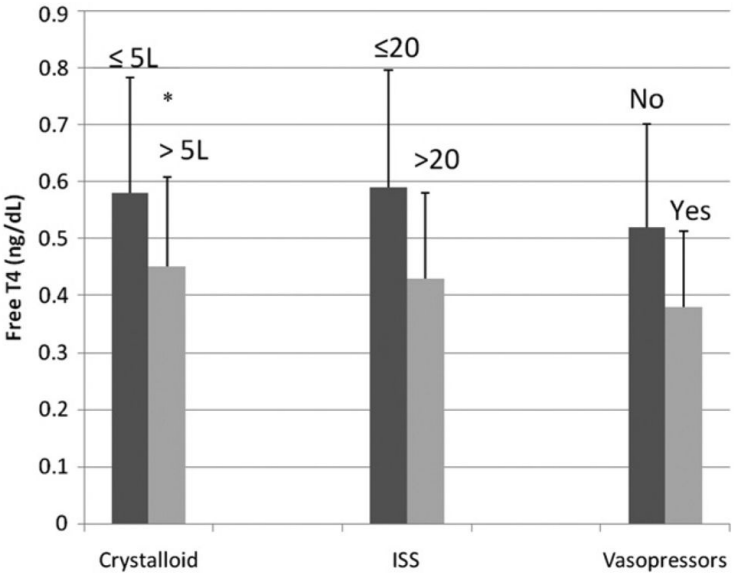

Fig. 4.

– Free T4 concentration on admission to the trauma bay as a function of crystalloid requirement, injury severity score, and the need for vasopressor support. The trauma bay free T4 levels (average with standard deviation) were compared according to crystalloid within 12 h of admission (≤5 *versus* >5 liters), injury severity score (ISS ≤20 *versus* >20), and need for vasopressors within 48 h of ICU admission (No *versus* Yes). **P* < 0.05 considered statistically significant.

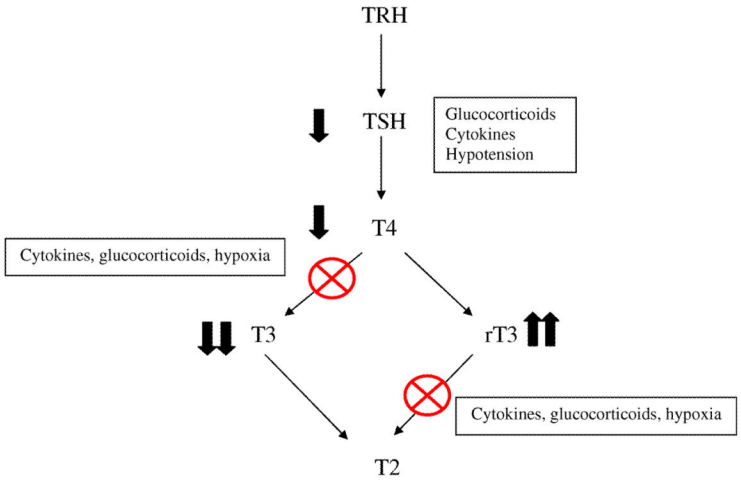

Fig. 5.

– Changes in hypothalamic-pituitary-thyroid axis following traumatic injury. (Color version of figure is available online.)

Table 1

Comparison of patient demographics, injury mechanism, and injury severity score based on volume of packed red blood cells infused within 12 h.

Transfused PRBC units/12 h	**≤5 (*n* = 7)**	**>5 (*n* = 11)**
Age (SD)	31 ± 17	31 ± 12
Male sex (*n*, %)	6/7 (86%)	10/11 (91%)
Penetrating mechanism (*n*, %)	5/7 (71%)	8/11 (73%)
Injury severity score	25 ± 12	28 ± 18
Lactate (mmol/L)	8.1 ± 4.2	11.4 ± 7.5

There were no statistically significant differences between patients who received ≤5 units PRBC when compared with those who received >5 units.

Table 2

Comparison of the units of blood product received and free and total T3 concentrations.

Resuscitation time (h)	Free T3 concentration (pg/dL)*			Total T3 concentration (ng/dL)*		
	>5 units	≤5 units	*P* value	>5 units	≤5 units	*P* value
TB	1.92 ± 1.01	3.88 ± 2.04	<0.025	55.86 ± 8.95	87.44 ± 44.41	<0.087
ICU	<0.92†	<0.92†	—	<50†	<50†	—
24 h	<0.92†	<0.92†	—	<50†	<50†	—
48 h	<0.92†	<0.92†	—	<50†	<50†	—

TB = trauma bay.

*Normal range for free T3 values in healthy volunteers: 2.30–4.20 pg/dL; normal range for total T3 values in healthy volunteers: 87–130 ng/dL.

†Values fall below the sensitivity of the assay.