Triiodothyronine supplementation in a sheep model of intensive care

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Abstract. Triiodothyronine (T3) concentrations in plasma decrease during acute illness and it is unclear if this contributes to disease. Clinical and laboratory studies of T3 supplementation in disease have revealed little or no effect. It is uncertain if short term supplementation of T3 has any discernible effect in a healthy animals. Observational study of intravenous T3 (1 μg/kg/h) for 24 h in a healthy sheep model receiving protocol-guided intensive care supports (T3 group, n=5). A total of 45 endpoints were measured including hemodynamic, respiratory, renal, hematological, metabolic and endocrine parameters. Data were compared with previously published studies of sheep subject to the same support protocol without administered T3 (No T3 group, n=5). Plasma free T3 concentrations were elevated 8-fold by the infusion (pmol/l at 24 h; T3 group 34.9±9.9 vs. No T3 group 4.4±0.3, P<0.01, reference range 1.6 to 6.8). There was no significant physiological response to administration of T3 over the study duration. Supplementation of intravenous T3 for 24 h has no physiological effect on relevant physiological endpoints in healthy sheep. Further research is required to understand if the lack of effect of short-term T3 may be related to kinetics of T3 cellular uptake, metabolism and action, or acute counterbalancing hormone resistance. This information may be helpful in design of clinical T3 supplementation trials.

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Introduction

Thyroid hormone concentrations in blood change during acute illness. This typically involves a rapid decrease in triiodothyronine (T3) with reciprocal increase of reverse-T3, a slow decline of thyroxine (T4), while thyroid stimulating hormone levels are preserved. The extent of these hormonal changes is proportional to severity of disease and it remains unclear if this contributes to disease, or represents an epiphenomenon (1-11).

Controlled clinical trials of T3 supplementation in patients having cardiac surgery and in organ transplantation have reported little effect (12,13). A randomized, blinded, placebo-controlled trial of T3 (with and without hydrocortisone) in a sheep model of septic shock illustrated that increasing plasma T3 concentrations in blood did not markedly alter hemodynamics, nor any other physiological variable (14). Nevertheless, further clinical studies of T3 have been proposed in patients with COVID-19, sepsis, acute respiratory distress syndrome and myocardial infarction (15).

While administration of T3 in critical illness has appeared safe, there have been concerns about adverse effects (11,16-18). These have been based on clinical features seen in those with prolonged exposure to excessive thyroid hormone and established hyperthyroidism, such as tachycardia, increased metabolism and hyperthermia. Studying the effects of

short-term T3 supplementation in a non-diseased state may further clarify safety, provide insights why T3 has not been efficacious and facilitate studies of thyroid hormone physiology. For these reasons we examined the clinical effects of a 24-h infusion of T3 administered to a healthy sheep receiving intensive care support.

Materials and methods

Study design. This was an observational prospective study of administering T3 in a healthy sheep model of intensive care. Ethics approval was obtained from the Institute of Medical and Veterinary Science/Central Northern Adelaide Health Service and The University of Adelaide Animal Ethics Committees (project numbers 157/08, 80/10 and M-2010-089). The study was conducted according to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (2004) (19).

Sheep model. Five female sheep (*Ovis aries*) aged at least 3 years and not lactating, were randomly chosen from a herd of similarly aged paddock-raised healthy agricultural stock, then housed with other animals in pens with free access to food and water. Individual sheep were managed according to an intensive care model described previously (14). Briefly, female sheep (weight, 56-65 kg) were anaesthetized with isoflurane for insertion of carotid and pulmonary artery catheters, tracheostomy, urinary catheter and venous cannula placed with radiological guidance into the coronary sinus, renal, hepatic and iliac veins. Following instrumentation (time 0 h), animals received protocol-directed sedation [ketamine (7.1±2.3 mg/kg/h) and midazolam (0.4±0.2 mg/kg/h)], ventilation, parenteral fluids and a noradrenaline infusion titrated to maintain the normal mean arterial pressure of sheep (75 mmHg).

After 2 h, animals were administered a 24-h intravenous infusion of T3 (liothyronine; GlobalRx Inc.) 1 μg/kg/h (time 2-26 h). This was the same dose administered previously in a septic sheep model (14). A pharmacist prepared the study drug solution each day of study. Sacrifice with phenobarbitone (6.5 g, iv) was performed at the completion of the study.

Endpoints. Clinical endpoints measured through the study period included hemodynamic, respiratory, renal, hematological, metabolic and endocrine parameters (Table SI). These 45 clinical endpoints were compared with a previously reported group of five non-septic sheep subjected to the same protocol but not administered T3 (14).

Assays. Biochemical analyses included serum electrolytes (Na^+, K^+, Cl^-, HCO_3^-), creatinine, urea, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT) and lactate (Olympus AU5400 chemistry analyzer; Olympus Corporation). Blood cell counts were obtained with a SYSMEX-XE-2100 hematology analyzer (TOA Medical Electronics, Co., Ltd.) and clotting times using STA-R Evolution (Stago Diagnostica). Blood pH, gases and haemoglobin-O_2 saturation were analyzed on a RAPID-Point 405 Blood-gas analyzer (Siemens Healthineers).

Plasma free-T3 and free-T4 concentrations were measured by Chemiluminescent Micro-particle Immuno-Assay using commercially available reagents and calibration solutions (Unicel DXi 800; Beckman Coulter, Inc.). Plasma cortisol concentrations were determined by radioimmunoassay (14,20).

Blood cultures were taken aseptically from the jugular vein at baseline, repeated at 12 and 26 h and analyzed on the Bactec system (Becton, Dickinson and Company).

Statistical analysis. Data are presented as means (± SD in tables; ± SEM in graphs). Group data over multiple time points were tested for statistical difference by linear mixed-effects models. If a statistically significant ($P<0.05$) 'group x time' interaction effect was found, a post-hoc test with Bonferroni correction was performed to determine the difference of adjusted means at each time point. Data were analyzed with SPSS (version 21; IBM Corp.) and GraphPad (version 8.2; Dotmatics).

Results

All sheep survived the study and maintained sterile blood cultures. Study groups were of comparable size and received similar amounts of parenteral fluids and sedation (Table SII).

Plasma hormone concentrations. Free-T3 plasma levels were markedly increased by T3 infusion, being nearly eight times higher than the group not given T3 (Table I). Free-T4 decreased over time and was not markedly different between groups. Cortisol declined from elevated baseline levels before increasing by the end of the study. This pattern of change and cortisol plasma concentration did not markedly differ between groups.

Clinical endpoints. There were no significant differences between study groups. Cardiac index, heart rate, circulatory pressures and the derived hemodynamic indices did not differ between the two groups over time (Figs. 1, S1 and S2). No animals required noradrenaline.

Partial pressure of carbon dioxide ($PaCO_2$) was similar in both groups with no difference in the amount of ventilation required or pulmonary compliance (Fig. 2). Arterial pH was not markedly different between groups, but lactate was slightly lower in the T3 group in the first 8 h (Fig. 3).

Urine flow, serum creatine, electrolytes, hematology and temperature did not differ between groups over time (Table II, Fig. 3). There was a slight difference in ALT between groups over time, but clinically insignificant. Haemoglobin-O_2 saturation in the pulmonary artery, coronary sinus, renal, hepatic and iliac veins was no different between the groups over time (Fig. S3).

Discussion

A 24-h intravenous infusion of T3 in healthy sheep managed with intensive care support produced supra-physiological plasma T3 concentrations, yet was associated with little or no significant physiological change when compared with a similarly managed group of sheep not administered T3. This is an important finding given the ongoing interest in clinical trials of T3 and adds further evidence that short term administration of T3 appears safe.

Table I. Plasma free-T3, free-T4 and cortisol in healthy sheep with (n=5) and without (n=5) a 24-h intravenous infusion of T3 (1 μg/kg/h commenced at 2 h). Means ± SD.

		0 h	12 h	26 h	Group x time	Time	Group
Free-T3, pmol/)	No T3	5.6±0.5	4.8±0.4	4.4±0.3	P<0.01		
	T3	4.1±0.8	26.9±14.4[a]	34.9±9.9[a]			
Free-T4, pmol/l	No T3	10.8±1.6	9.2±2.4	7.0±1.2	P=0.26	P<0.01	P=0.15
	T3	10.2±2.3	6.6±2.7	4.7±1.7			
Cortisol, nmol/l	No T3	241±45	37±27	144±169	P=0.24	P<0.01	P=0.40
	T3	150±41	66±44	126±70			

[a]P<0.05 for differences of adjusted means between No-T3 vs. T3 groups. T3, triiodothyronine; T4, thyroxine.

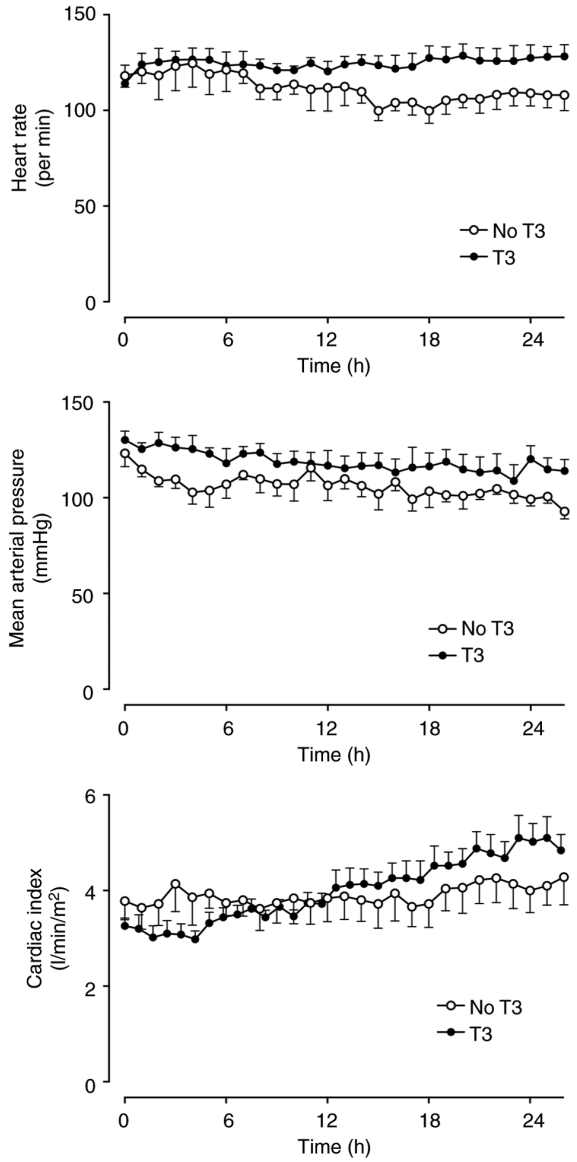

Figure 1. Heart rate, mean arterial pressure and cardiac index in a healthy sheep model of intensive care with (n=5) and without (n=5) a 24-h infusion of T3 (commenced at h 2). Mean ± SEM. The T3 group had a slightly higher mean arterial pressure [mean mmHg (95% confidence interval); No T3 105 (99-111) vs. T3 119 (114-124); P<0.01)] and this relationship did not change during the 24-h infusion of T3. Heart rate: Group x Time P=0.74, Group P=0.82, Time P=0.10. Mean arterial pressure: Group x Time P=0.99, Group P<0.01, Time P=0.68. Cardiac index: Group x Time P=0.62, Group P=0.89, Time P=0.79. T3, triiodothyronine.

While there was no significant difference between groups for the vast majority of the 45 endpoints measured, there were some parameters that differed slightly. Mean arterial, central venous and pulmonary artery pressures were slightly higher in the T3 group. However, these parameters differed between groups before the commencement of T3 infusion and did not change over time. Hence it is unlikely there is an obvious treatment effect of T3 within 24 h on hemodynamic pressures. Lactate concentrations were markedly higher in the group not given T3. This is unlikely to be important given that differences appeared early in the present study, concentrations were not markedly elevated and the large number of other parameters that did not differ.

Failing to observe a significant increase of cardiac index in animals given T3 was unexpected. Laboratory studies in cardiac myocytes and isolated hearts have reported prompt increases in contractility with T3 added to perfusate (21-24). Subsequently, several clinical trials have been conducted in patients having cardiac surgery. A meta-analysis of these studies concluded that T3 increased cardiac index but had inconclusive effects on other parameters (12). Most of these clinical studies used intravenous T3 doses of 0.175-0.333 μg/kg/h for 6-9 h, which is less than 1 μg/kg/h used for 24 h, and reported an effect on cardiac index at 4-6 h. Possibly there was some aspect of the sheep model that limited the ability to detect a change to cardiac output following T3. Ketamine, used as a sedating agent, is known to increase cardiac output in humans (25) and sheep (26) and may have obscured any hemodynamic effect of T3.

T3 rapidly stimulates Na^+/K^+-ATPase on alveolar membranes (27,28) and renal tubule cells (29) *in vitro*. This was not clinically apparent in the present study, as supra-physiological plasma T3 levels were not associated with any significant change to respiratory or renal function, or serum biochemistry. Lack of change to these variables has also been reported in clinical trials of T3 in neonatal respiratory failure (30) and renal transplant dysfunction (31).

Concerns that supplementing T3 would stimulate metabolism and O_2 demand (16), were not supported in the present study. While temperatures were higher in the group of sheep given T3, this did not differ between groups over time and likely reflects baseline differences and data variability. Sheep given T3 did not require more ventilation to control $PaCO_2$ compared with those not given T3. Haemoglobin-O_2 saturation

Table II. Biochemistry and haematological parameters in healthy sheep with (n=5) and without (n=5) a 24-h infusion of T3 (1 μg/kg/h commenced at 2 h). Means ± SD.

		0 h	2 h	12 h	26 h	Group x Time	Time	Group
Na^+, mmol/l	No T3	146±1	147±1	147±2	148±1	P=0.14	P=0.83	P<0.01
	T3	143±1	143±1	142±3	142±1			
K^+, mmol/l	No T3	3.8±0.3	3.3±0.4	3.7±0.5	3.8±0.2	P=0.87	P=0.11	P=0.05
	T3	3.5±0.3	3.0±0.2	3.5±0.3	3.6±0.3			
Cl^-, mmol/l	No T3	107±3	110±2	118±2	121±3	P=0.28	P<0.01	P=0.01
	T3	105±2	106±2	112±2	118±3			
HCO_3^-, mmol/l	No T3	29±3	24±2	18±1	17±2	P=0.27	P<0.01	P=0.06
	T3	31±2	29±3	21±4	16±6			
Anion Gap, mmol/l	No T3	14±3	16±3	15±2	13±1	P=0.89	P=0.67	P=0.10
	T3	11±2	10±3	12±3	12±7			
Urea, mmol/l	No T3	9±2	8±2	7±2	7±2	P=0.72	P<0.01	P=0.02
	T3	5±2	5±2	4±2	4±2			
Creatinine, μmol/l	No T3	97±19	84±10	75±14	76±16	P=0.10	P=0.22	P=0.71
	T3	83±20	77±15	84±40	110±39			
ALP, U/l	No T3	85±29[a]	64±16	51±16	42±10	P=0.27	P<0.01	P=0.11
	T3	53±23	45±14	38±8	32±17			
Bilirubin, μmol/l	No T3	4±2	7±1	11±5	10±3	P=0.91	P<0.01	P=0.21
	T3	2±1	4±2	8±5	8±8			
ALT, U/l	No T3	11±3	12±4	19±6	25±7[a]	P=0.01		
	T3	10±7	12±6	12±7	13±7			
aPTT, sec	No T3	33±9	33±4	34±6	39±5	P=0.26	P=0.02	P=0.65
	T3	30±4	32±6	41±9	42±8			
PT, sec	No T3	22±1	22±1	23±1	24±2	P=0.46	P=0.08	P=0.65
	T3	22±4	22±3	26±9	26±8			
Fibrinogen, g/l	No T3	1.6±0.3	1.5±0.3	1.9±0.5	2.7±0.7	P=0.42	P<0.01	P=0.12
	T3	2.0±0.2	2.1±0.3	2.3±0.4	3.3±0.3			
Hb, g/l	No T3	99±3	106±8	95±14	92±7	P=0.06	P=0.34	P<0.01
	T3	80±10	84±7	91±5	86±11			
WCC, $x10^9$/l	No T3	6.5±3.0	7.2±3.6	9.1±3.8	5.6±3.5	P=0.57	P<0.01	P=0.31
	T3	4.5±1.7	5.9±1.4	7.0±1.2	4.9±0.9			
PLTs, $x10^9$/l	No T3	163±79	160±61	115±36	106±27	P=0.20	P<0.01	P=0.70
	T3	192±46	174±35	85±38	108±26			

[a]P<0.05 for differences of adjusted means between No-T3 vs. T3 groups. T3, triiodothyronine; ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; Hb, hemoglobin; PT, prothrombin time; WCC, white cell count; PLTs, platelets.

of mixed venous blood and from the different organs remained stable over the duration of the study and did not differ between groups.

There were no obvious effects of supplementary T3 on plasma concentrations of T4 or cortisol. T3 can increase deiodinase-1 synthesis (32,33) and upregulate deiodinase-3 activity (34) favoring increased clearance of T4. Exogenous T3 can also suppress deiodinase-2 which would limit deiodination of T4 (35). Thus, T3 therapy could theoretically increase and/or decrease deiodination of T4. In the present study, T3 did not alter plasma levels of T4 and understanding how supra-physiological T3 alters the deiodinase enzymes requires further investigation. T3 can also upregulate steroid dehydrogenase and reductase enzymes leading to increased clearance of cortisol (36). However, this may take more than 24 h to become evident, or be balanced by increased cortisol secretion, as there were no changes to plasma cortisol concentrations in sheep given T3.

Why would the supra-physiological plasma levels of T3 achieved in this healthy sheep model not produce obvious clinical changes? First, a 24-h infusion of T3 may have been too short to allow T3 to exert any noticeable effect. Although T3 has rapid cell membrane effects *in vitro* (37), these may not manifest *in vivo* within 24 h in sheep. The genomic and mitochondrial effects of T3 may be responsible for clinical change, but require >24 h to manifest. Of note, studies that have reported T3-induced changes in heart rate (38), venous compliance (39), diastolic function (40), myocardial contractility (41) and metabolic rate (42) have administered hormone for at least seven days. Second, cellular concentration of T3

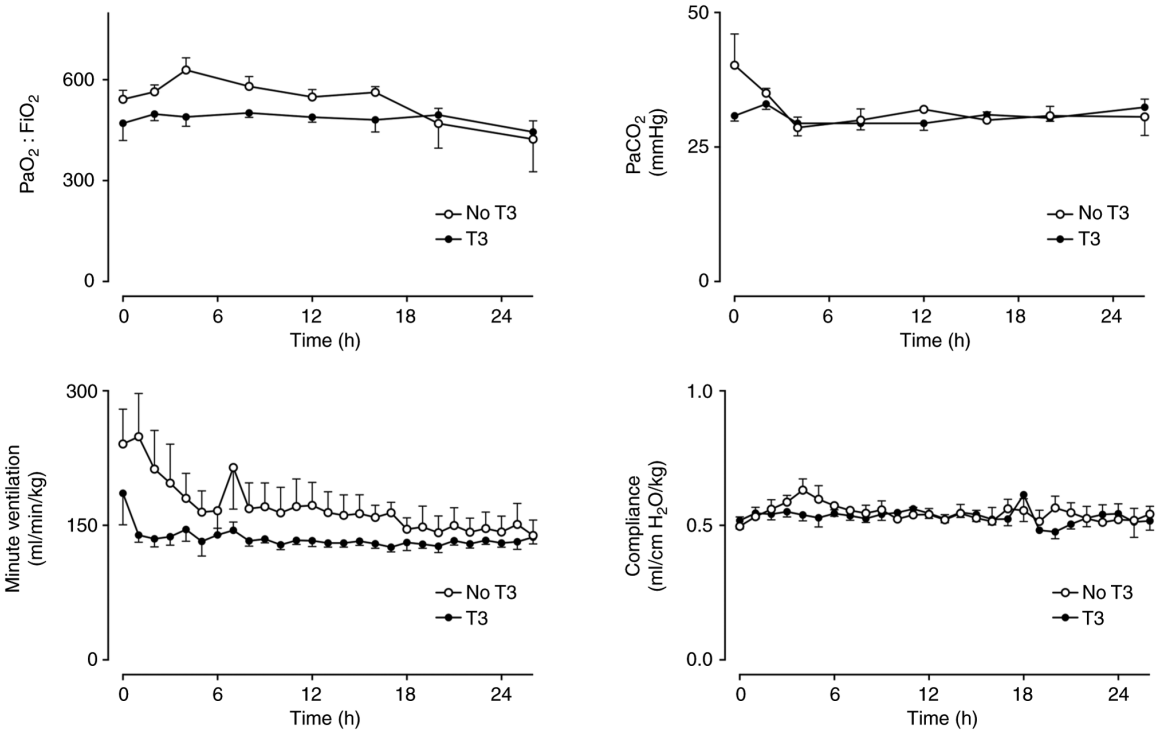

Figure 2. PaO_2:FiO_2, $PaCO_2$, V_A and pulmonary compliance in a healthy sheep model of intensive care with (n=5) and without (n=5) a 24-h infusion of T3 (commenced at h 2). Mean ± SEM. PaO_2:FiO_2: Group x Time P=0.46, Group P=0.24, Time P=0.22. $PaCO_2$: Group x Time P=0.24, Group P=0.31, Time P=0.13. V_A: Group x Time P=0.47, Group P=0.06, Time P=0.04. Compliance: Group x Time P=0.77, Group P=0.55, Time P=0.22. PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; V_A, minute ventilation; T3, triiodothyronine.

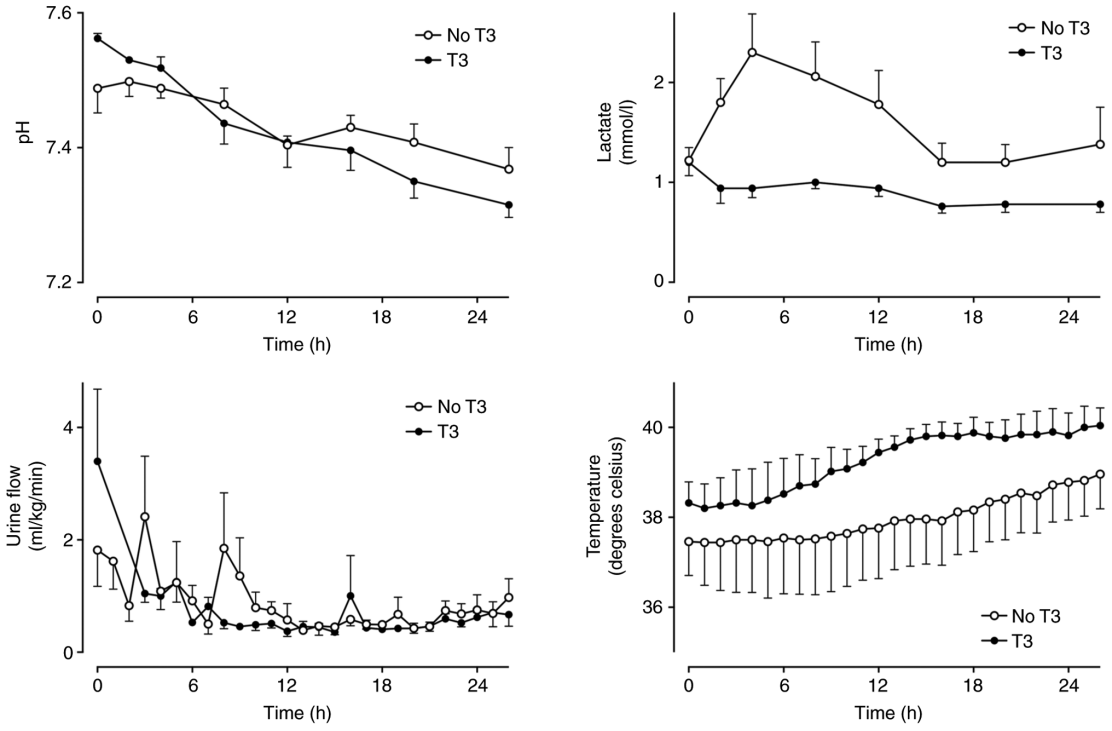

Figure 3. Arterial blood pH, serum lactate concentration, urine flow and core temperature in a healthy sheep model of intensive care with (n=5) and without (n=5) a 24-h infusion of T3 (commenced at h 2). Mean ± SEM. Urine data are missing for the T3 group at h 1 and 2. pH: Group x Time P=0.22, Group P=0.92, Time P<0.01. Lactate: Group x Time P=0.04, P<0.05 between groups at 2, 4 and 8 h. Urine: Group x Time P=0.36, Group P=0.40, Time P<0.01. Temperature: Group x Time P=0.95, Group P=0.28, Time P=0.01. T3, triiodothyronine.

may not reflect those in plasma. Cells may exhibit homeostatic mechanisms, such as deiodination, modulation of cell receptors and hormone transport mechanisms, that may limit exposure to excess plasma hormone concentrations. This will require

further study. Third, an acute clinical change following T3 administration may be more likely when restoring hormone levels in established hypothyroid states (38,42), rather than in euthyroid animals. Fourth, the effect of exogenous T3 may be species-specific, with sheep having limited response to acute therapy. When tested on hypothyroid lambs, T3 increased high energy phosphate compounds within 20 min but did not alter hemodynamics, coronary blood flow or myocardial O_2 consumption (43). Another sheep study reported increased cardiac output 2 h after a T3 bolus (1.2 μg/kg) that yielded much higher plasma concentrations (80 pmol/l) than the present study (44). Finally, most studies of T3 administered to euthyroid animals and humans have been unblinded and not randomized. This may have led to a greater likelihood to report an effect of T3 therapy. Notably, the only randomized, blinded, placebo-controlled study of T3 (100 μg i.v. bolus) administered to euthyroid human volunteers, reported no effect on cardiac output, heart rate or mean arterial pressure over 45 min (45). It is thus reasonable to conclude that T3 does not exert an acute effect on hemodynamics in euthyroid subjects.

There were several limitations to the present study. It was not randomized or blinded and the group of sheep given T3 were compared with a group of historical controls studied up to three years earlier. Despite the lag time between studies, sheep were obtained from the same herd, were of a similar size, received an identical management protocol and staffing expertise of the model was consistent over all studies. The number of sheep in each group was relatively small, which limits power of the study to detect a subtle effect of T3. A total of five animals were chosen, as this was the number of non-septic sheep in the earlier model validation studies.

The effects of supplementary T3 were studied in a group of healthy sheep receiving intensive care supports and compared with an earlier group not administered T3. The two groups of animals had similar baseline characteristics and were managed with identical protocols. The group receiving a 24-h infusion of T3 developed supra-physiological plasma levels while hemodynamic, metabolic and all other physiological parameters did not differ markedly between the groups over time. Administration of T3 for 24 h does not have substantial physiological effect in this healthy animal model and further study is required to understand cellular function and thyroid hormone metabolism with short-term T3 supplementation.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MJM was responsible for study conception, model development, study design and conduct, data collection and analysis and manuscript preparation. MJM, DJT and GLL were responsible for study design, project supervision and manuscript review. IJC was responsible for study design, assays and manuscript review. CHN was responsible for study conduct, data collection and manuscript review. LM was responsible for study conduct, animal care and manuscript review. SP was responsible for study conduct, animal care, data collection and manuscript review. BC was responsible for study conduct, animal care, data collection and manuscript review. TRK was responsible for model development, animal surgery, animal care and study conduct. All authors (TRK deceased) read and approved the final manuscript. MJM and CHN confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethics approval was obtained from the Institute of Medical and Veterinary Science/Central Northern Adelaide Health Service and The University of Adelaide Animal Ethics Committees (approval nos. 157/08, 80/10 and M-2010-089). The study was conducted according to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (2004).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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