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Impact of Triiodothyronine on the Survival of High-Risk Patients Undergoing Open Heart Surgery

Abstract

Experimental and clinical studies have shown the beneficial effects of triiodothyronine (T_3) following myocardial revascularization on cardiopulmonary bypass (CPB). In this study, open-label T_3 was administered to 68 high-risk patients undergoing open heart surgery. The New Jersey Risk Assessment was used to calculate the preoperative estimated surgical mortality. A loading dose of T_3 was administered: (a) at release of the aortic cross-clamp, (b) whenever the patient became CPB dependent, (c) if the patient exhibited low cardiac output after discontinuing CPB and (d) as pretreatment before initiating CPB. All therapeutic modalities were followed by a continuous T_3 infusion. Following T_3 therapy, CPB was discontinued in all patients. Based upon discriminant analysis, a total of 26 deaths were expected from the entire group, but only 7 patients died, therefore, the observed mortality was reduced by 72% ($p < 0.007$). The use of T_3 had a major impact on reducing surgical mortality, and may be advocated as a new therapeutic modality in patients with high estimated mortality undergoing open heart surgery.

Key Words
Cardiopulmonary bypass
Triiodothyronine

Introduction

In cardiac surgery, the preoperative estimated mortality (EM) depends on both cardiac and noncardiac risk factors [1]. Relevant cardiac risks include: low left-ventricular ejection fraction, postmyocardial infarction new-onset unstable angina, congestive heart failure (CHF), re-do coronary surgery, combined valve and coronary artery surgery and others. Noncardiac risk factors such as diabetes, hypertension, chronic obstructive lung disease, and chronic renal failure, also have a direct impact on the surgical outcome (postoperative day 30) [2]. The EM can be calculated by using several models, such as the VA [1–3], STS [4, 5] and others. The New Jersey Risk Assessment was used in the current study [6].

Despite advances in myocardial protection, myocardial depression often follows completion of open heart procedures [7–9]. There is a generalized body inflammatory response [10], complement activation, interleukin production and a profound derangement of the thyroid profile lasting for several days [11, 12]. The 'euthyroid sick syndrome' is characterized by a low FT_3, increase in plasma reverse T_3 (rT_3), normal or low total T_3 (TT_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH) lev-

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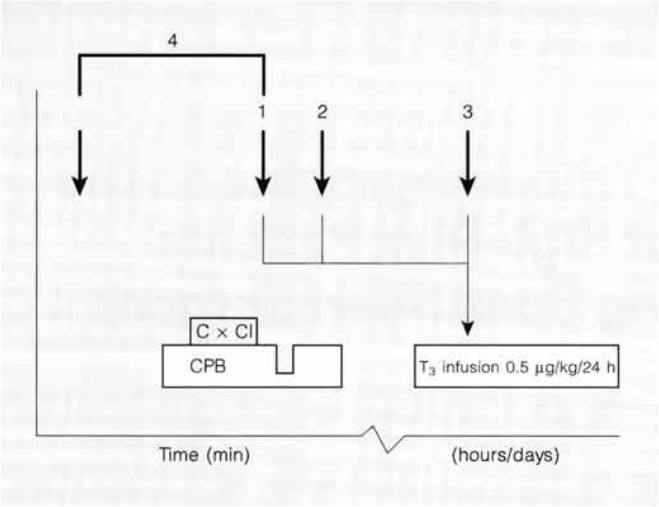


Fig. 1. Modalities of T_3 therapy: 1, T_3 is administered at the time of release of the aortic cross clamp; 2, T_3 is administered while patient remains CPB dependent; 3, T_3 is administered in the post-CPB period; 4, T_3 is administered before CPB (pretreatment) and a second dose at the time of release of the aortic cross clamp (C × Cl). Values are expressed in mean ± SD.

els [13]. In sick patients, the lower the FT_3/rT_3 ratios correlated with higher mortality [14, 15].

Experimental administration of T_3 in animals has shown a rapid reversal of the myocardial dysfunction which follows transient ischemic events, such as: (a) induction of experimental brain death [16–18], (b) stunned myocardium [19, 20], or (c) after prolonged cardioplegic arrest on cardiopulmonary bypass (CPB) [21, 22]. Similar observations were made in our preliminary clinical studies. After administering T_3 to 10 patients who were experiencing profound postcardiotomy myocardial depression, the T_3 enhanced the reversal of the myocardial dysfunction allowing for discontinuation of CPB, and also the use of intra-aortic balloon pump was no longer necessary after 1 h. This therapy also allowed for a rapid reduction in high inotropic requirements [23]. To confirm the beneficial effects of T_3, we studied a group of low-risk (EM 1–5%) patients undergoing myocardial revascularization in a prospective, randomized, double-blind, placebo-controlled study was conducted, which confirmed the beneficial impact of T_3 therapy [24]. In the T_3-treated patients, we observed significant hemodynamic improvement, requirement of less inotropic support and diuretics. The objective of this study was to observe the impact of T_3 (in an open-label fashion) on high-risk patients undergoing open heart surgery.

Patients and Methods

From April 1992 to April 1994, at the University of South Florida affiliated hospitals (James A. Haley VA Hospital and The Tampa General Hospital), T_3 was administered to 68 patients undergoing open heart surgery. The mean age was 61.92 years (range 35–81 years), and there were 64 men and 4 women. There were 29 elective, 7 urgent and 32 emergent surgical procedures. Coronary artery bypass grafts were performed in 32 patients, valve procedures in 9 patients, combined coronary artery bypass grafts with valve procedures in 27 patients, and an orthotopic heart transplant in 1 patient. Eighteen patients required preoperative use of the intra-aortic balloon pump for control of post-myocradial infarction unstable angina, despite heparin and intravenous nitroglycerin, and 10 patients received inotropic support. At the completion of the surgical procedure, unexpectedly, 12 patients became CPB dependent, receiving T_3 following prolonged CPB support. The preoperative mean EM was 29.67% (range 3–58%), patients were informed of the EM and consent to administer T_3 was obtained prior to enrollment. In emergent conditions, or if the patient received sedation, consent was obtained from a legal representative. This protocol and informed consent forms were approved by the Institutional Review Board of the University of South Florida and the Research and Development Committee of the James A. Haley VA Hospital.

CPB Management: Perioperative Monitoring

Standard hemodynamic monitoring values were obtained from a Swan Ganz catheter, and an arterial line. Moderate hypothermia (28–32 °C) was used, and the mean arterial pressure was maintained in the range of 50–60 mm Hg with a flow of 2 liters/m^2 using a Sarns roller pump. Blood cardioplegia was administered in an antegrade and retrograde fashion. Epinephrine was the inotropic agent of choice; however, a combination of other inotropic drugs was used whenever indicated. Nitroglycerin and sodium nitroprusside were used to maintain systemic vascular resistance in the range of 600–800 dyn. CPB was discontinued progressively under various loading conditions, and inotropic requirements were adjusted accordingly.

In 12 patients, further CPB support was required for various intervals as the heart failed to sustain adequate hemodynamics, despite receiving epinephrine in excess of 10 µg/min in combination with other inotropics (CI <1.8, MAP ≤ 60 mm Hg and PCWP ≥ 18 mm Hg). An attempt to discontinue CPB was initiated again. In the event of failure to support the circulation, the patients had a second, third or fourth bypass support runs.

Plasma FT_3 Measurement

Plasma FT_3 was measured by radioimmunoassay using a commercially available kit (Diagnostic Products Corporation, Calif., USA).

T_3 Therapeutic Modalities

T_3 was administered using four different regimens (fig. 1):

Regimen 1: n = 44, T_3 loading bolus (2–3 µg/kg) was administered at the time of release of the aortic cross clamp;

Regimen 2: n = 12, T_3 (1–2 µg/kg) was administered after the release of the aortic cross clamp, whenever the patient became CPB dependent.

Regimen 3: n = 4, T_3 (1 µg/kg) was administered in the postoperative period to patients exhibiting a low cardiac output state, despite high IABP support;

Table 1. Risk stratification and expected mortality

A Percentage EM – preoperative

Groups		Preoperative EM[1] according to discharge status, %	
		alive	dead
1	0–9	8, 4, 3, 9, 9	–
2	10–19	14, 12, 16, 18, 14, 18, 17, 19, 12, 15, 11, 16	–
3	20–29	18, 20, 25, 25, 22, 24, 20, 27, 24, 25, 29, 27, 27, 22, 20, 23, 24, 20, 25, 27, 27	21, 24
4	30–39	33, 38, 36, 32, 35, 34, 30, 35, 37	32, 38
5	40–49	41, 48, 49, 46, 48	45
6	50–59	50, 57, 57, 55, 57, 51, 54, 54, 51	58, 56

B Observed mortality

Groups	n	Observed deaths	EM mean ± SD, %	Expected deaths	O/E[2]	p value[3]
1	5	0	6.6 ± 2.88	0.33	0	<0.74
2	12	0	15.16 ± 2.62	2.02	0	<0.16
3	23	2	24.00 ± 2.72	5.28	0.37	<0.01
4	11	2	34.54 ± 2.62	3.79	0.26	<0.08
5	6	1	46.16 ± 2.92	2.77	0.52	<0.18
6	11	2	54.54 ± 2.80	5.99	0.33	<0.04
Total	68	7		20.17		$p < 0.0007$

[1] Each number represents the preoperative estimated mortality for each patient.
[2] O/E: Observed/Expected deaths; normally this ratio is equivalent to 1.
[3] Two-tailed p values are expressed.

Regimen 4: n = 8, T_3 pretreatment loading dose (1 μg/kg) was administered 30–60 min before initiating CPB, followed by a second T_3 bolus (1 μg/kg) at the time of aortic cross clamp release.
Maintenance infusion: 0.5 μg/kg/24 h was administered from 1 to 3 days according to hemodynamic parameters.

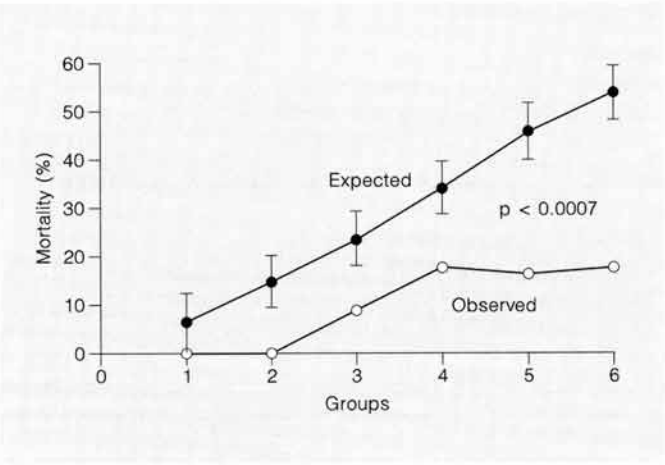
In 15 patients, following the loading bolus dose and during the infusion period, T_3 kinetic studies were performed measuring the half-life of the distribution phase ($t_{½}\alpha$), half-life of the elimination phase ($t_{½}\beta$) and the volume distribution.

Statistical Analysis

Calculation of EM for each patient was carried out using the New Jersey Risk Stratification Model. All patients were stratified and allocated at 10% intervals according to the EM. The total expected deaths were calculatd and the observed/expected ratio (O/E) expressed for each patient's interval. For the observed and estimated deaths, the level of significance was determined using a cumulative binomial probability distribution. The inotropic requirement for the CPB-dependent patients after the T_3 bolus was compared using Student's t test. The values are expressed as mean ± SD of the mean (table 1).

Results

Of these 68 high-risk patients, CPB was discontinued in 56 patients, 12 remained CPB dependent. T_3 was administered to 44 patients at the time of release of the aortic cross clamp, 4 patients received T_3 in the postoperative period. Eight had T_3 pretreatment followed by a second dose at the time of aortic cross clamp release. T_3 pretreatment was administered 30–60 min prior the initiation of CPB to patients experiencing low cardiac output state. While patients remained CPB dependent, T_3 was administered during the last CPB support run; a rapid cardiac functional recovery was observed, allowing the discontinuation of CPB support (table 2). Eight or more deaths were expected from the 12 CPB-dependent patients (including a primary cardiac graft failure following transplantation). Following the cardiac procedure, CPB was uneventfully discontinued in all patients. However, within 30 days, only 1 CPB-dependent patient died. Considering all patients together, 26 patients were expected to



die, however only 7 patients died. The EM was significantly reduced by 72% ($p < 0.0007$) (fig. 2). Of the 7 observed deaths (POD 30), 4 were cardiac; and 3 were noncardiac (table 3).

The preoperative FT_3 levels had a significant reduction from 2.01 ± 0.01 to 0.8 ± 0.07 pg/ml ($p < 0.0001$) prior to T_3 therapy. Following the initial T_3 bolus, FT_3 levels remained elevated for the first 2 h, however during

Fig. 2. Comparison of observed and expected mortality. 95% confidence intervals and the statistical differences are shown. Values are expressed in mean ± SD.

Table 2. CPB-dependent patients

Age	Sex	EM %	PS	C × CL min	CPB runs, min					Cardiac status	Cardiac procedure	Inotropic support[1] Epi/μg/kg/min		Outcome
					1	2	3	4	5			pre T_3	post T_3	
69	M	14	U	114	186	30	20			AS, CAD, pre-op MI, IABP	AVR, CABG × 2	0.14	0.05	alive
44	M	10	E	95	172	50	30			CAD, recent MI	CABG × 3	0.128	0.05	alive
62	M	18	E	100	160	30	20	18		CAD, MR LVEF 25% dobut.	CABG × 3, MVR	0.266 norepi.	0.05 0	alive
50	M	14	E	98	185	24				CAD, CABG, LVEF, 25%	redo CABG × 4	0.11	0.038	alive
66	M	24	E	66	239	48				CAD, CABG, recent MI, IABP	redo CABG × 3	0.10	0.025	alive
35	M	15	M	129	91	28	46	17	33	CAD, CM, HTx	oHTx norepi., Isup.	0.106 norepi., Isup.	0.053	alive
58	M	37	M	63	120	20				CAD, CRF, cath crash IABP	CABG × 4 norepi.	0.2 norepi., Amrin	0.05	alive
74	M	24	E	135	232	30				CAD, AS	CAGB × 1 AVR	0.22	0.22 POD7 RV MI	dead
62	M	7	E	106	144	31				CAD, prev. MIs, LVEF 20%	VABG × 4	0.08	0.02	alive
54	M	46	E	50	100	30				CAD, CABG MI, angina IABP	redo CABG × 2	0.15	0.05	alive
66	M	54	M	221	302	20				CAD, MR, MI angina, IABP LVEF 30%	CABG × 3, MVR	0.11	0.05	alive
53	M	16	M	103	120	26				CAD, acute MI post cath angina, IABP	CABG × 4	0.12	0.03	alive
Total 12				104.63 (13.79)	170.90 (18.16)	31.41 (2.55)	27.2 (5.10)	17.5 (0.5)	33			0.151 vs. (0.058)	0.06* (0.057)	11/12

EM = Estimated mortality; PS = preop. status; U = urgent; E = elective; M = emergent; A = aortic stenosis;
C × CL = aortic cross clamp; Epi = epinephrine, oHTx = Orthotopic heart transplant; IABP = intra-aortic balloon pump.

[1] Epinephrine requirement was reduced from 0.15 (0.058) to 0.06 (0.057) μg/kg/min $p < 0.0001$.

the infusion interval the FT_3 levels were within the normal range. The $t_{½}\alpha$ was of 0.42 ± 0.03 h and the $t_{½}\beta$ was of 1.69 ± 0.08 h. The volume distribution was 41.66 liters/kg.

Discussion

In this open study, the beneficial effects of T_3 following open heart surgery were confirmed. There was a significant improvement on the survival of high-risk patients undergoing a variety of cardiac procedures. The beneficial effecst of T_3 were seen not only in patients undergoing valvular surgery with normal coronary arteries, but also in patients undergoing myocardial revascularization in the presence of acute MI and new-onset angina exhibiting severaly compromised left-ventricular function and preoperative 'stunning'.

The beneficial effects of T_3 are multifactorial, impacting not only on the cardiovascular system but on other organs as well [25]. At the cardiac level it is well known that T_3 affects various ATPase [26, 27] and also upregulation of beta-receptors [27, 28]. It also increases coupling of the beta-receptor to adenylate cyclase [29]. T_3 also plays a role in calcium uptake and calcium release from the sarcoplasmic reticulum into the cytosol and activates various calcium-dependent ATPases [30–32], thus rapidly mobilizing and recompartmentalizing free ionic calcium from the cytosol into the sarcoplasmic reticulum [33, 34]. If this is the case, and also occurs in other organs, the calcium-induced injury which resembles the oxygen free radical injury [35] occurring during CPB may be reduced. T_3 also enhances metabolism at the mitochondrial level [36, 37] by increasing the activity of the adenine nucleotide translocase facilitating ATP mobilization from the mitochondria into the cytosol, thus, yielding high-energy phosphates required for the myosin ATPase [38].

The observed inotropic effects following T_3 administration have been documented within several minutes, and are probably extra-nuclear related, bypassing the DNA-RNA protein synthesis and independent of β-receptor stimulation. This rapid response is of great relevance

Table 3. Surgical mortality at postoperative day (POD) 30

Patient	Age	Sex	EM %	Status	Pre-diagnosis	Surgical procedure	Cause of death
1	72	M	58	M	MI, new onset angina, MTG, hep, IABP	CABG × 3	POD 20, SP initial course, transferred to floor, acute abdomen, laparotomy POD 18, small bowel infarct
2	74	M	24	E	CAD, AS, MI	AVR, CABG × 1 LAD endarterectomy	POD 7, new perioperative MI, ARDS, inotropes, low cardiac output
3	73	M	32	E	CAD, porcelain aorta	CABG × 3	POD 3, multiple perioperative MIs possibly from aortic emboli
4	62	M	21	M	CAD, unstable angina, hep, MTG, LVEF 20%	CABG × 3	POD 18, uneventful ICU course mediastinitis; POD 15, cardiac-arrhythmia asystole
5	60	M	56	M	CABG, MI, PTCA, acute graft dissection	redo CABG × 4	POD 9, perioperative MI, low cardiac output
6	74	M	45	E	aortic prost. valve stenosis MR +4, TR +4	redo AVR, MVR, Tann	POD 5, multiorgan failure, sepsis, PM severe cirrhosis
7	79[1]	M	38	E	AS, MR, CAD	AVR (SJ No. 19) M. Ann CABG × 2	POD 29, extubated, then ARDS pulmonary edema; severe aortic valve gradient ± 90 mm/Hg mediastinitis, sepsis

Patient 7 had a number 19 aortic prosthesis, postoperative gradient by TEE measured 80–110 mm Hg. The LV and RV functions remained good.

[1] Redo AVR was not performed as the patient developed ARDS and sepsis (mediastinitis).

to cardiac surgery [39–41]. This rapid recovery was also observed after inducing myocardial stunning in dogs [20]. By using load-independent pressure-volume relationship and sonomicrometers T_3 allowed total recovery of the myocardial dysfunction.

In our study, T_3 pretreatment was used for the first time in patients prior to the initiation of the open heart procedure. The rationale for this therapeutic modality was based on the previous experience of administering T_3 to brain-dead animals and unstable human brain-dead organ donors depending on high inotropic support [42–44]. The impact of T_3 resulted in a significant hemodynamic and biochemical improvement allowing rapid inotropic reduction. Following cardiac transplantation, these marginal donor hearts performed well in recipients [45].

Eight patients in a study exhibited a marked reduction of the systemic vascular resistance requiring the administration of norepinephrine in order to maintain adequate tissue perfusion pressure; however, diuresis remained excellent and no deleterious effects were observed, thus reconfirming that T_3 at the vascular level is a potent vasodilator [46]. It is quite possible that the T_3 loading dose of 3 μg/kg is the optimal pharmacological dose as is denoted by the marked vasodilation which followed administration. The concept that no thyroid replacement should be administered to patients exhibiting the 'euthyroid sick syndrome' as in those exposed to acute insults [47–49] seems no longer to be invalid, particularly in patients undergoing open heart surgery on CPB.

The marked reduction of half-life of the β-phase following exogenous T_3 administration was found to be approximately 8% of the endogenously produced T_3. This rapid reuptake may be directly related to the tissue T_3 depletion following CPB.

The conclusions of this study are limited by its open-label design and lack a placebo control. If, however, our assumption proves to be correct, T_3 may improve the survival of high-risk patients undergoing cardiac surgery.

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