

THYROID HORMONE TREATMENT AFTER CORONARY-ARTERY BYPASS SURGERY

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Abstract Background. Thyroid hormone has many effects on the cardiovascular system. During and after cardiopulmonary bypass, serum triiodothyronine concentrations decline transiently, which may contribute to postoperative hemodynamic dysfunction. We investigated whether the perioperative administration of triiodothyronine (liothyronine sodium) enhances cardiovascular performance in high-risk patients undergoing coronary-artery bypass surgery.

Methods. We administered triiodothyronine or placebo to 142 patients with coronary artery disease and depressed left ventricular function. The hormone was administered as an intravenous bolus of 0.8 μg per kilogram of body weight when the aortic cross-clamp was removed after the completion of bypass surgery and then as an infusion of 0.113 μg per kilogram per hour for six hours. Clinical and hemodynamic responses were serially recorded, as was any need for inotropic or vasodilator drugs.

Results. The patients' preoperative serum triiodothyronine concentrations were normal (mean [\pm SD] value, 81 ± 22 ng per deciliter [1.2 ± 0.3 nmol per liter]), and they

decreased by 40 percent ($P < 0.001$) 30 minutes after the onset of cardiopulmonary bypass. The concentrations in patients given intravenous triiodothyronine became supranormal and were significantly higher than those in patients given placebo ($P < 0.001$). However, the concentrations were once again similar in the two groups 24 hours after surgery. The mean postoperative cardiac index was higher in the triiodothyronine group (2.97 ± 0.72 vs. 2.67 ± 0.61 liters per minute per square meter of body-surface area, $P = 0.007$), and systemic vascular resistance was lower (1073 ± 314 vs. 1235 ± 387 dyn \cdot sec \cdot cm $^{-5}$, $P = 0.003$). The two groups did not differ significantly in the incidence of arrhythmia or the need for therapy with inotropic and vasodilator drugs during the 24 hours after surgery, or in perioperative mortality and morbidity.

Conclusions. Raising serum triiodothyronine concentrations in patients undergoing coronary-artery bypass surgery increases cardiac output and lowers systemic vascular resistance but does not change outcome or alter the need for standard postoperative therapy. (N Engl J Med 1995;333:1522-7.)

POOR cardiac performance is a major cause of morbidity and death in patients who undergo open-heart surgery, especially older patients and those with extensive disease or poor ventricular function.¹ Physicians therefore are challenged to improve perioperative management. Because of recent evidence that cardiopulmonary bypass results in altered thyroid hormone metabolism,^{2,3} interest has focused on the relation between decreased serum triiodothyronine concentrations and hemodynamic variables after cardiopulmonary bypass.⁴ There are similarities between hypothyroid patients and those undergoing cardiac surgery with respect to both serum triiodothyronine concentrations and decreased cardiac contractility and elevated peripheral vascular resistance^{5,6}; prior studies have suggested that perioperative triiodothyronine supplementation may improve outcome in patients with postoperative cardiovascular dysfunction.^{7,8} We now report the results of a trial in which triiodothyronine (liothyronine sodium) was administered to high-risk patients undergoing coronary-artery bypass surgery.

METHODS

Enrollment of Patients

We enrolled patients who underwent coronary-artery bypass surgery between April 1994 and February 1995 at New York Hospital-Cornell University Medical Center in New York City. Patients under 85 years of age, of either sex, were eligible if their ejection fractions had been 40 percent or less during cardiac catheterization within the

preceding two months. Criteria for exclusion included a planned concomitant valve procedure, a history of thyroid disease or thyroid hormone therapy, treatment with amiodarone, or ongoing inotropic support or use of an intraaortic balloon pump at the time of surgery. The protocol was approved by the institution's Committee on Human Rights in Research, and all patients gave informed consent.

Study Design

Immediately before surgery, the patients were randomly assigned to receive either triiodothyronine or placebo and were stratified according to their preoperative ejection fractions (less than 25 percent or 25 to 40 percent). All physicians and nurses involved in the patients' care were unaware of the treatment assignments, and with the exception of administration of the study drug, care during and after surgery did not differ between the two groups. Patients assigned to triiodothyronine received an intravenous bolus of 0.8 μg per kilogram of body weight (Triostat, SmithKline Beecham Pharmaceuticals, Philadelphia), given for two minutes at the time of removal of the aortic cross-clamp; an intravenous infusion of 0.113 μg per kilogram per hour for six hours; and a tapered final dose, decreased by 50 percent each hour and then stopped. The patients in the placebo group received 5 percent dextrose solution at the same infusion rates. Samples of arterial blood, for determination of serum triiodothyronine concentrations, were drawn after the induction of anesthesia (base line), 30 minutes after the start of cardiopulmonary bypass, 30 minutes and 6 hours after the infusion of the study drug began, and, in the last 22 patients enrolled, 15 hours after the end of the infusion. Serum thyroxine and thyrotropin concentrations were measured at base line. Serum thyroxine and triiodothyronine concentrations were determined by standard radioimmunoassays, and serum thyrotropin concentrations were measured by immunofluorescence. The coefficients of variation for each assay were less than 5 percent, and all samples from an individual patient were analyzed simultaneously.

Surgery and Anesthesia

The operation was performed by a group of six cardiothoracic surgeons using a standardized protocol for anesthesia and surgery. All the patients had invasive hemodynamic monitoring. Anesthesia was induced with thiopental (1 to 2 mg per kilogram) and fentanyl (25 μg per kilogram) and was maintained with a combination of fentanyl and midazolam or isoflurane. Pancuronium was administered for muscle relaxation.

Cardiopulmonary bypass was performed with aortic and right atri-

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Supported by a grant from SmithKline Beecham Pharmaceuticals.

al cannulation, priming with an asanguineous solution, membrane oxygenation, and nonpulsatile flow. Mean arterial pressure was maintained between 55 and 65 mm Hg. Moderate hypothermia (bladder temperature, 30 to 32°C) was routinely induced. Cardioplegic arrest was produced by the initial administration of a cold-blood, high-potassium solution and maintained with additional doses administered at approximately 20-minute intervals.

After grafting, the patients were rewarmed to 36°C and separated from cardiopulmonary bypass by the gradual reduction of venous return to the bypass circuit. Intravenous inotropic support, with either epinephrine (2 to 4 μg per minute) or dobutamine (333 to 500 μg per minute), was initiated if poor cardiac contractility or ventricular dysfunction became obvious during separation or if the cardiac index was less than 2.1 liters per minute per square meter. An additional supportive agent (amrinone) was given or an intraaortic balloon pump was put in place if initial therapy was inadequate. Electric pacing was instituted when needed to maintain a heart rate above 70 beats per minute.

Postoperative Management

The patients were continuously monitored in a cardiothoracic intensive care unit. The cardiac index was maintained above 2.1 liters per minute per square meter by the administration of epinephrine and dobutamine. Vasodilator (sodium nitroprusside) and vasopressor (nor-epinephrine) drugs were administered as needed to maintain arterial systolic blood pressure between 90 and 140 mm Hg. Sustained and nonsustained ventricular tachycardia and premature contractions that were more frequent than six per minute or multifocal were treated with lidocaine. For each patient, the total doses of the individual inotropic and vasodilator drugs administered, in micrograms per kilogram, were recorded during the six-hour period of study-drug infusion, and the mean total dose was calculated for all the patients who required support. Patients were weaned from mechanical ventilation when they were hemodynamically stable and alert, and they were usually discharged from the cardiothoracic intensive care unit after extubation and the discontinuation of all vasoactive-drug infusions.

Hemodynamic Measurements

Base-line hemodynamic measurements (heart rate, mean arterial pressure, central venous pressure, and pulmonary-capillary wedge pressure) were recorded in the operating room before the start of surgery and then 2, 4, 6, 12, and 16 hours after removal of the aortic cross-clamp. Mixed venous oxygen saturation was determined by standard blood gas analysis of pulmonary arterial-blood samples. Cardiac output — the average of three measurements — was determined by thermodilution. Derived measurements included the cardiac index (cardiac output divided by body-surface area) and systemic vascular resistance, calculated as (mean arterial pressure minus central venous pressure times 80) divided by cardiac output.

Measures of Clinical Outcome

Data on clinical outcome, including the need for and quantity of inotropic and vasodilator drugs, were obtained from flow sheets from the intensive care unit and from the patients' medical records by a research assistant who was unaware of the treatment assignments. Cardiac rhythm was monitored continuously in the intensive care unit with bedside monitors and, after discharge, with telemetry. Twelve-lead electrocardiograms were obtained immediately after the operations and on the first three mornings after surgery. Supraventricular and ventricular arrhythmias, and their treatment, were documented by the nurses. All physicians' notes were reviewed to determine the incidence of postoperative complications. Postoperative mortality was defined as the rate of death during hospitalization or within 30 days after surgery. Major morbid events were defined as adverse events that prolonged the patient's postoperative stay in the intensive care unit or the hospital or that led to clinical deterioration.

Statistical Analysis

All analyses were performed on an intention-to-treat basis. All enrolled patients were randomized, and none were excluded from the analysis. The demographic, base-line, and one-time outcome variables in the two groups were compared by two-sample t-test. Categorical variables were compared by chi-square test or, where applicable, Fisher's exact test. The values for continuous outcome variables at dif-

ferent points in time were compared by repeated-measures analysis of variance. We also used repeated-measures analysis to compare binary outcomes between groups at different points. Since several analyses were performed, a Bonferroni correction was made to minimize the possibility of a type I error. All statistical tests were two-sided. Statistical analysis was performed with SAS software (Cary, N.C.).

RESULTS

Study Population

The characteristics of the 142 patients with coronary artery disease who were randomly assigned to receive triiodothyronine or placebo are shown in Table 1. There were no significant differences between the two groups with respect to any of the characteristics listed.

Administration of Triiodothyronine

In both groups, the mean serum triiodothyronine concentration was in the low-normal range before the start of surgery and had decreased significantly — by approximately 40 percent — 30 minutes after the start of cardiopulmonary bypass (Fig. 1). In the placebo group, the concentrations remained low throughout the 24-hour period after removal of the cross-clamp. In the

Table 1. Preoperative Characteristics of Patients Undergoing Coronary-Artery Bypass Surgery and Intraoperative Data, According to Treatment Group.*

VARIABLE	TRIIODOTHYRONINE (N = 71)	PLACEBO (N = 71)
Age — yr	66±10	68±9
Male sex — no. (%)	61 (86)	60 (84)
Weight — kg	78±13	79±13
History of smoking — no. (%)	25 (35)	21 (29)
Diabetes mellitus — no. (%)	23 (32)	16 (23)
Congestive heart failure — no. (%)	22 (31)	25 (35)
Renal failure — no. (%)	5 (7)	6 (8)
History of myocardial infarction — no. (%)	49 (69)	51 (72)
Myocardial infarction in preceding 3 wk — no. (%)	20 (28)	23 (32)
Preoperative medications — no. (%)		
Intravenous nitroglycerin	24 (34)	18 (25)
Intravenous heparin	33 (47)	29 (41)
β -adrenergic antagonist	40 (56)	45 (63)
Calcium-channel blocker	32 (45)	31 (44)
Diuretic agent	17 (24)	19 (27)
Digoxin	9 (13)	13 (18)
Angiotensin-converting-enzyme inhibitor	27 (38)	23 (32)
Ejection fraction — %	32.5±8.5	32.1±8.9
Ejection fraction <25% — no. (%)	18 (25)	16 (23)
Stenosis of left main coronary artery — no. (%)	16 (23)	19 (27)
Urgent or emergency operation — no. (%)	45 (63)	47 (66)
Reoperation — no. (%)	8 (11)	7 (10)
Serum hormones†		
Triiodothyronine — ng/dl	81±21	81±23
Thyroxine — $\mu\text{g}/\text{dl}$	6.7±1.5	6.6±1.4
Thyrotropin — $\mu\text{U}/\text{ml}$	1.9±0.5	1.8±0.9
Intraoperative data		
No. of grafts	2.8±0.7	2.9±0.8
Internal-thoracic-artery graft — no. (%)	56 (79)	53 (75)
Total bypass time — min	81±37	89±41
Duration of cross-clamping — min	41±21	43±19
Lowest body temperature — °C	31±2	31±2
Reexploration for bleeding — no. (%)	5 (7)	5 (7)

*Plus-minus values are means \pm SD. There were no significant differences between the groups according to chi-square tests, Fisher's exact tests, or two-sample t-tests. To convert values for triiodothyronine and thyroxine to nanomoles per liter, multiply by 0.015 and 12.9, respectively.

†Normal ranges are as follows: serum triiodothyronine, 80 to 200 ng per deciliter (1.2 to 3.0 nmol per liter); thyroxine, 4.5 to 12.0 μg per deciliter (58 to 155 nmol per liter); thyrotropin, 0.4 to 4.0 μU per milliliter.

triiodothyronine group, they increased quickly to well above normal and remained high throughout the drug infusion. By the end of 24 hours the concentrations had returned to the preoperative range.

In both groups, the occurrence of at least one episode of supraventricular arrhythmia, including sinus tachycardia, was common. During the first 6 hours after removal of the cross-clamp, 71 percent of the treated group and 66 percent of the placebo group had such arrhythmias; in the next 18 hours the proportions were 40 percent and 35 percent, respectively. Similar numbers of patients in each group received pharmacologic treatment (39 percent and 34 percent, respectively) for these arrhythmias. The proportions of patients having any ventricular arrhythmia during the first 6 hours (42 percent in the triiodothyronine group and 44 percent in the placebo group) and the next 18 hours (24 percent and 24 percent) were also similar, as were the proportions treated for ventricular arrhythmias (22 percent and 21 percent).

Therapy

There were no significant differences between groups in the interventional support needed to separate patients from cardiopulmonary bypass. Three patients in the triiodothyronine group and seven in the placebo group were returned to bypass because of hemodynamic instability ($P=0.19$). In each group, 56 percent of the patients required inotropic support in order to be separated from bypass, including five patients in the triiodothyronine group and two in the placebo group who were treated with counterpulsation by an intraaortic balloon pump. Eight patients in each group received

amrinone. Vasopressor drugs were administered to 70 percent of the patients in the triiodothyronine group and to 65 percent of those in the placebo group at the time of separation from bypass. The proportions of patients requiring pacing immediately after removal of the cross-clamp were similar (50 percent in the treated group and 49 percent in the placebo group).

The percentages of patients in each group who required postoperative therapy with inotropic or vasodilator drugs were similar, as were the doses given (Fig. 2). During the six-hour period of study-drug infusion, 37 patients in the triiodothyronine group received a mean (\pm SD) total dose of epinephrine of 9.1 ± 7.3 μ g per kilogram, as compared with 8.9 ± 6.8 μ g per kilogram in 42 patients in the placebo group. The mean total (six-hour) dose of dobutamine administered to 14 patients in the triiodothyronine group was 1708 ± 1222 μ g per kilogram, as compared with 1402 ± 980 μ g per kilogram in 17 patients in the placebo group. Fifteen patients in the triiodothyronine group required inotropic drugs for longer than six hours, as compared with 21 patients in the placebo group ($P=0.22$). The mean total doses of sodium nitroprusside given over a period of six hours — 5.2 ± 4.5 μ g per kilogram in 46 patients treated with triiodothyronine and 6.5 ± 5.6 μ g per kilogram in 49 patients in the placebo group — were also similar. Fifteen percent of the patients in the triiodothyronine group received norepinephrine during the study-drug infusion, as compared with 18 percent of those in the placebo group ($P=0.64$). The need for temporary cardiac pacing in the two groups did not differ significantly, either during the first 6 hours (17 percent in the triiodothyronine group and 25 percent in the placebo group, $P=0.56$) or the next 18 hours (8 percent and 13 percent, $P=0.7$).

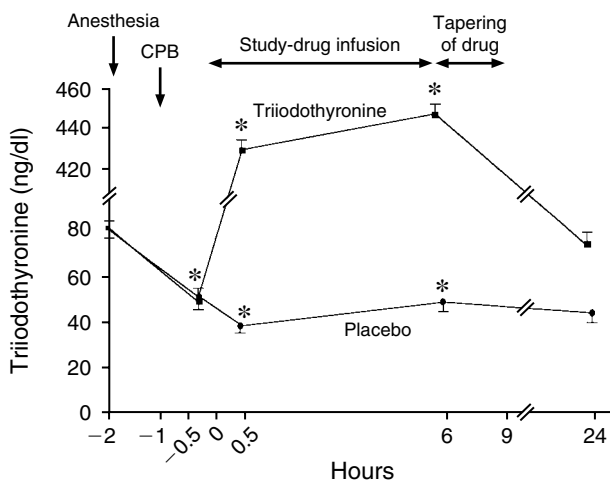


Figure 1. Mean (\pm SE) Serum Triiodothyronine Concentrations in Patients Who Received Triiodothyronine or Placebo during Coronary-Artery Bypass Surgery.

Base-line serum samples were drawn in the operating room after the induction of anesthesia. Zero denotes the time when the aortic cross-clamp was removed and infusion of the study drug was begun. At 24 hours, serum triiodothyronine was measured in 11 patients in each study group. To convert values for triiodothyronine to nanomoles per liter, multiply by 0.015. Asterisks indicate $P<0.001$ for the comparison with the base-line value. CPB denotes cardiopulmonary bypass.

Hemodynamic Measurements

There were no significant differences between the groups in heart rate, mean arterial blood pressure, central venous pressure, pulmonary-capillary wedge pressure, cardiac output, cardiac index, or systemic vascular resistance, either before the start of surgery or — for most of these variables — at any time after surgery (Table 2). Two hours after removal of the aortic cross-clamp, the cardiac index was higher in the triiodothyronine group (2.88 ± 0.73 liters per minute per square meter, as compared with 2.61 ± 0.60 liters per minute per square meter in the placebo group), and it remained higher four hours and six hours after removal (Fig. 3). Because the mean heart rates of the two groups were not significantly different, the increased cardiac output in the triiodothyronine group can be attributed to an increase in stroke volume. Systemic vascular resistance was lower in the triiodothyronine group two hours (1151 ± 369 vs. 1311 ± 389 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$), four hours, and six hours after the start of infusion (Fig. 3).

Clinical Outcome

There was no difference between the two groups in the duration of postoperative mechanical ventilation, the length of stay in the intensive care unit or the hos-

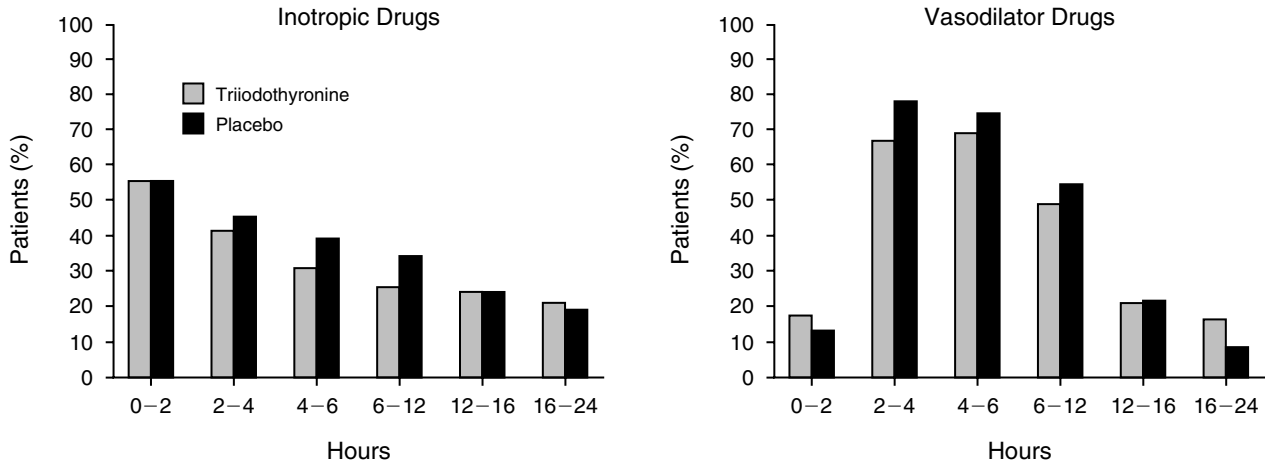


Figure 2. Patients in the Triiodothyronine and Placebo Groups Who Required Inotropic or Vasodilator Drugs after Coronary-Artery Bypass Surgery.

Zero denotes the time when the aortic cross-clamp was removed and infusion of the study drug was begun. No statistically significant differences between groups were detected.

pital, or perioperative mortality from either cardiac causes or all causes. The incidence of major postoperative complications was also similar in the two groups (Table 3).

DISCUSSION

The low serum concentrations of triiodothyronine and impaired cardiovascular hemodynamics in patients with hypothyroidism and patients who have undergone cardiopulmonary bypass,⁹ along with recent evidence that triiodothyronine may have acute inotropic and vasodilative effects,^{4,10} provided a rationale for investigating whether the perioperative administration of triiodothyronine might enhance cardiovascular performance. Experimental studies have found improvement in post-ischemic cardiac function if triiodothyronine is administered during reperfusion,¹¹⁻¹³ and several, largely uncontrolled, studies of patients undergoing coronary-artery bypass surgery^{7,8} or heart transplantation¹⁴ have suggested that the administration of triiodothyronine decreases perioperative mortality and the need for traditional inotropic agents. The results of our trial, however, do not support these conclusions.

The mechanism by which serum triiodothyronine concentrations decrease in patients undergoing cardiac surgery is uncertain, but it is probably associated with hypothermia, hemodilution, and the activation of inflammatory-response mediators.^{5,15} The decrease in serum triiodothyronine concentrations in these patients is considerably more rapid than that which occurs if the extrathyroidal conversion of thyroxine to triiodothyronine is inhibited, thus implicating — in the surgical patients — an increased volume of distribution of triiodothyronine and an increase in its clearance as con-

tributing factors. The half-life of the triiodothyronine administered in our trial was about half as long as normal,¹⁶ as estimated by the decline in serum triiodothyronine concentrations between 6 and 24 hours after the start of infusion. Although not measured separately in this study, serum concentrations of free triiodothyronine changed in parallel with those of total triiodothyronine in another study of patients undergoing bypass surgery.⁴

It has been suggested that the changes in thyroid function that occur in nonthyroidal illness are an adaptive physiologic response to illness.¹⁷⁻¹⁹ In our study, the administration of triiodothyronine provided hemodynamic benefits similar to those that occur during the treatment of hypothyroidism.⁵ The administration of thyroid hormone to patients with underlying cardiac illness, however, has been associated with untoward responses.²⁰ We noted no adverse cardiovascular effects — including any tachycardia or supraventricular arrhythmia — of the administration of triiodothyronine in doses that raised serum triiodothyronine concentrations transiently to well above the normal range. Although oxygen consumption was not measured, the enhanced cardiac performance during the administration of triiodothyronine, with no evidence of increased is-

Table 2. Perioperative Hemodynamic Variables in the Triiodothyronine and Placebo Groups, According to Length of Time after Removal of the Aortic Cross-Clamp.*

VARIABLE	2 HR AFTER REMOVAL		6 HR AFTER REMOVAL	
	TRIIODOTHYRONINE	PLACEBO	TRIIODOTHYRONINE	PLACEBO
Heart rate (beats/min)	95±1	93±14	101±12	98±14
Mean arterial pressure (mm Hg)	83±10	86±11	77±10	79±10
Central venous pressure (mm Hg)	7±3	7±3	9±3	9±2
Pulmonary-capillary wedge pressure (mm Hg)	10±4	9±3	10±3	9±3
Mixed venous oxygen saturation (%)	72±7	70±8	69±8	68±8

*Values are means ±SD. There were no significant differences between the groups, according to repeated-measures analysis of variance.

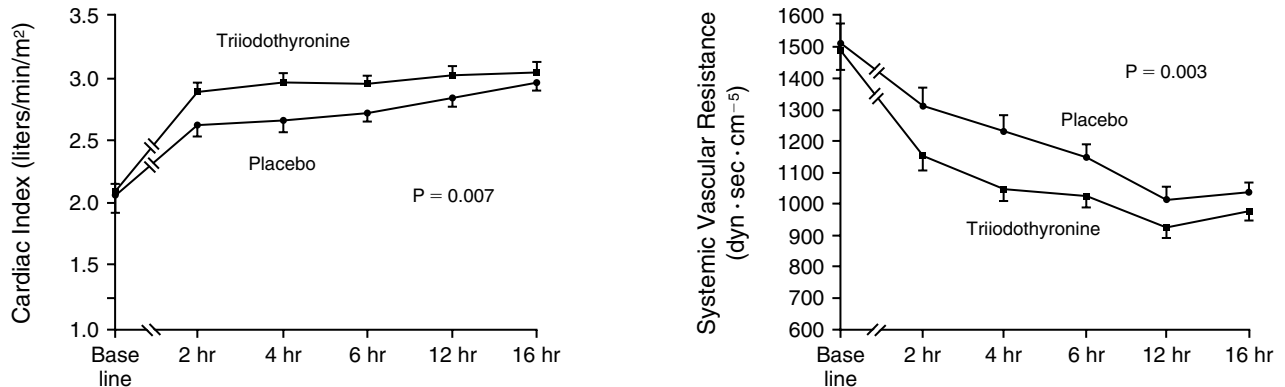


Figure 3. Cardiac Index and Systemic Vascular Resistance in the Triiodothyronine and Placebo Groups at Base Line and at Specified Intervals after Removal of the Aortic Cross-Clamp and Initiation of the Study-Drug Infusion.

chemia, does not point to a harmful shift in the relation between oxygen consumption and delivery. Experimental data have suggested that the acute inotropic effects of triiodothyronine after myocardial ischemia–reperfusion injury are accomplished without oxygen wasting.¹²

Our results confirm that triiodothyronine can act acutely as a cardiostimulant agent. It increases cardiac output while lowering systemic vascular resistance. Whether the hemodynamic enhancement during the administration of triiodothyronine was related primarily to direct, positive cardiac inotropism or to peripheral vasodilation is not known. Thyroid hormone has an acute effect on vascular resistance.²¹ In our experience, the acute cardiovascular effects of triiodothyronine appear moderate, as compared with those of commonly used β -adrenergic agonists and nitrovasodilator drugs, and were not independently sufficient to ensure adequate postoperative hemodynamics in patients with preexisting impairment of ventricular function. Although a molecular basis for the acute effects of triiodothyronine cannot be inferred from this study, the rapidity of those effects is consistent with putative nongenomic or extranuclear mechanisms.²² The potentiation of the effects

of β -adrenergic agonists, either endogenous or pharmaceutical, may also have a role in the process.²³⁻²⁵ Finally, triiodothyronine has direct relaxant effects on vascular smooth muscle.²¹

In this study the administration of triiodothyronine during cardiac surgery was safe and enhanced cardiovascular performance in the early postoperative period. Since it is difficult to identify patients who will have cardiovascular dysfunction, a low threshold for starting the use of inotropic drugs during weaning from cardiopulmonary bypass and tight pharmacologic control of postoperative cardiac and vascular function are standards of care at our institution; they were adhered to in the course of this study. Although triiodothyronine improved postoperative cardiovascular performance, we found no decrease in the requirements for traditional inotropic support. Therefore, our findings do not support the use of triiodothyronine as a substitute for standard drug therapy to maintain hemodynamic stability after cardiopulmonary bypass in patients with impaired ventricular function.

We are indebted to Dr. Nasser K. Altorki, Dr. Jeffrey P. Gold, Dr. Samuel Lang, and Dr. Todd K. Rosengart, the cardiothoracic surgeons of New York Hospital whose patients were enrolled in the study; to Dr. Martin Lesser and Dr. Barbara Napolitano for their statistical consultation; to Ms. Beverly Woytowich for her assistance as a research pharmacist; and to Mr. Richard Kung and the hospital's nuclear-medicine laboratory staff.

Table 3. Postoperative Outcome and Complications in the Triiodothyronine and Placebo Groups.*

VARIABLE	TRIIODOTHYRONINE (N = 71)	PLACEBO (N = 71)
	<i>median (interquartile range)</i>	
Postoperative intensive-care-unit stay (hr)	40 (25–70)	45 (26–71)
Postoperative mechanical ventilation (hr)	20 (18–24)	22 (18–28)
Postoperative hospital stay (days)	8 (7–10)	8 (7–12)
	<i>no. with event (%)</i>	
Mortality		
Total	4 (6)	3 (4)
Perioperative, from cardiac causes	2 (3)	1 (1)
Complications		
Pulmonary	7 (10)	11 (15)
Neurologic	3 (4)	3 (4)
Infectious	6 (8)	11 (15)

*The interquartile range is from the 25th to the 75th percentile. There were no significant differences between the groups according to chi-square tests, Fisher's exact tests, or two-sample t-tests.

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