

The Effects of Thyroid Hormones on the Heart Following Global Ischemia

A Clinical and Experimental Study

Volkan SINCI, M.D., Halim SONCUL, M.D.,
Serdar GUNAYDIN, M.D., Velit HALIT, M.D., F.A.C.S.,
Levent GOKGOZ, M.D., Oguz TATLICAN, M.D.,
Ali YENER, M.D., Ayse BILGEHAN, M.D.,*
and Ali ERSOZ, M.D.

SUMMARY

Cardiopulmonary bypass is associated with a reduction in plasma thyroid hormone concentrations in patients undergoing cardiac surgery. However, studies of the effects of cardiopulmonary bypass on thyroid function are limited and many studies report conflicting data concerning only the period of cardiopulmonary bypass.

In this study, we tried to clinically determine the effects of cardiopulmonary bypass on concentrations of thyroid hormones by comprehensive thyroid function tests in 10 patients before and after surgery, and observed the benefits of triiodothyronine supplementation after global ischemia on myocardial function experimentally in guinea pigs. In patients undergoing surgery, concentrations of total triiodothyronine and free triiodothyronine decreased progressively on the institution of cardiopulmonary bypass and remained below normal levels until 24 hours postoperatively.

In the guinea pig hearts studied in a Langendorf perfusion apparatus, T3 supplementation enhanced percentage recovery of ventricular contractile force, heart work and heart rate with respect to other groups receiving no T3 supplementation or T3 supplementation without any ischemic interval. (*Jpn Heart J* 35: 443-454, 1994)

Key words: Coronary artery bypass grafting Triiodothyronine Thyroid hormones

CARDIOPULMONARY bypass produces many alterations in endocrine homeostasis which may exert substantial hemodynamic effects postoperatively. The cause of transient postoperative left ventricular mechanical derangement is usually attributed to either inadequate intraoperative myocardial protec-

From the Department of Cardiovascular Surgery and *Biochemistry, Gazi University, School of Medicine, Ankara, Turkey.

Address for correspondence: Volkan Sinci, M.D., Kuleli Sok. No: 79/8 G.O.P. Ankara, Turkey.

Received for publication December 9, 1993.

Accepted March 14, 1994.

tion or reperfusion injury. Alternatively, however, it has been suggested that changes in thyroid hormone metabolism may contribute to cardiac dysfunction after open heart operations.¹⁻⁴⁾

Cardiopulmonary bypass leads to a 'euthyroid-sick' state characterized by a thyroid profile consisting of low plasma free triiodothyronine (FT3), a variable level of free thyroxine (FT4), and a significant increase in reverse triiodothyronine (rT3). Levels of total triiodothyronine, total thyroxine, and thyroid stimulating hormone remain unchanged.^{1,2,4,5)} Studies of the effects of cardiopulmonary bypass on thyroid function are limited and many studies report conflicting data limited to the period of cardiopulmonary bypass without any further follow-up or only experimental studies.

The purpose of this combined clinical and laboratory study was to clinically determine the effects of cardiopulmonary bypass on concentrations of thyroid hormones as determined by comprehensive thyroid function tests before and after surgery, and also to observe experimentally the benefits of triiodothyronine supplementation after global ischemia on myocardial function.

MATERIALS AND METHODS

This study was carried out in two different steps having two different goals. The first step consisted of patients undergoing elective coronary artery bypass surgery and the second step an animal study on an experimental model of cardiopulmonary bypass.

Clinical study patients: Ten patients (8 males, 2 females with an age range of 49-66, mean 58.6 ± 4) undergoing elective coronary artery bypass grafting were evaluated for thyroid function at specific intervals during, before and after surgery.

All patients were clinically euthyroid as determined by medical history and thorough physical examination. Patients enrolled were taking no medications that interfered with thyroid hormone metabolism or thyroid function tests. Patients included in the study received no albumin or other colloid solutions throughout the study interval. Patients requiring transfusion of blood products were excluded from the study.

Euthyroid status was also confirmed by a thyroid profile including TSH, total thyroxine, total triiodothyronine, FT3, FT4 and albumin levels, preoperatively.

Three of the patients had triple vessel disease: left anterior descending coronary artery + left circumflex artery + right coronary artery (LAD+LCX+RCA), 5 of them had two vessel disease (3: LAD+LCX and 2: LAD+RCA) and two of the patients had single LAD disease. Five of the patients reported previous myocar-

dial infarction. None of the patients had any risk factors including family history (diabetes, hypercholesterolemia, etc). Routine chest roentgenograms, ECG, complete chemistry profiles and Doppler echocardiographic data (cardiac dimensions, ejection fraction rates) were within normal ranges in all patients.

Procedure: A standard cardiopulmonary bypass technique was used in all patients. The circuit consisted of a roller pump (Cobe) and a membrane oxygenator (Maxima; Medtronic, Minneapolis, MN) with venous reservoir and an arterial filter. The system was primed with 1800 to 2000 ml of Ringer's lactate (Baxter, Deerfield, IL). Flow was maintained at 1.8 to 2.2 l/min/m² and moderate hypothermia (26°C to 30°C) was used in all cases. The mean durations of cardiopulmonary bypass and aortic clamp time were 84.2±8 and 48.3±7 minutes, respectively.

The postoperative interval was without complications in all patients studied. All patients demonstrated hemodynamic stability and there were no deaths.

The serum samples for thyroid function tests (total triiodothyronine, total thyroxine, FT3, FT4, TSH) were collected preoperatively, 15 min after institution of cardiopulmonary bypass, and at the 2nd, 8th and 24th hours, postoperatively.

The hormone levels were determined by RIA technique. The data were analyzed by t-test using a microsta PC program.

Experimental study: Hearts were obtained from male guinea pigs ($n = 30$) weighing 320–400 g (mean 360±90 g). All animals received care in compliance with the 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guide for the Care and the Use of Laboratory Animals' prepared by the US National Academy of Sciences and published by the US National Institute of Health (NIH Publication No. 80-23, revised 1978).

The animals were anesthetized with thiopental 20 mg/kg and given 200 units of heparin into the femoral vein. The hearts (1.5–2.2 g) were rapidly removed and cannulated via the aortic root.

Protocol: The hearts were mounted on a modified Langendorf perfusion apparatus simulating the cardiopulmonary bypass procedure and perfused with a gassed (oxygen 95%, CO₂ 5%) Krebs-Henseleit solution at a rate of 5 ml/min at 37°C. The composition was as follows: NaHCO₃- 25 mmol/l, NaCl- 118 mmol/l, 2KH₂PO₄-1.2 mmol/l, KCL-4.8 mmol/l, MgSO₄-1.2 mmol/l, CaCl₂-1.2 mmol/l and glucose 11.1 mmol/l.

The preischemic heart rate and ventricular contractility were recorded after waiting 10 min for a stabilization period. The animals were then allocated randomly into 3 groups (10 animals each). In group A, the hearts were arrested by stopping the Krebs-Henseleit perfusion (anoxic normothermic arrest) and kept in

normothermic ischemia (37°C) for the following 15 min. The hearts were then reperfused with Krebs-Henseleit solution. Heart rate and ventricular contractile force were recorded after a stabilization period of 20 min.

In Group B, the hearts were arrested by stopping the Krebs-Henseleit perfusion and after 15 min of global ischemia, reperfused with 3,5,3' triiodo-DL thyronine (Sigma Chemical Co, St. Louis, MO) containing Krebs-Henseleit solution at a rate of 1 µg/min. Data were collected after 20 min of a stabilization.

In Group C, after the first perfusion interval of Krebs-Henseleit solution, without ischemia, the hearts were reperfused with Krebs-Henseleit solution containing 3,5,3' triiodo-DL thyronine (Sigma Chemical Co., St. Louis, MO) and data were recorded after 20 min.

All hearts were preserved in a liquid nitrogen tank at -196°C in order to determine enzyme activities.

Parameters: For Groups A and B the following parameters were evaluated:

- 1) Percentage recovery of ventricular contractile force = $\frac{\text{Postischemic contractile force}}{\text{Postischemic contractile force}} \times 100$
- 2) Percentage recovery of heart work = $\frac{\text{Postischemic heart rate} \times \text{Postischemic contractile force}}{\text{Preischemic heart rate} \times \text{Preischemic contractile force}} \times 100$
- 3) Percentage recovery of heart rate = $\frac{\text{Postischemic heart rate}}{\text{Postischemic heart rate}} \times 100$

In Group C, the same parameters were evaluated as the ratio of perfusion with T3 containing Krebs-Henseleit reperfusion solution to Krebs-Henseleit solution alone.

In the hearts preserved in the liquid nitrogen tank, the enzyme activities of adenosine deaminase (ADA) and malonyl di-aldehyde were determined for Group A and Group B in order to assess the extent of myocardial injury.

Ventricular contractile force and heart rate were recorded through an isometric force transducer (UGO BASILE 700, Comserio-Varese Co., Italy) connected to a microdynamometer (UGO BASILE 7050).

ADA activity was determined by the Lowry method and malonyldialdehyde by the thiobarbituric acid method.^{6,7)} The results are presented as the mean and the standard error of the mean. Overall significance of the differences between groups was determined by t-test using a microsta PC programme.

RESULTS

Clinical study

Concentrations of total thyroxine (T4) remained within the normal physiological range for all times sampled either during cardiopulmonary bypass or in the early postoperative period. Concentrations of free thyroxine (FT4) increased to slightly above normal during cardiopulmonary bypass and returned to normal levels for the 2nd, 8th and 24th hour postoperative measurements.

Concentrations of total triiodothyronine (T3) and free triiodothyronine (FT3) decreased progressively on the institution of cardiopulmonary bypass and remained below normal levels throughout the postoperative period ($p < 0.05$) (Figure 1). Comparisons of concentrations 24 hours postoperatively with preoperative concentrations demonstrated a 57% and 78% decrease in FT3 and total T3 levels, with respect to preoperative measurements, respectively

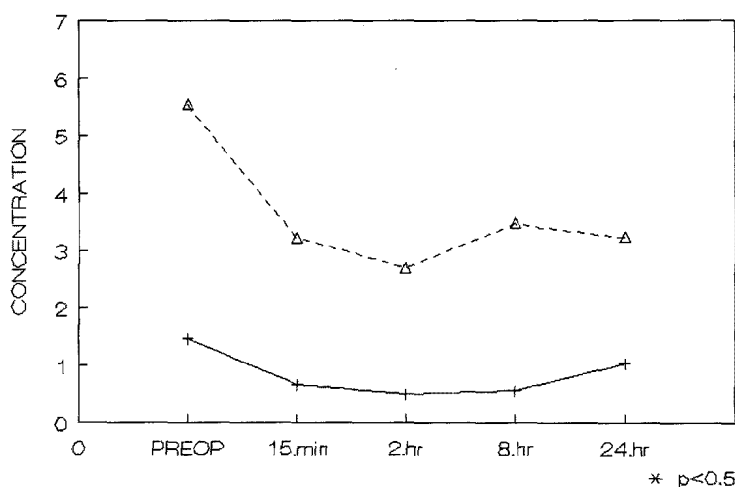


Figure 1. Preoperative, perioperative and postoperative concentrations of total T3 and FT3. + =total T3* (nmol/l) --Δ--=FT3 (pmol/ml)

Table. Preoperative, Perioperative and Postoperative Measurement of Thyroid Function in Patients Undergoing Surgery

Hormones	Preoperative	After CPB (15 min)	Postoperative (2 hours)	Postoperative (8 hours)	Postoperative (24 hours)
Mean total T4 (nmol/l)	91.2±9.4	104.6±10.8	93.1±7.6	88.6±8.8	90.3±9.9
Mean free T4 (ng/dl)	1.8±0.12	2.4±0.19	1.6±0.11	1.7±0.15	1.7±0.13
Mean total T3* (nmol/l)	1.46±0.16	0.66±0.07	0.5±0.06	0.56±0.04	1.04±0.09
Mean free T3* (pmol/ml)	4.08±0.71	2.57±0.38	2.21±0.4	2.92±0.58	2.20±0.53
TSH (μ/mol)	3.8±0.42	3.66±0.51	3.81±0.6	3.71±0.42	3.77±0.48

* $p < 0.05$

($p < 0.05$) (Table).

There were no significant postoperative changes with respect to preoperative measurements in TSH concentrations.

Experimental study

Group A: In this group, the hearts were reperfused with Krebs-Henseleit solution after global ischemia of 15 min. The mean percentage recovery of ventricular contractile force and mean percentage recovery of heart work were $63.9 \pm 7\%$ and $47.3 \pm 9\%$, respectively. The mean preischemic heart rate was $60.6 \pm 9/\text{min}$ and decreased to $46.4 \pm 10/\text{min}$ in the postischemic period, 74.4% of baseline % (Figure 2).

The RIA measurements in the preserved hearts revealed that the mean concentration of ADA was 12.1 ± 1.4 nmol/min/mg proteins and the mean concentration of MDA was 0.046 ± 0.009 nmol MDA/g tissue.

Group B: In this group, the hearts were reperfused with T3 containing Krebs-Henseleit solution after global ischemia of 15 min. The mean percentage recovery of ventricular contractile force and the mean percentage recovery of heart work were $90.3 \pm 7\%$ and $100.4 \pm 8\%$, respectively. The mean percentage recovery in heart rate was 90.3% (Figure 3).

The RIA measurements in the preserved hearts revealed that the mean concentration of ADA was 10.0 ± 1.1 nmol/min/mg proteins and the mean concentration of MDA was 0.03 ± 0.001 nmol MDA/g tissue.

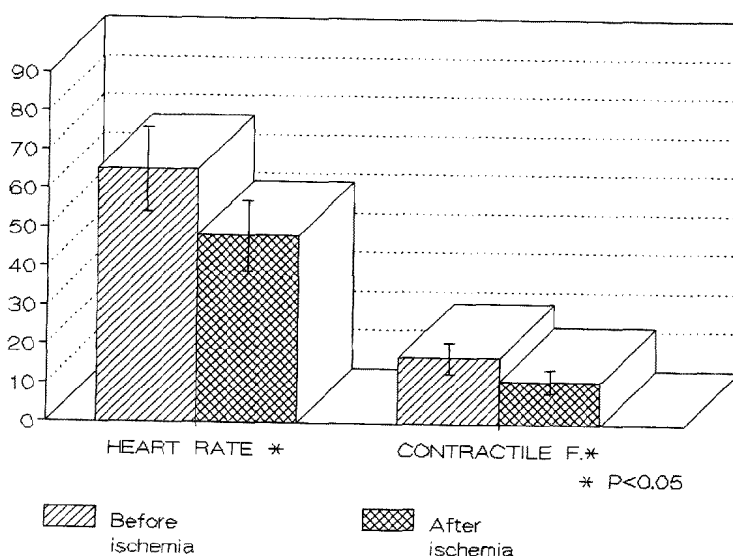


Figure 2. Heart rate and contractile force before and after ischemia (Krebs group)

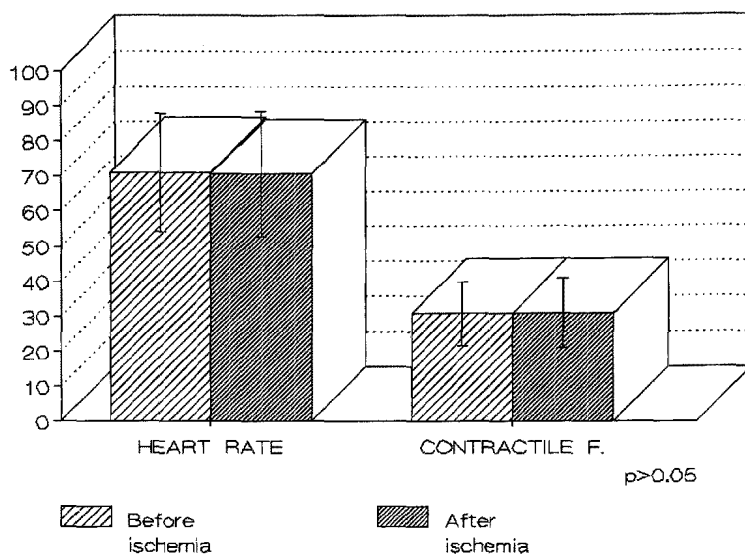


Figure 3. Heart rate and contractile force before and after ischemia (T3 + Krebs group)

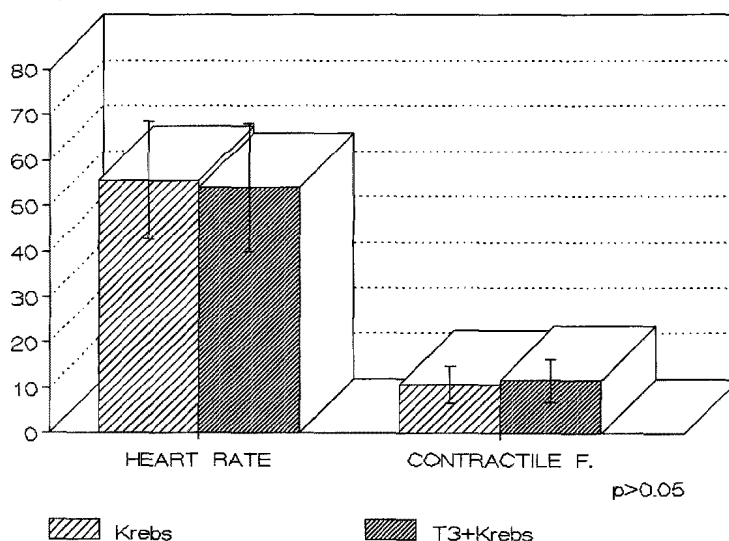


Figure 4. Heart rate and contractile force in hearts perfused with Krebs and T3+Krebs (No ischemia)

Group C: The hearts were reperfused with T3 containing Krebs-Henseleit solution without an ischemic interval. The mean percentage change in ventricular contractile force and percentage change of heart rate were $110.7 \pm 8\%$ and $106.6 \pm 8\%$, respectively. The mean percentage change in heart rate was $96.5 \pm 7\%$

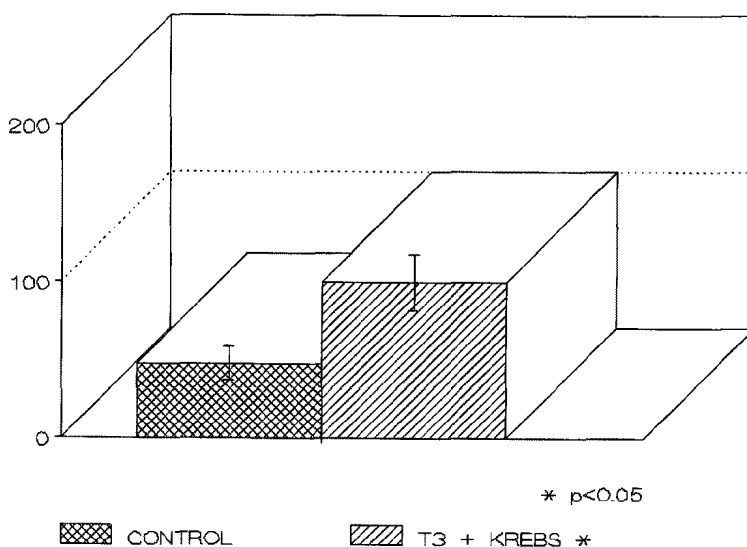


Figure 5. Percentage recovery of heart work in control and postischemic T3+Krebs group

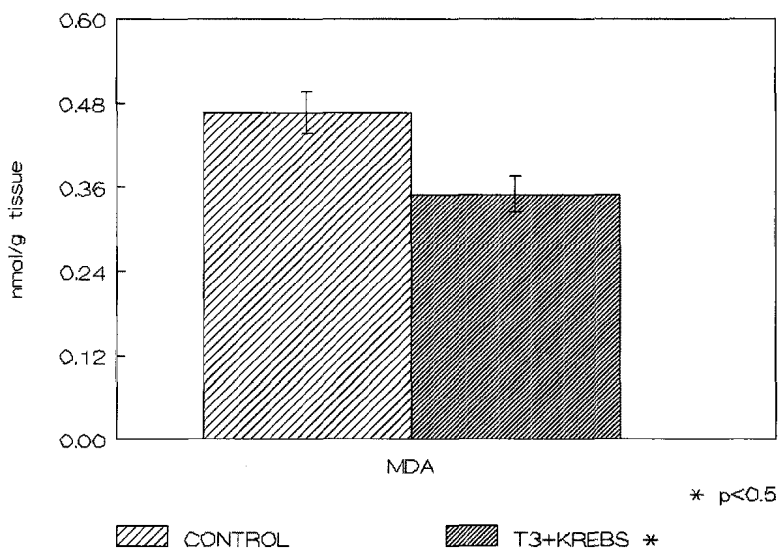


Figure 6. Concentrations of malonyl di-aldehyde in control and postischemic T3+Krebs groups

(Figure 4).

As can easily be noticed, there is a significant difference between Group A and Group B with respect to percentage recovery in ventricular contractile force, heart rate and percentage recovery of heart work, showing that Group B has

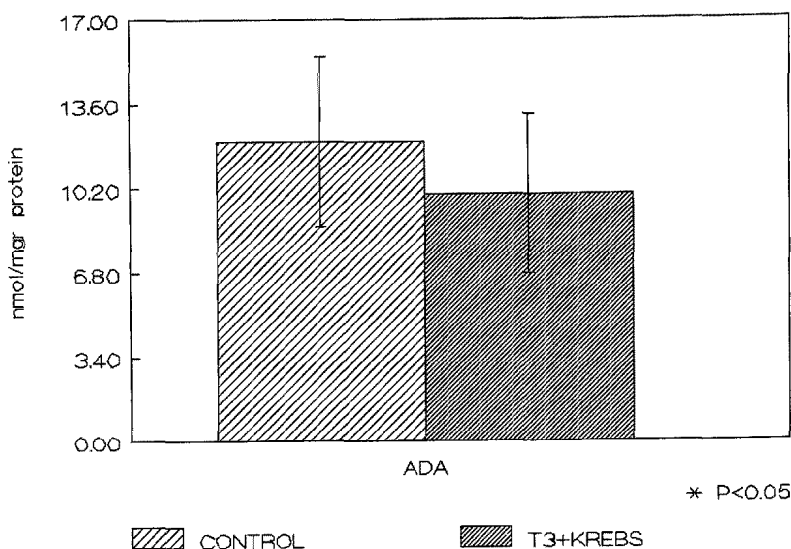


Figure 7. Concentrations of adenosine deaminase in control and postischemic T3+Krebs groups

much better ventricular performance compared to Group A after global ischemia ($p < 0.05$) (Figure 5). There is also a marked difference in enzyme activities showing that myocardial damage and ATP consumption is much less in Group B in comparison with Group A ($p < 0.05$) (Figures 6 and 7).

DISCUSSION

It is becoming increasingly evident that cardiopulmonary bypass affects thyroid hormone metabolism, leading to a euthyroid-sick state characterized by low levels of circulating FT3. The 'low T3 syndrome' is a part of a non-specific phenomenon of what is considered a general stress reaction.^{8,9} In this sense, it is a beneficial adaptive response to stress causing a reduction in metabolic demands and is accompanied by elevation of reverse T3, which is a metabolically inactive product of thyroxine breakdown.¹⁰

T3 may act on several metabolic pathways in the myocardium.¹¹ Aerobic metabolism is activated in the entire myocardium, enhancing substrate metabolism, replenishing the high energy phosphate stores within the myocardium and correcting the tissue lactic acidosis. The effects of T3 on various ATPases, such as calcium ATPase, modulation of the Na/K ATPase essential for the electrical depolarization-repolarization phenomenon, and the impact on myosin and troponin ATPases have been described. T3 has also been shown to lead to an increase in intracellular calcium within the cytosol; this is an important compo-

ment of myocardial contractility. It also plays an important function in catecholamine interaction and in the upregulation of B-adrenergic receptors. T3 is one of the major regulators of the synthesis of ventricular myosin isoenzymes. T3 also controls the adenine nucleotide translocase system, which transports ATP out of the mitochondria in the cytosol.^{8,12,13)}

In an experimental study with baboons, it was postulated that a combination of global ischemia and depletion of T3 results in reduced mitochondrial function, inhibition of tricarboxylic acid cycle and increased metabolism and depletion of myocardial phosphates.¹⁴⁾

Administration of T3 to patients who manifest the euthyroid-sick syndrome is controversial. Studies are limited and optimal management has not been determined. Thyroid hormone supplementation to patients with severe burn injury or severe primary non-thyroidal illnesses has shown no benefit. Also preoperative thyroid hormone replacement in patients with coronary artery disease may precipitate acute myocardial ischemia or infarction.¹⁾

An evaluation of the beneficial effects of T3 administered at hourly intervals was assessed in brain-dead patients referred for organ donation, and successful results were obtained.^{15,16)}

An experimental study in pigs demonstrated a marked inotropic effect when T3 was administered after a period of myocardial ischemia and cardiopulmonary bypass. This was associated with a significant reduction in mortality compared with the mortality in control pigs.^{3,4)} Although in another study T3 showed no inotropic properties in rabbit hearts, it significantly improved postischemic left ventricular function.¹⁷⁾

Novitzky et al demonstrated a significant improvement in cardiac function in dog hearts reperfused with T3 after a period of ischemia.⁵⁾

In patients with a left ventricular ejection fraction below 30%, T3 administration at the end of operation and during the initial 24 hours after operation was associated with a significantly reduced need for conventional inotropic agents and diuretics; also in patients with a left ventricular ejection fraction over 40%, T3 administration resulted in significantly improved stroke volume and cardiac output with reduced systemic and pulmonary vascular resistances.¹³⁾ In another group of patients, TRH administered during cardiopulmonary bypass elicited a markedly blunted TSH response which might be the consequence of the elevation of FT4 and FT3 due to heparin administration.¹⁸⁾

In our study, the clinical results showed a good correlation with the other studies. The concentrations of total T3 and FT3 decreased progressively after the institution of cardiopulmonary bypass and remained below normal throughout the study intervals, whereas there was no significant difference in the concentrations of either total T4, FT4 or TSH.

The results of the experimental study make it clearly evident that T3 reperfusion is beneficial for the improvement of cardiac function since there were better results in Group B than in Group A. Most authors demonstrated that T3 supplementation enhanced left ventricular functional recovery only after a period of ischemic injury. Our data confirm this fact, since there was no significant difference in Group C in which, without an ischemic period, T3 supplementation did not have a marked advantage over other groups.

These data provide further support for investigational trials of T3 supplementation in the improvement of cardiac function and prevention and treatment of low cardiac output syndrome after cardiopulmonary bypass.

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