Anesthesiology
1997; 87:102–9

Positive Inotropic and Lusitropic Effects of Triiodothyronine in Conscious Dogs with Pacing-induced Cardiomyopathy

Iyad N. Jamali, M.D., Paul S. Pagel, M.D., Ph.D.,† Douglas A. Hettrick, Ph.D.,‡ Dermot Lowe, M.B., F.F.A.R.C.S.I.,§ Judy R. Kersten, M.D.,‡ John P. Tessmer, B.S.,‖ and David C. Warltier, M.D., Ph.D.#*

Background: **The effects of triiodothyronine (T_3) on systemic hemodynamics, myocardial contractility (preload recruitable stroke work slope; M_w), and left ventricular (LV) isovolumic relaxation (time constant; τ) were examined before and after the development of pacing-induced cardiomyopathy in conscious dogs.**

Methods: **Dogs (n = 8) were chronically instrumented for measurement of aortic and LV pressure, dP/dt_{max}, subendocardial segment length, and cardiac output. Dogs received escalating doses (0.2, 2.0, and 20.0 mg/kg, intravenous) of T_3 over 5 min at 1-h intervals, and peak hemodynamic effects were recorded 10 min after each dose and 24 h after the final dose. Dogs were then continuously paced at 220–240 beats/min for 21 ± 2 days. Pacing was temporarily discontinued after the development of severe LV dysfunction, and administration of T_3 was repeated.**

Results: **T_3 produced immediate and sustained (24 h) increases ($P < 0.05$) in M_w and dP/dt_{max} in dogs before the initiation of pacing, consistent with a positive inotropic effect. No changes in τ occurred. Rapid ventricular pacing over 3 weeks increased baseline heart rate (sinus rhythm) and LV end-diastolic pressure, decreased mean arterial and LV systolic pressures, and caused LV systolic (decreases in M_w and dP/dt_{max}) and diastolic (increases in τ) dysfunction. T_3 caused immediate and sustained increases in M_w (63 ± 7 during control to 82 ± 7 mmHg after the 2 mg/kg dose) and decreases in τ (65 ± 8 during control to 57 ± 6 ms after the 20 mg/kg dose), indicating that this hormone enhanced myocardial contractility and shortened LV relaxation, respectively, in the presence of chronic LV dysfunction. In contrast to the findings in dogs with normal LV function, T_3 did not affect heart rate and calculated indices of myocardial oxygen consumption and reduced LV end-diastolic pressure (27 ± 3 during control to 20 ± 2 mmHg after the 2 mg/kg dose) in cardiomyopathic dogs.**

Conclusions: **The findings indicate that T_3 produces favorable alterations in hemodynamics and modest positive inotropic and lusitropic effects in conscious dogs with LV dysfunction produced by rapid LV pacing. (Key words: Heart: diastole; diastolic function; isovolumic relaxation. Heart: failure; rapid pacing; cardiomyopathy; myocardial contractility; preload recruitable stroke work. Hormones: triiodothyronine.)**

RECOGNITION that abnormalities in thyroid hormone metabolism may occur in patients with congestive heart failure has stimulated research attempting to define the role of thyroid hormone therapy in this clinical setting. A major finding in heart failure is the reduction of free triiodothyronine (T_3) levels. Reversal of such decreases in free T_3 concentration *via* the administration of exogenous T_3 has been proposed to increase left ventricular function and improve the short-term prognosis of patients with heart failure.[1] Several investigations in experimental animals and humans have suggested the feasibility and usefulness of this therapeutic approach. T_3 has been shown to enhance the functional recovery of stunned myocardium[2–4] and to improve contractility in models of myocardial infarction and ventricular remodeling.[5,6] T_3 also produced beneficial hemodynamic effects in patients with acute myocardial infarction,[7,8] after sudden cardiac death,[9] and during[10] and after cardiopulmonary bypass.[11] Thyroid hormone therapy has recently been shown to improve functional capacity in patients with idiopathic dilated cardiomyopathy.[12]

* Fellow in Medicine, Division of Cardiovascular Diseases.

† Associate Professor of Anesthesiology.

‡ Assistant Professor of Anesthesiology.

§ Research Fellow in Anesthesiology.

‖ Senior Research Scientist.

Professor of Anesthesiology, Pharmacology and Toxicology, and Medicine (Division of Cardiovascular Diseases) and Vice Chairman for Research of Anesthesiology.

Received from the Departments of Medicine (Division of Cardiovascular Diseases), Anesthesiology, and Pharmacology and Toxicology, the Medical College of Wisconsin and the Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin. Submitted for publication November 21, 1996. Accepted for publication March 4, 1997. This work was supported by a FAER Young Investigator Award (JRK), US PHS grant HL 54820 (DCW), and Anesthesiology Research Training Grant GM 08377 (DCW).

Address reprint requests to Dr. Warltier: Medical College of Wisconsin, MEB, Room 462C, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226.

However, the influence of T_3 on systemic hemodynamics and invasively derived indices of left ventricular systolic and diastolic function in the cardiomyopathic heart have not been described.

The present investigation tested the hypothesis that T_3 enhances myocardial contractility, improves left ventricular isovolumic relaxation, and produces beneficial hemodynamic effects in conscious, unsedated dogs with rapid ventricular pacing-induced cardiomyopathy. This experimental model produces time-dependent biventricular dilation, increases in left and right ventricular filling pressures,[13,14] abnormalities in intracellular calcium (Ca^{2+}) homeostasis,[15] left ventricular systolic and diastolic dysfunction,[16,17] and derangements in thyroid hormone metabolism[18] similar to those found in patients with dilated congestive cardiomyopathy.[19] Pacing-induced cardiomyopathy is relatively easy to produce in dogs[13,14] and provides a suitable model to study the cardiovascular effects of T_3 in the setting of severe left ventricular dysfunction.

Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. All procedures conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiologic Society and were performed according to the *Guide for the Care and Use of Laboratory Animals* (Department of Health, Education, and Welfare — Department of Health and Human Services publication [NIH] 85-23, revised 1996).

Surgical Preparation

The surgical implantation of instruments has been previously described in detail.[20] Briefly, during general anesthesia and using aseptic techniques, a left thoracotomy was performed in conditioned mongrel dogs for placement of instruments for measurement of aortic, left atrial, and intrathoracic pressures (heparin-filled catheters), subendocardial segment length (ultrasonic crystals), and relative cardiac output (ascending thoracic aortic ultrasonic flow transducer). A miniature micromanometer was placed in the left ventricle for measurement of continuous left ventricular pressure and the peak rate of increase of left ventricular pressure (dP/dt_{max}). A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of left ventricular preload used to generate left ventricular pressure-segment length diagrams. Stainless steel pacing electrodes were sutured to the epicardial surface of the left ventricular free wall and attached to an external programmable pacemaker. All instruments were firmly secured, tunneled between the scapulae, and exteriorized *via* several small incisions. The pericardium was left open; the chest wall was closed in layers, and the pneumothorax was evacuated by a chest tube. Each dog was fitted with a jacket to prevent damage to the instruments and catheters that were housed in a jacket pocket. The pacing electrodes were attached to a programmable pacemaker that also was stored in a jacket pocket.

All dogs received fentanyl as needed after surgery. Dogs were allowed to recover a minimum of 7 days before experimentation. All dogs were treated with intramuscular antibiotics (cephalothin, 40 mg/kg, and gentamicin, 4.5 mg/kg) and trained to stand quietly in a sling during hemodynamic monitoring. Segment length signals were monitored by ultrasonic amplifiers. End-systolic (ESL) and end-diastolic segment length (EDL) were measured 30 ms before $-dP/dt_{min}$ and immediately before the onset of left ventricular isovolumic contraction, respectively. Percent segment shortening (%SS) was determined using the equation: $\%SS = (EDL - ESL) \cdot 100 \cdot EDL^{-1}$. The pressure work index (PWI), an estimate of global myocardial oxygen consumption, was calculated using a previously validated formula.[21] Hemodynamic data were continuously recorded on a polygraph and simultaneously digitized by a computer interfaced with an analog to digital converter for recording and subsequent analysis of left ventricular pressure-segment length waveforms and diagrams.

Experimental Protocol

Each dog ($n = 8$; weight, 26.9 ± 0.7 kg, mean $\pm$ SEM) fasted overnight, and fluid deficits were replaced before experimentation with 0.9% saline (500 ml), which was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. Left ventricular pressure-segment length diagrams used to assess myocardial contractility were obtained as previously described.[20] The slope (M_w) of the regional preload recruitable stroke work relation derived from a series of differentially preloaded left ventricular pressure-segment length diagrams was used to quantify alterations in myocardial contractility.[22] A time constant of isovolumic relaxation (τ) was determined from the left ventricular pressure waveform at end-expiration using the derivative method.[23] After baseline sys-

temic hemodynamics and left ventricular pressure-segment length diagrams had been recorded during steady-state conditions, escalating doses (0.2, 2.0, and 20.0 mg/kg, intravenous) of T_3 (3,3′,5-triiodo-L-thyronine; Sigma Chemical, St. Louis, MO) were administered over 5 min at 1-h intervals. The drug vehicle for T_3 consisted of 25% ethanol (95%), 25% polyethylene glycol (5%), and 50% normal saline. No hemodynamic effects were produced by the drug vehicle alone. Peak changes in systemic hemodynamics were recorded, and left ventricular pressure-segment length diagrams were obtained using the techniques described above 10 min after the administration of each dose of T_3. Hemodynamics and pressure-length diagrams were also obtained 24 h after T_3 administration. Plasma concentrations of T_3 were evaluated after each intervention using radioimmunoassay in five dogs.

Dogs were continuously paced at ventricular rates between 220 and 240 beats/min for 21 ± 2 days to produce severe left ventricular dysfunction as indicated by chamber dilation, increases in left ventricular end-diastolic pressure, decreases in myocardial contractility, and increases in τ.[20] Dogs were brought to the laboratory on each day to confirm the functional integrity of the pacemaker and to monitor the development of pacing-induced cardiomyopathy. Pacing was temporarily discontinued during and restarted immediately after daily hemodynamic monitoring. After the development of pacing-induced cardiomyopathy, baseline hemodynamics, left ventricular pressure-segment length waveforms and diagrams, and plasma T_3 concentrations were recorded during steady-state conditions 30 min after pacing had been discontinued (sinus rhythm). Dogs then received T_3 in the doses described previously, and pacing was reinstated after data had been recorded. Hemodynamics, left ventricular pressure-length diagrams, and plasma T_3 concentrations were also obtained 24 h after the final dose of T_3. Thus, the effects of T_3 on systemic hemodynamics, myocardial contractility, and isovolumic relaxation were studied in the same conscious, unsedated dogs before and after the development of rapid ventricular pacing-induced cardiomyopathy.

Statistical Analysis

Statistical analysis of the data within and between groups before and after rapid ventricular pacing and during and after administration of T_3 was performed by multiple analysis of variance (ANOVA) with repeated measures, followed by Student's *t* test (two-tailed) with Duncan's adjustment for multiplicity. Changes were considered to be statistically significant when the *P* value was < 0.05. All data are expressed as mean ± SEM.

Results

Triiodothyronine caused significant ($P < 0.05$) increases in heart rate, rate-pressure product, pressure-work index, and cardiac output in conscious dogs with normal left ventricular function (table 1). These variables remained elevated 24 h after T_3 administration. Mean arterial pressure, left ventricular systolic and end-diastolic pressures, EDL, ESL, systemic vascular resistance, and stroke volume were unchanged. Increases in M_w (88 ± 5 during control to 109 ± 4 mmHg after the 2 mg/kg dose) and dP/dt_{max} (2286 ± 143 during control to 2593 ± 193 mmHg/s after the 2 mg/kg dose) occurred with administration of T_3, consistent with an immediate positive inotropic effect. T_3-induced increases in myocardial contractility remained intact 24 h after administration of this hormone. No changes in τ occurred, suggesting that T_3 does not shorten the isovolumic relaxation phase of diastole in the normal heart.

Chronic rapid ventricular pacing produced marked changes in systemic hemodynamics and left ventricular function (*e.g.*, table 1 *vs.* table 2). Significant increases in baseline heart rate (sinus rhythm), left ventricular end-diastolic pressure, EDL, and ESL and decreases in mean arterial and left ventricular systolic pressures were observed after 21 ± 2 days of pacing. No changes in calculated indices of myocardial oxygen consumption (rate-pressure product and pressure-work index), cardiac output, or systemic vascular resistance occurred with pacing. A decline in stroke volume was observed concomitant with an increase in heart rate. Rapid ventricular pacing caused a direct negative inotropic effect as indicated by reductions in M_w (88 ± 5 before to 63 ± 7 mmHg after pacing), dP/dt_{max}, and %SS. Pacing also increased τ (39 ± 1 before to 65 ± 8 ms after pacing), consistent with a negative lusitropic effect.

Triiodothyronine caused hemodynamic effects in dogs with pacing-induced cardiomyopathy that were somewhat different from those in dogs with normal left ventricular function (table 2). Left ventricular end-diastolic pressure was significantly reduced (27 ± 3 during control to 20 ± 2 mmHg after the 2 mg/kg dose), and heart rate, rate-pressure product, and pressure-

Table 1. Hemodynamic Effects of Triiodothyronine in Conscious Dogs with Normal Left Ventricular Function

	N	Before Pacing	Triiodothyronine Dose ($\mu g \cdot kg^{-1}$)			24 Hours
			0.2	2	2.0	
HR (bpm)	8	74 ± 6	94 ± 7*	86 ± 6	91 ± 7*	97 ± 6*
MAP (mmHg)	8	104 ± 4	105 ± 5	105 ± 2	105 ± 3	110 ± 5
RPP ($mmHg \cdot bpm \cdot 10^3$)	8	9.3 ± 0.8	11.7 ± 1.0*	11.0 ± 0.9	11.5 ± 1.1*	12.9 ± 1.2*
LVSP (mmHg)	8	124 ± 5	127 ± 6	128 ± 2	127 ± 5	134 ± 4*
LVEDP (mmHg)	8	9 ± 2	9 ± 1	10 ± 1	9 ± 1	9 ± 2
dP/dt_{max} ($mmHg \cdot s^{-1}$)	8	2,286 ± 143	2,590 ± 214*	2,593 ± 193*	2,413 ± 173	2,668 ± 113*§
EDL (mm)	8	21.2 ± 1.7	21.0 ± 1.7	21.3 ± 1.8	21.1 ± 1.9	21.5 ± 1.6
ESL (mm)	8	15.1 ± 1.2	14.7 ± 1.1	15.4 ± 1.4	15.3 ± 1.5	15.1 ± 1.1
SS (%)	8	28.7 ± 1.3	29.3 ± 2.5	27.7 ± 2.3	27.1 ± 2.6	29.6 ± 2.0
M_w (mmHg)	7	88 ± 5	107 ± 4*	109 ± 7*	94 ± 8‡	120 ± 8*§
L_w (mm)	7	13.8 ± 1.3	15.3 ± 1.8	15.8 ± 1.9	16.2 ± 2.2*	15.6 ± 1.5
τ (ms)	8	39 ± 1	37 ± 1	37 ± 1	37 ± 2	37 ± 2
CO ($L \cdot min^{-1}$)	6	2.2 ± 0.2	2.9 ± 0.2*	2.8 ± 0.4*	2.5 ± 0.3	2.8 ± 0.2*
SVR ($dyne \cdot s \cdot cm^{-5}$)	6	3,870 ± 560	2,930 ± 220*	3,260 ± 430	3,550 ± 470	3,050 ± 150
SV (ml)	6	34 ± 4	32 ± 4	34 ± 3	30 ± 4	31 ± 2
PWI ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	6	7.7 ± 0.3	9.9 ± 0.9*	9.3 ± 1.0	9.1 ± 0.8	10.0 ± 0.6*
$[T_3]$ ($ng \cdot ml^{-1}$)	5	0.49 ± 0.06	0.73 ± 0.11	3.2 ± 0.47*	24.4 ± 3.8*†‡	1.0 ± 0.18§

Data are mean ± SEM.

HR = heart rate; MAP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; τ = time constant of isovolumic relaxation; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; PWI = pressure work index; $[T_3]$ = plasma triiodothyronine concentration.

* Significantly ($P < 0.05$) different from control before pacing.

† Significantly ($P < 0.05$) different from 0.2 $\mu g \cdot kg^{-1}$ triiodothyronine.

‡ Significantly ($P < 0.05$) different from 2 $\mu g \cdot kg^{-1}$ triiodothyronine.

§ Significantly ($P < 0.05$) different from 20 $\mu g \cdot kg^{-1}$ triiodothyronine.

work index were unchanged during administration of T_3 to cardiomyopathic dogs in contrast to the findings in dogs before pacing. No changes in mean arterial and left ventricular systolic pressures, EDL, ESL, and systemic vascular resistance were observed. T_3 increased M_w (63 ± 7 during control to 82 ± 7 mmHg after the 2 mg/kg dose) and dP/dt_{max} (1585 ± 120 during control to 1769 ± 167 mmHg/s after the 20 mg/kg dose) in cardiomyopathic dogs, indicating a positive inotropic effect. The magnitude of increases in M_w and dP/dt_{max} caused by T_3 was similar in dogs with and without pacing-induced cardiomyopathy (figs. 1A and 1B). An increase in stroke volume was observed 24 h after the administration of T_3 in cardiomyopathic dogs concomitant with increases in contractility despite significant reductions in left ventricular end-diastolic pressure. Decreases in τ (65 ± 8 during control to 57 ± 6 ms after the 20 mg/kg dose) occurred in dogs after chronic rapid ventricular pacing (fig. 1C). Similar to the findings in normal dogs, alterations in hemodynamics and left ventricular function produced by T_3 in cardiomyopathic dogs persisted 24 h after administration of this hormone.

Discussion

The present results in conscious dogs with normal left ventricular function indicate that T_3 causes acute increases in myocardial contractility, confirming the findings of several previous investigations in normal papillary muscle[24,25] and isolated heart preparations.[26-28] The present results also show that T_3 produces immediate and sustained declines in left ventricular end-diastolic pressure, increases of myocardial contractility, improvements in isovolumic relaxation, and modest increases in cardiac output in dogs with pacing-induced cardiomyopathy. Importantly, these beneficial hemodynamic effects occurred in the absence of increases in heart rate and calculated estimates of global myocardial oxygen consumption in dogs with severe left ventricular dysfunction. These findings contrast with those ob-

Table 2. Hemodynamic Effects of Triiodothyronine in Conscious Dogs with Left Ventricular Dysfunction

			Triiodothyronine Dose ($\mu g \cdot kg^{-1}$)			
	N	After Pacing	0.2	2	2.0	24 Hours
HR (bpm)	8	102 ± 7*	101 ± 5	98 ± 5	102 ± 5	93 ± 6†¶
MAP (mmHg)	8	92 ± 4*	93 ± 5	94 ± 4*	97 ± 4	93 ± 3*
RPP ($mmHg \cdot bpm \cdot 10^3$)	8	11.4 ± 1.1	11.4 ± 1.0	11.0 ± 0.7	11.8 ± 0.8	10.6 ± 0.9
LVSP (mmHg)	8	109 ± 6*	111 ± 8	109 ± 6*	110 ± 6*	115 ± 6*
LVEDP (mmHg)	8	27 ± 3*	23 ± 2*†	20 ± 2*†	21 ± 2*†	21 ± 1*†
dP/dt_{max} ($mmHg \cdot s^{-1}$)	8	1,585 ± 120*	1,827 ± 177*†	1,745 ± 141*†	1,769 ± 167*†	2,094 ± 192*†‡§¶
EDL (mm)	8	26.4 ± 1.9*	26.4 ± 1.9*	26.6 ± 1.9	26.4 ± 1.9	26.7 ± 1.9
ESL (mm)	8	21.1 ± 1.5*	20.9 ± 1.5*	20.9 ± 1.6*	20.9 ± 1.6*	20.5 ± 1.6*
SS (%)	8	20.0 ± 1.9*	20.8 ± 2.0*	21.3 ± 1.7*	21.0 ± 1.7	22.9 ± 2.1*†
M_w (mmHg)	7	63 ± 7*	80 ± 7*†	82 ± 7*†	78 ± 6†	94 ± 7*†‡§¶
L_w (mm)	7	16.9 ± 1.8	18.0 ± 1.9†	18.4 ± 1.8†	18.3 ± 1.8†	17.5 ± 2.0
τ (ms)	8	65 ± 8*	59 ± 7*	59 ± 7*	57 ± 6*†	52 ± 6*†‡
CO ($L \cdot min^{-1}$)	6	2.3 ± 0.3	2.6 ± 0.4*	2.5 ± 0.3	2.5 ± 0.3	2.6 ± 0.3
SVR ($dyne \cdot s \cdot cm^{-5}$)	6	3,420 ± 520	2,910 ± 350	3,050 ± 320	3,180 ± 300	2,960 ± 270
SV (ml)	6	24 ± 4*	28 ± 5	27 ± 5	25 ± 4	30 ± 4†¶
PWI ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	6	8.4 ± 0.6	9.0 ± 0.9	8.7 ± 0.6	9.2 ± 0.7	8.6 ± 0.4
$[T_3]$ ($ng \cdot ml^{-1}$)	5	0.40 ± 0.10	0.78 ± 0.08	3.1 ± 0.57†	32.1 ± 3.2†‡§	1.6 ± 0.46¶

Data are mean ± SEM.

HR = heart rate; MAP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; τ = time constant of isovolumic relaxation; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; PWI = pressure work index; $[T_3]$ = plasma triiodothyronine concentration.

* Significantly ($P < 0.05$) different from corresponding value in dogs with normal left ventricular function (table 1).

† Significantly ($P < 0.05$) different from control before pacing.

‡ Significantly ($P < 0.05$) different from 0.2 $\mu g \cdot kg^{-1}$ triiodothyronine.

§ Significantly ($P < 0.05$) different from 2 $\mu g \cdot kg^{-1}$ triiodothyronine.

¶ Significantly ($P < 0.05$) different from 20 $\mu g \cdot kg^{-1}$ triiodothyronine.

served in dogs before pacing, in which the positive inotropic actions of T_3 occurred concomitant with tachycardia and increases in rate-pressure product and pressure-work index. The results in cardiomyopathic dogs suggest that myocardial oxygen consumption remained constant during and after administration of T_3 because increases in myocardial contractility were balanced by simultaneous reductions in left ventricular end-diastolic pressure. This conclusion requires qualification because coronary sinus oxygen tension was not measured and because myocardial oxygen consumption was not directly determined *in vivo*. The baseline plasma T_3 concentrations observed in conscious dogs before and after the development of pacing-induced cardiomyopathy (0.49 ± 0.06 and 0.40 ± 0.10 ng/ml, respectively) were similar to those reported previously in an identical model.[18] However, these T_3 levels are below the normal range (0.71 to 1.82 ng/ml) for healthy dogs in the absence of chronic surgical instrumentation. Thus, the present results should also be qualified because the effects of T_3 on systemic hemodynamics and left ventricular function were examined in normal and cardiomyopathic dogs with laboratory evidence of hypothyroidism.

The modest positive inotropic and lusitropic effects of T_3 observed in the present investigation are supported by the findings of several previous studies in experimental models of acute or chronic left ventricular dysfunction. T_3 has been shown to enhance contractile function without producing adverse increases in myocardial oxygen consumption or decreases in mechanical efficiency after global hypothermic ischemia in isolated canine hearts.[29] T_3 and related structural analogs of thyroid hormone also have been shown to produce positive inotropic effects in stunned myocardium.[2-4] The immediate and sustained actions of T_3 in cardiomyopathic dogs in the present investigation also are firmly supported by the previous observations of Morkin *et al.*[5] and Mahaffey *et al.*[4] in rats and rabbits, respectively, showing that T_3 causes increases in dP/dt_{max} and bene-

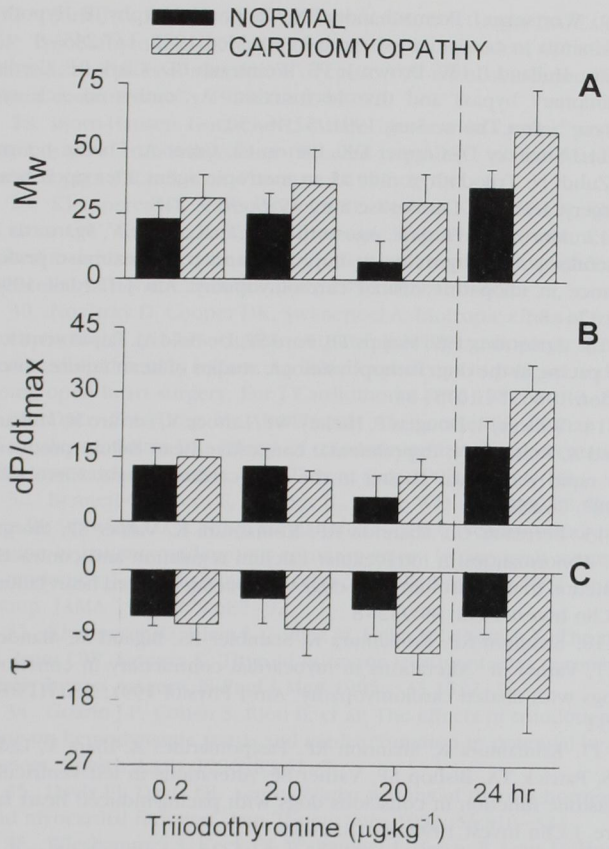

Figure 1. Histograms illustrating the percent change from control of regional preload recruitable stroke work slope (M_w, *A*), left ventricular dP/dt_{max} (*B*), and the time constant of isovolumic relaxation (τ; *C*) produced immediately by escalating doses of triiodothyronine (T_3; 0.2, 2.0, and 20.0 mg/kg, intravenous) and 24 h after T_3 administration in dogs before (normal; solid bars) and after the development of rapid ventricular pacing-induced left ventricular dysfunction (cardiomyopathy; hatched bars). *Significantly ($P < 0.05$) different from normal.

ficial reductions in left ventricular end-diastolic pressure and τ in heart failure produced by myocardial infarction and ventricular remodeling.

Thyroid hormone therapy produces beneficial effects in patients after acute myocardial infarction[7,8] and sudden cardiac death.[9] Clinical evidence has suggested that T_3 supplementation may acutely enhance cardiac performance, hasten the recovery of normal hemodynamics, and reduce the need for inotropic support in patients with left ventricular dysfunction after cardiopulmonary bypass,[10,11,30,31] although these conclusions have been challenged by recently published data.[32-34] Oral administration of T_4 for 1 week has also been shown to increase ejection fraction, cardiac output, and exercise tolerance in patients with dilated cardiomyopathy.[12] Thus, the present results with T_3 in conscious, cardiomyopathic dogs are also qualitatively supported by the majority of previous findings in patients with acute left ventricular dysfunction or chronic congestive heart failure.

Triiodothyronine has been shown to acutely enhance the activity of Ca^{2+}-ATPases in the sarcolemmal membrane and the sarcoplasmic reticulum (SR).[35] These actions lead to increased SR Ca^{2+} uptake and more efficient Ca^{2+} extrusion from the cardiac myocyte during diastole, effects that may have contributed to observed decreases in τ in cardiomyopathic dogs in the present investigation. Reversible declines in the rate of left ventricular isovolumic relaxation have also been observed previously in patients with acute hypothyroidism concomitant with reductions in myocardial contractility.[36] Thus, enhanced sarcolemmal and SR Ca^{2+}-ATPase activity during the administration of T_3 may partially attenuate abnormalities of intracellular Ca^{2+} homeostasis that are central to the pathogenesis of diastolic dysfunction in rapid pacing-induced[15] and clinical heart failure.[37] Potentiation of SR Ca^{2+}-ATPase activity by T_3 probably contributes to immediate increases in myocardial contractility by increasing the quantity of Ca^{2+} stored in this organelle for subsequent release during the next systole. T_3 has also been shown to directly enhance Ca^{2+} influx across the sarcolemmal membrane[38-40] *via* the voltage-dependent Ca^{2+} channel.[38,41] This increase in Ca^{2+} influx associated with membrane depolarization may contribute to the acute positive inotropic actions of T_3 not only by directly increasing Ca^{2+} availability for contractile activation but also by simultaneously stimulating Ca^{2+}-induced Ca^{2+} release from the SR.

The persistent increases in M_w and dP/dt_{max} and decreases in τ observed in dogs with pacing-induced left ventricular dysfunction 24 h after administration of T_3 are consistent with the known time-course of nuclear thyroid hormone receptor upregulation[42,43] and the subsequent transcription and translation of SR Ca^{2+}-ATPase.[44] T_3 may favorably alter the composition of myosin heavy chain isoforms in the failing heart,[45] although recent evidence suggests that this effect plays a relatively minor role in chronic T_3-induced increases in contractility in heart failure caused by myocardial infarction and ventricular remodeling.[6] β-Adrenoceptor downregulation, reduced adenylyl cyclase activity, and decreased production of cyclic adenosine monophosphate (cAMP) are characteristic features that contribute to depressed contractility in failing myocardium. Although the β-adrenoceptor-linked signal transduction is

not responsible for the inotropic actions of T_3 in normal myocardium,[27] T_3 may enhance β-adrenoceptor density[46] and sensitivity[47] in hypothyroid states, including those associated with heart failure. Such an improvement in β-adrenoceptor viability by T_3 may contribute to the transient and sustained positive inotropic effects of this hormone in failing myocardium. This hypothesis remains to be tested; the stability of heart rate observed during and after the administration of T_3 to cardiomyopathic dogs suggests that the beneficial actions of this thyroid hormone on left ventricular systolic and diastolic function were not based solely on alterations in β-adrenoceptor activity.

In summary, the present results indicate that T_3 produces immediate and sustained increases in myocardial contractility and improvement in isovolumic relaxation in conscious dogs with rapid ventricular pacing-induced cardiomyopathy. These positive inotropic and lusitropic effects were not accompanied by increases in myocardial oxygen consumption because T_3 caused favorable reductions in left ventricular end-diastolic pressure without changes in heart rate.

The authors thank Ms. Angela M. Barnes for preparation of the manuscript.

References

1. Hamilton MA: Prevalence and clinical implications of abnormal thyroid hormone metabolism in advanced heart failure. Ann Thorac Surg 1993; 56(Suppl 1):S48–S53

2. Novitzky D, Matthews N, Shawley D, Cooper DKC, Zuhdi N: Triiodothyronine in the recovery of stunned myocardium in dogs. Ann Thorac Surg 1991; 51:10–7

3. Kadletz M, Mullen PG, Ding M, Wolfe LG, Wechsler AS: Effect of triiodothyronine on postishemic myocardial function in the isolated heart. Ann Thorac Surg 1994; 57:657–62

4. Yokoyama Y, Novitzky D, Deal MT, Snow TR: Facilitated recovery of cardiac performance by triiodothyronine following a transient ischemic insult. Cardiology 1992; 81:34–45

5. Morkin E, Pennock GD, Raya TE, Bahl JJ, Goldman S: Studies on the use of thyroid hormone and a thyroid hormone analogue in the treatment of congestive heart failure. Ann Thorac Surg 1993; 56(Suppl 1):S54–S60

6. Mahaffey KW, Raya TE, Pennock GD, Morkin E, Goldman S: Left ventricular performance and remodeling in rabbits after myocardial infarction. Effects of a thyroid hormone analogue. Circulation 1995; 91:794–801

7. Pedersen F, Perrild H, Rasmussen SL, Skovsted L: "Low T_3-syndrome" in acute myocardial infarction. Relationship to beta-adrenergic blockade and clinical course. Eur J Clin Pharmacol 1984; 26:669–73

8. Wiersinga WM, Lie KI, Touber JL: Thyroid hormones in acute myocardial infarction. Clin Endocrinol 1981; 14:367–74

9. Wortsman J, Premachandra BN, Chopra IJ, Murphy JE: Hypothyroxinemia in cardiac arrest. Arch Intern Med 1987; 147:245–8

10. Holland II FW, Brown Jr PS, Weintraub BD, Clark RE: Cardiopulmonary bypass and thyroid function: A "euthyroid sick syndrome". Ann Thorac Surg 1991; 52:46–50

11. Novitzky D, Cooper DK, Barton CI, Greer A, Chaffin J, Grim J, Zuhdi N: Triiodothyronine as an inotropic agent after open heart surgery. J Thorac Cardiovasc Surg 1989; 98:972–8

12. Moruzzi P, Doria E, Agostoni PG, Capacchione V, Sganzerla P: Usefulness of L-thyroxine to improve cardiac and exercise performance in idiopathic dilated cardiomyopathy. Am J Cardiol 1994; 73:374–8

13. Armstrong PW, Stopps TP, Ford SE, De Bold AJ: Rapid ventricular pacing in the dog: Pathophysiologic studies of heart failure. Circulation 1986; 74:1075–84

14. Wilson JR, Douglas P, Hickey WF, Lanoce V, Ferraro N, Muhammad A, Relchek N: Experimental congestive heart failure produced by rapid ventricular pacing in the dog: cardiac effects. Circulation 1987; 75:857–67

15. Perreault CL, Shannon RP, Komamura K, Vatner SF, Morgan JP: Abnormalities in intracellular calcium regulation and contractile function in myocardium from dogs with pacing-induced heart failure. J Clin Invest 1992; 89:932–8

16. Shannon RP, Komamura K, Stambler BS, Bigaud M, Manders WT, Vatner SF: Alterations in myocardial contractility in conscious dogs with dilated cardiomyopathy. Am J Physiol 1991; 260:H1903–H11

17. Komamura K, Shannon RP, Pasipoularides A, Ihara T, Lader AS, Patrick TA, Bishop SP, Vatner SF: Alterations in left ventricular diastolic function in conscious dogs with pacing-induced heart failure. J Clin Invest 1992; 89:1825–38

18. Panciera DL, Refsal KR: Thyroid function in dogs with spontaneous and induced congestive heart failure. Can J Vet Res 1994; 58:157–62

19. Johnson RA, Palacios I: Dilated cardiomyopathies of the adult. N Engl J Med 1982; 307:1051–8

20. Pagel PS, McGough MF, Hettrick DA, Lowe D, Tessmer JP, Jamali IN, Warltier DC: Levosimendan enhances left ventricular systolic and diastolic function in conscious dogs with pacing-induced cardiomyopathy. J Cardiovasc Pharmacol 1997; 29:In Press

21. Rooke GA, Feigl EO: Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res 1982; 50:273–86

22. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC, Rankin JS: Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985; 71:994–1009

23. Raff GL, Glantz SA: Volume loading slows left ventricular isovolumic relaxation rate: evidence of load-dependent relaxation in the intact dog heart. Circ Res 1981; 48:813–24

24. Murayama M, Goodkind MJ: Effect of thyroid hormone on the frequency-force relationship of atrial myocardium from the guinea pig. Circ Res 1968; 23:743–51

25. Taylor RR, Covell JW, Ross J Jr: Influence of the thyroid state on left ventricular tension-velocity relations in the intact, sedated dog. J Clin Invest 1969; 48:775–84

26. Buccino RA, Spann Jr JF, Pool PE, Sonnenblick EH, Braunwald E: Influence of the thyroid state on the intrinsic contractile properties and energy stores of the myocardium. J Clin Invest 1967; 46:1669–82

27. Ririe DG, Butterwort JF,4th, Royster RL, MacGregor DA, Zaloga GP: Triiodothyronine increases contractility independent of beta-adrenergic receptors or stimulation of cyclic-3′,5′-adenosine monophosphate. ANESTHESIOLOGY 1995; 82:1004-12

28. Bjorn-Hansen Gotzsche L: Acute increase in cardiac performance after triiodothyronine: Blunted response in amiodarone-treated pigs. J Cardiovasc Pharmacol 1994; 23:141-8

29. Klemperer JD, Zelano J, Helm RE, Berman K, Ojamaa K, Klein I, Isom OW, Krieger K: Triiodothyronine improves left ventricular function without oxygen wasting effects after global hypothermia ischemia. J Thorac Cardiovasc Surg 1995; 109:457-65

30. Novitzky D, Cooper DK, Swanepoel A: Inotropic effect of triiodothyronine (T_3) in low cardiac output following cardioplegic arrest and cardiopulmonary bypass: An initial experience in patients undergoing open heart surgery. Eur J Cardiothorac Surg 1989; 3:140-5

31. Dyke CM, Ding M, Abd-Elfattah AS, Loesser K, Dignan RJ, Wechsler AS, Salter DR: Effects of triiodothyronine supplementation after myocardial ischemia. Ann Thorac Surg 1993; 56:215-22

32. Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwinn DA: Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery: A randomized, double-blind, placebo-controlled trial. Duke T_3 study group. JAMA 1996; 275:687-92

33. Klemperer JD, Klein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ, Isom OW, Krieger K: Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med 1995; 333:1522-7

34. Goarin J-P, Cohen S, Riou B, et al: The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. Anesth Analg 1996; 83:41-7

35. Davis PJ, Davis FB: Acute cellular actions of thyroid hormone and myocardial function. Ann Thorac Surg 1993; 56:S16-S23

36. Wieshammer S, Keck FS, Waitzinger J, Henze E, Loos U, Hombach V, Pfeiffer EF: Acute hypothyroidism slows the rate of left ventricular diastolic relaxation. Can J Physiol Pharmacol 1989; 67:1007-10

37. Morgan JP: Abnormal intracellular modulation of calcium as a major cause of cardiac contractile dysfunction. N Engl J Med 1991; 325:625-32

38. Kim D, Smith TW, Marsh JD: Effect of thyroid hormone on slow calcium channel function in cultured chick ventricular cells. J Clin Invest 1987; 80:88-94

39. Han J, Leem C, So I, Kim E, Hong S, Wonkyung H, Sung H, Earm YE: Effects of thyroid hormone on the calcium current and isoprenaline-induced background current in rabbit ventricular myocytes. J Mol Cell Cardiol 1994; 26:925-35

40. Segal J: Calcium is the first messenger for the action of thyroid hormone at the level of the plasma membrane: First evidence for an acute effect of thyroid hormone on calcium uptake in the heart. Endocrinology 1990; 126:2693-702

41. Bjorn-Hansen Gotzsche L: L-Triiodothyronine acutely increases Ca^{2+} uptake in the isolated, perfused rat heart. Changes in L-type Ca^{2+} channels and b-receptors during short- and long-term hyper- and hypothroidism. Eur J Endocrinol 1994; 130:171-9

42. Ladenson PW, Kieffer JD, Farwell AP, Ridgway EC: Modulation of myocardial L-triiodothyronine receptors in normal, hypothyroid, and hyperthyroid rats. Metabolism 1986; 35:5-12

43. Shanker R, Neeley WE, Dillmann WH: Time course of response of individual messenger RNAs in the rat heart to T_3. J Mol Cell Cardiol 1987; 19:595-601

44. Rohrer D, Dillmann WH: Thyroid hormone markedly increases the mRNA coding for sarcoplasmic reticulum Ca2+-ATPase in the rat heart. J Biol Chem 1988; 263:6941-4

45. Polikar R, Burger AG, Scherrer U, Nicod P: The thyroid and the heart. Circulation 1993; 87:1435-41

46. Insel PA: Adrenergic receptors: Evolving concepts on structure and function. Am J Hypertens 1989; 2:112S-8S

47. Polikar R, Kennedy B, Maisel A, Zeigler M, Smith J, Dittrich H, Nicod P: Decreased adrenergic sensitivity in patients with hypothyroidism. J Am Coll Cardiol 1990; 15:94-8