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


Background: The effects of triiodothyronine (T₃) on systemic hemodynamics, myocardial contractility (preload recruitable stroke work slope; Mₑ), 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/dtₘₐₓ, subendocardial segment length, and cardiac output. Dogs received escalating doses (0.2, 2.0, and 20.0 mg/kg, intravenous) of T₃ 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 T₃ was repeated.

Results: T₃ produced immediate and sustained (24 h) increases (P < 0.05) in Mₑ, and dp/dtₘₐₓ 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 Mₑ, and dp/dtₘₐₓ) and diastolic (increases in τ) dysfunction. T₃ caused immediate and sustained increases in Mₑ (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, T₃ 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 T₃ 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 (T₃) levels. Reversal of such decreases in free T₃ concentration via the administration of exogenous T₃ has been proposed to increase left ventricular function and improve the short-term prognosis of patients with heart failure. Several investigations in experimental animals and humans have suggested the feasibility and usefulness of this therapeutic approach. T₃ has been shown to enhance the functional recovery of stunned myocardium, and to improve contractility in models of myocardial infarction and ventricular remodeling. T₃ also produced beneficial hemodynamic effects in patients with acute myocardial infarction, after sudden cardiac death, and during and after cardiopulmonary bypass. Thyroid hormone therapy has recently been shown to improve functional capacity in patients with idiopathic dilated cardiomyopathy.
However, the influence of T, 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, 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 bi-ventricular dilation, increases in left and right ventricular filling pressures, 13,14 abnormalities in intracellular calcium (Ca2+) 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, 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/dtmax). 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/dtmax and immediately before the onset of left ventricular isovolumic contraction, respectively. Percent segment shortening (%SS) was determined using the equation: %SS = (EDL — ESL) · 100/EDL. 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 ± SEM) fasted overnight, and fluid deficits were replaced before experimentation with 0.9% saline (500 ml), which was continued at 3 ml·kg−1·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 (Mw) 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 T3 (3,3',5-triiodo-L-thyronine; Sigma Chemical, St. Louis, MO) were administered over 5 min at 1-h intervals. The drug vehicle for T3 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 T3. Hemodynamics and pressure-length diagrams were also obtained 24 h after T3 administration. Plasma concentrations of T3 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 T3 concentrations were recorded during steady-state conditions 30 min after pacing had been discontinued (sinus rhythm). Dogs then received T3 in the doses described previously, and pacing was reinstated after data had been recorded. Hemodynamics, left ventricular pressure-segment length diagrams, and plasma T3 concentrations were also obtained 24 h after the final dose of T3. Thus, the effects of T3 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 T3 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 T3 administration. Mean arterial pressure, left ventricular systolic and end-diastolic pressures, EDL, ESL, systemic vascular resistance, and stroke volume were unchanged. Increases in Maw (88 ± 5 during control to 109 ± 4 mmHg after the 2 mg/kg dose) and dp/dtmax (2286 ± 143 during control to 2593 ± 193 mmHg/s after the 2 mg/kg dose) occurred with administration of T3, consistent with an immediate positive inotropic effect. T3-induced increases in myocardial contractility remained intact 24 h after administration of this hormone. No changes in τ occurred, suggesting that T3 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 Maw (88 ± 5 before to 65 ± 7 mmHg after pacing), dp/dtmax, 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-
**T₃ AND LV FUNCTION**

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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Before Pacing</th>
<th>Triiodothyronine Dose (µg·kg⁻¹)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>8</td>
<td>74 ± 6</td>
<td>94 ± 7*</td>
<td>86 ± 6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>8</td>
<td>104 ± 4</td>
<td>105 ± 5</td>
<td>105 ± 2</td>
</tr>
<tr>
<td>RPP (mmHg·bpm⁻¹·10⁻²)</td>
<td>8</td>
<td>9.3 ± 0.8</td>
<td>11.7 ± 1.0*</td>
<td>11.0 ± 0.9</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>8</td>
<td>124 ± 5</td>
<td>127 ± 6</td>
<td>128 ± 2</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>8</td>
<td>9 ± 2</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>dP/dt_max (mmHg·s⁻¹)</td>
<td>8</td>
<td>2,286 ± 143</td>
<td>2,590 ± 214*</td>
<td>2,593 ± 193*</td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>8</td>
<td>21.2 ± 1.7</td>
<td>21.0 ± 1.7</td>
<td>21.3 ± 1.8</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>8</td>
<td>15.1 ± 1.2</td>
<td>14.7 ± 1.1</td>
<td>15.4 ± 1.4</td>
</tr>
<tr>
<td>SS (%)</td>
<td>8</td>
<td>28.7 ± 1.3</td>
<td>29.3 ± 2.5</td>
<td>27.7 ± 2.3</td>
</tr>
<tr>
<td>M₀ (mmHg)</td>
<td>7</td>
<td>88 ± 5</td>
<td>107 ± 4*</td>
<td>109 ± 7*</td>
</tr>
<tr>
<td>L₀ (mm)</td>
<td>7</td>
<td>13.8 ± 1.3</td>
<td>15.3 ± 1.8</td>
<td>15.8 ± 1.9</td>
</tr>
<tr>
<td>τ (ms)</td>
<td>8</td>
<td>39 ± 1</td>
<td>37 ± 1</td>
<td>37 ± 1</td>
</tr>
<tr>
<td>CO (L·min⁻¹)</td>
<td>6</td>
<td>2.2 ± 0.2</td>
<td>2.9 ± 0.2*</td>
<td>2.8 ± 0.4*</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻³)</td>
<td>6</td>
<td>3,870 ± 560</td>
<td>2,930 ± 220*</td>
<td>3,260 ± 430</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>6</td>
<td>34 ± 4</td>
<td>32 ± 4</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>PVI (ml·min⁻¹·100 g⁻¹)</td>
<td>6</td>
<td>7.7 ± 0.3</td>
<td>9.9 ± 0.9*</td>
<td>9.3 ± 1.0</td>
</tr>
<tr>
<td>T₃ (ng·ml⁻¹)</td>
<td>5</td>
<td>0.49 ± 0.06</td>
<td>0.73 ± 0.11</td>
<td>3.2 ± 0.47*</td>
</tr>
</tbody>
</table>

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; M₀ and L₀ = 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; PVI = pressure work index; [T₃] = plasma triiodothyronine concentration.

*Significantly (P < 0.05) different from control before pacing.
†Significantly (P < 0.05) different from 0.2 µg·kg⁻¹ triiodothyronine.
‡Significantly (P < 0.05) different from 2 µg·kg⁻¹ triiodothyronine.
§Significantly (P < 0.05) different from 20 µg·kg⁻¹ triiodothyronine.

work index were unchanged during administration of T₃ 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. T₃ increased M₀ (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 M₀ and dP/dt_max caused by T₃ 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 T₃ 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 T₃ 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 T₃ causes acute increases in myocardial contractility, confirming the findings of several previous investigations in normal papillary muscle[23,25] and isolated heart preparations. The present results also show that T₃ 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-

Anesthesiology, V 87, No 1, Jul 1997
Table 2. Hemodynamic Effects of Triiodothyronine in Conscious Dogs with Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>After Pacing</th>
<th>Triiodothyronine Dose (µg · kg⁻¹)</th>
<th>0.2</th>
<th>2</th>
<th>2.0</th>
<th>24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>8</td>
<td>102 ± 7*</td>
<td>101 ± 5</td>
<td>98</td>
<td>5</td>
<td>102</td>
<td>5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>8</td>
<td>92 ± 4*</td>
<td>93 ± 5</td>
<td>94</td>
<td>4</td>
<td>97</td>
<td>4</td>
</tr>
<tr>
<td>RPP (mmHg · bpm · 10³)</td>
<td>8</td>
<td>11.4 ± 1.1</td>
<td>11.4 ± 1.0</td>
<td>11.0 ± 0.7</td>
<td>11.8 ± 0.8</td>
<td>10.6 ± 0.9</td>
<td>10.6 ± 0.9</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>8</td>
<td>109 ± 6*</td>
<td>111 ± 8</td>
<td>109</td>
<td>6</td>
<td>110</td>
<td>6</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>8</td>
<td>27 ± 3*</td>
<td>23 ± 2†</td>
<td>20</td>
<td>2</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>dP/dt max (mmHg · s⁻¹)</td>
<td>8</td>
<td>1,585 ± 120†</td>
<td>1,827 ± 177††</td>
<td>1,745 ± 141††</td>
<td>1,769 ± 167††</td>
<td>2,094 ± 192††</td>
<td>3,094 ± 192††</td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>8</td>
<td>26.4 ± 1.9*</td>
<td>26.4 ± 1.9</td>
<td>26.6 ± 1.9</td>
<td>26.4 ± 1.9</td>
<td>26.7</td>
<td>1.9</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>8</td>
<td>21.1 ± 1.5*</td>
<td>20.9 ± 1.5</td>
<td>20.9 ± 1.6</td>
<td>20.9 ± 1.6</td>
<td>20.5</td>
<td>1.6</td>
</tr>
<tr>
<td>SS (%)</td>
<td>8</td>
<td>20.0 ± 1.9*</td>
<td>20.8 ± 2.0</td>
<td>21.3 ± 1.7</td>
<td>21.0 ± 1.7</td>
<td>22.9</td>
<td>2.1†</td>
</tr>
<tr>
<td>Mₑ (mmHg)</td>
<td>7</td>
<td>63 ± 7*</td>
<td>80 ± 7†</td>
<td>82</td>
<td>7</td>
<td>78</td>
<td>6†</td>
</tr>
<tr>
<td>Lₑ (mm)</td>
<td>7</td>
<td>16.9 ± 1.8</td>
<td>18.0 ± 1.9††</td>
<td>18.4 ± 1.8††</td>
<td>18.3 ± 1.8††</td>
<td>17.5</td>
<td>2.0</td>
</tr>
<tr>
<td>CO (L · min⁻¹)</td>
<td>6</td>
<td>65 ± 8*</td>
<td>59 ± 7†</td>
<td>59</td>
<td>7</td>
<td>57</td>
<td>6†</td>
</tr>
<tr>
<td>SVR (dyne · s · cm⁻⁵)</td>
<td>6</td>
<td>3,420 ± 520</td>
<td>2,910 ± 350</td>
<td>3,050 ± 320</td>
<td>3,180 ± 300</td>
<td>2,960</td>
<td>270</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>6</td>
<td>24 ± 4*</td>
<td>28 ± 5</td>
<td>25</td>
<td>5</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>PWI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>6</td>
<td>8.4 ± 0.6</td>
<td>9.0 ± 0.9</td>
<td>8.7 ± 0.6</td>
<td>9.2 ± 0.7</td>
<td>8.6</td>
<td>0.4</td>
</tr>
<tr>
<td>[T₃] (ng · ml⁻¹)</td>
<td>5</td>
<td>0.40 ± 0.10</td>
<td>0.78 ± 0.08</td>
<td>3.1 ± 0.57††</td>
<td>3.2 ± 3.2††</td>
<td>1.6</td>
<td>1.46††</td>
</tr>
</tbody>
</table>

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; Mₑ and Lₑ = preload recruitable stroke work slope and length intercept, respectively; t = time constant of isovolumic relaxation; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; PWI = pressure work index; [T₃] = 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 µg · kg⁻¹ triiodothyronine.
§ Significantly (P < 0.05) different from 2 µg · kg⁻¹ triiodothyronine.
†† Significantly (P < 0.05) different from 20 µg · kg⁻¹ triiodothyronine.

served in dogs before pacing, in which the positive inotropic actions of T₃ 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 T₃, 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 T₃ concentrations observed in conscious dogs before and after the development of pacing-induced cardiomyopathy (0.49 ± 0.06 ng/ml and 0.49 ± 0.10 ng/ml, respectively) were similar to those reported previously in an identical model. However, these T₃ 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 T₃ 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 T₃ observed in the present investigation are supported by the findings of several previous studies in experimental models of acute or chronic left ventricular dysfunction. T₃ 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. T₃ and related structural analogs of thyroid hormone also have been shown to produce positive inotropic effects in stunned myocardium. The immediate and sustained actions of T₃ in cardiomyopathic dogs in the present investigation also are firmly supported by the previous observations of Morkin et al. and Mahaffey et al. in rats and rabbits, respectively, showing that T₃ causes increases in dP/dt max and bene-

Anesthesiology, V 87, No 1, Jul 1997
T₃ AND LV FUNCTION

![Graphs showing changes in Mₑ, dP/dt_max, and triiodothyronine concentration over time.]

Figure 1. Histograms illustrating the percent change from control of regional preload recruitable stroke work slope (Mₑ, A), left ventricular dP/dt_max (B), and the time constant of isovolumic relaxation (τ; C) produced immediately by escalating doses of triiodothyronine (T₃; 0.2, 2.0, and 20.0 mg/kg, intravenous) and 24 h after T₃ 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.

official 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 and sudden cardiac death. Clinical evidence has suggested that T₃ 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, although these conclusions have been challenged by recently published data. Oral administration of T₃ for 1 week has also been shown to increase ejection fraction, cardiac output, and exercise tolerance in patients with dilated cardiomyopathy. Thus, the present results with T₃ 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 Ca²⁺-ATPases in the sarcolemmal membrane and the sarcoplasmic reticulum (SR). These actions lead to increased SR Ca²⁺ uptake and more efficient Ca²⁺ 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. Thus, enhanced sarcolemmal and SR Ca²⁺-ATPase activity during the administration of T₃ may partially attenuate abnormalities of intracellular Ca²⁺ homeostasis that are central to the pathogenesis of diastolic dysfunction in rapid pacing-induced and clinical heart failure.

Potentiation of SR Ca²⁺-ATPase activity by T₃ probably contributes to immediate increases in myocardial contractility by increasing the quantity of Ca²⁺ stored in this organelle for subsequent release during the next systole. T₃ has also been shown to directly enhance Ca²⁺ influx across the sarcolemmal membrane via the voltage-dependent Ca²⁺ channel. This increase in Ca²⁺ influx associated with membrane depolarization may contribute to the acute positive inotropic actions of T₃ not only by directly increasing Ca²⁺ availability for contractile activation but also by simultaneously stimulating Ca²⁺-induced Ca²⁺ release from the SR.

The persistent increases in Mₑ and dP/dt_max and decreases in τ observed in dogs with pacing-induced left ventricular dysfunction 24 h after administration of T₃ are consistent with the known time-course of nuclear thyroid hormone receptor upregulation and the subsequent transcription and translation of SR Ca²⁺-ATPase, T₃ may favorably alter the composition of myosin heavy chain isoforms in the failing heart, although recent evidence suggests that this effect plays a relatively minor role in chronic T₃-induced increases in contractility in heart failure caused by myocardial infarction and ventricular remodeling. 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 T₃ in normal myocardium. T₃ may enhance β-adrenoceptor density and sensitivity in hypothyroid states, including those associated with heart failure. Such an improvement in β-adrenoceptor viability by T₃ 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 T₃ 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 T₃ 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 T₃ caused favorable reductions in left ventricular end-diastolic pressure without changes in heart rate.

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T₃ AND LV FUNCTION


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