Coronary Blood Flow, Myocardial Oxygen Consumption, and Myocardial Metabolism in Normal and Hyperthyroid Human Subjects

By Leonard Leight, M.D., Valentino DeFazio, M.D., Frederick N. Talmers, M.D., Timothy J. Regan, M.D., and Harper K. Hellems, M.D.

The pronounced clinical effects of hyperthyroidism upon the cardiovascular system strongly suggest a direct participation of cardiac tissue in the metabolic effects of excess thyroid hormone. Although limited study of the human heart has failed to support this view, experimental hyperthyroidism has revealed an increased myocardial oxidative activity and diminished myocardial concentration of high-energy phosphate compounds.

This limitation in the source of immediately available energy for muscular contraction, and, hence, of cardiac work capacity, might represent a biochemical lesion responsible for the clinical demonstration of impaired exercise response in hyperthyroid patients.

To explore further the influence of thyroid hormone excess on the myocardium, a study of carbohydrate metabolism, oxygen consumption, and coronary flow was undertaken in a group of individuals with typical hyperthyroidism and, for comparative purposes, in a group of hospitalized individuals free of cardiac and metabolic disease.

Methods and Material

The data presented were obtained from 17 normal individuals and 13 hyperthyroid patients. The former group was made up of individuals convalescent from a variety of acute diseases, and at the time of study had no detectable cardiovascular or metabolic disease. The latter group was made up of patients with history, physical, and laboratory findings typical of hyperthyroidism.

The 17 normal individuals ranged in age from 22 to 54 years, with a mean age of 34.4 years. The 13 hyperthyroid individuals had an age range from 18 to 54 years, and a mean age of 26.6 years. All subjects were fasting for at least 8 hours prior to study. No attempt was made to modify the ward diet in the days preceding the study. The patients in both groups were sedated with Nembutal, 100 mg., or demerol, 50 mg., to obtain a reasonably basal state. Catheterization of the coronary sinus was carried out in the right anterior oblique position and an indwelling needle inserted in either the radial or brachial artery. Coronary blood flow was determined by the nitrous oxide method of Kety and Schmidt as modified for the heart, utilizing the saturation technic and a coefficient of 1.1 for the partition of nitrous oxide between myocardium and blood.

Just prior to the onset of nitrous oxide administration, blood was drawn simultaneously from the coronary sinus and a peripheral artery for oxygen, carbon dioxide, glucose, lactic acid, and pyruvic acid determinations, and for the nitrous oxide blood blanks. In addition to an integrated sample over the first minute of nitrous oxide administration, 5 other samples were collected during the first 5 minutes and 45 seconds of nitrous oxide administration, and a total of 8 samples of blood were obtained from the artery and coronary sinus over a period of 9 minutes.
and 15 seconds of nitrous oxide administration. Samples were collected at as constant a rate as possible over a 30-second interval; the midpoint of each collection period was plotted as a discrete point. In order to compensate for the varying dead space of different size catheters, the volume of each catheter used was measured and this volume cleared from the catheter and discarded prior to each sampling of blood from the coronary sinus for nitrous oxide determination. The sampling from the coronary sinus catheter was so timed as to correct for the dead space of the particular catheter, so that the bloods collected for analysis represented true simultaneous sampling of arterial and coronary sinus blood. Arterial blood was obtained directly from the needle, no intervening tube being used.

While coronary flow studies were attempted in 17 normal and 13 hyperthyroid patients, the nitrous oxide curves were satisfactory in all aspects in only 8 normal and 5 hyperthyroid patients. Studies were rejected because of one or more of the following reasons: obvious deviation from a steady state during the study; failure of the venous and arterial curves to reach equilibrium; and irregularities in either the venous or arterial curve which precluded the construction of a smooth curve.

Cardiac output, utilizing the Fick principle, was determined either with right atrial blood obtained from the proximal lumen of a double-lumen catheter (distal lumen in coronary sinus), or with pulmonary artery blood as the mixed venous sample either just after or just before the start of the coronary blood flow. Attempts were made to determine cardiac output and coronary blood flow at as close an interval as possible. Oxygen consumption was determined by analysis of expired air and room air for oxygen on a Pauling oxygen analyzer. Corrections were not made for the paramagnetic effect of nitrous oxide on the Pauling oxygen analyzer, since in our experience the small amount of nitrous oxide present in the expired air introduced no significant error in the calculation of oxygen consumption. Mean pressures were obtained by electric integration, using Sanborn electromanometers and recorded on a Sanborn polyviso.

Blood gas analyses were carried out the day of study. Bloods for oxygen and carbon dioxide were analyzed in duplicate by the method of Van Slyke and Neil. Nitrous oxide was determined as described by Kety. Blood concentrations of glucose, lactic acid, and pyruvic acid were determined in duplicate, using the methods of Somogyi, Barker and Summerson, and Friedemann and Haugen, respectively.

The oxygen consumption per 100 Gm. left ventricle/min. was obtained as follows:

\[
O_2 \text{ consumption (ml./100 Gm. left ventricle/min.)} = \frac{\text{arterial } O_2 \text{ content (vol. %)}}{- \text{ coronary sinus } O_2 \text{ content (vol. %)}} \times \text{coronary flow (ml./100 Gm./min.)}
\]

The coronary blood flow per 100 Gm. left ventricle/min. expressed as per cent of cardiac output was calculated as follows:

\[
\text{Per cent of cardiac output} = \frac{\text{coronary flow (ml./100 Gm./min.)}}{\text{cardiac output (ml./min.)}} \times 100
\]

The myocardial oxygen consumption per 100 Gm. left ventricle/min. expressed as per cent of total oxygen consumption per minute was calculated as follows:

\[
\text{Per cent of total } O_2 \text{ consumption} = \frac{\text{myocardial } O_2 \text{ consumption (ml./100 Gm./min.)}}{\text{total } O_2 \text{ consumption (ml./min.)}} \times 100
\]

The coefficient of extraction of oxygen and the metabolites were obtained with the following equation:

\[
\text{Coefficient of extraction (toward arterial level/100 ml.)} = \frac{\text{arterial level/100 ml.}}{- \text{coronary sinus level/100 ml.}} \times 100
\]

Coronary vascular resistance was calculated as follows:

\[
\text{Coronary vascular resistance (mm. Hg/ml./100 Gm./min.)} = \frac{\text{mean arterial pressure (mm. Hg)}}{\text{coronary flow (ml./100 Gm./min.)}}
\]

The work of the left ventricle against pressure was expressed as follows:

\[
\text{Left ventricular work (kilogram-meters-minute) = \frac{\text{cardiac output (ml./minute)}}{\times \text{mean arterial pressure (mm. Hg) \times 13.6}}}
\]

The contribution of lactic acid, pyruvic acid, and glucose to the aerobic metabolism of the left ventricle was indicated by converting the arterial-coronary sinus difference of these metabolites to their energy equivalents. The factors used to indicate the milliliters of oxygen necessary to metabolize 1 mg. of each metabolite were 0.75 for glucose and lactic acid and 0.67 for pyruvic acid.

The energy equivalent for glucose, for example, would then be calculated as follows:

\[
\text{Energy equivalent for glucose (mg. %)} = \frac{\text{glucose arterial-coronary sinus difference (mg. %) \times 0.75}}{\text{oxygen arterial-coronary sinus difference (Vol. %)}} \times 100
\]

The per cent of the oxygen difference across the myocardium accounted for by glucose, lactic acid, and pyruvic acid was determined by adding the individual energy equivalents.
RESULTS

As expected, the cardiac output in the hyperthyroid group was higher than in the normal group, the mean for the 2 groups being 11.70 L./min. and 6.01 L./min., respectively (tables 1 and 2).

The mean coronary blood flow in the hyperthyroid group was 155 ml./100 Gm. left ventricle/min., compared to a mean of 103 ml./100 Gm./min. in the 8 normal individuals. One hyperthyroid individual (L.R.) had a coronary blood flow which fell within the normal range (table 2). The increased left ventricular coronary flow in the hyperthyroid group appeared to represent no greater proportion of the cardiac output than did the coronary flow among the normal patients. This is shown in tables 1 and 2, and is illustrated in figure 1, where the coronary flow for both groups is plotted against the per cent of cardiac output that each flow represents.

The mean coefficient of oxygen extraction by the myocardium was essentially similar in both groups although the oxygen A-V difference across the myocardium tended to be lower in the hyperthyroid group. This reflected a somewhat lower hemoglobin concentration in the latter group. However, in no patient was the hemoglobin reduced to levels below 9 Gm. per cent. It is not until the hemoglobin drops below the latter figure that there appears to be an effect on myocardial hemodynamics.

The mean myocardial oxygen consumption among the hyperthyroid patients was 13.3

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**Table 1.**—Coronary Blood Flow and Myocardial Oxygen Consumption in Eight Normal Individuals

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Cardiac output (ml/min.)</th>
<th>Arterial coronary sinus O2 A-V difference (Vol. %)</th>
<th>O2 Coefficient of extraction (%)</th>
<th>Coronary blood flow (ml/100 Gm./min.) as % of Cardiac output</th>
<th>Myocardial O2 consumption (ml./100 Gm./min.)</th>
<th>Myocardial O2 consumption per 100 Gm./min. as % of total O2 consumption (%)</th>
<th>Body O2 consumption (ml./100 Gm./min.)</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Coronary vascular resistance (mm.Hg./ml./100 Gm./min.)</th>
<th>Left ventricular work (Kg.M./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.R.</td>
<td>45</td>
<td>3250</td>
<td>12.3</td>
<td>69.8</td>
<td>95</td>
<td>2.9</td>
<td>224</td>
<td>11.7</td>
<td>5.2</td>
<td>93</td>
<td>0.98</td>
</tr>
<tr>
<td>L.H.</td>
<td>25</td>
<td>7250</td>
<td>10.1</td>
<td>61.2</td>
<td>120</td>
<td>1.8</td>
<td>261</td>
<td>13.0</td>
<td>4.9</td>
<td>83</td>
<td>0.64</td>
</tr>
<tr>
<td>J.S.</td>
<td>36</td>
<td>7480</td>
<td>10.8</td>
<td>70.9</td>
<td>68</td>
<td>0.9</td>
<td>243</td>
<td>7.3</td>
<td>3.0</td>
<td>90</td>
<td>1.3</td>
</tr>
<tr>
<td>R.M.</td>
<td>34</td>
<td>5180</td>
<td>10.8</td>
<td>72.3</td>
<td>91</td>
<td>1.8</td>
<td>159</td>
<td>9.8</td>
<td>6.1</td>
<td>106</td>
<td>1.2</td>
</tr>
<tr>
<td>G.D.</td>
<td>54</td>
<td>4380</td>
<td>6.7</td>
<td>49.8</td>
<td>101</td>
<td>2.3</td>
<td>162</td>
<td>6.8</td>
<td>4.2</td>
<td>92</td>
<td>0.91</td>
</tr>
<tr>
<td>F.B.</td>
<td>27</td>
<td>5620</td>
<td>11.1</td>
<td>66.8</td>
<td>129</td>
<td>2.3</td>
<td>219</td>
<td>14.3</td>
<td>6.5</td>
<td>120</td>
<td>0.92</td>
</tr>
<tr>
<td>C.S.</td>
<td>46</td>
<td>8250</td>
<td>10.6</td>
<td>68.3</td>
<td>98</td>
<td>1.2</td>
<td>245</td>
<td>10.4</td>
<td>4.2</td>
<td>95</td>
<td>0.97</td>
</tr>
<tr>
<td>S.N.</td>
<td>24</td>
<td>6680</td>
<td>9.6</td>
<td>57.0</td>
<td>113</td>
<td>1.7</td>
<td>191</td>
<td>10.6</td>
<td>5.3</td>
<td>98</td>
<td>0.85</td>
</tr>
</tbody>
</table>

| Averages | 36.4  | 6011                     | 10.3                                          | 64.5                            | 103                                                            | 1.9                                        | 213                                                                            | 10.5                             | 4.9                             | 97                             | 0.97                          | 7.9                            |

**Table 2.**—Coronary Blood Flow and Myocardial Oxygen Consumption in Five Hyperthyroid Individuals

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Cardiac output (ml/min.)</th>
<th>Arterial coronary sinus O2 A-V difference (Vol. %)</th>
<th>O2 Coefficient of extraction (%)</th>
<th>Coronary blood flow (ml/100 Gm./min.) as % of Cardiac output</th>
<th>Myocardial O2 consumption (ml./100 Gm./min.)</th>
<th>Myocardial O2 consumption per 100 Gm./min. as % of total O2 consumption (%)</th>
<th>Body O2 consumption (ml./100 Gm./min.)</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Coronary vascular resistance (mm.Hg./ml./100 Gm./min.)</th>
<th>Left ventricular work (Kg.M./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.M.</td>
<td>54</td>
<td>7300</td>
<td>9.7</td>
<td>62.0</td>
<td>154</td>
<td>2.1</td>
<td>246</td>
<td>14.9</td>
<td>6.1</td>
<td>115</td>
<td>0.75</td>
</tr>
<tr>
<td>J.J.</td>
<td>24</td>
<td>13600</td>
<td>8.6</td>
<td>64.8</td>
<td>168</td>
<td>1.2</td>
<td>331</td>
<td>14.4</td>
<td>4.3</td>
<td>90</td>
<td>0.53</td>
</tr>
<tr>
<td>J.B.</td>
<td>43</td>
<td>13820</td>
<td>7.0</td>
<td>59.3</td>
<td>157</td>
<td>1.1</td>
<td>238</td>
<td>11.0</td>
<td>4.6</td>
<td>80</td>
<td>0.51</td>
</tr>
<tr>
<td>L.R.</td>
<td>32</td>
<td>14930</td>
<td>10.2</td>
<td>60.7</td>
<td>117</td>
<td>0.78</td>
<td>397</td>
<td>11.9</td>
<td>3.0</td>
<td>76</td>
<td>0.65</td>
</tr>
<tr>
<td>M.H.</td>
<td>41</td>
<td>8870</td>
<td>7.9</td>
<td>68.1</td>
<td>180</td>
<td>2.3</td>
<td>228</td>
<td>14.2</td>
<td>6.2</td>
<td>98</td>
<td>0.54</td>
</tr>
</tbody>
</table>

| Averages | 38.8  | 11704                     | 8.7                                           | 62.6                            | 155                                                            | 1.5                                        | 288                                                                            | 13.3                             | 4.8                             | 92                             | 0.60                          | 13.1                           |
The myocardial carbohydrate metabolism was studied in a total of 17 normal and 13 hyperthyroid individuals (tables 3 and 4). There was no statistically significant difference in carbohydrate metabolism between the 2 groups. A value for $p$ of 0.08 or greater was found when the following categories were compared: arterial glucose, lactic acid, and pyruvic acid; energy equivalent for glucose, lactic acid, and pyruvic acid; per cent of total oxygen A-V difference accounted for by carbohydrate metabolites; and lactic acid/pyruvic acid ratio.

The mean arterial glucose was identical in 2 groups, 76 and 75 mg. per cent, among the normal and hyperthyroid individuals, respectively. The range of variation of arterial glucose was narrow, 49 to 90 mg. per cent in the normal and 62 to 88 mg. per cent in the hyperthyroid individuals. Excluding the individual (F.B., table 3) with an arterial glucose of 49 mg. per cent, the range in the normal was 64 to 90 mg. per cent. Both the arterial-coronary sinus glucose difference and the coefficient of extraction for glucose showed considerable variation within both groups, with no difference between the groups. The mean extraction of glucose was small, averaging 4.9 per cent among the normal group and 4.8 per cent in the hyperthyroid group. Although there was a marked variation among individuals within both groups in the per cent of the oxygen A-V difference across the myocardium accounted for by glucose, the mean energy equivalent for glucose averaged close to 25 per cent for both groups. In neither group was there a correlation between the arterial glucose level and either the A-V difference of glucose across the myocardium, the glucose coefficient of extraction, or the glucose energy equivalent.

Lactic acid metabolism in the normal and hyperthyroid groups also showed striking similarities. In both groups, the mean extraction of lactic acid was about 33 per cent of the arterial level. The per cent of the simultaneously observed oxygen A-V difference across the myocardium accounted for by lactic acid metabolism was 15 per cent, with no difference between the groups.
<table>
<thead>
<tr>
<th>Glucose Metabolism</th>
<th>Lactic Acid Metabolism</th>
<th>Pyruvic Acid Metabolism</th>
<th>% Of Arterial-coronary sinus A-V difference accounted by glucose, lactic acid, pyruvic acid</th>
<th>Arterial lactic acid: pyruvic acid ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt.</td>
<td>Arterial level mg.%</td>
<td>Arterial-coronary sinus A-V difference mg.%</td>
<td>Coefficient of extraction %</td>
<td>Energy equivalent %</td>
</tr>
<tr>
<td>A.N.</td>
<td>69</td>
<td>0</td>
<td>0</td>
<td>10.2</td>
</tr>
<tr>
<td>L.B.</td>
<td>64</td>
<td>9.4</td>
<td>35.2</td>
<td>3.2</td>
</tr>
<tr>
<td>F.B.</td>
<td>49</td>
<td>14</td>
<td>28.6</td>
<td>93.4</td>
</tr>
<tr>
<td>E.S.</td>
<td>64</td>
<td>7</td>
<td>10.9</td>
<td>45.7</td>
</tr>
<tr>
<td>L.H.</td>
<td>64</td>
<td>-12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G.D.</td>
<td>77</td>
<td>8</td>
<td>10.4</td>
<td>89.6</td>
</tr>
<tr>
<td>R.B.</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R.M.</td>
<td>88</td>
<td>7</td>
<td>8.1</td>
<td>48.7</td>
</tr>
<tr>
<td>J.S.</td>
<td>80</td>
<td>6</td>
<td>7.5</td>
<td>41.8</td>
</tr>
<tr>
<td>G.M.</td>
<td>77</td>
<td>7</td>
<td>9.0</td>
<td>38.3</td>
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<tr>
<td>A.L.</td>
<td>90</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E.S.</td>
<td>75</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.S.</td>
<td>86</td>
<td>-4</td>
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<td>0</td>
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<tr>
<td>H.V.</td>
<td>77</td>
<td>-3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S.N.</td>
<td>85</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J.R.</td>
<td>87</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.M.</td>
<td>76</td>
<td>7</td>
<td>11</td>
<td>31.4</td>
</tr>
<tr>
<td>Averages</td>
<td>76</td>
<td>3</td>
<td>4.9</td>
<td>23.1</td>
</tr>
</tbody>
</table>

* In computing average, all values greater than 100% were considered to be 100%.
† All negative values considered as 0 in computing average.

<table>
<thead>
<tr>
<th>Glucose Metabolism</th>
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<th>Pyruvic Acid Metabolism</th>
<th>% Of Arterial-coronary sinus A-V difference accounted by glucose, lactic acid, pyruvic acid</th>
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<td>Pt.</td>
<td>Arterial level mg.%</td>
<td>Arterial-coronary sinus A-V difference mg.%</td>
<td>Coefficient of extraction %</td>
<td>Energy equivalent %</td>
</tr>
<tr>
<td>I.B.</td>
<td>85</td>
<td>3</td>
<td>3.5</td>
<td>21.1</td>
</tr>
<tr>
<td>A.J.</td>
<td>78</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V.H.</td>
<td>73</td>
<td>3</td>
<td>4.1</td>
<td>24.5</td>
</tr>
<tr>
<td>I.M.</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E.H.</td>
<td>74</td>
<td>1</td>
<td>1.4</td>
<td>6.6</td>
</tr>
<tr>
<td>W.S.</td>
<td>70</td>
<td>8</td>
<td>11.4</td>
<td>52.6</td>
</tr>
<tr>
<td>B.P.</td>
<td>62</td>
<td>12</td>
<td>19.3</td>
<td>95.1</td>
</tr>
<tr>
<td>F.R.</td>
<td>74</td>
<td>6</td>
<td>8.1</td>
<td>44.6</td>
</tr>
<tr>
<td>L.R.</td>
<td>70</td>
<td>2</td>
<td>2.8</td>
<td>16.2</td>
</tr>
<tr>
<td>L.R.</td>
<td>88</td>
<td>3</td>
<td>3.5</td>
<td>22.1</td>
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<tr>
<td>M.M.</td>
<td>88</td>
<td>1</td>
<td>1.1</td>
<td>7.8</td>
</tr>
<tr>
<td>J.B.</td>
<td>70</td>
<td>5</td>
<td>7.1</td>
<td>53.8</td>
</tr>
<tr>
<td>J.J.</td>
<td>67</td>
<td>-10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Averages</td>
<td>75</td>
<td>3</td>
<td>4.8</td>
<td>26.5</td>
</tr>
</tbody>
</table>

* In computing average, all values greater than 100% were considered to be 100%.
† All negative values considered as 0 in computing average.
averaged, in both groups, somewhat less than that accounted for by glucose, the energy equivalent for lactic acid averaging 17.4 and 15.5 per cent among the normal and hyperthyroid groups, respectively. As with glucose, there was no relation between the arterial lactate level and lactic acid utilization by the myocardium.

The pyruvic acid usage by the myocardium in the normal and hyperthyroid patients was also similar. The arterial level in both groups was low, averaging close to 1 mg. per cent. The energy equivalent for pyruvic acid was negligible in both groups, averaging an identical 1.9 per cent.

In neither group was there a relationship between the arterial level of one metabolite and the arterial-coronary sinus difference, coefficient of extraction, or energy equivalent of the other metabolites.

It is of interest that the ratio of arterial lactic acid to arterial pyruvic acid showed similar ranges in both groups (Tables 3 and 4), and averaged less than the previously described ratio of 12.2 in normal human subjects. The lactic acid levels in the hyperthyroid group tended to be lower than in the normal group, averaging 6.4 mg. per cent in the former and 8.0 mg. per cent in the latter group. The mean arterial pyruvate levels were similar in both groups, averaging 1.01 mg. per cent in the hyperthyroid and 0.91 mg. per cent in the normal group. These findings militate strongly against the presence of thiamine deficiency among the hyperthyroid patients.

**DISCUSSION**

The findings in this report indicate that the coronary flow per unit of left ventricular weight is elevated in hyperthyroidism. The increased coronary flow in this disease appears to represent no greater proportion of the simultaneously determined cardiac output than does the coronary flow in normal individuals. Although, as indicated in figure 1, the relationship between coronary flow and cardiac output is not linear in either group, the range of scatter is similar in both groups. No attempt is made to infer that the coronary flow is increased as a result of the increased cardiac output in hyperthyroidism. Both these parameters may be altered by a common factor.

The myocardial oxygen consumption in the 2 groups showed considerable overlapping. However, as previously illustrated, there appeared to be no difference between the 2 groups when the myocardial oxygen consumption was related to total body oxygen consumption (figure 2), indicating that the myocardial oxygen consumption in hyperthyroidism represents the same percentage of whole-body oxygen consumption as in the normal group. This increased myocardial oxygen usage in hyperthyroidism appears to be brought about by an increased coronary blood flow in the presence of a normal percentage extraction of arterial oxygen by the myocardium.

The above results are in agreement with those of Rowe and associates, who found the coronary flow and myocardial oxygen consumption elevated prior to surgery in a group of hyperthyroid individuals. Bing reported only a slight increase in coronary blood flow in hyperthyroidism and a lower than normal myocardial oxygen consumption. Satisfactory explanation for such discrepancies is not readily apparent.

Conflicting results have been reported on the effect of thyroid substances on the heart of experimental animals. These inconsistencies are probably related to the use of various types of preparations and the study of different anatomic regions of the heart. Ulrick and Whitehorn reported a significant increase in oxygen consumption of both atrial and ventricular tissue of the hyperthyroid rat in vitro, the former tissue showing a greater change than the latter. Dock and Lewis, utilizing the heart-lung preparation of the rat, found that the increase in myocardial oxygen consumption of the hyperthyroid rat was entirely explicable on the basis of the increased heart weight and rate. Leblond and Hoff reported an increased heart rate produced by thyroxin in the intact thyroidecomized rat. These authors did not measure myocardial oxygen consumption. Gordon and Heming, using minced or sliced heart muscle of the hyperthyroid rat, could show only a transient increase in myocardial oxygen consumption following by a depression.
McEachern, who was able to demonstrate an increased oxygen consumption of the intact atrium of the hyperthyroid guinea pig in vitro, also found an increase in oxygen consumption followed by a depression when using minced or sliced atrial tissue obtained from the hyperthyroid guinea pig, suggesting that the use of sliced or minced tissue may give misleading results.

The mean coronary blood flow of 103 ml./100 Gm./min. in the normal group in this study is comparable to a mean flow of 96 ml./100 Gm./min. found by Goodale and Hackel in 4 normal human beings. The range in their subjects was 91 to 103 ml./100 Gm./min., compared to a range of 88 to 129 ml./100 Gm./min. in the present study. Bing has reported a somewhat lower mean coronary blood flow of 77 ml./100 Gm./min. among normal subjects. He found a mean myocardial oxygen consumption of 9.4 ml./100 Gm./min., compared to a higher mean figure of 10.5 ml./100 Gm./min. among the 8 normal persons in this series.

Discrepancies between the value of coronary flow in the normal subjects in this series and those reported by other authors may be accounted for by differences in technic. If corrections for dead space existing in the coronary sinus catheter are not made, but samples are drawn simultaneously from artery and coronary sinus without such correction, the determined coronary sinus nitrous oxide concentration will be lower than actually existing in the coronary sinus blood at a given instant, particularly during the first portion of the curve where rapid changes in nitrous oxide concentrations are occurring. This will tend to widen the arteriovenous difference of nitrous oxide and consequently make the calculation of coronary flow falsely low. We have used the saturation technic throughout, finding little advantage or convenience in the desaturation method. The results by both these technics are comparable.

As previously demonstrated, the study of the carbohydrate metabolism in the normal and hyperthyroid patients revealed great similarity, and there was very little pattern that could be deduced from the results obtained. Certainly on the basis of, and within the limitations of, the present studies, there is no abnormality of the myocardial carbohydrate metabolism in hyperthyroidism. As others have found in man and dogs, the heart is capable of utilizing glucose, pyruvic acid, and lactic acid. The contribution of the latter two metabolites to the aerobic metabolism of the heart is sharply restricted by their relatively low arterial levels. Usage of glucose appears to be variable, and the total contribution of the sum of the 3 metabolites studied to the aerobic metabolism of the heart varied markedly (figures 3 and 4). The respiratory quotient also showed considerable variation and, in our hands, in no way appeared to correlate with the degree of carbohydrate usage. Respiratory quotient for each patient is shown above the appropriate bar graph in figures 3 and 4.

No relationship could be demonstrated between the usage of one metabolite and the utilization of any other. There was no correlation between the work of the left ventricle and the carbohydrate usage. These findings are in conformity with those previously reported by Bing and by Goodale and Hackel. A relationship could not be demonstrated between the arterial level of any of the metabolites and their extraction by the myocardium, results which are in disagreement with the previously quoted authors. However, the range of the arterial concentration of the metabolites, especially glucose, was relatively narrow in the present study. No attempt was made to raise
acutely the blood level of any of the metabolites. In other studies,\textsuperscript{21} in which the arterial lactic and pyruvic acid concentrations were rather markedly increased by fructose administration, there occurred an increased extraction of these metabolites by the myocardium. Though the greater uptake tended to be associated with the higher blood levels, this relationship was not linear.

It would appear to us that the nutritional state of the body, which is not necessarily reflected in the arterial level of the carbohydrate substances measured in this study, would be of importance in determining the metabolism of the myocardium. It may be that this factor as well as the arterial level of the metabolites is important in determining uptake by the myocardium. According to Peters,\textsuperscript{22} after an overnight fast, 60 per cent of the energy of the body is provided by fat. That the human myocardium can utilize fat and ketones has been amply demonstrated.\textsuperscript{23} At any rate, it is of interest that on a routine ward diet and following only an overnight fast, considerable part or all of the metabolism of the left ventricle may be provided for by substances other than carbohydrates.

Some of the cases in both groups in the present study had a negative arterial-coronary sinus difference across the myocardium for the various metabolites studied. In several cases, the negative A-V difference was small and probably within the error of the method of determination. However, in some cases it does not appear to be explicable on this basis. We can offer no explanation of these findings at this time.

Perhaps there is no disease in which the effects on the component parts of the circulation in the human being have been studied so carefully as in hyperthyroidism. Our data and that of others\textsuperscript{24} indicate that in the majority of cases of hyperthyroidism, although the cardiac output is elevated, the over-all arteriovenous oxygen difference is normal. Studies of the component parts of the circulation give varying results. The response of the heart in hyperthyroidism with increased output and normal arteriovenous oxygen difference is the result of a high skin and muscle flow,\textsuperscript{25} and probably of diminished oxygen A-V difference in these areas; of a normal splanchnic flow and high splanchnic oxygen A-V difference with a resultant high splanchnic oxygen consumption\textsuperscript{24}; of a normal cerebral blood flow; of oxygen A-V difference and oxygen consumption\textsuperscript{26}; of a normal renal blood flow\textsuperscript{27}; and, as reported here, of a high coronary blood flow, normal arterial-coronary sinus oxygen difference, and increased myocardial oxygen consumption. In all probability, in other states in which high cardiac output is present, considerable regional differences in hemodynamics exist.

The needs of the heart in hyperthyroidism appear to be met in the same fashion as in other situations in which cardiac output is increased. As a result of exercise, the nonfailing heart responds in similar fashion to the hyperthyroid heart, i.e., increase in coronary blood flow, decrease in coronary vascular resistance, unchanged arterial-coronary sinus oxygen difference, and increase in myocardial oxygen consumption.\textsuperscript{28} Similar findings are reported in the case of peripheral arteriovenous fistula.\textsuperscript{1} In severe anemia, in which case the cardiac output is almost always high, both the coronary blood flow and myocardial oxygen consumption are elevated.\textsuperscript{1}

Thus, in terms of its carbohydrate metabolism and its myocardial hemodynamics, there appears to be nothing unique about the heart in hyperthyroidism. An important question
that remains to be answered is what regulates the response of the heart to an increased work load. Hypertension, the most common cardiovascular abnormality in which the work of the left ventricle is increased, is apparently not accompanied by either an increase in coronary blood flow or myocardial oxygen consumption per 100 Gm. left ventricle. The meager data available indicate that no change in coronary blood flow or myocardial oxygen consumption accompanies aortic stenosis, while in coarctation of the aorta and aortic insufficiency both these parameters are increased. Reasons and mechanisms for these reported differences in myocardial hemodynamics are obscure.

**Summary**

In a series of 5 hyperthyroid patients, the mean coronary blood flow and myocardial oxygen consumption/100 Gm. left ventricle/min. averaged 155 and 13.3 ml. respectively. The corresponding values in 8 normal patients were 103 and 10.5 ml. The coefficient of oxygen extraction across the myocardium was similar in both groups.

The per cent of total cardiac output and oxygen consumption accounted for by the heart was similar in both groups.

On the basis of studies performed on 17 normal and 13 hyperthyroid patients, it is concluded that the myocardial metabolism of glucose, lactic acid, and pyruvic acid does not deviate from the normal among hyperthyroid patients.

Usage of carbohydrate substances showed marked and unexplained variations in both groups. No relationship between the arterial level of a metabolite and its myocardial extraction could be demonstrated. The oxygen A-V difference across the myocardium accounted for by the sum of all the metabolites studied averaged 39 per cent among the normal and 43.7 per cent among the hyperthyroid patients.

On the basis of studies of myocardial hemodynamics and carbohydrate metabolism there appears to be no unique effect of thyroid hormone on the heart.

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**Summary in Interlingua**

In un serie de 5 patientes hyperthyroide, le valor median del fluxo de sanguine coronari e del consumption myocardial de oxygeno per 100 g ventriculo sinistre per minuta eseva medianmente 155 e 13.3 ml, respectivamente. Le valores correspondentemente in 8 normal patientes eseva 103 e 10.5 ml. Le coefficiente de extraction oxygenic a transverso le myocardio eseva simile in le duo gruppess.

Le procentaje del total rendimento cardiae e del total consumption oxygenic attribuibile al corde eseva simile in le duo gruppess.

Super le base de studios execute in 17 normal e 13 hyperthyroide patientes, nos conclude que le metabolismo myocardial de glucosa, acido lactic, e acido pyruvic in patientes hyperthyroide non devia ab le norma.

Le uso de substantias de hydrato de carbon exhibiva marcate sed inexplicate variationes in le duo gruppess. Il non eseva possibile demonstrar un relation inter le nivello arterial de un metabolito e su extraction myocardial. Le differentia atrio-ventricular de oxygeno a transverso le myocardio que eseva explicabile per le summa del metabolitos studiate amontava medianmente a 39 pro cento inter le patientes normal e a 43.7 pro cento inter le hyperthyroides.

Super le base de nostre studios del hemodynamica myocardial e del metabolismo de hydratos de carbon il pare justificate concluder que il existe nulle specific effecto de hormon thyroide super le corde.

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Coronary Blood Flow, Myocardial Oxygen Consumption, and Myocardial Metabolism in Normal and Hyperthyroid Human Subjects
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