Myocardial Metabolism in Progressive Muscular Dystrophy

By J. F. Sundermeyer, M.D., S. Gudbjarnason, Ph.D., V. E. Wendt, M.D., P. B. den Bakker, M.D., and R. J. Bing, M.D.

Myocardial involvement as well as skeletal muscle involvement occurs in a high proportion of cases of human progressive muscular dystrophy. This cardiac involvement constitutes a specific cardiomyopathy. Clinical evidence of myocardial involvement by the dystrophic process includes labile tachycardia in over 50 per cent of cases, congestive heart failure, various arrhythmias, cardiac murmurs, and cardiomegaly.\(^1\)\(^-\)\(^5\) Electrocardiographic abnormalities occur in up to 80 per cent of patients.\(^3\) These changes include sinus tachycardia, bundle-branch block, premature ventricular contractions, shortened P-R intervals, T-wave changes, elevation of S-T segments, and abnormal Q waves.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^6\)\(^-\)\(^8\) Pathologically, the myocardium shows the characteristic gross and histopathologic changes of skeletal muscle as seen in progressive muscular dystrophy, except that the myocardium is usually not so severely involved.\(^3\)\(^,\)\(^7\) In addition, specific cardiac lesions include increased subepicardial fat and occasional epicardial thickening.\(^7\) Subendocardial fibroelastosis may also occur.\(^1\)\(^,\)\(^9\)

The clinical findings and the pathologic changes of the heart in progressive muscular dystrophy have recently been reviewed by Levin, Baens and Weinberg.\(^1\)

Although the metabolic changes of skeletal muscle in human progressive muscular dystrophy have been studied extensively, the metabolism of the myocardium has not been investigated. It is the purpose of this communication to report the cardiac metabolism of 11 patients suffering from this disease.

Materials and Methods

A total of 11 patients with progressive muscular dystrophy was studied by means of coronary sinus catheterization.\(^10\) The patients ranged in age from 9 to 41 years; however, most of them were 16 to 22 years old. The average duration of the disease in this group was 12 years (table 1). The shortest duration was 4 years and the longest 19. Nine of the 11 patients had the pseudohypertrophic type of muscular dystrophy, and two (F.D. and J.G.) had the facioscapulohumeral type (table 1). The electrocardiographic changes are recorded in table 2. All these patients were physically seriously handicapped. All but two (F.D. and J.G., table 1) were confined to a wheelchair, and A.L. (table 1) had marked difficulties in walking. The patients were postabsorptive, and none was premedicated. Two patients (J.G. and M.Z.) were studied at rest and during exercise. Exercise consisted of moving the legs against a resistance. The work they performed was estimated to be about 20 Kg. meters per minute.

Coronary blood flow was measured by the nitrous oxide desaturation method in four patients as previously described.\(^11\) Cardiac output was measured in six of the 11 patients by the Stewart-Hamilton method by injecting cardiogreen dye into the right atrium and sampling through a Gilford densitometer from either the brachial or the femoral artery.\(^12\)\(^,\)\(^13\)

Simultaneous coronary sinus and either brachial or femoral arterial blood samples were drawn for the determination of oxygen, glucose, inorganic phosphate, pyruvate, lactate, and for malic dehydrogenase and aldolase activities. Blood oxygen concentration was determined by the manometric method of Van Slyke and Neill.\(^14\) Glucose was determined by the method of Hugget and Nixon\(^15\) and pyruvate was also measured enzymatically.\(^16\) Lactate was determined by a method modified from Hohorst,\(^17\) inorganic phosphate by the method of Wahler and Wollenberger;\(^18\) malic dehydrogenase activity in plasma was measured as previously reported,\(^19\) and plasma aldolase activity by means of a combined enzymatic test.\(^20\)

Hereafter, differences in concentrations of substrates or the activity of enzymes between the
PROGRESSIVE MUSCULAR DYSTROPHY

Clinical Data on Eleven Patients with Progressive Muscular Dystrophy

<table>
<thead>
<tr>
<th>Name of patient, sex, and type of PMD</th>
<th>Date studied</th>
<th>Age of patient at onset of PMD</th>
<th>Electrocardiogram</th>
<th>Urine creatinine mg./24 hr.</th>
<th>Urine creatinine Gm./24 hr.</th>
<th>S-GOT units</th>
<th>S-LD units</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. J. 22 M D</td>
<td>11/15/60</td>
<td>5</td>
<td>A</td>
<td>1810</td>
<td>0.7</td>
<td>57</td>
<td>390</td>
</tr>
<tr>
<td>G. P. 17 M</td>
<td>11/21/60</td>
<td>Infancy</td>
<td>A</td>
<td>297</td>
<td>0.2</td>
<td>15</td>
<td>130</td>
</tr>
<tr>
<td>F. D. 41 F</td>
<td>12/20/60</td>
<td>22</td>
<td>A</td>
<td>622</td>
<td>0.75</td>
<td>18</td>
<td>150</td>
</tr>
<tr>
<td>R. Me. 10 D</td>
<td>1/6/61</td>
<td>2</td>
<td>N</td>
<td>292</td>
<td>0.2</td>
<td>88</td>
<td>1480</td>
</tr>
<tr>
<td>A. L. 9 D</td>
<td>2/7/61</td>
<td>5</td>
<td>A</td>
<td>392</td>
<td>0.3</td>
<td>102</td>
<td>1100</td>
</tr>
<tr>
<td>J. G. 18 F</td>
<td>2/28/61</td>
<td>Infancy</td>
<td>N</td>
<td>818</td>
<td>0.9</td>
<td>40</td>
<td>660</td>
</tr>
<tr>
<td>S. S. 20 D</td>
<td>3/7/61</td>
<td>13</td>
<td>A</td>
<td>1095</td>
<td>0.3</td>
<td>34</td>
<td>280</td>
</tr>
<tr>
<td>L. F. 16 D</td>
<td>3/9/61</td>
<td>3</td>
<td>A</td>
<td>253</td>
<td>0.2</td>
<td>37</td>
<td>150</td>
</tr>
<tr>
<td>B. M. 17 D</td>
<td>3/28/61</td>
<td>5</td>
<td>N</td>
<td>368</td>
<td>0.2</td>
<td>63</td>
<td>550</td>
</tr>
<tr>
<td>M. Z. 22 D</td>
<td>5/9/61</td>
<td>5</td>
<td>A</td>
<td>1179</td>
<td>0.9</td>
<td>95</td>
<td>470</td>
</tr>
<tr>
<td>L. D. 10 D</td>
<td>5/24/61</td>
<td>5</td>
<td>A</td>
<td>1306</td>
<td>0.3</td>
<td>89</td>
<td>1040</td>
</tr>
</tbody>
</table>

Abbreviations: PMD, progressive muscular dystrophy; S-GOT, serum glutamic-oxalacetic transaminase; S-LD, serum lactic dehydrogenase; D, Duchenne; FSH, facioscapulohumeral; A, abnormal; N, normal.

arterial and coronary sinus blood will be referred to as myocardial balances. A positive myocardial balance indicates a lower value in the coronary sinus blood than in the arterial blood; when the balance is negative, the value in the coronary sinus blood exceeds that in arterial blood.

Calculations

The per cent glucose oxygen extraction ratio was determined from the coronary arteriovenous differences of glucose and oxygen as described before:

\[
\text{Glucose oxygen extraction ratio per cent} = \frac{O_2 \text{ equivalent of extracted glucose}}{\text{myocardial oxygen extraction}} \times 100.
\]

The oxygen equivalent of glucose is 0.75 \times \text{mg. per cent of glucose extraction.}

The ratio of the molar concentration of lactate to pyruvate is a reflection of the ratio of the molar concentration of DPNH to DPN. The ratio of DPNH to DPN determines the oxidation-reduction potential of the system. Therefore, it is possible to determine the oxidation-reduction potential (E_o or redox potential) of the arterial and venous blood from the ratio of the molar concentration of lactate to that of pyruvate \( \frac{(La)}{(Py)} \). Klingenberg and Bucher state that the oxidation-reduction potential of the lactate-pyruvate system in blood and in the normal resting tissues are very close to each other. However, they arrived at this conclusion primarily through their work on the liver. Nevertheless, it has been shown in this laboratory that changes in the oxidation-reduction...
The differences in oxidation-reduction potentials between arterial and coronary venous blood are plotted against the myocardial glucose extraction. Negative coronary arteriovenous differences in oxidation-reduction potentials are associated with low glucose extractions; positive coronary arteriovenous differences in oxidation-reduction potential are associated with a higher myocardial glucose extraction. (ΔE_h mv represents the coronary arteriovenous difference in oxidation-reduction potential expressed as millivolts. A positive difference in oxidation-reduction potential suggests anaerobic metabolism.)

potential of the myocardium were reflected by those occurring in coronary sinus blood as calculated from the ratio \( \frac{L_a}{P_y} \). The redox potential of the extramitochondrial DPN-DPNH system (E_h) has been estimated at -240 mv. The redox potential is calculated from the formula

\[
E_h = E_o + \frac{RT}{nF} \ln \left( \frac{[OX]}{[RED]} \right)
\]

Where E_o is the redox potential when the oxidized substrate (OX) equals the reduced (RED). The value for the pyruvate-lactate system is -204 mv and the value for

\[
\frac{RT}{nF} \ln \left( \frac{[OX]}{[RED]} \right) = 30.7 \log \left( \frac{[OX]}{[RED]} \right)
\]

(R is the gas constant, T the absolute temperature, n represents the number of electrons, and F the faraday). Thus, by substitution:

\[
E_h = -204 + 30.7 \log \left( \frac{P_y}{L_a} \right)
\]

The change in redox potential across the heart is determined by subtracting the venous from the arterial redox potentials. A positive difference in oxidation-reduction potential between the arterial and coronary sinus blood indicates a relative increase in the ratio \( \frac{L_a}{P_y} \) in the coronary venous blood and therefore a shift toward anaerobic metabolism by the myocardial cells.

Results

Cardiac indices ranged from 3.7 to 5.6, and the average for the group was 4.7 L per minute per square meter of body surface (table 3). Thus, all the individuals had elevated cardiac outputs. The coronary blood flows in the four patients in whom it was determined were in the range of 53 to 92, with an average of 72 ml per minute per 100 Gm. of left ventricle. This is within the normal range (table 3).

The biochemical data are arranged in table 3. The pyruvate and lactate balances were positive in all patients except two (L.F. and J.G.). Glucose was extracted by all patients; its extraction appeared to be a function of the arterial glucose concentration, as has been

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**Table 2**

Electrocardiographic Changes in Eight Patients with Progressive Muscular Dystrophy

<table>
<thead>
<tr>
<th>Name</th>
<th>Electrocardiographic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. J.</td>
<td>Deep Q in lead III  Abnormal Q in leads V_n, V_r  S-T segment straightened in leads I, V_n, V_r, V_t  T wave small, diphasic in leads I, V_n, V_r, V_r</td>
</tr>
<tr>
<td>G. P.</td>
<td>Had right bundle-branch block on 10/10/60  Normal tracing on 11/22/60</td>
</tr>
<tr>
<td>F. D.</td>
<td>6/21/60 T waves very small in standard and unipolar limb leads V_n, V_r, diphasic in leads II, III, aV_n, aV_r, S-T segment straightened in all leads except V_r, V_n, V_t  12/19/60 Improved but nonspecific damage still present</td>
</tr>
<tr>
<td>A. L.</td>
<td>Sinus tachycardia  T small, diphasic in lead III</td>
</tr>
<tr>
<td>S. S.</td>
<td>Abnormal QI on 3/8/61  Abnormal QI plus elevated S-T segments in leads V_t through V_i on 7/8/60</td>
</tr>
<tr>
<td>L. F.</td>
<td>3/8/61 T inverted in lead III and diphasic in aV_r  Deep Q (&lt;.03) second in leads V_n, V_r, 9/20/60 Sinus tachycardia</td>
</tr>
<tr>
<td>M. Z.</td>
<td>Ventricular premature contraction  S-T straightened and T wave flat in lead III</td>
</tr>
<tr>
<td>L. D.</td>
<td>P-R 0.08 second  Deep but not prolonged Qs in leads V_n, V_r, V_t</td>
</tr>
</tbody>
</table>

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progressive muscular dystrophy

previously reported. The inorganic phosphate concentration in blood was elevated, confirming the findings of Danowski and coworkers. There was no significant myocardial extraction or release of inorganic phosphate. The malic dehydrogenase activity in plasma was above normal in four of the eight patients; the myocardial balance of this enzyme was negative in two patients (B.M. and M.Z.), becoming positive in one (M.Z.) during exercise (table 3). The serum aldolase was elevated in four of the seven patients in whom it was determined. In one of these (J.G.) the positive myocardial balance became negative on exercise (table 3). The oxygen extraction by the heart ranged from 8.6 vol. per cent to 12.3 vol. per cent, with an average of 11.1 vol. per cent in 10 patients. These values are slightly elevated. The myocardial glucose oxygen extraction ratio was less than 100 per cent in all individuals, demonstrating breakdown of substrates other than glucose. The coronary arteriovenous redox potential differences were positive in most of the patients, indicating a shift toward glycolysis.

Discussion

The relationship of the myocardial extraction of glucose to the difference in the redox potential existing between arterial and coronary vein blood is illustrated in figure 1. It may be seen that the more positive coronary arteriovenous redox potential differences are accompanied by a higher myocardial glucose extraction, the myocardial glucose extraction and the ratio \( \frac{L_a}{F_Y} \) increasing together. This relationship indicates that the increased extraction of glucose is accompanied by a rise in glycolysis rather than respiration.

Figure 2 illustrates the relationship between the per cent glucose oxygen extraction ratio and the differences in coronary arteriovenous redox potentials. As already indicated in figure 1, most of the patients had positive coronary arteriovenous differences in redox potentials. As shown in figure 2, glucose oxygen extraction ratios are less than 100 per cent in all patients studied, indicating myo-
### Table 3

**Myocardial Metabolism on Eleven Patients with Progressive Muscular Dystrophy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cardiac output L/min/1.73 M²</th>
<th>Coronary blood flow ml/min/100 Gm. LV</th>
<th>Myocardial oxygen extraction (Vol %)</th>
<th>Glucose (mg%)</th>
<th>Pyruvate (mg%)</th>
<th>Lactate (mg%)</th>
<th>Malic dehydrogenase activity (units)</th>
<th>Aldolase activity (units)</th>
<th>Inorganic phosphate</th>
<th>Oxidation-reduction potential (Eh) *</th>
<th>Myocardial oxygen extraction ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. J.</td>
<td>5.4</td>
<td>92</td>
<td>12.3</td>
<td>58</td>
<td>.51</td>
<td>.13</td>
<td>6.07</td>
<td>.042</td>
<td>139</td>
<td>6</td>
<td>4.2</td>
</tr>
<tr>
<td>G. P.</td>
<td>3.52</td>
<td>62</td>
<td>10.7</td>
<td>70.7</td>
<td>2.7</td>
<td>.281</td>
<td>3.41</td>
<td>1.09</td>
<td>266.6</td>
<td>0</td>
<td>83.3</td>
</tr>
<tr>
<td>F. D.</td>
<td>5.6</td>
<td>9.2</td>
<td>17.2</td>
<td>87.2</td>
<td>11.2</td>
<td>.246</td>
<td>4.7</td>
<td>.16</td>
<td>116.5</td>
<td>6.5</td>
<td>5.48</td>
</tr>
<tr>
<td>R. Me.</td>
<td>12.2</td>
<td>100</td>
<td>16.0</td>
<td>338.180</td>
<td>7.80</td>
<td>3.11</td>
<td>200</td>
<td>8</td>
<td>20</td>
<td>3.5</td>
<td>+2.3</td>
</tr>
<tr>
<td>A. L.</td>
<td>5.15</td>
<td>82</td>
<td>10.3</td>
<td>86.2</td>
<td>10.6</td>
<td>.374</td>
<td>4.44</td>
<td>-0.20</td>
<td>125</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>J. G.</td>
<td>5.3</td>
<td>76</td>
<td>9.2</td>
<td>98.6</td>
<td>11.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>110</td>
<td>35</td>
<td>17.5</td>
</tr>
<tr>
<td>J. G.</td>
<td>12.2</td>
<td>87.8</td>
<td>12.6</td>
<td>.0908</td>
<td>.0403</td>
<td>4.33</td>
<td>1.76</td>
<td>—</td>
<td>27.5</td>
<td>-5</td>
<td>—</td>
</tr>
<tr>
<td>L. F.</td>
<td>11.6</td>
<td>62.8</td>
<td>1.8</td>
<td>.181</td>
<td>-.024</td>
<td>4.79</td>
<td>1.82</td>
<td>220</td>
<td>90</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>B. M.</td>
<td>8.7</td>
<td>76.8</td>
<td>6.2</td>
<td>40</td>
<td>-18</td>
<td>41</td>
<td>25</td>
<td>—</td>
<td>4.08</td>
<td>+7.6</td>
<td>59.5</td>
</tr>
<tr>
<td>M. Z.</td>
<td>3.1</td>
<td>53</td>
<td>12.2</td>
<td>96.0</td>
<td>4</td>
<td>.414</td>
<td>4.48</td>
<td>1.35</td>
<td>310</td>
<td>-30</td>
<td>—</td>
</tr>
<tr>
<td>M. Z.</td>
<td>4.2</td>
<td>80</td>
<td>13.2</td>
<td>91.5</td>
<td>10.5</td>
<td>.626</td>
<td>.303</td>
<td>9.2</td>
<td>345</td>
<td>19</td>
<td>—</td>
</tr>
<tr>
<td>L. D.</td>
<td>11.4</td>
<td>—</td>
<td>—</td>
<td>.456</td>
<td>.370</td>
<td>7.70</td>
<td>4.02</td>
<td>—</td>
<td>100</td>
<td>7</td>
<td>—</td>
</tr>
</tbody>
</table>

*For explanation of calculation of per cent glucose oxygen extraction ratio and oxidation-reduction potential see text.*
that increasing the extracellular concentration of inorganic phosphate resulted in its intracellular elevation. Fitch and Dinning\textsuperscript{31} have demonstrated a high rate of turnover between extracellular and intracellular inorganic phosphate in vitamin E-deficient rabbits and rats. It has been shown repeatedly that an elevated intracellular inorganic phosphate concentration stimulates glycolysis.\textsuperscript{37, 32-34} That this is possibly the case in patients with progressive muscular dystrophy is shown by the fact that an elevated concentration of blood inorganic phosphate is accompanied by increased myocardial glucose extraction (fig. 3), and that the increase in myocardial glucose extraction is directly related to an increase in glycolysis and heart muscle as shown in figure 1.

What is the mechanism of the elevation in the inorganic phosphate concentration in blood? It has been shown that either anaerobiosis or uncoupling of oxidative phosphorylation results in increased intracellular concentrations of inorganic phosphate with increase in the rate of glycolysis.\textsuperscript{35} The data presented here show increased inorganic phosphate in blood along with aerobic glycolysis in heart muscle in the presence of a normal or slightly elevated myocardial oxygen extraction. This combination suggests uncoupling of oxidative phosphorylation. Further evidence of this is the finding of Danowski and co-workers\textsuperscript{38} that children with progressive muscular dystrophy have an elevated basal metabolic rate and protein-bound iodine. The studies presented here also reveal an increased cardiac output (table 3). Experimental muscular dystrophy in vitamin E-deficient animals has been thought to be accompanied by uncoupling of oxidative phosphorylation.\textsuperscript{37, 38} However, several investigators studying skeletal muscle in human progressive muscular dystrophy have concluded that the major metabolic defect in carbohydrate metabolism is a marked diminution of glycolysis.\textsuperscript{39-41} These conclusions were based on the low intramuscular levels of certain glycolytic enzymes and the decreased lactate production by homogenates of dystrophic muscle.

The dangers and limitations of attempting to interpret the pathways of intermediary metabolism in the myocardial cell from the coronary arteriovenous differences of substrates are well appreciated.\textsuperscript{42} From changes in the relationships between the concentrations of substrates in arterial and coronary sinus blood, however, certain tentative conclusions may be drawn. Thus, the relative increase in the ratio $\frac{La}{Py}$ between the arterial and coronary sinus blood reflects a similar change in the oxidation-reduction potential of

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure3}
\caption{This shows the relationship between the arterial blood concentrations of inorganic phosphate and the myocardial glucose extraction. Section A shows the absence of correlation in patients with diseases other than muscular dystrophy such as hypertension, metastatic carcinoma, and low-output congestive heart failure. Section B shows that in patients with muscular dystrophy there is a linear relationship between the inorganic phosphate in blood and the myocardial glucose extraction.}
\end{figure}
the heart muscle cell.\textsuperscript{21,22} Equally, the relationship between myocardial glucose extraction and the myocardial redox potential may provide information about the rate of glycolysis in heart muscle. Finally, the data obtained from arterial and coronary sinus blood have shown that an elevated inorganic phosphate concentration in blood increases rate of glycolysis in the myocardial cell.

Summary

Myocardial metabolism was studied in 11 patients with progressive muscular dystrophy. Coronary blood flow was measured in four, the cardiac output in six patients. The blood concentrations of oxygen, glucose, inorganic phosphate, pyruvate, and lactate, and the serum activities of malic dehydrogenase and aldolase were determined in simultaneously drawn coronary sinus and arterial blood samples.

The cardiac outputs were elevated in all patients. Myocardial extractions of pyruvate and lactate were negative in two patients. Inorganic phosphate concentrations in blood were elevated. Malic dehydrogenase and aldolase were released by the heart in several patients. Differences in oxidation-reduction potential between arterial and coronary venous blood were positive, suggesting glycolysis in the heart muscle. This was accompanied by increased myocardial extraction of glucose. Apparently aerobic glycolysis occurred, since sufficient oxygen was present to account for all glucose extracted.

Stimulation of glycolysis by inorganic phosphate was suggested by the relationship between the elevated inorganic phosphate concentration in blood and the myocardial glucose extraction. This suggests the possibility of uncoupling of oxidative phosphorylation in the myocardium.

Acknowledgment

We are grateful to Dr. Alex Newman, Director of the Physical Therapy and Rehabilitation Clinic of Detroit Memorial Hospital, without whose cooperation and enthusiasm this study would not have been possible. We also wish to thank Dr. Achilles Skoulas of Detroit Memorial Hospital who was of great assistance in selecting patients for study.

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