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Myocardial Metabolism in Cyanotic Congenital Heart Disease Studied by Arteriovenous Differences of Lactate, Phosphate, and Potassium at Rest and during Atrial Pacing

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With the technical assistance of H. Maris

SUMMARY To study myocardial metabolism in chronic hypoxia due to cyanotic congenital heart disease, coronary arteriovenous differences of lactate (L), pyruvate (P), inorganic phosphate (Pi) and potassium (K) were measured in 14 cyanotic patients and seven controls, at rest and during atrial pacing. At rest, there was no difference in any parameter between cyanotic and noncyanotic patients. During atrial pacing (150–175/min) for 10 min, a moderate drop in L-extraction occurred in the control patients with some increase in L/P ratio in coronary venous blood.

Cyanotic patients fell into two groups: in nine (group I), the arterial oxygen saturation (SaO2) dropped with pacing. Their L-extraction fell sharply, from 28.1 ± 3.12 to −2.8 ± 5.51 and L production occurred in five. There was a significant increase in coronary venous L/P ratio. Five cyanotic patients (group II) showed no drop in SaO2 with pacing, and L extraction as well as L/P ratio remained stable. Uptake of Pi was noted in all patients at rest; during pacing this disappeared in controls and group I cyanotics but not in group II. No K changes were seen in any patient.

Thus, myocardial metabolism is normal at rest in patients with cyanotic CHD; during atrial pacing, a shift toward anaerobic metabolism occurs if SaO2 drops; cyanotic patients whose SaO2 remains stable appear to withstand pacing better than controls.

IN PATIENTS WITH CYANOTIC CONGENITAL HEART DISEASE (CCHD), the myocardium is constantly perfused with hypoxic blood. Little is known about the effect of this chronic hypoxia on myocardial metabolism and the possible effects on the heart muscle. Microinfarcts of the left ventricle in tetralogy of Fallot have been described,1 and

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might be the cause of the left ventricular dysfunction which has sometimes been found after surgical correction of the defect.8 The question arises whether hypoxia due to CCHD might induce changes in myocardial metabolism similar to those seen in ischemia of coronary heart disease, i.e., decreased lactate extraction, and release of phosphate and potassium into coronary venous blood.8 The present study was designed to assess whether such changes occur in CCHD either at rest, or during the stress of atrial pacing.8

*Preliminary accounts have been presented to the American College of Cardiology, the British Cardiac Society and the European Society for Clinical Investigation.
Patients and Methods

Fourteen patients with CCHD (age range, 6–15 years) and seven control patients (age range, 5–14 years) were studied during routine heart catheterization. Individual data on diagnosis, sex, and age, and hemodynamic data are given in Table 1. All catheterizations were done under light sedation with a mixture of pethidine, promethazine and chlorpromazine. After hemodynamic data were obtained, but before angiograms were taken, a bipolar electrode catheter with a sampling lumen (“Gorlin” 7F or “Zucker” 6F) was introduced into the coronary sinus. The correct position was confirmed by oximetry and a hand injection of a small amount of contrast material. An arterial catheter was placed into the ascending aorta or femoral artery.

Paired samples were withdrawn simultaneously from the artery and coronary sinus; two sets of samples were taken at rest, separated by a five minute interval. Atrial pacing (AP) was then started from the coronary sinus at rates of 150–175 beats/min. Paired samples were again withdrawn after 5 and 10 min of atrial pacing.

Blood samples were analyzed for oxygen saturation (SO2) (Instrumentation Laboratory Cooxymeter), PaO2, pH, PCO2. Lactate (L) and pyruvate (P) were determined by the enzymatic method (Boehringer), inorganic phosphate (P) by the Malachite green method and potassium (K) by Flame photometer. Myocardial lactate extraction is calculated by the formula

\[ \frac{L(\text{artrial}) - L(\text{venous})}{L(\text{artrial})} \times 100 \]

Table 1. Clinical Data of Patients and Control Subjects

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex/Age</th>
<th>Diag</th>
<th>Site of RVO obstruction</th>
<th>Anoxic spells</th>
<th>Heart Rate</th>
<th>Hemodynamic Data</th>
<th>Pressures (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pacing</td>
<td>RV</td>
<td>PA</td>
</tr>
</tbody>
</table>

Group I, Cyanotic CHD

B.H. | M/6 | TF | infund. | + | 100 180 | 92/5 | 12/5 | 8 | 94/4 | 94/74 | 85
K.M. | F/8 | Severe PS + ASD | valve | - | 90 150 | 157/23 | 15/4 | 10 | 95/5 | 95/70 | 75
E.S. | M/11 | TF | infund. | + | 64 155 | 100/10 | 15/4 | 10 | 95/5 | 95/70 | 75
K.H. | M/13 | Severe PS + ASD | valve | - | 120 155 | 120/19 | 15/4 | 10 | 95/5 | 95/70 | 75
S.N. | F/6 | TF | infund. | - | 110 170 | 100/9 | 10/5 | 7 | 100/4 | 100/70 | 75
P.T.L. | F/13 | TF | infund. | + | 75 155 | 105/8 | 26/14 | 16 | 100/9 | 102/64 | 80
K.P.C. | M/10 | TF | infund. | + | 100 175 | 106/8 | 17/9 | 11 | 106/8 | 106/80 | 90
H.M.P-H. | F/9 | TF | infund. | + | 95 150 | 100/8 | 13/8 | 9 | 85/12 | 85/65 | 75
G.O. | F/9 | TF | infund. | + | 95 150 | 100/8 | 13/8 | 9 | 85/12 | 85/65 | 75

Group II, Cyanotic CHD

R.K. | M/12 | TF | valve | - | 80 155 | 118/12 | 18/13 | 14 | 115/11 | 105/70 | 85
T.C.N. | M/15 | Pseudotruncus | - | - | 70 150 | 95/14 | 15/4 | 14 | 95/12 | 90/56 | 75
N.V.D. | M/12 | TF | infund. | - | 100 165 | 100/6 | 20/12 | 14 | 100/6 | 105/15 | 80
E.L.A. | M/10 | PS + VSD | valve | - | 95 170 | 95/4 | 20/12 | 14 | 95/7 | 95/70 | 80
T.M. | M/13 | Pseudotruncus | - | - | 90 160 | 96/10 | 100/9 | 100/9 | 100/11 | 80

Controls

T.O. | M/14 | NSHD | 90 170 | 21/2 | 21/5 | 8 | 86/6 | 88/56 | 72
Ch.M. | M/14 | Minimal AS | 95 165 | 23/4 | 15/9 | 12 | 93/8 | 93/64 | 77
J.S. | F/8 | Small ASD | 105 170 | 39/4 | 24/9 | 13 | 116/8 | 106/60 | 76
de M.A. | F/5 | Small PDA | 70 175 | 25/5 | 23/12 | 15 | 110/10 | 110/60 | 80
F.B. | M/10 | Minimal PS | 85 170 | 33/6 | 22/13 | 16 | 90/11 | 90/65 | 77
C.A. | F/8 | Minimal PS | 75 155 | 40/5 | 22/9 | 15 | 100/58 | 100/72 | 72
E.S. | M/8 | Small PDA | 75 160 | 25/6 | 22/12 | 15 | 89/9 | 89/54 | 76

Abbreviations: TF = tetralogy of Fallot; PS = pulmonic valve stenosis; ASD = atrial septal defect; VSD = ventricular septal defect; PDA = patent ductus arteriosus; AS = aortic stenosis; NSHD = no significant heart disease; RVO = right ventricular outflow. Overbar indicates mean pressure.

Statistical Procedures

Values were expressed as means ± standard errors of the mean for the number of observations given. P values of less than 0.05 were regarded as significant using a paired t-test (rest vs pacing) or a nonpaired t-test (differences between groups).

Results

Individual data for lactate extraction, coronary venous lactate/pyruvate ratio, arteriovenous differences for inorganic phosphate and potassium are given in Table 2, along with means, standard errors, and P values.

At rest, the average myocardial lactate extraction ratio was almost identical in control patients (25.5 ± 6.3%) and in cyanotic patients (28.9 ± 2.0%). A net uptake of inorganic phosphate was found in cyanotics as well as controls (positive arteriovenous difference). There was no such arteriovenous gradient of potassium.

With atrial pacing, there was a drop in lactate extraction among controls, slight in most, but with production of lactate seen in one subject after 10 min of pacing (mean at rest, 25.5 ± 6.35, at the end of atrial pacing: 14.0 ± 6.60, P < 0.001). The cyanotic patients fell into two distinct groups defined by their different response in arterial oxygen saturation to pacing (fig. 1). Group I, composed of nine patients, responded to AP by increasing their right-to-left shunt so that their arterial oxygen saturation fell markedly (from 77 ± 2.5% to 55 ± 5.0%); all but two had tetralogy of Fallot with predominant infundibular subpulmonic stenosis. Group II, composed of five patients, showed either no
change in \( \text{SaO}_2 \) or a drop of less than 10% of the resting value. These patients had either pulmonary atresia with large bronchial collaterals supplying the lungs, or pulmonary stenosis which was predominantly valvular.

These two groups showed different \textit{metabolic} responses to atrial pacing, as seen in fig. 2A and B. In addition to the decreased \( \text{SaO}_2 \), group I showed a marked fall in myocardial lactate extraction, from 28.1 ± 3.12% to −2.8 ± 5.51% (\( P < 0.001 \)); lactate production occurred in five. Pacing had to be interrupted after 5 min in a number of cases because of increasing cyanosis and to prevent possible hypoxic spells. Group II, however, (fig. 2B) did not show any change in lactate extraction during the whole period of pacing; group II, therefore, differs from group I patients who had lactate production on the average during atrial pacing and from control patients who had a slight but significant drop in lactate extraction with atrial pacing (fig. 3).

Changes in coronary venous L/P ratio were less marked but concordant with the lactate data: the ratio increased significantly in control patients with atrial pacing (rest: 10.6 ± 1.99; pacing 13.1 ± 2.43, \( P < 0.05 \)); the change was somewhat more marked in group I cyanotic patients (value at rest, 10.8 ± 1.15; with pacing, 13.9 ± 1.68, \( P < 0.001 \) but there was no change in group II).

The net \( P_i \) uptake observed in all groups at rest disappeared with pacing in control patients and group I cyanotics, and a slightly negative coronary arteriovenous

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**Table 2. Oxygen, Lactate, and Electrolyte Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>( \text{SaO}_2 % )</th>
<th>Lactate arterial (mmol/L)</th>
<th>Lactate extraction %</th>
<th>L/P v</th>
<th>( \Delta \text{A-V Pi} ) (mg/L)</th>
<th>( \Delta \text{A-V K} ) (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyanotic CHD, Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.H.</td>
<td>81</td>
<td>59</td>
<td>0.50</td>
<td>0.91</td>
<td>19</td>
<td>−1</td>
</tr>
<tr>
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<td>68</td>
<td>0.29</td>
<td>0.40</td>
<td>53</td>
<td>5</td>
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<tr>
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<td>0.58</td>
<td>26</td>
<td>−2</td>
</tr>
<tr>
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<td>69</td>
<td>0.29</td>
<td>0.29</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>P.T.L.</td>
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<td>66</td>
<td>0.49</td>
<td>0.50</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>K.P.C.</td>
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<td>69</td>
<td>0.48</td>
<td>0.45</td>
<td>20</td>
<td>−15</td>
</tr>
<tr>
<td>H.M.P.-H.</td>
<td>82</td>
<td>53</td>
<td>1.03</td>
<td>1.05</td>
<td>37</td>
<td>−3</td>
</tr>
<tr>
<td>G.O.</td>
<td>72</td>
<td>64</td>
<td>0.55</td>
<td>0.56</td>
<td>28</td>
<td>10</td>
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<tr>
<td>X</td>
<td>76.0**</td>
<td>58.1</td>
<td>0.55</td>
<td>0.69</td>
<td>28.1**</td>
<td>−2.8</td>
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<tr>
<td>SEM</td>
<td>2.38</td>
<td>3.02</td>
<td>0.075</td>
<td>0.130</td>
<td>3.12</td>
<td>5.51</td>
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<td><strong>Cyanotic CHD, Group II</strong></td>
<td></td>
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<td>R.K.</td>
<td>74</td>
<td>72</td>
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<td>0.87</td>
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<td>0.63</td>
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<td>31</td>
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<td>0.66</td>
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<td>E.L.L.A.</td>
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<td>78</td>
<td>0.44</td>
<td>0.35</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>T.M.</td>
<td>72</td>
<td>73</td>
<td>0.34</td>
<td>0.32</td>
<td>26</td>
<td>28</td>
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<td>X</td>
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<td>0.57</td>
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<td>0.053</td>
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<tr>
<td>( P (I \text{ vs II}) )</td>
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<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T.O.</td>
<td>96</td>
<td>96</td>
<td>0.54</td>
<td>0.72</td>
<td>12</td>
<td>−18</td>
</tr>
<tr>
<td>Ch.M.</td>
<td>96</td>
<td>96</td>
<td>0.87</td>
<td>0.74</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>J.S.</td>
<td>96</td>
<td>96</td>
<td>0.73</td>
<td>0.49</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>de M.A.</td>
<td>96</td>
<td>96</td>
<td>0.44</td>
<td>0.45</td>
<td>28</td>
<td>21</td>
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<tr>
<td>F.B.</td>
<td>94</td>
<td>95</td>
<td>0.52</td>
<td>0.54</td>
<td>27</td>
<td>23</td>
</tr>
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<td>C.A.</td>
<td>97</td>
<td>96</td>
<td>0.59</td>
<td>0.44</td>
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<tr>
<td>E.S.</td>
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<td>97</td>
<td>0.32</td>
<td>0.29</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>X</td>
<td>96.0</td>
<td>96.0</td>
<td>0.57</td>
<td>0.32</td>
<td>25.5**</td>
<td>14.0</td>
</tr>
<tr>
<td>SEM</td>
<td>0.38</td>
<td>0.22</td>
<td>0.009</td>
<td>0.060</td>
<td>6.35</td>
<td>6.60</td>
</tr>
<tr>
<td>( P (v I \text{ vs II}) )</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>( P (v II \text{ vs NS}) )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
difference was observed. In group II patients there was no change in $P_A$ uptake (fig. 4).

No arteriovenous differences in potassium could be demonstrated in any group, neither at rest nor with pacing.

**Discussion**

The effect of chronic hypoxia on myocardial metabolism has been previously studied at high altitude, but few reports on myocardial metabolic changes in cyanotic congenital heart disease have appeared. Both Rudolph and Scheuer have shown that coronary blood flow is somewhat decreased in congenital cyanotic heart disease (CCHD), but no major changes in substrate utilization by the heart muscle were demonstrated at rest. In particular, signs of anaerobic metabolism were lacking. Our results in patients at rest are in agreement with these studies. Values for lactate extraction, coronary venous, lactate/pyruvate ratios and ion concentrations were similar in controls and cyanotic patients. During pacing, however, reactions different from normal were observed in CCHD.

Inducing rapid heart rates by atrial pacing has proved a useful stress test in coronary artery disease as it increases myocardial oxygen requirement. In many cases of CCHD, it appears to have an additional effect, previously described by King and Franch. It decreases $SaO_2$ by increasing the right-to-left shunt. The mechanism by which this occurs is probably twofold: On the one hand, pacing is known to decrease left and right ventricular cavity size; on the other hand, it increases contractility. Both of these changes are likely to increase the degree of infundibular stenosis in tetralogy of Fallot, thus increasing the right-to-left shunt. A decrease in $SaO_2$ with pacing is therefore observed in the typical tetralogy with predominantly infundibular subpulmonic stenosis. A decrease in systemic resistance might have played a role in one case of pulmonary valve stenosis with atrial septal defect (case 2), in which a
fall in arterial blood pressure occurred during pacing. But in tetralogy of Fallot, arterial blood pressure does not usually fall during atrial pacing.13

Five of our 14 cyanotic patients did not show any changes in arterial oxygen saturation during pacing. These patients had either predominantly valvular pulmonary stenosis or pulmonic atresia with ventricular septal defect and large bronchial collateral arteries supplying the lungs. In these cases, the changes in ventricular geometry and contractility do not influence the right-to-left shunt, thus SaO2 remained unchanged during pacing.

The two groups outlined above had different myocardial metabolic responses to pacing. A shift toward anaerobic metabolism, with a sharp drop in lactate extraction or even lactate production, occurred in those whose right-to-left shunt increased, accompanied by release of phosphate in coronary venous blood or at least a disappearance of the uptake seen at rest. It is possible that the same shift occurs in these patients during myocardial stresses occurring in daily life, such as exercise, emotional upset, tachycardia, and of course, anoxic spells. It is the patient with reactive infundibular stenosis who is likely to have such spells. Therefore, it is not surprising to find that spells were observed in many patients of our group I (5 out of 9), but never in patients of group II (table 1).

Thus, the heart of the patient with classical tetralogy and reactive infundibular stenosis is probably subjected to many episodes of decreased oxygen supply in times of increased oxygen demand, and a repeated shift toward anaerobic metabolism could result in damage to some myocardial cells and fibrosis.1 This in turn would explain poor left ventricular performance after surgical correction of the defect.

Patients in our group II, with no changes in SaO2 saturation during pacing, showed a steady metabolic pattern during fast atrial pacing. This is in marked contrast to the cyanotic patients of group I, but also somewhat different from control patients.

In our study, the control patients reacted to fast atrial pacing with a slight or moderate decrease in myocardial lactate extraction. This change remains statistically significant for the group even when one excludes the patient who showed actual lactate production with atrial pacing. A tendency toward falling lactate extraction during rapid pacing seems to occur in normal adults as well,10, 11, 14 though it is less marked than in the present study. In contrast, group II cyanotic patients did not show any change in lactate extraction with pacing. This is not the only difference between group II and controls: indeed the P1-extraction, seen at rest in all groups, disappears with pacing in controls, but remains stable in group II. This adds to the impression that cyanotic patients of group II react to the stress of pacing with fewer metabolic changes than the control patients and suggests that adaptation of the heart muscle to work at chronically low SaO2 has occurred. This is in keeping with the findings at high altitude, where O2 consumption of the myocardium, for a given workload, appears to be smaller than at sea level.1

Of particular interest in this context is the study by Moffitt et al.,15 who measured coronary venous lactate in patients undergoing open heart surgery: he was able to demonstrate that myocardial L-production was lower in patients operated for cyanotic heart disease than in those operated for noncyanotic heart defects.

Changes in uptake or release of inorganic phosphate (P1) in the present study occurred simultaneously with a drop in lactate extraction. These parallel changes are to be expected because ATP breakdown occurs during anaerobic metabolism, with P1 release as one end-product.4 On the other hand, P1 enhances glycolysis through the activation of phosphofructokinase; thus, P1 release, increased glucose utilization, decreased lactate uptake and release of lactate are expected to be observed together.5 In the experimental model, there may be constant relationship between these changes.8 In addition, the loss of potassium in coronary venous blood was also observed after coronary ligation6 or during progressive ischemia.14 The reason for the K loss is as yet unknown. No such ion changes were observed in our study, where arteriovenous differences in K were close to zero in all patients and controls, at rest and with pacing. This might be surprising in view of the fixed relation between P1 and K loss in the experimental model observed by Case.14 However, studies in dogs have already shown that this relationship does not hold for all models of ischemia or anoxia,7 and phosphate release seems to be a more sensitive index of tissue anoxia than does release of potassium. It is possible that the degree of myocardial oxygen deprivation in our study was not sufficient to result in potassium release.

The clinical implications of the present study need further evaluation. One might speculate that patients with reactive infundibular stenosis, with or without hypoxic spells, are at risk from myocardial fibrosis secondary to repeated episodes of inadequate O2 supply to the myocardial cell. Therefore, early operative intervention is required. On the other hand, in group II patients, in whom myocardial adaptation appears to have taken place and episodes of acute hypoxia do not seem to occur, operation would probably be less urgent; but if the operation were proceeded with, there might be less risk of deterioration of postoperative myocardial function.2 Long term postoperative studies will show whether the patients of group II have a better left ventricular function than those of group I.

Acknowledgment

We would like to thank Prof. F.W. Duchosal for support and encouragement, Mr. J-P. Killisch and J.J. Adatte for technical assistance and Mrs. M. Meldem for typing the manuscript.

References

7. Moret PR, Bopp P, Grosgrain J, Hatam K, Ahmad M, Odler J: Com-
Comparative Effects of Physical Training and Diet in Normalizing Serum Lipids in Men with Type IV Hyperlipoproteinemia

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SUMMARY  The effect of mild physical training (PT) (group A), Type IV hyperlipoproteinemia (HLP) diet (group B), and PT plus Type IV HLP diet on serum lipids (group C) in 46 men with Type IV HLP was studied. Significant reductions in mean triglyceride (TG) levels from 163, 229, 196, to 136, 145, 116 mg/100 ml serum were found for groups A, B, and C, respectively. Following six weeks of intervention, cholesterol levels also dropped for all groups with the greatest reductions occurring in groups B and C. Minimal weight losses were found for all groups while groups A and C displayed significant reductions in body fatness, but both of these changes appeared independent of lipid reductions.

It was concluded that either mild PT or HLP diet or both are effective means of lowering TG levels in Type IV HLP individuals. Furthermore, it appears that patients need to participate regularly in formal programs in order to maintain adherence to these interventions.

HYPERTRIGLYCERIDEMIA is often associated with hyperprebeta-lipoproteinemia (Type IV HLP), and hypertriglyceridemia has in turn been recognized as one of the metabolic disorders associated with coronary heart disease. While dietary management is a recognized means of reducing serum triglyceride (TG) levels, there is evidence that physical activity may also be a means of lowering serum triglyceride concentrations. However, little is known about the comparative effectiveness of these interventions in normalizing hypertriglyceridemia in men with Type IV HLP. Therefore, the purpose of this study was to compare the effectiveness of physical training, of dietary management, and of physical training and dietary management combined, in reducing serum TG concentrations. In addition, we investigated the effect of these interventions on serum cholesterol and insulin levels and on the presence or absence of prebeta lipoprotein bands on paper electrophoresis.

Methods

Subjects

Forty-six men with Type IV HLP were selected from a group of approximately 400 faculty members identified as having hyperlipidemia during examinations in the Periodic Health Appraisal Unit, The University of Michigan. Type IV HLP was defined as fasting serum TG levels greater than 150 mg/100 ml plus the presence of a definite prebeta band on lipoprotein electrophoresis, and the absence of fasting chylomicronemia. Criteria for exclusion from the study included persons with insulin-dependent diabetes; those receiving drugs which affect lipid metabolism; and those having cardiac or other medical conditions that would contraindicate physical training. Informed consent was obtained from each subject prior to his commencement of the study.

Each subject had three 12-hour postabsorptive blood samples drawn on consecutive mornings to establish baseline serum lipid levels and to ensure that at least two of the three initial values met the above criteria. Weight was measured at each visit; during one of the initial three visits, anthropometric measurements were made. Following the blood
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