Hyperbaric Oxygenation (HBO) as a Complementary Treatment of Patients with Multibacillary Lepromatous Leprosy

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I. Introduction

The progress that has been reached in combined chemotherapy of leprosy has failed to eliminate totally the development of resistance to and intolerability of drugs. Therapeutical modalities capable of improving the results of chemotherapy are still needed.

Thus we thought it would be of interest to review the results we obtained with hyperbaric oxygenation (HBO) in the treatment of lepromatous patients and to create a base for further experience with this tool in this field.

II. Aspects explored

We studied patients with multibacillary lepromatous-leprosy and we focused on biochemical, histopathological, bacteriological and clinical aspects.

1. Effect of HBO on cell metabolism

We showed in a previous study that the metabolic quotient (microliters of oxygen consumed by 1 mg. of dry tissue in one hour: \( -QO_2 \)) was reduced in lepromatous tissue as compared with normal tissue(1).

We were interested to see how HBO affected the activity of cellular metabolism in patients with leprosy, pretreated with chemotherapy and without it.

Method

HBO was administrated to 60 patients in one place-chambers at 21°C and with a pressure of 3 absolute atmospheres (Ata) during 90 minutes (15-compressing, 60-maintaining the pressure...
and 15 minutes-decompressing).

Those groups were formed:
A. 20 patients without treatment received HBO on three consecutive days; the metabolic quotient was determined before the series of HBO, immediately after it and at 4 months
B. 20 patients on treatment with sulfadimtoxine and sulfametoxine: treated and assessed as above
C. 20 patients on chemotherapy as above received HBO on 21 consecutive days; the metabolic quotient was assessed before and at the end of the series of HBO.

The metabolic quotient ("-QO₂") was determined with the respirometer of Warburg and expressed in microliters of O₂ per mg/hour(²,³).

Results

Table 1 presents the results of the "-QO₂" in the lepromatous tissue.

The metabolic quotient proved to be considerably reduced at the onset in the 3 groups of patients. The normal value in epidermic tissue being minus 3.41 ml O₂/mg/hour±S.D. 0.21, the values found in lepromatous tissue were as follows:
A. -QO₂: −0.73 (S.D. 0.24)
B. -QO₂: −0.66 (S.D. 0.13)
C. -QO₂: −0.73 (S.D. 0.12)

The metabolic quotient raised at 4 months after the HBO by 83% in patients of group A, by 281% in patients of group B and by 236% immediately following the 3 weeks series of HBO in patients of group C.

2. Effect of HBO on adenosintriphasphate (ATP) in blood

The ATP was determined by the enzymatic technique of Adam(⁴).

Method

The determinations were done in basal conditions in 60 individuals, divided into 3 groups:
A. 20 patients without chemotherapy; HBO was administered on 3 consecutive days as outlined in 1.; ATP was determined before and immediately after the HBO series
B. 20 patients on antimicrobial therapy, treated with HBO and followed as above
C. 20 individuals (medical students and members of the Navy) serving as control.

<table>
<thead>
<tr>
<th>Group</th>
<th>before HBO</th>
<th>after HBO</th>
<th>120 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>-0.73±0.24 (ST. D.)</td>
<td>-0.93±0.23 (ST. D.)</td>
<td>-1.34±0.28 (ST. D.)</td>
</tr>
<tr>
<td>Group B</td>
<td>-0.66±0.13 (ST. D.)</td>
<td>-1.11±0.15 (ST. D.)</td>
<td>-2.42±0.26 (ST. D.)</td>
</tr>
<tr>
<td>Group C</td>
<td>-0.73±0.12 (ST. D.)</td>
<td>-2.46±0.26 (ST. D.)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Mean values of ATP concentration in blood (mg/100ml) "assessed with the enzymatic method by Adam (4)"

<table>
<thead>
<tr>
<th>Group</th>
<th>before HBO</th>
<th>after HBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29.5±2.64 (S. D.)</td>
<td>31.4±3.92 (S. D.)</td>
</tr>
<tr>
<td>B</td>
<td>30.4±2.62 (S. D.)</td>
<td>23.4±2.35 (S. D.)</td>
</tr>
<tr>
<td>C</td>
<td>16±2.73 (S. D.)</td>
<td>16.7±2.74 (S. D.)</td>
</tr>
</tbody>
</table>

Results

The results of ATP determinations in blood are listed in Table 2. Leprosy patients had higher basic levels than controls; the concentrations of ATP decreased by 23% in patients on chemotherapy after HBO.

3. Effect of HBO on serum lipase

Dhople had shown that there is an inverse relationship between the bacteriological index and the serum lipase(5), an observation that prompted us to explore this enzyme in patients with leprosy subjected to HBO.

Method

A homogenous group of 24 patients with lepromatous leprosy, pretreated with antimicrobial drugs, were studied. The serum lipase was assessed by the method of Cherry and Crandall, for which the normal range is 0-1.5 lipase units per 100 ml(6).

Results

The serum lipase values before and after HBO are shown in Table 3. The mean value of the enzyme increases significantly (p 0.01) following the HBO therapy.

Table 3 Serum lipase values in lipase units of lepra patients treated with HBO "determined with the method of Cherry and Crandall"

<table>
<thead>
<tr>
<th>Case No</th>
<th>before HBO</th>
<th>after HBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.67</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>0.80</td>
</tr>
<tr>
<td>3</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>4</td>
<td>0.85</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>0.70</td>
<td>1.15</td>
</tr>
<tr>
<td>6</td>
<td>1.15</td>
<td>1.00</td>
</tr>
<tr>
<td>7</td>
<td>0.63</td>
<td>1.65</td>
</tr>
<tr>
<td>8</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>9</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>10</td>
<td>0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>11</td>
<td>0.82</td>
<td>1.30</td>
</tr>
<tr>
<td>12</td>
<td>0.15</td>
<td>0.25</td>
</tr>
<tr>
<td>13</td>
<td>0.17</td>
<td>0.38</td>
</tr>
<tr>
<td>14</td>
<td>0.48</td>
<td>0.53</td>
</tr>
<tr>
<td>15</td>
<td>0.18</td>
<td>0.28</td>
</tr>
<tr>
<td>16</td>
<td>1.38</td>
<td>1.38</td>
</tr>
<tr>
<td>17</td>
<td>0.05</td>
<td>0.25</td>
</tr>
<tr>
<td>18</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>19</td>
<td>0.10</td>
<td>0.13</td>
</tr>
<tr>
<td>20</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>21</td>
<td>0.20</td>
<td>0.38</td>
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<tr>
<td>22</td>
<td>0.10</td>
<td>0.12</td>
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<tr>
<td>23</td>
<td>0.30</td>
<td>0.38</td>
</tr>
<tr>
<td>24</td>
<td>0.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Mean value before HBO : 0.45 lipase units
Mean value after HBO : 0.57 lipase units

4. Effects of HBO on the ultrastructure of a leproma

Method

Skin biopsies from lepomas were performed in two patients before and following a series of 21 daily HBO sessions. Care was taken to use the same spot at both occasions.
The specimens were processed for an examination by electron microscopy.

**Results**

The changes in the ultrastructure of lepromatous skin after HBO consisted in the appearance of multivesicular foamy structures, remnants of cytoplasmatic elements and signs collagenous proliferation (see Fig. 1).

5. **Effect of HBO on the global evolution of a patient**

After having focused on changes induced by HBO in single aspects, we proceeded to observe the global evolution of patients exposed to this therapy.

The study comprised 20 patients with lepromatous leprosy, pretreated with antimicrobial drugs: 8 at stage L₁, 7 at stage L₂ and 5 at stage L₃ of the disease. HBO at 3 Ata was administered on two consecutive days. Assessments were done before and following the HBO therapy.

6. **Clinical evolution**

We observed the following changes after HBO. The skin acquired a normal colour. The extremities regained a normal temperature. The sensibility of affected areas improved. The patients slept better and their appetite improved. The specific lesions changed as follows.

In patients at stage L₁: definitive improvement (disappearance of infiltration and of maculae, flattening of lepromas) in five cases.

At stage L₂: three patients improved definitively and four patients moderately. At stage L₃: some improvement in two and no change in three patients.

7. **Bacteriology**

The examination of a smear of the affected skin revealed disappearance of bacteriae in 45% and signs of bacterial involution in 55% patients. Splitting the results in stages:

- L₁: −62.5% negative bacterioscopy
  37.5% morphological changes of bacteriae

- L₂: −42.8% negative finding
  57.2% morphological alterations

- L₃: −20% negative outcome
  80% considerable morphological effects (fragmentation and granulation of the bacilli)

8. **Biochemical aspects**

The figures of pH, −HCO₃ and pCO₂ revealed some tendency towards acidosis induced by
HBO (more so by the second session) that reverted in the following hours.

9. Histopathological aspects

The examination of biopsy from the leproma revealed:
- alterations in the Virchow’s cells (vacuolisation, pycnosis and cariolyssis) in 88% of cases.
- reticular fibrosis in 66% of instances
- collagen fibrosis in 77% of instances
- leucocytic infiltration in 55% of cases

Solid bacilli were detected in 2.2%, morphologic changes in 55.5% and absence of bacilli in 22.3% of examinations.

10. Tolerability

Adverse effects (such as headache, vomiting, dezziness or other manifestation of oxygen intolerance) were not observed during the HBO therapy and leprotic reactions were not precipitated (neither lepromatous nodular erythema nor asymptomatic papulour/macular reaction).

III. Discussion

The considerable increase in oxygen consumption by the lepromatous tissues induced by HBO may correspond to a certain recovery of metabolic functions of cells and to the activation of metabolism in the lipidic vacuoles with bacilli in involution. It is noteworthy, that the metabolic quotient remained elevated as long as four months after a series of three HBO sessions. The fact that the greatest increase in oxygen consumption by leproma occurred in patients on chemotherapy could imply the existence of a synergism between drug action and HBO.

The higher basic levels of blood ATP in leprosy patients as compared with controls could be due to metabolic abnormalities of skin tissue in leprosy patients. Since ATP levels in blood are lowered by HBO in patients on chemotherapy and not in the patients without it, this could be an additional evidence for a synergistic action between HBO and chemotherapy.

We mentioned already the observation by Dhople(5), that a higher degree of bacterial activity goes along with lower serum lipase levels. If this is so, then the increase of lipase levels in patients on HBO points to an direct or indirect antibacterial effect of this therapy.

The favorable clinical evolution of leprosy patients undergoing HBO therapy seems to substantiate the relevance of the above described biochemical, structural and bacteriological findings in patients with this disease.

It is up to future studies to confirm the findings of our past work and to complement it with efforts to explore if and how immunomodulatory effects are induced by HBO therapy in patients with leprosy.

IV. Summary and Conclusions

144 patients with multibacillary lepromatous leprosy and 20 healthy volunteers underwent HBO therapy (with 3 Ata during 1.5 hours, including compression and decompression) on 2 to 21 consecutive days. The metabolic quotient (i.e. oxygen consumption by tissues), the blood level of adenosintrisphosphate and the serum levels of lipase showed trends towards nor-
malisation, mainly in patients on antimicrobial drug therapy. Involution in lepromas on ultrastructure examination and improvements in the clinical conditions were found. HBO may evolve to a useful adjunct to chemotherapy in lepromatous leprosy.

Bibliography

6) Cherry, I and Crandall, I.,: Amer. J. Physiol. 100, 266 (1932).

Complementary references

菌陽性らい患者の補助療法としての高圧酸素付加 (HBO)

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キーワード：高圧酸素付加，HBO療法，酸素係数，アデノシン三磷酸塩，血清リパーゼ

菌陽性のらいらい患者144例と健康志願者20名とにHBO療法（加圧及び減圧を含めて3気圧で1時間半）を2日から21日間続けて行った。代謝係数（すなわち組織による酸素消費）、アデノシン三磷酸塩の血液濃度、血清リパーゼ濃度は、抗菌薬剤治療下の患者では主として、正常化への傾向を示した。超微構造検査によるらいらいの衰退像と臨床症状の改善とが見出された。HBOはらいらいの化学療法に役立つ補助手段に発展するかも知れない。