Laser biostimulation in end-stage multivessel coronary artery disease – a preliminary observational study

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Abstract

Background: Low-energy laser radiation through its direct influence on tissue repair processes without heating effect may have vital importance in the therapy of patients with advanced coronary artery disease (CAD).

Aim: The introductory assessment of the effects of laser biostimulation applied to patients with advanced multivessel CAD.

Methods: 39 patients with advanced CAD were assigned (mean age 64.8±9.6, male gender 64%, CCS class 2.5±0.5, EF=46±11%, 69% with a history of acute myocardial infarction), to undergo two sessions of irradiation of low-energy laser light on skin in the chest area from helium-neon B1 lasers. The time of irradiation was 15 minutes while operations were performed 6 days a week for one month. Before including the patients in the experimental group a full clinical evaluation, basic biochemical tests, ECG, 24h Holter recordings, 6-minute walk test, treadmill test using Bruce protocol and full echocardiographic examination were performed. After the first and second period of laser therapy with a one-month break between them analogical parameters with the initial examination were measured.

Results: No side effects associated with the laser biostimulation or performed clinical tests were noted. Lower CCS class (2.5±0.5 ⇒ 2.2±0.4 ⇒ 2.0±0.4, p<0.001), higher exercise capacity (5.1±2.2 ⇒ 5.8±2.2 ⇒ 6.6±2.5 [METs], p=0.023), longer exercise time (257±126 ⇒ 286±127 ⇒ 325±156 [s], p=0.06), less frequent angina symptoms during the treadmill test (65% ⇒ 44% ⇒ 38%, p=0.02), longer distance of 6-minute walk test (341±93 ⇒ 405±113 ⇒ 450±109 [m], p <0.001), lower systolic blood pressure values (SP 130±14 ⇒ 125±12 ⇒ 124±14 [mmHg], p=0.05) and trend towards less frequent 1 mm ST depression lasting 1 min during Holter recordings were noted.

Conclusions: An improvement of functional capacity and less frequent angina symptoms during exercise tests without a significant change in the left ventricular function were observed. Laser biostimulation in short-term observation was a very safe method. These encouraging results should be confirmed in a larger, placebo-controlled study.

Key words: laser biostimulation, low-energy laser irradiation, advanced coronary artery disease

Introduction

Laser biostimulation (low level laser therapy, LLLT) has been applied in medicine for more than 30 years. Its action consists of direct impact on the intracellular mechanisms and activation of heat-independent tissue repair processes without tissue damage. The LLLT effects may be either local or systemic, thus involving not only sites of direct influence of laser radiation.

Since the first application of LLLT more than 2000 scientific reports with respect to this still controversial issue have been published. Although most of these controversies regarding the impact of laser radiation have
been solved, nowadays the main interest of scientific research is its impact on intracellular processes, their excitation pathways and the possibility of interactions between activated cells at the tissue level [1-3].

Studies performed mostly on animal models and in vitro provided evidence of LLLT effects: anti-inflammatory, improved microcirculation and cardioprotective effects. Reduced infarct area after artificially induced myocardial infarction (MI) as well as favourable influence on postinfarct myocardial remodelling were noted [4, 5]. The aforementioned action may have an important impact on quality of life and prognosis in patients with multi-vessel coronary artery disease (CAD) who are not suitable for the conventional techniques of myocardial revascularisation. The early studies on LLLT performed in humans involved patients suffering from MI treated with intravascular irradiation. Reduction of ischaemic area, decreased levels of myocardial necrosis markers and reduced incidence of cardiac arrhythmia were observed [6, 7]. Also, exposure to external irradiation of patients with ischaemic heart disease was beneficial as it reduced angina complaints, inhibited lipid peroxidation processes [8] and improved rheology of blood, showing a protective effect on the erythrocyte membranes [9] and a drop in the arterial blood pressure and pulse pressure.

We are not aware of any studies investigating the influence of low energy laser irradiation applied externally to the chest in patients with advanced multi-vessel CAD (either clinical or reports). Our concept is to apply external low energy laser irradiation to the chest. A potential biostimulation impact, through a local and systemic effect on inflammatory reaction alleviation, stimulation of microcirculation development and tissue regenerative processes, may be potentially beneficial in advanced CAD.

The purpose of the study was to assess the safety and efficacy of low energy laser therapeutic procedures in patients with advanced multi-vessel CAD not suitable for myocardial revascularisation. Many clinical parameters as well as results of laboratory tests were evaluated to find any indices of potential impact of the laser therapy in the examined population.

Methods

The study protocol was approved by the Local Bioethical Committee of the Medical University of Łódź.

Inclusion criteria were as follows:
1) multi-vessel CAD documented with coronary angiography and not suitable for revascularisation, either percutaneous or surgical,
2) advanced angina: class II or III according to the Canadian Cardiovascular Society (CCS) functional classification [10],
3) optimised medical therapy according to the current standards of patient management in cardiology and ACC/AHA guidelines [11],
4) informed written consent to participate in the study.

At the time of enrolment the following conditions were absent (exclusion criteria):
1) significant structural valvular disease or congenital malformation,
2) acute coronary syndrome,
3) serious systemic disease that might have a significant impact on patient prognosis. Diabetes mellitus was not considered a contraindication.

Finally, 39 patients hospitalised in the Second Chair and Department of Cardiology, Medical University of Łódź, were enrolled. After initiation of optimised medical therapy all patients were discharged with successful control of clinical symptoms achieved. Patients were treated according to the ACC/AHA guidelines [11] with aspirin, statins, angiotensin-converting enzyme inhibitors and beta-blockers, and this therapy was not changed significantly throughout the study period.

Baseline clinical assessment consisted of complete clinical examination, basic biochemical studies, chest X-ray, resting ECG, treadmill test and 6-minute walk test as well as complete echocardiographic examination with Doppler measurements.

The same parameters as at baseline were evaluated after two four-week cycles of laser therapy procedures with one-month intervals between the cycles.

The degree of clinical significance of CAD was classified according to the Canadian Cardiovascular Society classification [10]. History of MI, typical atherosclerosis risk factors (arterial hypertension, diabetes mellitus, smoking, familiar history of atherosclerosis, total cholesterol level, LDL-C, HDL-C and triglyceride concentrations) were also taken into account.

Six-minute walk test

All patients underwent walk test with calculation of walking distance covered by each individual within 6 minutes. Patients were instructed to walk without stopping at a pace as fast as possible not to provoke either angina or heart failure symptoms. This test was carried out at the Department of Cardiology with the facilities of an immediate qualified response team.
**Treadmill test**

Treadmill test was performed on a computer-based system (Marquette Electronics Inc, Milwaukee, USA) and according to the Bruce protocol [12]. Typical criteria of terminating the exercise test were applied. Physical capacity was expressed as MET units (metabolic equivalents of exercise). The duration of exercise was also recorded.

**Holter examination**

Holter examination was carried out using a Pathfinder 700 DelMar Reynolds Medical device (Hertford, United Kingdom). Three Lifecard CF-type channel recorders were utilised.

Reversible depressions of ST segments meeting criteria called the “1 × 1 × 1” rule were considered significant, and included:

1) ST depression of at least 1 mm in the horizontal or sloping manner recorded within 80 ms after the J point,
2) ST depression lasting at least 60 seconds,
3) episodes detected as isolated if they were separated by at least one-minute long isoelectric ST segments.

**Echocardiography**

In the echocardiographic study (M and 2D mode), global as well as regional left ventricular (LV) myocardial contractility were assessed according to the 16-segment model of the American Echocardiographic Society recommendations [13]. A four-stage system of contractility assessment was employed, where 1 meant normokinesia, 2 – hypokinesia, 3 – akinesia, and 4 – dyskinesia. A LV contractility index was calculated in the typical manner as the sum of the score of individual segments and divided by the number of analysed segments. Ejection fraction (EF) was evaluated using the Simpson equation (four-chamber apical and LV long-axis projection). In patients with atrial fibrillation, measurements were taken for three consecutive cardiac cycles and then mean values were calculated. Flow through the cardiac valves and cardiac chambers were examined employing methods of pulse wave Doppler, continuous wave Doppler and colour blood flow visualisation techniques.

**Laser therapy procedures**

The patients were exposed to laser irradiation of low energy produced by helium-neon B1 laser and transmitted by optic fibre that assured complete therapy safety. The B1 biostimulator used in this study is based on a laser type semiconductor that generates garish red light of a wavelength of 632 nm. This laser emits continuous energy of 10 mW at the tissue level. The irradiation time was 15 minutes and procedures were repeated 6 days a week for one month. The procedures were supervised by a trained study nurse responsible for the assessment of possible local complications. Throughout the whole study, a physician and engineer team of Politechnika Łódzka was available, being responsible for proper functioning and safety of the laser equipment employed in this study.

**Statistical analysis**

Data are expressed as means and standard deviations. Differences between the individual parameters in the patient groups were analysed using a test for unpaired variables (Anova). A p value <0.05 was considered significant.

**Results**

The baseline clinical parameters and risk factors are outlined in Table I. The study involved 39 patients at the mean age of 65 years. The majority of them had a history of MI (69%) and there was a relatively high contribution of females (36%) in the group. The examined population had a significant burden of such risk factors as arterial hypertension (67%), diabetes mellitus (26%), smoking history (59%), overweight (64%), and relatively well controlled lipid disturbances (mean total cholesterol concentration 183 mg/dL). Left ventricular EF was well preserved with a mean value of 46%, while exercise capacity was poor – mean 257 seconds. Fifty-one percent of patients presented angina of CCS class III and 49% of class II, all had multi-vessel CAD documented in coronary angiography. The mean follow-up time from coronary angiography to the final examination was 15 weeks.

There were no adverse events associated with laser biostimulation, either systemic or local. In three patients procedures were temporarily discontinued because of respiratory tract infections.

The results of control examinations are presented in Table II and as graphs in Figure 1. After the first irradiation statistically significant improvement in CCS class and longer distance of 6-minute walk were observed. These beneficial effects remained stable after the subsequent cycle, and additionally after the second cycle statistically significant improvement in exercise capacity as measured during exercise stress tests [METS], lower incidence of ischaemia-limited stress tests, less frequent occurrence of supraventricular premature beats and lower systolic arterial pressure were found. A trend towards prolongation of exercise time (by 67 seconds) and a lower incidence of transient
depression of ST segment of at least 1 mm in the ambulatory ECG monitoring were also noted. No favourable changes with respect to LV performance were observed.

Discussion

The low energy laser radiation also called laser biostimulation may be considered a phototherapy method and even a form of physiotherapy. The aforementioned designations apply to radiation of energy ranging between a few to a dozen or so J/cm² and power not exceeding several hundred MW, most often in the range from 1 to 30 mW, penetrating tissue to the depth of 20-50 mm. This level of power is not sufficient to produce a thermal effect and the increase of temperature does not exceed 0.1-0.5°C. The features of such radiation involve a reduction of inflammation, increased rate of cellular regeneration and higher activity of repair processes, including wound healing. Simultaneously, such radiation prevents negative, uncontrolled cellular hypertrophy activated by an inflammatory response. It should be emphasised that biological effects are observed much deeper than the level of direct radiation penetration. Owing to these features, LLLT has been applied widely in many medical disciplines, including cardiology, where it has been tried on coronary artery segments during angioplasty and stenting procedures to prevent restenosis as a result of physiological activation of endothelial hyperplasia with simultaneous inhibition of neointima proliferation [14, 15].

The observed improvement in the CCS class and decrease of angina symptoms in the examined patient group was supported by the results of the exercise...
stress tests. However, it should be remembered that exercise stress tests were significantly less frequently terminated due to clinical symptoms of myocardial ischaemia, while the rate of stress tests limited by the ECG changes did increase. This improvement may be a result of the analgetic effect of LLLT, well documented in the medical literature. Such an effect may be associated with cellular membrane hyperpolarisation, changes of cellular redox status, increased endorphin and prostaglandin release and improvement of the intracellular metabolic processes, and also with an impact on the functional status of arterial and capillary vessels or with enhanced lymphatic drainage from inflammation-involved sites.

The possible mechanisms of LLLT that influence the ischaemic heart include angiogenesis activation [16, 17] and beneficial impact on microcirculation. Helium-neon lasers were employed in those studies, as in our project. Increased release of VEGF and activation of smooth muscle and endothelial cell production were found. Thus, they may be of importance in angiogenesis activation. These reports are of particular interest with respect to the recent publications revising the dogma of the absence of regeneration processes in the ischaemic myocardium [18, 19]. It is suggested that restoration processes might be of fundamental importance for cardiac homeostasis.

Low energy laser radiation causes vascular dilatation via nitric oxide (NO) (decreased intracellular Ca\(^{2+}\) concentration in vascular smooth muscle cells controlled by NO). It is supposed that alongside cytokines, lymphokines and free oxygen radicals produced by phagocytes, NO as a second transmitter is also responsible for the systemic effect of low energy laser therapy [20]. Also the impact of LLLT on rheological blood parameters seems interesting. Favourable changes of blood rheological features were observed after in vitro exposure to a radiation. They included decreased blood viscosity, increased compliance of erythrocytes and decreased sedimentation index [21]. It seems that the mechanisms described above may be responsible for the reduction of arterial blood pressure, improvement in functional circulatory status and lower incidence of ischaemic events observed in our study.

### Table II. Selected clinical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>p</th>
<th>p 0 vs. 1</th>
<th>p 0 vs. 2</th>
<th>p 1 vs. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS class (mean)</td>
<td>2.5±0.5</td>
<td>2.2±0.4</td>
<td>2.0±0.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.072</td>
<td></td>
</tr>
<tr>
<td>6-minute walking test [m]</td>
<td>341±193</td>
<td>405±113</td>
<td>450±109</td>
<td>0.012</td>
<td>&lt;0.001</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>Exercise stress test capacity [METS]</td>
<td>5.1±2.2</td>
<td>5.8±2.2</td>
<td>6.6±2.5</td>
<td>0.170</td>
<td>0.023</td>
<td>0.319</td>
<td></td>
</tr>
<tr>
<td>Exercise stress test duration [s]</td>
<td>257±126</td>
<td>287±127</td>
<td>325±156</td>
<td>0.339</td>
<td>0.066</td>
<td>0.318</td>
<td></td>
</tr>
<tr>
<td>Exercise stress test ischaemia symptom-limited (n)</td>
<td>64</td>
<td>48</td>
<td>34</td>
<td>0.207</td>
<td>0.018</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>Stress test terminated due to ECG changes (n)</td>
<td>39</td>
<td>42</td>
<td>48</td>
<td>0.804</td>
<td>0.445</td>
<td>0.629</td>
<td></td>
</tr>
<tr>
<td>ST depression during stress test</td>
<td>72</td>
<td>58</td>
<td>65</td>
<td>0.230</td>
<td>0.568</td>
<td>0.561</td>
<td></td>
</tr>
<tr>
<td>ExSV during stress test (n)</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>0.075</td>
<td>0.023</td>
<td>0.346</td>
<td></td>
</tr>
<tr>
<td>ExV during stress test (n)</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>0.362</td>
<td>0.991</td>
<td>0.388</td>
<td></td>
</tr>
<tr>
<td>ST depression of 1 mm (Holter) within 1 minute (sum/number of patients)</td>
<td>36/8</td>
<td>3/3</td>
<td>3/3</td>
<td>0.121</td>
<td>0.104</td>
<td>0.290</td>
<td></td>
</tr>
<tr>
<td>HR mean [min⁻¹]</td>
<td>69.6±9.2</td>
<td>72.0±12.3</td>
<td>69.8±11.5</td>
<td>0.345</td>
<td>0.346</td>
<td>0.990</td>
<td></td>
</tr>
<tr>
<td>Systolic pressure [mmHg]</td>
<td>130.1±13.5</td>
<td>125.4±11.6</td>
<td>124.0±14.1</td>
<td>0.130</td>
<td>0.051</td>
<td>0.576</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure [mmHg]</td>
<td>77.4±8.3</td>
<td>75.8±6.7</td>
<td>74.8±7.3</td>
<td>0.341</td>
<td>0.203</td>
<td>0.675</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure [mmHg]</td>
<td>51.9±10.0</td>
<td>49.3±9.3</td>
<td>48.9±11.3</td>
<td>0.267</td>
<td>0.168</td>
<td>0.685</td>
<td></td>
</tr>
<tr>
<td>WMSI</td>
<td>1.4±0.3</td>
<td>1.3±0.3</td>
<td>1.3±0.3</td>
<td>0.975</td>
<td>0.759</td>
<td>0.761</td>
<td></td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>46±12</td>
<td>47±12</td>
<td>46±12</td>
<td>0.943</td>
<td>0.922</td>
<td>0.879</td>
<td></td>
</tr>
<tr>
<td>LV diastole [mm]</td>
<td>51.9±8.0</td>
<td>51.2±8.4</td>
<td>51.3±9.4</td>
<td>0.915</td>
<td>0.797</td>
<td>0.882</td>
<td></td>
</tr>
<tr>
<td>LV systole [mm]</td>
<td>40.2±8.9</td>
<td>40.3±7.2</td>
<td>42.8±9.1</td>
<td>0.782</td>
<td>0.456</td>
<td>0.593</td>
<td></td>
</tr>
<tr>
<td>LA [mm]</td>
<td>41.1±6.7</td>
<td>43.4±6.2</td>
<td>42.8±5.9</td>
<td>0.116</td>
<td>0.100</td>
<td>0.648</td>
<td></td>
</tr>
</tbody>
</table>

0 – before exposure to radiation, 1 – after first irradiation, 2 – after second irradiation, p – level of statistical significance (Anova). Abbreviations: ExSV – supraventricular extrasystolia during exercise, ExV – ventricular extrasystolia during exercise, other abbreviations as in Table I
Figure 1. Graphs presenting changes of selected parameters
0 – before irradiation, 1 – after the first irradiation, 2 – after the second irradiation: CCS classification (CCS), exercise capacity during treadmill exercise stress test expressed as METS (METS), exercise time during treadmill stress test (EX-TIME), 6-minute walk test (Walk), percentage of positive exercise stress tests in ECG recordings (ECG-Pos%), percentage of positive symptom-limited exercise stress tests (Clin-Pos%).
The results presented herein seem to justify considering LLLT a safe procedure because no complications related to irradiation, either systemic or local, were observed in the short-term follow-up. However, an evaluation of the late effects of the irradiation is mandatory because one must be aware of the possible mutagenic impact of free radicals produced in the irradiated cells and the likelihood of inheritance of the intracellular changes, although no evidence of cyto- and genotoxic effects of such radiation have been found so far.

There is strong evidence of cardioprotective effects of LLLT and the mechanisms of its influence on tissue are becoming better recognised. It is seems that in the near future an important issue will be to establish the optimum site of irradiation, radiation dose, time and wavelength of light.

To conclude, an observed improvement in the functional circulatory status and alleviation of angina symptoms may improve quality of life in patients with severe CAD. It is impossible at this time to answer the question as to whether the biostimulation procedures do improve patient prognosis and further follow-up study involving more patients and a control group will be mandatory. Although no changes in LVEF were observed, a statistically significant decrease of arterial blood pressure was noted that may have a favourable impact on subjects in this particular patient population.

**Study limitations**

This study involved a relatively small number of 39 patients, and lacked a sham procedure group, precluding objective analysis of clinical parameter changes. Although the examinations were performed by the same physician team, our study methods are of limited accuracy and reproducibility. In the study presented herein we focused on a presentation of the examined patient group and aimed to show no complications associated with therapy based on a novel LLLT method. Additionally, a favourable impact of the therapeutic environment and reproducibility of follow-up examinations may have resulted in a placebo effect possibly affecting the results of the exercise stress tests. It should be mentioned that some of the patients that were diagnosed before initiation of irradiation had received optimum medical therapy according to the Polish Cardiac Society and ACC/AHA guidelines. Taking into account the prolonged period of time needed to reach full action of some drugs, the observed hypotensive effect might be a result of the aforementioned circumstances, although the final clinical assessment was performed more than 3 months after initiation of irradiation, and the medical therapy did not change significantly throughout the study.

**Conclusions**

In our clinical study, no adverse events of laser biostimulation were seen. Analysis of results suggests a slight, though statistically significant, improvement of exercise capacity and decrease of arterial pressure in patients with advanced ischaemic heart disease not suitable for any revascularisation. However, no improvement of LV performance was noted as a result of biostimulation. These promising results should be confirmed in another study with a placebo control group.

**References**


Kardiologia Polska 2007; 65: 1


Biostymulacja laserowa w zaawansowanej chorobie wieńcowej – obserwacja wstępna

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Streszczenie

Wstęp: Niskoenergetyczne promieniowanie laserowe poprzez wpływ na tkankowe procesy naprawcze bez efektu cieplnego może mieć znaczenie w terapii pacjentów z zaawansowaną chorobą wieńcową.

Cel: Wstępna ocena efektów zabiegów laseroterapii u pacjentów z zaawansowaną, wielonaczyniową postacią choroby wieńcowej.

Metodyka: Badaniem objęto grupę 39 pacjentów (średnia wieku 65,0±9,4; 64% mężczyzn; średnia klasa wg CCS 2,5±0,5; średnia EF 46±11%, 69% – historia zawału w wywiadzie) z rozpoznaniem ciężkiej postaci choroby wieńcowej serca, potwierdzonej w koronarografii, bez możliwości rewaskularyzacji. Pacjenci byli poddani 2 cyklom naświetlań okolicy przedsercowej światłem laserowym emitowanym przez lasery helowo-neonowe B1, wykonywanym przez 1 mies. z 4-tygodniową przerwą. Przed i po każdym cyklu naświetlań przeprowadzano pełne badanie kliniczne, EKG spoczynkowe, test 6-minutowego marszu, próbę wysiłkową wg protokołu Bruce’a, badanie metodą Holtera i badanie echokardiograficzne.

 Wyniki: Nie obserwowano powikłań związanych z biostymulacją laserową i przeprowadzanymi badaniami klinicznymi. Obserwowano poprawę klasy CCS (2,5±0,5 ⇒ 2,2±0,4 ⇒ 2,0±0,4; p <0,001), większą wydolność podczas prób wysiłkowych (5,1±2,2 ⇒ 5,8±2,2 ⇒ 6,6±2,5 [METS], p=0,023), z dłuższym czasem wysiłku (257±126 ⇒ 286±127 ⇒ 325±156 [s], p=0,06) i mniejszym odsetkiem prób ograniczonych objawami (65% ⇒ 44% ⇒ 38%, p=0,02), zwiększenie odległości 6-minutowego marszu (341±93 ⇒ 405±113 ⇒ 450±109 [m], p <0,001), niższe wartości skurczowego ciśnienia tętniczego (SP 130±14 ⇒ 125±12 ⇒ 124±14 [mmHg], p=0,05) i trend do rzadszego występowania obniżeń odcinka ST (>1 mm i trwających >1 min) w badaniu metodą Holtera.

Wnioski: Zaobserwowano poprawę parametrów wydolnościowych układu krążenia i rzadsze epizody niedokrwienia podczas prób wysiłkowych, bez zauważalnej poprawy w funkcji lewej komory. Biostymulacja laserowa w obserwacji krótkiej okazała się procedurą bezpieczną, zaś zachęcające wyniki badania powinny zostać potwierdzone w badaniu przeprowadzonym na szerszej grupie pacjentów, z uwzględnieniem grupy placebo w protokole badania.

Słowa kluczowe: biostymulacja laserowa, niskoenergetyczne promieniowanie laserowe, zaawansowana choroba wieńcowa

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