Evaluation of the impact of transmyocardial laser (CO_2) revascularisation on myocardial perfusion – 6-months observations

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Abstract

BACKGROUND: Transmyocardial laser revascularisation (TMLR) is a relatively new surgical approach to symptomatic coronary artery disease patients otherwise inoperable by classical revascularisation methods. Perfusion improvement after TMLR is considered as one possible mechanism causing alleviation of symptoms in a significant percentage of operated patients. The goal of this work was to assess the history of myocardial perfusion during the first 6 months after sole TMLR operation.

METHODS: TMLR was performed by using high-power (800 W) CO_2 laser. Tc-99m-Sestamibi single photon emission computed tomography (SPECT), both in rest and stress, was performed 4 times: before TMLR [SPECT-0], very early (mean: 3 weeks) after TMLR [SPECT-I], 3 months after TMLR [SPECT-II] and 6 months after TMLR [SPECT-III] in every patient. The group consisted of 25 patients, including 21 patients with previous myocardial infarctions. The patients subjected to the operation were those suffering from angina in spite of pharmacological therapy, with diffuse changes in the peripheral parts of coronary arteries, with left ventricle (LV) ejection fraction not lower than 0.30 and with at least one transient or small persistent defect in preoperative SPECT. Perfusion was assessed in 13 of 17 segments of the LV (after exclusion of 4 septal segments). Only a history of transient or small persistent perfusion defects ('*viable*' segments) detected in SPECT-0 is discussed.

RESULTS: In comparison to SPECT-0: in SPECT-I perfusion did not change in 52% of segments, improved — in 31%, and deteriorated — in 17%; in SPECT-II perfusion did not change in 48% of segments, improved — in 34%, and deteriorated — in 18%; in SPECT-III perfusion did not change in 52%, improved — in 25%, and deteriorated — in 22% of segments. No significant difference in the number of segments with perfusion preservation, improvement or deterioration in comparison to SPECT-0 was found in SPECT-I,-II or -III. In SPECT-II in comparison to SPECT-I, no changes in perfusion were found in 66% of segments, perfusion improved in 20% and deteriorated in 14%. In SPECT-III in comparison to SPECT-II, no changes in perfusion were found in 79% of segments, perfusion improved in 5% and deteriorated in 15%.

CONCLUSIONS: Our evaluation of the history of segments with preoperatively transient or small persistent («viable») defects indicates that during the first 6 months after TMLR: 1) perfusion is better than before the operation in about one third of the segments, and 2) in some of these segments there are dynamic perfusion changes (improvement or deterioration) from one to the next postoperative moment of observation.

Key words: myocardial perfusion, SPECT, Tc-99m-Sestamibi, transmyocardial laser revascularisation

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Introduction

Transmyocardial laser revascularisation (TMLR) is a surgical approach, performed as a sole operation or in combination with coronary artery bypass grafting (CABG), applied to symptomatic coronary artery disease patients in whom complete revascularisation of myocardium by classical methods (CABG or percutaneous transluminal coronary angioplasty PTCA) is not achievable because of diffuse changes in the peripheral parts of the coronary arteries (1). Since the early nineties high power (800 W) carbon dioxide lasers have been used, which allow creation of channels in the contracting myocardium (2). During TMLR transmyocardial channels from the epicardium to endocardium are created by the use of laser energy, which causes the myocardium to evaporate. Laser pulses are delivered to the treated area approx-

imately 1cm apart. Perfusion improvement after TMLR is considered among other possible mechanisms causing alleviation of symptoms in a significant percentage of operated patients. Two main theories on perfusion improvement consider direct revascularisation and stimulation of angiogenesis. However the demonstration of improved myocardial perfusion in clinical studies has not been convincingly performed and large discrepancies exist among published results (3–12). The goal of this work was to assess in detail the history of myocardial perfusion three times during the first 6 months after sole TMLR operation, to study the dynamic of perfusion changes.

Material and methods

Patients and study design. The patients subjected to the operation were those suffering from angina in spite of pharmacological therapy, with diffuse changes in the peripheral parts of coronary arteries, with left ventricle (LV) ejection fraction not lower than 0.30 (the criteria imposed by the Ethics Committee of the Institute of Cardiology in Warsaw), and with at least one transient (total or partial) or small persistent defect in preoperative myocardial perfusion study.

The group consisted of 25 patients (23 males, 38–73 years old, mean: 59 ± 9 years). Nineteen patients (76%) had a history of previous myocardial infarctions. Left ventricle ejection fraction, evaluated on the basis of contrast ventriculography, was 0.30–0.74 (mean: 0.48 ± 0.15). Before the operation, the patients presented II–IV class of angina (mean: 3.2 ± 0.5) according to the Canadian Cardiovascular Society (CCS). Four patients (16%) had undergone CABG 1–8 years before.

In all patients Tc-99m-Sestamibi stress single-photon emission computed tomography (SPECT) was performed 4 times: before TMLR (26 ± 21 days, SPECT-0), as early as possible after TMLR (23 ± 9 days, SPECT-I), approximately 3 months after TMLR (99 ± 13 days, SPECT-II) and approximately 6 months after TMLR (189 ± 16 days, SPECT-III).

Informed consent was obtained from each patient. The study protocol was approved by the institute's ethics committee.

Transmyocardial laser revascularisation. TMLR was performed by using high power 800 W CO_2 laser (The Heart Laser, PLC Medical Systems Inc., Milford, MA, USA), after sternotomy, on the beating heart, without extracorporeal circulation. During the operation 23–52 (mean: 34 ± 7) channels per patient heart were created with transmyocardial penetration confirmed by intraoperative transoesophageal echocardiography.

Imaging protocol. Stress and rest studies were performed after separate tracer injections, on consecutive days, in a random sequence. Stress tests were performed according to a modified Bruce protocol (MAX-1 Marquette exercise system with Series 1900 treadmill). After at least 4 hours fasting, a dose of 0.3 mCi (1.11 MBq) per 1 kg of body weight of Tc-99m-Sestamibi was injected. SPECT data acquisition commenced 60 to 120 minutes after tracer injection in rest and 45–90 minutes after injection in stress. Image sets were obtained from 64 projections over 180-degree arc beginning at 45-degree right anterior oblique and ending at 45-degree left posterior oblique projection. A low-energy high-resolution, parallel-hole collimator and a 64 x 64 matrix with no zoom were used. Processing was performed with filtered back-projection using one-dimensional Butterworth filter with a cut-off frequency of 0.4 of Nyquist frequency and the order of 7; interslice weighting 1–2–1 was applied after transverse reconstruction. Images were corrected for nonuniformity and for centre of rotation displacement. From transaxial tomograms short-axis, vertical long-axis, and horizontal long-axis tomograms were derived. From the short-axis slices, the BULL'S-EYE maps in stress and in rest were generated. SPECT imaging was done by a single-head gamma camera (ORBITER 75, Siemens) connected to a MaxDELTA 2000 computer system (Siemens).

Image analysis. Perfusion assessment was performed visually on the basis of vertical long-axis tomograms, horizontal long-axis tomograms and the BULL'S-EYE maps. Perfusion was evaluated after dividing the LV into 17 segments (four segments corresponded to the anterior wall, four to the lateral wall, four to the inferior wall, four to the septum and one to the apex). Perfusion was assessed in 13 of 17 segments of the LV (after exclusion of 4 septal segments, never treated by laser during the operation). Our research follows up the history of transient or small persistent perfusion defects, defined as 'viable segments', observed in the preoperative SPECT study. A transient perfusion defect in the segment was described when there was a higher relative uptake of Tc-99m MIBI in the rest study than in stress. A small persistent perfusion defect was described when there was no uptake increase in rest and when the 'severity' of the uptake defect was assessed as 'one' in 4-grade intensity scale [0 — no defect, 1 — small defect, 2 — large defect, 3 — very large defect (i.e. lack of perfusion)].

In post-TMLR studies, perfusion improvement in a segment was described if the defect severity decreased in the stress and/or the rest images. Perfusion deterioration in a segment was described if the defect severity increased in the stress and/or the rest images.

Each SPECT study was assessed by three observers experienced in nuclear cardiology and the results were established by consensus.

Statistical analysis. All continuous variables were represented as mean and standard deviation. Mean values were first evaluated by F-test ($p = 0.05$) for variances equality and then the t-test ($p = 0.05$) for means with equal or non-equal variances was used to compare them. Rates of segments with perfusion preserved, improved or deteriorated were described as variables with binomial distribution and 95-percent confidence intervals ($CI_{0.95}$) were calculated for assessment of the equality of the rates.

Results

In SPECT-0, 183 segments were diagnosed as transient perfusion defects (n = 163) or small persistent defects (n = 20). In SPECT-I perfusion did not change in 52% of segments ($CI_{0.95}$ = 43–58%), perfusion improved in 31% ($CI_{0.95}$ = 24–38%), and perfusion deteriorated in 17% ($CI_{0.95}$ = 12–23%) of segments (Figure 1).

In SPECT-II, also in comparison to SPECT-0, perfusion did not change in 48% of segments ($CI_{0.95}$ = 39–54%), perfusion improved in 34% ($CI_{0.95}$ = 27–41%), and perfusion deteriorated in 18% ($CI_{0.95}$ = 12–24%) (Figure 1).

In SPECT-III, also in comparison to SPECT-0, perfusion did not change in 52% of segments ($CI_{0.95}$ = 43–58%), perfusion im-

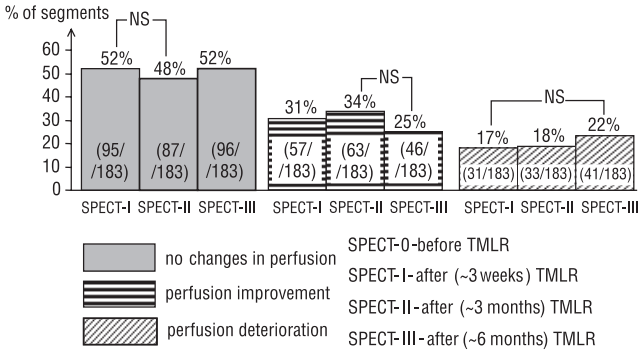

Figure 1. State of perfusion in preoperatively «viable» segments (n = 183) in SPECT-I, -II, and –III, always in comparison to preoperative SPECT-0.

proved in 25% ($CI_{0.95}$ = 19–31%), and perfusion deteriorated in 22% ($CI_{0.95}$ = 16–29%) (Figure 1).

No significant difference in the number of segments with perfusion preservation, improvement or deterioration in comparison to SPECT-0 was found in SPECT-I, -II or -III (Figure 1).

In SPECT-II in comparison to SPECT-I, no changes in perfusion were found in 66% ($CI_{0.95}$ = 57–72%) of observed segments, perfusion improved in 20% ($CI_{0.95}$ = 14–26%), and perfusion deteriorated in 14% ($CI_{0.95}$ = 9–19%) of segments. In SPECT-III in comparison to SPECT-II, no changes in perfusion were found in 79% ($CI_{0.95}$ = 71–83%) of segments, perfusion improved in 5% ($CI_{0.95}$ = 3–10%), and perfusion deteriorated in 15% ($CI_{0.95}$ = 10–21%) of segments (Figure 2). A significantly lower number of segments with perfusion improvement between 3rd and 6th month after operation was observed than earlier (between 3rd week and 3rd month after operation). Figure 3 shows an example of dynamic perfusion changes in a patient submitted to TMLR (in this patient during 6-month observation after TMLR perfusion improved or deteriorated but it was always better than before TMLR).

Angina (defined according to CCS classification) improved from before treatment class 3.2 ± 0.5 to class 1.9 ± 0.6 shortly after operation, class 1.8 ± 0.6 three months after, and class 1.6

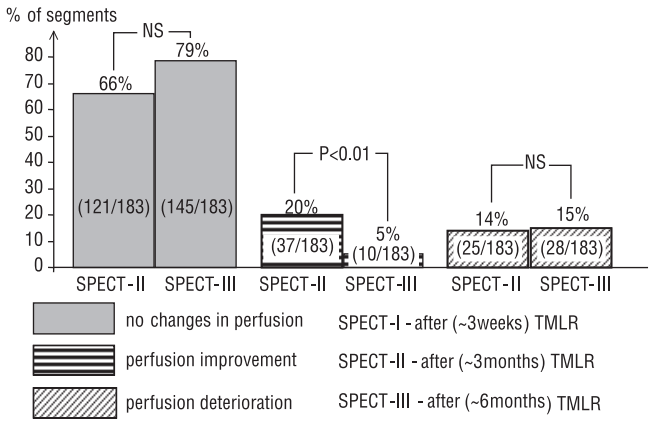

Figure 2. Changes of perfusion in preoperatively «viable» segments (n = 183) in SPECT-II and SPECT-III (always in comparison to the preceding SPECT).

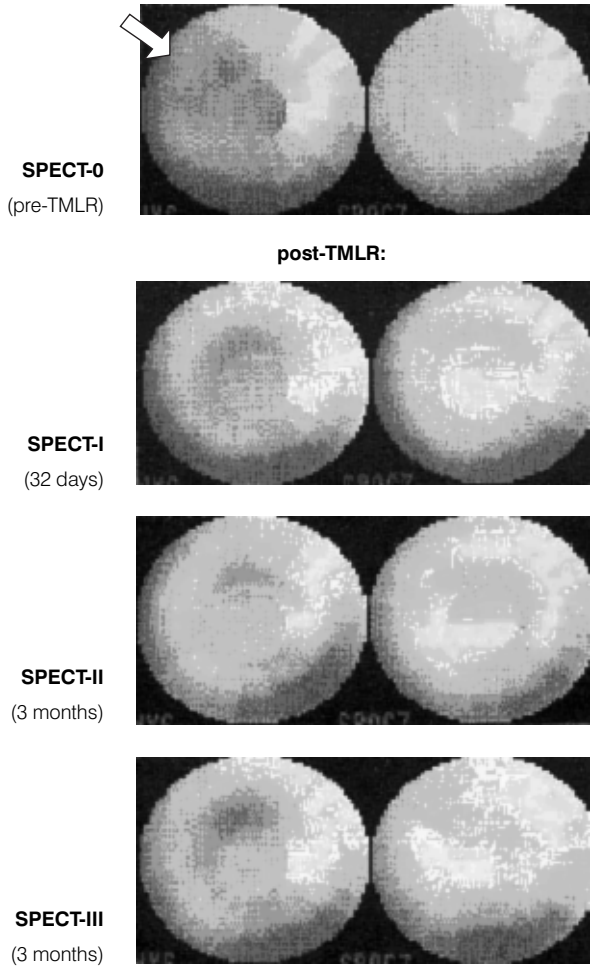

Figure 3. Example of perfusion changes in a patient submitted to TMLR (73-year-old male, 15 years after infero-posterior myocardial infarction). White colour corresponds to maximal uptake of Tc-99m-Sestamibi in the study. BULL'S-EYE in the left represents stress perfusion, in the right — rest perfusion. In pre-TMLR study (SPECT-0), transient perfusion defect in apex and antero-septal region is present. In early post-TMLR study (SPECT-I), significant perfusion improvement in this region is observed. In SPECT-II further perfusion improvement is observed. Three months later (SPECT-III) perfusion deterioration in stress is observed (in comparison to the preceding study). In all the studies also constant perfusion defect in inferior wall is present (transient in apical part and persistent in basal part of the wall). During 6-month observation after TMLR perfusion is always better than before TMLR.

± 0.6 six months after operation. In comparison to preoperative state, shortly after operation angina decreased by at least one class in 23/25 patients (92%, $CI_{0.95}$ = 74–99%), three months after operation — in the same 23/25 patients, and six months after operation — in 24/25 patients (96%, $CI_{0.95}$ = 80–100%).

Discussion

The laser perforation is often combined with CABG procedure whenever it is possible to achieve more complete revascularisation. After such treatment evaluation of the contribution of transmyocardial laser channels to postoperative results is nearly im-

possible. To join the international efforts in assessing the efficacy of high-power carbon-dioxide laser on myocardial perfusion we selected from a cohort of patients only those submitted to sole TMLR.

Our results suggest that TMLR gives an objective advantage in the form of regional perfusion improvement in a portion (approximately 30% and up to 41% taking into account the upper limit of confidence intervals) of segments with abnormal perfusion but preserved viability.

The results from previous works in which perfusion was assessed after sole CO_2 laser perforation are divergent. Some of them conclude that perfusion improves after TMLR. Horvath et al. (5) (in a group of n = 11 patients studied by Tc-99m-Sestamibi) observed perfusion improvement in transient defects (and, to a lesser extent, also in persistent defects) 3 months after TMLR and further improvement 6 months after operation. These results were confirmed in a later multicenter study in patients studied by Tc-99m-Sestamibi or Tl-201 (6). Our results are not easily comparable with results from those two reports as we included small fixed defects to 'viable' defects and in Horvath's works reversible defects are separated from any fixed defects. Lately there were also published two reports about one year results of randomised, controlled trials (11,12). March (11) reported the results from 12 United States investigation sites comprising patients randomly assigned to undergo sole TMLR or to receive continued medical management. Perfusion was evaluated by Tl-201 dipyridamole-redistribution-reinjection protocol and the LV was divided into 24 segments. There was significant improvement in perfusion for the TMLR group as shown by a reduction in the number of reversible defects at 3-, 6-, and 12-month follow-up. The biggest improvement was observed 12 months after TMLR when 20% of preoperatively reversible defects disappeared. We observed perfusion improvement on the level of approximately 30% of transient defects, but our definition of improvement was more tolerant (not only full perfusion normalisation but also any perfusion improvement in stress and/or rest). The UK single-centre trial reported by Schofield et al. (12) comprised patients randomly assigned to TMLR or antianginal therapy. Perfusion was evaluated by Tc-99m-Sestamibi protocol and LV was divided in 5 segments. In the TMLR group the number of segments with reversible ischemia decreased from 31% preoperatively to 20% at 3-month and to 22% at 6-month follow-up, but in that study the total number of the reversible defects existing at the moment of observation were calculated (old and new reversible defects) so our results cannot be compared with them.

On the other hand, Lubeck et al. (7), using Tc-99m-Sestamibi SPECT in rest and after dipyridamole found that 6 months after TMLR rest perfusion improved only in 6 of 162 evaluated segments (4%) and was worse in 26 segments (16%) with the conclusion that subjective clinical improvement claimed by approximately 80% of patients could not be explained by perfusion improvement. Also Nagele et al. (9) in patients in whom pre- and 6-month postoperative Tc-99m-Sestamibi study with dipyridamole were complete showed no significant difference in the number of ischemic and hibernating segments. The work of Nitzsche et al. (10), where PET was used for perfusion (and metabolism) evaluation, also indicated at 6-month follow-up that perfusion at rest and under stress in the lased ischemic segments remained unchanged. Frazier at al. (3), using SPECT with Tl-201 in stress and after redistribution observed that perfusion evaluated 3 and 6 months after TMLR did not change in comparison to pre-TMLR studies. But PET with N-13 ammonia applied in the same study and analysed separately for subepicardial and subendocardial layers of myocardium suggested that perfusion in subendocardium improves after TMLR.

Perfusion improvement observed in about 30% of transient or small persistent perfusion defects in our group of patients involves a relatively large percentage of segments submitted to laser perforation and this suggests that laser can be responsible for clinical state improvement in some patients — similar to the studies performed by Horvath and colleagues. During TMLR, channels permit blood flow from the LV to myocardium and its diffusion to interstitial tissue or further transportation via vessels crossing the channels. Many experimental papers show, however, that channels do not stay open over time. Consequently another explanation proposed for perfusion improvement observed in some studies is angiogenesis stimulated by laser (perfusion improvement by collateral circulation in stimulated collateral vessels). Probably both of these effects (direct perfusion and neovascularisation) are incorporated in TMLR and both may contribute to perfusion improvement to different degrees at different times after the operation. To ascertain the mechanisms longer follow-ups are necessary. It is possible that with our 6-month observation we are still in a period demonstrating only the short-term benefit offered by direct perfusion due to open channels (our slightly deteriorating results in the last SPECT support this speculation).

Alleviation of symptoms was significantly more frequent (observed in nearly all the patients) in every postoperative evaluation than parallel perfusion improvement. So it is possible that other mechanisms, like heart denervation, can contribute to pain alleviation (13).

The dynamic type of perfusion changes (only a part of defects stays in the same state from one post-TMLR study to the other) does not have an easy interpretation. Perfusion improvement with time during the first six months following operation in some of the preoperatively viable segments can be associated with the long process of angiogenesis. Perfusion deterioration in another part of segments can be associated with channel fibrosis.

Conclusion

Our evaluation of the history of segments with preoperatively transient or small persistent («viable») defects indicates that during the first 6 months after TMLR: 1) perfusion is better than before the operation in about one third of the segments, and 2) in some of these segments there are dynamic perfusion changes (improvement or deterioration) from one to the next postoperative moment of observation.

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