Technetium 99m-labeled tetrofosmin and iodine 123-labeled metaiodobenzylguanidine scintigraphy in the assessment of transmyocardial laser revascularization

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Objective: Transmyocardial laser revascularization is a new technique that improves symptoms in patients with refractory angina not amenable to conventional revascularization. The aim of this study was to assess whether transmyocardial laser revascularization produces changes in innervation, perfusion scintigraphy, or both that could explain the benefit to patients.

Methods: Sixteen patients (12 men and 4 women; mean age, 60 ± 8 years) with coronary artery disease were studied. Transmyocardial laser revascularization was performed in 39 myocardial areas supplied by a stenotic vessel. A technetium 99m-labeled tetrofosmin stress-rest tomographic scan and iodine 123-labeled metaiodobenzylguanidine planar scans were performed before and after transmyocardial laser revascularization (3 and 12 months later) to evaluate myocardial perfusion and innervation. Stress and rest perfusion images were quantified on a polar map. Ischemia uptake was also defined as the difference between rest and stress uptake for each area. Innervation planar images were visually analyzed and semiquantified.

Results: A significant decrease in angina class from baseline was observed at 3, 6, and 12 months after transmyocardial laser revascularization ($P < .005$). A significant decrease in ischemia uptake was also found between the pre-transmyocardial laser revascularization and the post-transmyocardial laser revascularization studies in treated areas ($P < .001$). A significant improvement in stress myocardial perfusion at 3 and 12 months after transmyocardial laser revascularization was only found in treated areas that were considered ischemic in the pre-transmyocardial laser revascularization study ($P < .05$). At 3 months, a significant myocardial innervation worsening was observed in treated areas ($P < .001$), with partial recovery at 12 months ($P < .05$).

Conclusion: The transmyocardial laser revascularization mechanism involves both perfusion improvement and denervation, mainly at 3 months, that partially recovered at 12 months.

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Transmyocardial laser revascularization (TMR) is a new technique for the treatment of refractory angina not amenable to either percutaneous angioplasty or bypass surgery.¹ Two different types of laser systems have been described, the CO₂ laser and the holmium-YAG laser. Clinical trials have demonstrated that both of these lasers significantly improve angina in those patients who are not candidates for conventional therapies.² However, the mechanism of TMR action is still poorly

Figure 1. Polar map divided into 9 regions of interest. 1 and 2, Anterior area; 3 and 4, septal area; 5 and 6, inferior area; 7 and 8, lateral area; 9, apical area.

understood. Its beneficial action on anginal class has been attributed to an improvement in regional blood flow through the newly created channels or to the stimulation of a neo-angiogenesis process, but significant differences in myocardial perfusion have been demonstrated in only a few publications.² Another mechanism for angina relief could be sympathetic denervation, which might improve angina without influencing myocardial perfusion in the early post-operative period, as has been observed in one positron emission tomography study.³

The aim of this study was to clarify the mechanism of action of TMR on anginal symptoms by testing the 2 hypotheses during the first year after TMR by using conventional nuclear medicine procedures. Therefore a prospective study was conducted to determine whether TMR with a holmium-YAG laser produces differences in myocardial perfusion, myocardial sympathetic innervation, or both, 3 or 12 months after revascularization and whether there is any possible relationship to the changes in functional class.

Materials and Methods

Patients

This study included 16 consecutive patients (12 men and 4 women; mean age, 60 ± 8 years) who underwent TMR as a part of a prospective study that was approved by the hospital ethics committee. All of the patients had coronary artery disease, had a preoperative Canadian Cardiovascular Society Score (CCSS) for angina of III or IV, and were not candidates for conventional coronary interventions. Six patients had type II diabetes mellitus, 12 had hypercholesterolemia, and 8 had hypertension. Eleven patients had a past history of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. None had recent myocardial infarction. Two patients had single-vessel disease, and 14 patients had multivessel disease (ie, 2 vessels in 3 patients and 3 vessels in 11 patients). Mean preoperative left ventricular ejection fraction was 57% ($57\% \pm 13\%$; range, 28%-77%). Informed consent was obtained from each patient enrolled.

Surgical Procedure

TMR was performed in 39 myocardial areas, defined as apical, anterior, lateral, or inferior, as is usually the case in perfusion tomographic studies. All treated areas were supplied by significant ($>70\%$) stenotic vessels, as determined by means of coronary arteriography. This criteria was also applied in innervation studies, although only planar scans were obtained.

Cardiac exposure was accomplished through a limited left anterior thoracotomy in the fifth intercostal space. A commercially available, 20-W, pulsed holmium-YAG laser (Eclipse, Cardiogenesis, Soophell, Ranch, Calif) was used to create transmyocardial channels. The laser was calibrated to deliver 6 to 8 W per pulse, and energy was delivered at the rate of 5 pulses per second through a flexible 1-mm optical fiber. Energy application was not gated to the cardiac cycle or in synchrony with diastole. The epicardial holes were performed every square centimeter throughout the apical two thirds of the left ventricle. Hemostasis was achieved by means of epicardial digital pressure, and the thoracotomy was closed in a routine fashion. A mean of 2.44 ± 0.89 areas were treated per patient, and a mean of 14.3 ± 3.2 channels were created per myocardial area (mean, 34 ± 14 channels; 10-43 channels per patient). Patients were monitored in the intensive care unit immediately after the operation. No bleeding complications were encountered in any patient.

Study Design

Anginal class was recorded at baseline and at 3, 6, and 12 months after TMR by a blinded individual with the CCSS score for angina. Technetium 99m-labeled tetrofosmin (^{99m}Tc -tetrofosmin) pharmacologic stress-rest single-photon emission computed tomography (SPECT) and a iodine 123-labeled metaiodobenzylguanidine (^{123}I -MIBG) innervation scan (planar and SPECT) were also performed at baseline and after TMR (3 and 12 months). Ten of the 39 areas treated had to be excluded in the innervation tomographic analysis because of a high level of extramyocardial activity. Because of this, only innervation planar scans were analyzed.

Scintigraphic Studies

A standard dipyridamole protocol was used for the pharmacologic stress testing. ^{99m}Tc -Tetrofosmin stress-rest imaging was performed according to the stress-rest protocol in which 7 to 9 mCi (260-333 MBq) of ^{99m}Tc -tetrofosmin are administered at stress, with stress imaging obtained 60 minutes later. Three hours later, 21 to 25 mCi (777-925 MBq) of ^{99m}Tc -tetrofosmin were injected at rest, obtaining rest imaging 60 minutes later. All images were processed according to standard protocols. The coronal slices were also generated to obtain a bull's-eye (polar map) that was later divided into different regions of interest (Figure 1). The ^{99m}Tc -tetrofosmin uptake of the left ventricular myocardium at stress and rest were measured quantitatively on the polar map by using an automatic program. Ischemia uptake was also defined as the difference between rest and stress uptake for each region of interest. The regions were matched with the myocardial treated areas, as shown in Figure 1. All the studies were analyzed by using the same protocol and criteria.

The innervation study was done between 4 and 20 days after the perfusion SPECT. The thyroid gland was blocked with 20 Lugol drops.⁴ Three hours later, 8 to 10 mCi (296-370 MBq) of

^{123}I -MIBG, an analog of norepinephrine, was injected. The study was performed 4 hours after injection to allow for clearance of nonspecific tissue uptake,⁵ and planar images (anterior and 45° and 70° left anterior oblique images) were acquired. Laser- and non-laser-treated areas in the different studies were visually evaluated by 3 experienced observers by means of consensus, as previously reported, and semiquantified as absent uptake (0), severe defect (1), moderate defect (2), mild defect (3), or normal area (4). The observers had no knowledge of the clinical data, perfusion scans, or coronary arteriography results.

Statistical Analysis

All measures recorded at baseline and follow-up were compared by using the Wilcoxon signed-rank test. Results are expressed as means $\pm$ SD.

Results

Clinical Data

One patient died at 6 months of a noncardiac cause (pneumonia), one patient did not undergo the 12-month perfusion study because of technical problems, and in another patient the 3-month scintigraphy was not performed because of a rib fracture. In the remaining patients the follow-up was completed.

CCSSs for angina during follow-up are presented in Figure 2, A. Considering the preoperative status, 14 of 16 patients improved their angina class at 3 months. In 11 patients improvement persisted at 6 and 12 months. In 5 patients there was an anginal class worsening between the 3rd and 12th months but without complete recovery to the basal status. There were only 2 patients who did not change anginal class during the first year. Overall, anginal class improved significantly from the preoperative period (3.38 ± 0.50) to 3 months (1.63 ± 0.72 , $P < .001$), 6 months (1.80 ± 0.86 , $P < .005$), and 12 months (1.93 ± 0.80 , $P < .005$) after TMR.

Perfusion Studies

Areas with normal uptake ($>85\%$) or absent uptake ($<20\%$) in the pre-TMR study did not change after the operation.

In laser-treated areas a significant decrease in ischemic (rest-stress) myocardial uptake was found between the pre-TMR study (8.00 ± 6.45) and the 3-month (1.03 ± 5.65 , $P < .001$) and 12-month (-0.05 ± 7.05 , $P < .001$) post-TMR studies (Figure 2, B, and 3).

No statistical differences were found in stress or rest perfusion uptake between laser- and nonlaser-treated areas during follow-up. However, in the subgroup of patients with ischemic areas before TMR, a significant improvement was also found at stress in treated areas (Figure 3) between the pre-TMR study (68.56 ± 15.77) and the 3-month (73.49 ± 14.15 , $P < .05$) and 12-month (69.52 ± 15.15 , $P < .05$) post-TMR studies (Figure 3).

A. Anginal class (CCSS)

B. Ischaemia uptake (Rest-Stress) in treated areas

C. Innervation in treated areas

Figure 2. A, Evolution of anginal class in the different patients. B, Evolution of ischemia uptake (rest-stress myocardial uptake) in laser-treated areas. C, Evolution of myocardial innervation in laser-treated areas. Data are shown for before the operation (pre-TMR) and at 3 and 12 months after the operation (post-TMR).

Innervation Studies

Five areas were excluded from this evaluation because of a high level of lung or liver activity ($n = 3$). Areas without uptake did not change during follow-up (8/34). Of the 26 areas with basal uptake, innervation worsened at 3 months in 15 and did not change in 10. The remaining area corresponded to a patient not undergoing the 3-month studies. Nine of the worsened areas had improved innervation at 12 months (Figure 2, C, and 4). Of the remaining 6 worsened areas, 3 did not change, and 2 continued to worsen at 12 months, whereas one corresponded to a patient who died at

Figure 3. ^{99m}Tc -Tetrofosmin stress-rest SPECTs. The patient was referred for right coronary artery disease. TMR was performed on the inferior area. Before the operation, the stress tomography showed a moderate inferior defect that improved at rest. Twelve months after the operation, the inferior territory had improved its perfusion at stress and had decreased ischemic uptake (rest-stress) compared with basal study.

6 months. Overall, a significant decrease in innervation from baseline (2.50 ± 1.58) was found in the laser-treated areas at 3 months (1.94 ± 1.56 , $P < .001$) and 12 months (2.29 ± 1.53 , $P < .01$). It is worth noting that a significant innervation improvement was detected from 3 to 12 months ($P < .05$). Finally, of the 9 normal preoperative innervation areas, 6 did not change during follow-up.

Considering the results on a patient-per-patient basis, in 10 of the 15 patients who were studied at 3 months, there was both angina improvement and denervation in at least one of the laser-treated areas. Moreover, in 4 of the 5 patients whose anginal class worsened between the 3rd and 12th months, there was also a reinnervation in at least one of the laser-treated areas.

Discussion

Evolution in Clinical Symptoms

TMR has been introduced as therapy for patients with medically refractory angina and diffusely diseased vessels that are not amenable to conventional revascularization therapies.^{1,2,6} In almost all published TMR studies, perfusion scintigraphic reversible ischemia is a main inclusion criterion.⁷ In our study the main inclusion criterion was the presence of severe refractory angina and diffuse coronary artery disease determined by means of coronary arteriography independently of the perfusion scan. In spite of this, a

significant improvement in angina class was documented at 3, 6, and 12 months with respect to the preoperative status. Only 2 patients experienced no improvement in clinical symptoms. In one of these patients with previous myocardial infarction, the only treated area had less than 20% perfusion uptake on the polar map and absent uptake in the innervation study.

In our study angina class improved at 3 months after TMR but tended to worsen later on without reaching the preoperative status. In line with our results, different authors⁸⁻¹⁰ found a trend toward worsening over time; in contrast, patients studied by Frazier and colleagues¹¹ had improved angina status with time.

Perfusion Improvement

Improved anginal status has been thought to be secondary to increased myocardial perfusion,^{12,13} either through patent TMR myocardial channels or through a process of neoangiogenesis developing in the treated areas. Permeability of laser channels is controversial. Although there is histologic evidence of early occlusion of laser channels,¹⁴ inflammatory cells recruited in response to laser-induced myocardial injury might release angiogenic growth factors¹⁵ that might result in neovascularization. This is a slow process beginning 2 to 3 weeks after TMR, with a progressive increase thereafter.¹³

Figure 4. ^{123}I -MIBG left anterior oblique 45° planar scans. The patient was referred for right coronary and left circumflex artery disease. TMR was performed on the inferior and lateral areas. The planar scans showed an inferolateral moderate defect before the operation, a severe defect at 3 months, and a partial recovery at 12 months.

Four different randomized studies comparing TMR with medical treatment have been published.^{2,8,11,16} In all, 4 TMRs produced a significantly better clinical outcome, but only one found an improvement in myocardial perfusion.¹¹ This discrepancy could be due to a difference in patient selection, scintigraphic methods, or surgical technique.¹⁷

In our study a significant decrease in ischemia uptake was found in laser-treated areas between the pre-TMR and post-TMR studies (3 and 12 months), as has been observed in other published studies.⁷ When analyzing only laser-treated areas that were considered ischemic before the operation, a significant stress perfusion improvement was also found between pre-TMR studies and the 3- and 12-month post-TMR studies.

Denervation

The second mechanism thought to be involved in TMR is denervation.³ Denervation might damage cardiac nerve fibers¹⁸ that convey pain, improving angina without influencing myocardial perfusion. In our experience, as has been reported by others,¹⁹ it is difficult to obtain adequate tomographic innervation scans because the reconstruction process can vary widely from one trained observer to another, especially in the most denervated myocardium. Therefore only planar scans were considered in our study.

It is known that adrenergic function is more sensitive to ischemia than the associated perfusion abnormality²⁰ and that repetitive episodes of ischemia can induce a permanent loss of neuronal MIBG uptake in the myocardium.²¹ This fact might explain the lack of correlation between perfusion and innervation uptake.

There has been one positron emission tomography study that demonstrates denervation induced by TMR in human subjects without long-term follow-up,³ but myocardial de-

nervation has never been demonstrated in conventional scintigraphic studies until now. In our study innervation was worse in the visual analysis at 3 months than preoperatively in 15 laser-treated areas ($P < .005$). At 12 months, 9 of these 15 areas had improved ($P < .05$). As has been described in the "Results" section, in 10 of the 15 patients who were studied at 3 months, there was both angina improvement and denervation in at least one of the laser-treated areas. Moreover, in 4 of the 5 patients whose anginal class worsened between the 3rd and 12th months, there was also a reinnervation in at least one of the laser-treated areas. Therefore these results would indicate that reinnervation can take place in the long term (12 months), as found in patients undergoing heart transplantation.²² This hypothesis could explain why angina class in our patients seems to worsen during follow-up.

Six normal preoperative areas did not change in terms of innervation on visual analysis during the entire study. Although the analysis was not sensitive enough to detect minimal changes, it is possible that some differences in their response could be related to variations in surgical technique or patients' differences.¹⁷ Therefore dose response could be related to the number of channels made and might influence evaluation of TMR efficacy.²³

It must be underlined that denervation might have a detrimental effect on the heart. Because laser energy ablates myocardial tissue, there is concern that TMR might decrease angina by creating myocardial zones of necrosis. However, neither differences in fixed perfusion defects² nor a significant difference in the rate of survival at 12 months between the TMR and medically treated groups have been demonstrated,^{2,11} and none of our patients had a myocardial infarct or severe arrhythmia during the follow-up period.

Study Limitations

First, the number of patients and the areas involved were relatively small. However, this limitation is partially overcome by the fact that each patient has been studied at 3 different time points. Second, MIBG uptake might be influenced by medication.²⁴ Although this drug interaction could be an important limitation, the study was designed as a paired data trial, and patients were not advised to discontinue therapy during the follow-up period. Also, the presence of diabetes might interfere with the biodistribution of MIBG. We have found only 2 areas with worse innervation at 12 months when compared with the 3-month study, and both of these corresponded to a diabetic patient. Finally, a third limitation might derive from the nonexact anatomic matching between the treated areas and the scintigraphic areas, especially when MIBG is used. In this regard, however, it is worth noting that perfusion quantification was automatic and that MIBG planar image evaluation and final correlation were made by 3 observers without knowledge of the clinical data.

Conclusion

The mechanism of TMR action is probably multifactorial, including both perfusion improvement and myocardial denervation, mainly in the early postoperative period, in laser-treated areas. Larger long-term studies are warranted to confirm the possibility of reinnervation at 12 months after TMR.

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