Cardiac denervation after clinical transmyocardial laser revascularization: Short-term and long-term iodine 123-labeled meta-iodobenzylguanide scintigraphic evidence

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Objectives: This study was designed to investigate whether transmyocardial laser revascularization induces myocardial denervation and to correlate this with myocardial perfusion and clinical status.

Methods: Transmyocardial laser revascularization was performed with a Holmium:YAG (n = 3) or xenon chloride excimer laser (n = 5). Preoperative and postoperative iodine 123-labeled meta-iodobenzylguanide SPECT scintigraphy to assess cardiac innervation and perfusion scintigraphy were also performed. Furthermore, New York Heart Association functional angina class and quality of life were assessed.

Results: In all patients postoperative iodine 123-labeled meta-iodobenzylguanide SPECT showed significantly decreased uptake and therefore sympathetic myocardial denervation at up to 16 months' follow-up (average preoperative and postoperative summed defect scores of 14.8 ± 5.3 and 24.5 ± 4.2 , respectively; $P = .00005$). In 86% of segments, the decreased meta-iodobenzylguanide uptake could be correlated to the treated area. In all patients angina was reduced by 2 or more classes at 12 months' follow-up, and quality of life improved significantly.

Conclusions: Transmyocardial laser revascularization-induced improvement of angina and quality of life can be explained by destruction of nociceptors or cardiac neural pathways, changing the perception of anginal pain.

Transmyocardial laser revascularization (TMLR) is a therapy for severe angina pectoris refractory to antianginal medication, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. At low operative risk, CO₂ and Holmium:YAG TMLR relieve angina pectoris¹⁻⁵ and improve quality of life (QOL)^{1-3,6} and exercise time.^{1,2,4,5} Furthermore, nonrandomized xenon chloride (XeCl) excimer TMLR achieves similar anginal relief.^{7,8} However, the angina-relieving mechanism is still poorly understood and probably multifactorial, reducing acceptance of TMLR. The original idea that direct perfusion from the left ventricle through the laser channels improves myocardial perfusion⁹ currently has little support.¹⁰ Other hypotheses are TMLR-induced stimulation of angiogenesis¹¹ or destruction of cardiac nociceptors and afferent nerve fibers,¹² which is investigated in the study reported here. Only one other clinical study has reported sympathetic myocardial denervation after Holmium:YAG TMLR.¹³ However, in that study 2 of 8 patients postoperatively showed increased myocardial innervation, and 5 had diabetes mellitus, introducing possible interference through diabetic neuropathy. Furthermore, denervation location was not correlated with the treated area.

In the present study we divided the heart in segments and related changes in sympathetic innervation with treated area, perfusion, and clinical performance in patients treated with Holmium:YAG or excimer TMLR. We excluded confounding factors, such as preoperative myocardial infarction and diabetes mellitus, in all but one patient.

Methods

Study Design

Patients were recruited from a randomized clinical trial (RCT) investigating the clinical efficacy of Holmium:YAG and XeCl excimer TMLR. Inclusion criteria were angina pectoris of New York Heart Association functional class III-IV/IV (not eligible for percutaneous transluminal coronary angioplasty or coronary artery bypass grafting as determined by an experienced cardiac surgeon and interventional cardiologist at the trial center), a scintigraphically proved reversible perfusion defect, a left ventricular ejection fraction of 35% or greater, and a life expectancy of greater than 1 year. Exclusion criteria were ventricular arrhythmias requiring treatment, clinically manifest heart failure, severe intrinsic hemorrhagic disorders, and lack of informed consent.

Between March 1998 and June 2001, 30 of 118 patients screened for TMLR were included in the RCT, of which 8 were included in the study reported here. All other RCT patients were excluded either because of diabetic neuropathy or because of previously documented myocardial infarction (maximal CK-MB of $>25 \mu\text{g/L}$) because denervation and regeneration of neural tissue occurs in varying degrees in viable myocardium adjacent to infarcted myocardium. Iodine 123-labeled meta-iodobenzylguanide (^{123}I -MIBG) SPECT scintigraphy was performed at baseline and postoperatively at 1 ($n = 5$), 4 ($n = 1$), 9 ($n = 1$), or 16 ($n = 1$) months' follow-up. Myocardial perfusion was evaluated by means of technetium 99m-labeled tetrofosmin ($^{99\text{m}}\text{Tc}$ -TF) SPECT scintigraphy at baseline (at 3 months $\pm$ 3 weeks before TMLR) and at 3 and 12 months' follow-up. Angina class, QOL, and exercise time were assessed at baseline and at 3, 6, and 12 months. The in-hospital medical ethical committee approved the study, and all patients provided written informed consent. The funding agency played no role in data interpretation.

Angina Class, QOL, and Exercise Time

Angina class was assessed by one investigator (JAPvdS); QOL was assessed by using the Seattle Angina Questionnaire (SAQ)¹⁴ and the EuroQol Standardized Questionnaire's Visual Analog Scale (VAS),¹⁵ which ranges from 0% (worst imaginable health) to 100% (best imaginable health). Exercise time was assessed by using a modified Bruce protocol.

Myocardial Perfusion Scintigraphy

Myocardial perfusion scintigraphy was performed according to the guidelines of the American Society of Nuclear Cardiology¹⁶ by using $^{99\text{m}}\text{Tc}$ -TF and a 2-day stress-rest protocol. Stress was induced by means of exercise (bicycle ergometry) or, if exercise was contraindicated or suboptimal, pharmacologically ($0.14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ adenosine for 6 minutes). For each individual patient, the stress modality used at baseline was also used at follow-up.

All patients fasted for 4 hours before perfusion scintigraphy. $^{99\text{m}}\text{Tc}$ -TF (approximately 500 MBq; Nycomed Amersham, Buck-

inghamshire, United Kingdom) was injected at maximal exercise or after 4 minutes of pharmacologic stress and also at rest. SPECT was performed 1 hour after $^{99\text{m}}\text{Tc}$ -TF injection. Images were obtained with the patient in the prone position by using a 3-headed gamma camera (MultiSPECT-3; Siemens, Hoffman Estate, Ill) with low-energy and high-resolution collimators, a 20% energy window centered on the $^{99\text{m}}\text{Tc}$ 140-keV photopeak, 20 views per camera head, and 45 seconds per view in a 64×64 matrix by using the camera autocontour facility and standard filtered back projection without applying attenuation correction. Short-axis slices were obtained and used for a segmental bull's-eye reconstruction. Stress and rest images were scored by using a validated and widely used 3-dimensional sampling and analysis algorithm, which generates a 5-point $^{99\text{m}}\text{Tc}$ -TF uptake score (a measure for myocardial perfusion) for each myocardial segment.¹⁷ Uptake was classified as normal (0), equivocal abnormal (1), mildly abnormal (2), moderately abnormal (3), or severely abnormal (4). With this classification, the algorithm used the stress and rest scans to calculate (per patient) a summed stress score, a summed rest score (SRS), and a summed difference score (SDS), which is generated from the summed stress score and SRS. Because the 2 basal-septal segments represent the membranous part of the septum, they were excluded from the SDS, leaving the sum of 18 segments. This 18-segment SDS was used in further analyses. The nuclear medicine physicians (HJV and BLFvE-S), blinded to treated area and ^{123}I -MIBG SPECT, reviewed the generated scores per segment. In case of artifact scoring by the algorithm program, scores were manually adjusted.

^{123}I -MIBG SPECT

MIBG and noradrenaline have similar molecular structures, and both use the same uptake and storage mechanisms in sympathetic nerve endings.¹⁸ ^{123}I labeling of MIBG enables scintigraphic visualization of the cardiac sympathetic nervous system, and uptake is therefore a measure of innervation. Because β -blocker therapy affects MIBG uptake, it is noteworthy that the dosage of β -blockers of each individual patient at preoperative MIBG scintigraphy was identical to that at postoperative MIBG scintigraphy.

All patients received a single oral dose of 100 mg of potassium iodine to block thyroid uptake of free radioactive iodine 1 hour before administration of the radiopharmaceutical. SPECT was performed 4 hours after intravenous administration of 185 MBq of ^{123}I -MIBG (Nycomed Amersham), as described above for $^{99\text{m}}\text{Tc}$ -TF SPECT, by using medium-energy collimators, an energy window centered on the ^{123}I 159-keV photopeak, and 60 seconds per view. Data reconstruction was performed with a Wiener filter. Short-axis slices were obtained and used to construct the same segmental bull's-eye, as described above. The fully automatic border-detection feature of a 3-dimensional sampling and analysis algorithm¹⁷ was used to delineate myocardial borders. Despite MIBG uptake in the lungs and liver, in only 1 of 16 scans was manual correction of the automatic delineation required (performed by the 2 nuclear medicine specialists), and therefore in 15 ^{123}I -MIBG SPECT scans the automatic delineation was successful.

The program described above could not be used for the ^{123}I -MIBG SPECT analysis because it is not validated for ^{123}I -MIBG SPECT. Therefore ^{123}I -MIBG SPECT results before and after TMLR were visually analyzed by the 2 nuclear medicine physi-

Figure 1. Results of the Seattle Angina Questionnaire (SAQ) and EuroQol Questionnaire's visual analogue scale (VAS). *VAS and all SAQ domains; † VAS and SAQ domains with exception of treatment satisfaction.

cians, who were blinded to treated area and perfusion scintigraphy. However, for each segment, an identical 5-point scoring system was used for MIBG uptake: normal (0), equivocal abnormal (1), mildly abnormal (2), moderately abnormal (3), or severely abnormal (4). For each patient, a preoperative summed score, a postoperative summed score, and a summed myocardial denervation score, defined as the postoperative summed score minus the preoperative summed score, was calculated for 18 segments.

Operative Technique and TMLR Procedure

A left lateral thoracotomy was performed in the fifth or sixth intercostal space, and TMLR was performed in the ischemic area of the left ventricular wall as preoperatively assessed by means of perfusion scintigraphy. Approximately 1 channel per square centimeter was created with excimer TMLR, and 1 channel per 1.5 cm² was created with Holmium:YAG TMLR. Transmyocardial penetration was confirmed by using transesophageal echocardiography.

The Holmium:YAG laser (NSLX-6; CardioGenesis Corp, Sunnyvale, Calif; wavelength of 2.1 μ m, 2.0 J per pulse, pulse duration of 350 μ s, 19 Hz) was used with a 1.9-mm diameter spherically tipped fiber and its own trigger device. The myocardium was perforated by gently and manually advancing the fiber during 2 to 3 triggered cardiac cycles (3 pulses per cycle). With the XeCl excimer laser (Max-20; Medolas, Munich, Germany; 308 nm, 37–40 mJ per pulse, 110 ns, 40 Hz), which was combined with a hospital-built electrocardiographic trigger device, the myocar-

dium was perforated by gently and manually advancing a 1-mm-diameter flat-tipped fiber during 3 to 4 triggered cardiac cycles (4–5 pulses per cycle).

Basal-septal and midseptal segments were not treated to prevent damage to the bundle branches. Apicoseptal segments were sometimes treated through the apex. Immediately after the procedure, the surgeon recorded the treated segments by drawing them into a bull's-eye presentation of the heart. Postoperative care was identical to that after cardiac surgery. Preoperative antianginal medication was resumed on the first postoperative day. Myocardial damage was assessed on the basis of maximal CK-MB.

Statistical Analysis

Student *t* tests (all paired and 2 tailed) were used for statistical analyses of preoperative and postoperative angina class, QOL, exercise time, myocardial perfusion scintigraphy (SDS), and ¹²³I-MIBG SPECT scintigraphy (summed scores). Results are given as means $\pm$ SD.

Results

Tables 1 and 2 summarize preoperative, perioperative, and postoperative patient characteristics. Deliberately, the number of Holmium:YAG laser channels was lower than with the excimer laser because at the laser settings used, 1.9-mm Holmium:YAG fibers induce more mechanical and thermal

TABLE 1. Preoperative patient characteristics

Patient no.	Sex	Age (y)	Previous CABG	Previous PTCA	LVEF (%)	DM	Cardiac medication
1	M	61	+	—	56	—	β -b/Ca/Ni
2	M	51	+	—	53	—	β -b/Ca
3	M	53	+	+	61	—	β -b/Ni
4	M	60	+	—	50	—	β -b/Ca/Ni
5	F	57	—	+	58	—	β -b/Ca/Ni
6	M	48	+	—	61	+	β -b/Ca/Ni
7	M	59	+	+	60	—	β -b/Ca/Ni
8	M	60	+	—	55	—	β -b/Ca/Ni

CABG, Coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; β -b, beta-blocker; Ca, calcium antagonist; Ni, long-acting nitrate.

TABLE 2. Perioperative and postoperative patient characteristics

Patient no.	Laser	No. of channels	CK-MB _{max} (μ g/L)	NYHA preoperative	NYHA 3 mo follow-up	NYHA 12 mo follow-up
1	Excimer	64	23	3	2	1
2	Holmium:YAG	43	36	4	2	2
3	Excimer	59	101†	4	2	2
4	Excimer	50	43	4	2	2
5	Holmium:YAG	27	28	4	2	2
6	Excimer	50	29	4	2	2
7	Holmium:YAG	23	18	4	1	2
8	Excimer	42	25	4	1	2
Mean $\pm$ SD	Excimer:	53 $\pm$ 9	44 $\pm$ 33	3.8 $\pm$ 0.5	1.8 $\pm$ 0.5*	1.6 $\pm$ 0.6*
	Holmium:YAG	31 $\pm$ 11	27 $\pm$ 9	4.0 $\pm$ 0	1.7 $\pm$ 0.6*	2.0 $\pm$ 0*

* $P < .05$ compared with preoperative value.

†Because of a small subendocardial infarction that neither affected wall motion nor ^{123}I -MIBG scintigraphy value.

NYHA, Angina class according to the classification of the New York Heart Association.

injury than 1-mm excimer fibers. The average in-hospital stay was 9 days for both the Holmium:YAG and excimer TMLR groups. None of the patients died during follow-up.

Angina Class, QOL, and Exercise Time

Angina improved by 2 or more classes (New York Heart Association) in 7 of 8 patients at 3 months' follow-up and in all 8 patients at 12 months' follow-up (Table 2). Overall, QOL (Figure 1) was significantly improved at 3 months' follow-up in all 5 domains of the SAQ and in the VAS. These improvements were still significant at 12 months' follow-up with the exception of the treatment satisfaction domain of the SAQ. No differences were seen between patients undergoing treatment with the Holmium:YAG and excimer lasers. Overall, TMLR did not improve exercise time (526 $\pm$ 201 seconds preoperative vs 558 $\pm$ 217 and 549 $\pm$ 222 seconds at 3 and 12 months).

Myocardial Segments Treated With TMLR

Of 144 segments (8 patients, 18 segments per patient), 74 were treated with TMLR (range, 6-14 segments per patient). Furthermore, 63 of 144 segments demonstrated a reversible

perfusion defect preoperatively; 58 of these were eligible for TMLR (the other 5 were midseptal segments), and 46 (79%) of these 58 segments were actually treated with TMLR. Consequently, 46 (62%) of 74 treated segments preoperatively showed a reversible perfusion defect. Of the remaining 28 treated segments, 7 showed a minimal rest score (of 1 or 2), and the remaining 21 showed no defects. Figure 2 summarizes the results.

^{123}I -MIBG SPECT and Myocardial Perfusion Scintigraphy

Table 3 summarizes the scintigraphic results. Preoperatively, 27 of 62 segments with a decreased MIBG uptake corresponded with areas at risk on perfusion scintigraphy. All patients had a positive summed myocardial denervation score, and MIBG uptake decreased after TMLR in 45% of treated segments (Figure 2). If we assume that there was no significant difference in the maximum preoperative and postoperative MIBG uptake (that in each individual was in a nontreated basal segment and preoperatively was at the same cardiac location as postoperatively), we can conclude that none of the 144 segments showed increased innerva-

tion. Overall, in 50 segments MIBG uptake was decreased after TMLR, and 33 (66%) of these had been treated. No significant differences in MIBG uptake were found between Holmium:YAG and excimer TMLR. On average, perfusion remained unchanged at 3 and 12 months. No postoperative increase in scar size was observed (average SRS was 4.4 ± 5.2 at baseline vs 6.1 ± 5.0 at 3 months [$P = .2$] and 4.1 ± 4.6 at 12 months). Figure 3 shows a patient example.

Discussion

Our results support previous evidence that denervation plays a role in anginal relief after TMLR.¹³ To our knowledge, this is the first segmental analysis of innervation correlated to perfusion and TMLR-treated area. Also, because no patient had diabetic neuropathy (because only one diabetic was included with no signs of neuropathy), the possible interference of diabetic neuropathy with the studied denervation effects is minimized.

Denervation Hypothesis

The denervation hypothesis originates from the observation that TMLR can relieve angina within days. Because functional angiogenesis is unlikely to occur within days, anginal relief through direct intervention in (neural) pain sensation by means of cardiac denervation is thought to play a role. Anginal perception is believed to be transported to the brain through cardiac nociceptors and afferent fibers.¹⁹ The latter are located superficially in the epicardium²⁰ and thus are easily accessible by means of TMLR. Other indications that interference in neural pathways can contribute to anginal relief are the beneficial effects on angina of neuromodulating therapies, such as spinal cord stimulation and thoracic epidural anesthesia.^{21,22} Also, diabetics frequently experience silent ischemia (without anginal complaints) because diabetic neuropathy often destroys sympathetic myocardial fibers.²³ Moreover, patients lack angina after heart transplantation, despite development of extensive coronary artery disease.

Experimental Evidence

Experimental myocardial denervation studies after TMLR show conflicting results.¹⁰ In a canine model Kwong and colleagues¹² reported that Holmium:YAG TMLR destroys cardiac nerve fibers, as assessed on the basis of cardiac afferent nerve function (epicardial bradykinin) and tyrosine hydroxylase measurements 2 weeks postoperatively. Using the same assessment and follow-up, Yamamoto and associates²⁴ reported radiofrequency TMR-associated denervation in canines comparable with that after TMLR. In contrast, Minisi and coworkers²⁵ and Hirsch and colleagues²⁶ reported no effect of Holmium:YAG TMLR in canines by using various acute neural assessments. However, Arora and associates²⁷ also studied TMLR effects (after 4 weeks),

Figure 2. Venn diagram of segments treated with TMLR (dark gray) preoperatively showing a reversible perfusion defect (light gray) and a positive myocardial denervation score (white). As an example, 28 segments preoperatively showed a reversible perfusion defect, were treated with TMLR, and postoperatively did not show denervation. Of the 14 segments that preoperatively showed a reversible perfusion defect, were not treated, and did not show denervation, 5 were midseptal segments, which cannot be treated. Consequently, a total of 58 reversible perfusion defect segments were eligible for TMLR.

and they concluded that remodeling of the intrinsic cardiac nervous system might account, at least in part, for delayed symptomatic benefits in patients undergoing TMLR. Finally, one study, using the same assessment techniques as described in the clinical study reported here (MIBG SPECT) in a 3-day survival porcine model, has reported a negligible effect of endocardial Holmium:YAG channels (percutaneous myocardial revascularization [PMR]) on denervation.²⁸ This might be explained by the epicardial location of the sympathetic fibers (less damaged by PMR) and because PMR affects myocardium to a lesser extent. These differences might also explain the reported difference in clinical efficacy between TMLR and PMR.²⁹

Clinical Evidence

Al-Sheikh and coworkers¹³ have investigated sympathetic innervation and myocardial ischemia with positron emission tomography imaging by using ¹¹C-hydroxyephedrine and ¹³N-ammonia, respectively. In 8 patients undergoing Holmium:YAG, positron emission tomographic imaging was performed at baseline and 2 months postoperatively. All patients experienced improvement of 2 or more angina classes. As in our study, TMLR did not significantly affect myocardial perfusion. ¹¹C-hydroxyephedrine measurements showed decreased innervation after TMLR in 6 of 8 patients and, surprisingly, increased innervation in 2 patients. Pathophysiologically, this increase is difficult to explain. Nevertheless, the authors concluded that TMLR causes sympathetic myocardial denervation without affecting perfusion.

Compared with the study of Al-Sheikh and coworkers,¹³ our design has several advantages. First, only one of our patients had diabetes (vs 5 of 8 in Al-Sheikh and coworkers' study), which minimizes the possible interference of neuropathy with the scintigraphic results. In this patient (with

Figure 3. Bull's-eye representation of myocardial innervation and perfusion in a representative case (patient 4) showing denervation after TMLR. Eight months postoperative ^{123}I -MIBG scintigraphy (B) shows, compared with preoperative values (A), anterolaterally decreased uptake corresponding with the TMLR-treated area. C displays the difference between preoperative and postoperative ^{123}I -MIBG scintigraphy compatible with denervation in the TMLR-treated area. No improvement in ischemia was observed in the TMLR-treated area 12 months postoperatively (E) compared with preoperative values (D, both panels displayed as reversibility plots). The level of radioactivity (A and B) and difference (C, D, and E) is encoded from low (black) through medium (yellow) to high (white). F shows the 18-segment model of the left ventricle: 4 basal, 6 midventricular, 6 preapical, and 2 apical segments. The gray segments, representing the membranous part of the interventricular septum, were excluded in all analyses. *Segments never treated with TMLR. MPS, Myocardial perfusion scintigraphy; ANT, anterior; LAT, lateral; INF, inferior; SEPT, septal.

TABLE 3. Results of ^{123}I -MIBG SPECT and myocardial perfusion scintigraphy

Patient no.	^{123}I -MIBG SPECT scintigraphy			Myocardial perfusion scintigraphy		
	Preoperative SS	Postoperative SS	SMDS	Preoperative SDS	3 mo SDS	12 mo SDS
1	19	26	7	6	9	8
2	19	28	9	28	16	23
3	12	22	10	39	26	14
4	14	26	12	14	21	22
5	8	24	16	6	12	6
6	21	30	9	9	7	11
7	18	24	6	3	6	6
8	7	16	9	8	3	3
Mean $\pm$ SD	14.8 $\pm$ 5.3	24.5 $\pm$ 4.2*	9.8 $\pm$ 3.1	14.1 $\pm$ 12.7	12.5 $\pm$ 7.9	11.6 $\pm$ 7.5

SS, Summed score; SMDS, summed myocardial denervation score; SDS, summed difference score.

* $P = .00005$ compared with preoperative value (and $P = .0002$ when excluding patient 6, who had diabetes mellitus type II).

type II diabetes) no clinical signs of neuropathy were identified. Furthermore, even when excluding this patient from analyses, the observed denervation in the remaining 7 patients was still highly significant ($P = .0002$). Second, we

assessed denervation at 1, 4, 9, and 16 months and found clinical benefit and denervation at all follow-up times. Given the controversy concerning the long-term efficacy of TMLR, this is an important finding, even though it was

investigated in only a few patients. Third, this study compares for each of 18 segments in the areas that showed denervation versus the TMLR-treated areas. Of 74 TMLR-treated segments, 33 (45%) segments showed denervation. Apparently, not every transmyocardial laser perforation destroys nerves or at least not enough to significantly decrease MIBG uptake. However, because all patients postoperatively showed decreased MIBG uptake and all experienced significant clinical improvement, we hypothesize that this incomplete denervation of treated segments is sufficient to relieve angina. Inversely, 33 (66%) of 50 denervated segments were treated. Of the remaining 17 nontreated segments, 10 were preapical or apical segments. As also postulated by Al-Sheikh and coworkers,¹³ denervation of nontreated (pre-) apical segments might result from proximal (upstream) lesions that interrupt sympathetic nerve fibers that connect with the apex. Consequently, we concluded that in 86% (43/50) of all segments that showed denervation, decreased MIBG uptake could be attributed to TMLR. Why denervation occurred in the remaining 7 nontreated segments is unclear. Although myocardial ischemia might play a role in cardiac neuronal damage,³⁰ only 3 of the 7 remaining nontreated segments showed ischemia, leaving unexplained denervation in 4 segments. These denervated segments were distributed over 3 patients (with 1 month's follow-up): 1 segment showed a denervation score of 2, and 3 segments showed denervation scores of only 1. Given our method of recording the treated area, it is entirely possible that a shift or uncertainty of some centimeters might occur in the TMLR polar plot compared with in the scintigraphic scans. As a result, this could have led to minor errors in our analysis, and this might explain some of the inconsistencies. We have considered 3 other possible explanations for the denervation in the 4 segments: (1) spontaneous denervation, (2) thoracotomy-related denervation, or (3) a variation in observed MIBG uptake. However, we rejected them because (1) in our opinion spontaneous denervation is unlikely given the short time span used in this study, (2) there is no theoretic basis for decreased MIBG uptake solely induced by the thoracotomy, and (3) any uptake-related variation would be expected to be 2 sided. Because none of the investigated segments showed increased innervation, this last explanation also seems unlikely.

Finally, we performed both Holmium:YAG and excimer TMLR. Despite differences in laser-tissue interaction,¹⁰ no laser-specific differences in denervation or myocardial damage (CK-MB) were observed. However, for this comparison, groups were too small to draw definite conclusions. If denervation would be the only working mechanism of TMLR, it is highly likely that the antianginal effect would decrease with reinnervation of the myocardium. Similarly, a return of anginal complaints is observed after reinnervation

of transplanted hearts. However, a sustained relief might be induced if the initial TMLR-induced anginal relief caused by denervation results in, for instance, a change in lifestyle with increased exercise (inducing increased capillary shear rates and arteriogenesis).

Conclusion

In all patients undergoing Holmium:YAG and excimer TMLR, evidence of denervation was found, whereas no improvement was seen in perfusion. The coinciding improvement in angina and QOL suggests that myocardial denervation plays an important role in the efficacy of TMLR. Consequently, further research is indicated to investigate whether other methods to induce myocardial denervation might be at least as effective, simpler, and cheaper in relieving angina and improving QOL in patients with severe refractory angina.

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