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REPERFUSION IN ACUTE ISCHEMIC MYOCARDIUM BY TRANSMYOCARDIAL REVASCULARIZATION USING CO_2 LASER

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INDEXING WORDS

acute myocardial ischemia; CK-MB; CO_2 laser; transmyocardial laser revascularization

SYNOPSIS

Transmyocardial laser revascularization (TMLR) is currently applied to provide clinical benefits in the patients with end-stage coronary artery disease. However, this method is so far indicated only for chronic status of ischemic heart disease. In this study, we have investigated in the canine model whether acute ischemic myocardium could be reperfused by TMLR using CO_2 laser. A CO_2 laser was used to create transmural myocardial channels. The ischemic areas of 3 cm in diameter were created on the left ventricle with multiple coronary ligations. Laser procedure was carried out 30 minutes after coronary ligation in TMLR group (n=6), while laser treatment was not performed after coronary ligation in acute myocardial infarction (AMI) group (n=6). The level of MB isozyme of creatinine kinase (CK-MB) derived from coronary sinus was measured at 0, 3, 6, 12, 18, 24, and 48 hours after coronary ligations, and the pattern of serial CK-MB changing was analyzed. Animals were sacrificed 48 hours after treatment and histologically investigated. The time to peak level of CK-MB in TMLR group appeared significantly earlier (13.0±2.4 hours) than that in AMI group (22.0±3.1 hours). The value of CK-MB of 24 hours after ligation in TMLR group (1985±805 IU/L) was significantly lower than that in AMI group (4759±778 IU/L). The channels on the gross section after 48 hours of TMLR were patent with some of fibrin network. Red blood cells were scattered in the lumens. It was suggested that acute ischemic myocardium was directly reperfused through the open laser channels from the left ventricular chamber in the canine model.

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INTRODUCTION

There are a large number of patients with severe ischemic heart disease which cannot be treated by surgical operations, percutaneous techniques and maximum medications. For those patients with such end-stage coronary artery disease, transmyocardial laser revascularization (TMLR) is an alternate method to improve anginal status and blood perfusion into ischemic myocardium.

The original concept of TMLR is based on the reptilian heart[12]. Its myocardium is directly perfused with communicating channels between the left ventricular cavity and coronary arterial trees. In practice, myocardial wall is penetrated by high power CO_2 laser to create channels from pericardial surface into the left ventricle so that oxygenated blood from the left ventricular cavity could directly perfuse to the ischemic myocardium. Mirhoseini and Cayton[13] provided the initial experimental description of TMLR in 1981. In 1986, Okada et al.[15] reported the first successful clinical case of sole TMLR operation using the CO_2 laser in the world. With the recent development of an 800-W CO_2 laser, a number of clinical investigations of TMLR have been reported, and many of them suggested that this new technique was clinically effective for the patients with chronic symptom of end-stage coronary disease[2,7,16].

However, TMLR is uncertain to be beneficable in the acute phase of myocardial ischemia. There are few reports about the possibility of TMLR to salvage acute ischemic myocardium[14,20] using holmium yttrium-aluminum-garnet (Ho:YAG) laser, concluding that direct laser revascularization could not reperfuse to acute ischemic myocardium. In this study, we experimentally investigated whether TMLR using CO_2 laser might be effective for acute myocardial infarction.

MATERIALS AND METHODS

Laser procedure

A CO_2 laser (Model IRX104, Nippon Infrared Industries Co.,LTD. Yokohama Japan) was used with a wavelength in the infrared range at 10.6 μm. The CO_2 laser guiding by Helium-Neon beam was delivered to the heart synchronized with the R wave on the ECG. The output energy was adjusted at 100 W, and the duration of exposure was 0.2 second. Spot size of laser channel was 1mm in diameter.

Surgical procedure

Twelve mongrel dogs weighting 10 ± 2.3 kg (range, 8 to 13 kg) were used. All animals were premedicated with intramuscular ketamine (15 mg/kg) and intravenous sodium thiopental (20 mg/kg) administration, intubated and ventilated with room air. Anesthesia was maintained with intermittent administration of sodium thiopental. Antibiotic coverage was given in the pre- and

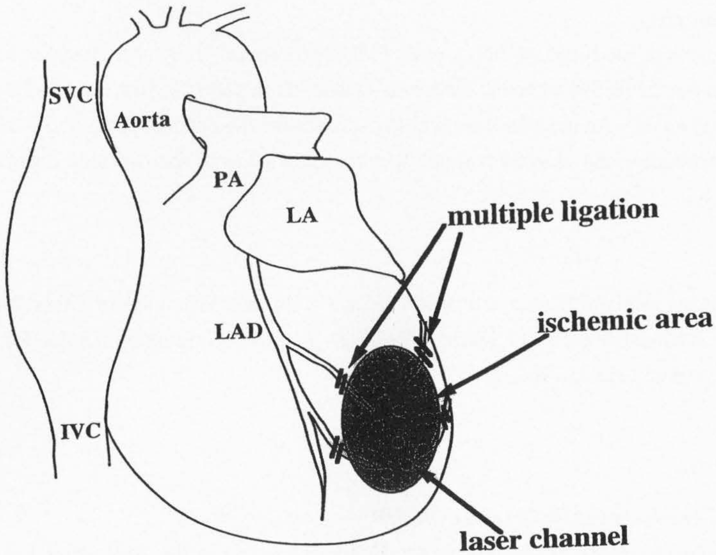

Fig. 1. Schema of experimental procedure in TMLR group. Laser channels in the ischemic area were made 30 minutes after multiple ligation.

post-operative period. After left anterolateral thoracotomy through the fifth or sixth intercostal space, the pericardium was opened, and the heart was fully exposed. Peripheral branches of left anterior descending artery (LAD) and circumflex (CX) artery were ligated to create an ischemic area of 3 cm in diameter on the free wall of left ventricle (Fig. 1). In TMLR group of six dogs, a CO_2 laser was applied to make channels at 30 minutes after ligations. Ten to twelve laser channels were made in the area of acute ischemic myocardium. In AMI group of six dogs, no laser treatment was done on the ischemic area. After the laser procedure, persistent bleeding from the channel into the left ventricular cavity was easily controlled by gentle finger pressure with a gauze compression. Bleeding could be controlled within ten minutes, and the chest was closed. Venous samples for analysis of serial changes of creatine kinase MB (CK-MB) were taken from the coronary sinus.

CK-MB determination

Venous samples for enzyme analysis were taken at seven points; before ligation and 3, 6, 12, 18, 24, and 48 hours after ligations. The samples were immediately centrifuged at 3000 rpm. for 10 minutes. The serum was frozen and stored at -20 °C, and successively used for CK-MB determination with an immunoassay method (Merck auto CK-MB).

Statistical evaluation

The statistical evaluation was carried out by the unpaired t-test. And values were indicated as a mean ± standard error and $p<0.05$ was evaluated as a significant difference.

Histological analysis

Animals were sacrificed 48 hours after TMLR procedure. For histological examinations, myocardium in representative ischemic areas was embedded in paraffin, sectioned and stained with hematoxylin and eosin. An independent pathologist evaluated the channel patency and the situation within and surrounding the channel without specific knowledge of the previous treatment of the ischemic region.

Animal care

All animals received human care in accordance with the "Principles of Laboratory Animal Care" by the National Society for Medical Research and the "Guiding Principles for Research Involving Animals and Human Beings,".

RESULTS

Analysis of the changing pattern of serum CK-MB

The serial changings of CK-MB in the TMLR group and in the AMI group are shown in Fig. 2. The levels of CK-MB at 24 hours after ligation were 1985±805 IU/L in the TMLR group and 4759±778 IU/L in the AMI group, and significant difference was recognized between two groups ($p<0.05$). Figure 3 shows the time to reach the maximal level of CK-MB in each animal of two groups. The average time to reach peak CK-MB was 13.0±2.4 hours in TMLR group and 22.0±1.3 hours in AMI group, which was significantly different between two groups ($p<0.001$).

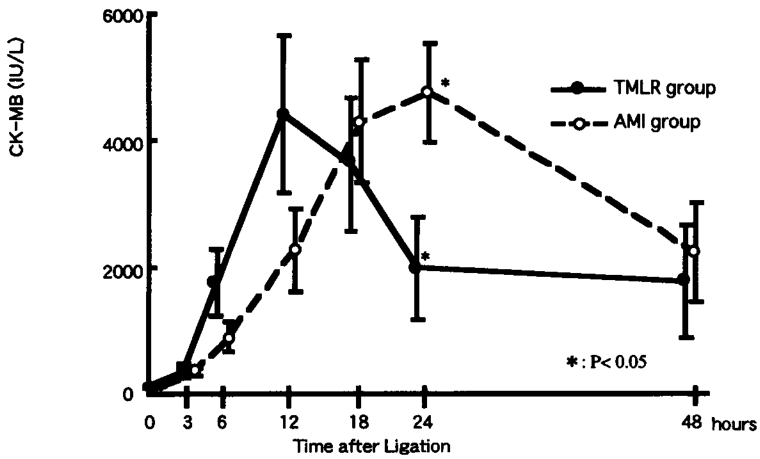

Fig. 2. Serial CK-MB changing over the time course of the experiments in TMLR group (n = 6) and AMI group (n = 6).

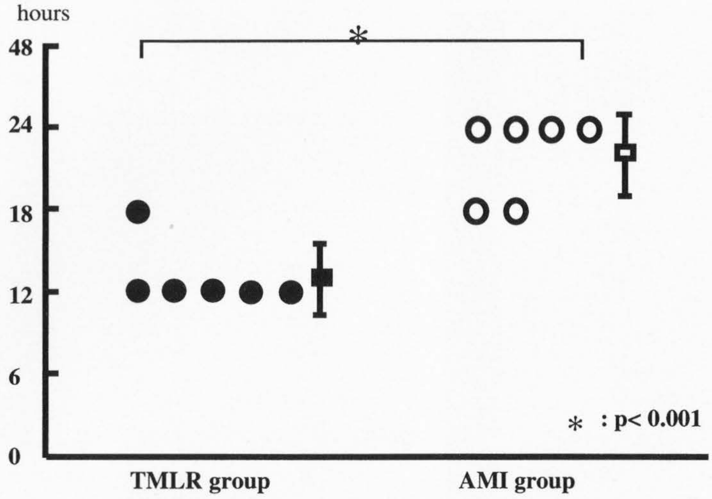

Fig. 3. The average time to peak CK-MB in each dog was plotted in TMLR group (● : n = 6) and AMI group (O :n = 6).

Fig.4. Macroscopic findings 48 hours after TMLR.
: Laser Channel on the Epicardium.

Histological findings

The myocardium 48 hours after TMLR was histologically examined. On macroscopic findings, the channels of about 1mm diameter could be easily identified on the surface of the epicardium (Fig. 4). However, the channels on the endocardial site was somewhat different to

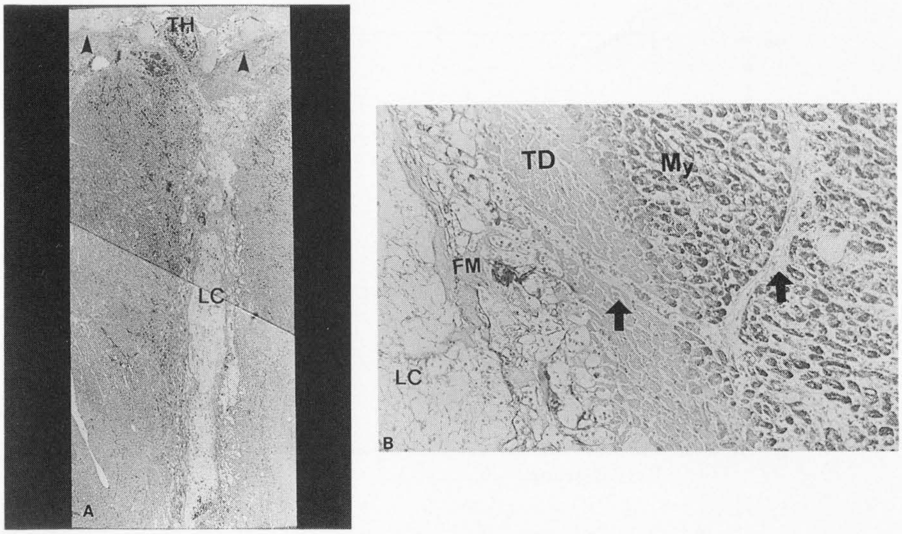

Fig.5. Laser channel 48 hours after TMLR, longitudinal section. : (A) H-E stain×40. and (B) PTAH stain×200. ▲: epicardium site, TH: Thrombus, FM: Fibrin mass, TD: Thermal damage, My: Myocardium, LC: Laser channel.
⬆ : Small vessel communicating between lumen and myocardium.

identify, because the diameter of the channel lumen on the endocardial site was much smaller than that on the epicardial site. The white thin layer, which was made by thermal injury, could be observed around the channel. On microscopic finding, the channels were patent on the gross inspection of the endocardium (Fig. 5, Fig. 6 a.,b). Fibrin networks were recognized and red blood cells were scattered in the channel lumen. There was a paucity of thrombus and fibrin mass at the edge in the channel lumen. Numerous leukocytes were emigrated, and myocytes necrosis with contraction band due to thermal damage was evident around the channel. However, the laser channel maintained connection with small native vessels beyond the damaged layer.

DISCUSSION

Initially, the direct transmyocardial revascularization was attempted to create transmural conduits by various products and methods, such as acupuncture or Vineberg's operation[6,11,18]. However, these experimental and clinical trials brought minimal success. Mirhoseini and Cayton[13] firstly reported that the laser channels created in the acute ischemic myocardium reduced mortality rates in the canine model, and the patency of these channels was confirmed histologically. Okada et al.[16] also reported three year patency of the laser channel in the canine model.

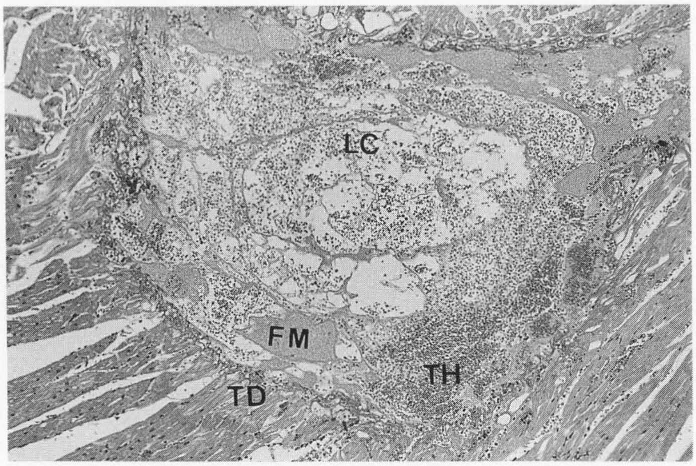

Fig.6. Laser channel 48 hours after TMLR, transverse section. : M-T stain ×100. FM: Fibrin mass, TD: Thermal damage, LC: Laser channel.

In 1990's, TMLR operation was clinically attempted for patients with end-stage coronary artery disease in many countries. Significant improvement of angina class and myocardial perfusion in reversible areas have been reported by several investigators[7,8,19]. Patients' symptom improved immediately after the procedure and continued to improve at least more than one year, nevertheless the mechanism of the effectiveness of TMLR is controversial. Kwong et al.[10] reported that TMLR had an influence on perception of angina pain due to neurophysiological effect by the destruction of the nerve endings. Some reports[1,4] suggested a marked angiogenesis as a main mechanism of TMLR in their experimental researches. We hypothesized that ischemic myocardium would be reperfused the oxygenated blood through laser channels, and investigated reperfusion effect of TMLR using CO_2 laser in acute ischemic model.

The circular acute ischemic areas of 3 cm in diameter were created by multiple ligations of peripheral branches of coronary arteries beside the apex. These ischemic areas had minimal collateral influence from surrounding myocardium. Using this model, we investigated whether TMLR might provide immediate benefit in acute myocardial ischemia, by determination of CK-MB as a cardiac marker. The level of serum CK-MB in the TMLR group has reached to the maximum earlier and decreased earlier compared with that in the AMI group. The average time to peak CK-MB in each dog appeared significantly earlier in the TMLR group than in AMI group. Clinically, an early peak of serum CK-MB is regarded as one of useful assessments of successful recanalization by PTCA or thrombolytic therapy[1] in patients with acute myocardial infarction. This phenomenon was explained by the wash-out effect of CK-MB from the ischemic myocardium. Therefore, acute ischemic myocardium in our model was assessed to be reperfused by TMLR using a CO_2 laser.

As we showed in the histological findings, certainly, there were agglomerated red blood cells and fibrin mass appeared at the inside edge of the channel lumen 48 hours after laser procedure. The laser channel was apparent to stay open. Current clinical reports[3,5] doubted the channel patency even in the acute phase after laser treatment. They revealed the channels were partially or completely filled with fibrin and leukocytes in the patients who died a few days after TMLR surgery. However, the possibility exists that they were lead to unsuccessful results because of the early channel closure. We considered that the situation of the channel lumen and surrounding tissue in dead cases were not equal to those in living cases.

Investigators[14,20] using Ho:YAG laser resulted that the laser channels failed to increase blood flow in the ischemic tissue, improve regional ischemic myocardial function, and enhance wash-out of accumulated lactate. However, there are some significant differences between the CO_2 laser and the Ho:YAG laser. The energy of the CO_2 laser is delivered with a hand piece, penetrates straight through the tissue with a single pulse, and is highly absorbed by biological tissue and water. The CO_2 laser theoretically vaporizes tissue with minimal thermal damage surrounding the channel and creates the conduits to make a communication with native sinusoids. By contrast, the Ho:YAG laser energy is delivered through a fiber optic cable which drills into the myocardium with repeated pulses. Myocardial tissue is so widely damaged by the energy of Ho:YAG laser that vessel communications might be destroyed. Furthermore, the flow pattern through a transmural channel of both laser was different. Vigorous pulsatile bleeding was seen during systole through the epicardial laser entry point on using the CO_2 laser. On the other hand, not pulsatile bleeding but blood oozing could be recognized through the laser channel[17]. These was the reason why our study resulted that acute ischemic myocardium could be reperfused by CO_2 laser.

Some reports[4,9,10] suggested the importance of angiogenesis as a mechanism of TMLR in their experimental studies and concluded that anginal reduction in clinical patients just after TMLR operation was due to denervation or placebo effects. This theory could not explain the pattern of serial CK-MB changing that we showed. It might be possible that TMLR using CO_2 laser become an option in the treatment of acute myocardial infarction.

CONCLUSION

From the pattern of serial CK-MB changing and pathological findings 48 hours after TMLR in our canine model, it was suggested that acute ischemic myocardium was directly reperfused by new blood flow through the open laser channels from the left ventricle chamber.

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