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EXPERIMENTAL INVESTIGATIONS ON RELATIONSHIPS BETWEEN MYOCARDIAL DAMAGE AND LASER TYPE USED IN TRANSMYOCARDIAL LASER REVASCULARIZATION (TMLR)

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INDEXING WORDS

coronary artery disease; CO_2 laser; Ho:YAG laser; TMLR; thermal damage

SYNOPSIS

Transmyocardial laser revascularization (TMLR) using a CO_2 laser is clinically attempted in end-stage ischemic heart disease that is not treated by conventional bypass grafting or transluminal angioplasty. Besides, clinical trials of TMLR using a Ho:YAG laser have started recently. In this study, we compared the degree of damage to normal myocardium using these 2 types of lasers.

Hearts of adult mongrel dogs were exposed under general anesthesia. Dogs were divided into 2 groups; those with channels made in the left ventricle by CO_2 laser (CO_2 group, n=5) and those with channels made by Ho:YAG laser (Ho:YAG group, n=5). The chest was temporarily closed, then serum MB isozyme of creatinine kinase (CK-MB) and troponin T (TnT) were measured sequentially. Twenty-four hours after laser irradiation, hearts were isolated for pathological studies with hematoxylin-eosin and Masson's trichrome stains. The CO_2 group produced CK-MB with a peak of 1162.2 ± 462.2 IU/l and the Ho:YAG group 1804.0 ± 992.4 IU/l after 12 hours, and

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there was a significant difference between two groups ($p<0.01$). The CO_2 group produced TnT with a peak of 1.2 ± 0.4 ng/ml and the Ho:YAG group 11.6 ± 4.1 ng/ml after 6 hours, and the peak value in Ho:YAG group was significantly higher than that in the CO_2 group ($p<0.001$). Thirty channels were confirmed histologically in the CO_2 group, and the width of thermal damage layer around the cannel lumen was 249 ± 83 μ m. Twenty-seven channels were confirmed histologically in the Ho:YAG group, and the width of thermal damage layer was 760 ± 288 μ m. Thermal damage in the Ho:YAG group was significant greater than that in the CO_2 group ($p<0.01$).

We concluded that TMLR using a CO_2 laser is more suitable for end-stage myocardial ischemia than a Ho:YAG laser in terms of myocardial damage.

INTRODUCTION

Mirhoseini et al. firstly attempted transmyocardial laser revascularization (TMLR) in combination with coronary artery bypass grafting (CABG) in 1985,[6] thereafter, TMLR using a carbon dioxide (CO_2) laser has been the mainstream for the treatment of end-stage ischemic heart disease that is not treatable by conventional CABG or percutaneous transluminal coronary angioplasty (PTCA).[1,3,4,7] In Japan, TMLR was not clinically applied since Okada et al. had done a first successful clinical application of TMLR using a CO_2 laser for ischemic heart disease with severe constrictive pericarditis in 1985, [8] but in 1997 came into limited use.

TMLR using a holmium:yttrium-aluminum garnet (Ho:YAG) laser began to be applied recently and short-term results were not so different from those using a CO_2 laser. [5] The Ho:YAG laser is cheaper and easier to use than the CO_2 laser. Because it can be transmitted by fiberoptic catheter, TMLR from the endocardial side using angioscope or TMLR under thoracoscopic guidance are potentially applicable.

Although TMLR was initially limited to the patients with good cardiac function, indication of it is gradually expanding. In some recent reports, TMLR was attempted for patients whose ejection fraction (EF) was under 40%. However, some cases of them required long-term intraaortic balloon pumping (IABP) support due to

temporarily deteriorated cardiac function or faced death by heart failure. The cause of heart failure after TMLR is thought to be due to the existence of myocardial edema around the channel induced by laser irradiation. There was no experimental or clinical report which compared quantitatively the degree of myocardial damage by types of laser used. In this study, we irradiated with CO_2 laser and Ho:YAG laser on normal myocardium, and measured serum MB isozyme of creatinine kinase (CK-MB) and Troponin T (TnT) to find the degree of myocardial damage. Furthermore, we pathologically studied the myocardial damage 24 hours after TMLR and assessed the suitability of TMLR for end-stage ischemic heart disease.

MATERIALS AND METHODS

Subjects

Animal experiments conformed to ''Guidelines for Animal Experiments at the Medical Department of Kobe University''. Ten adult mongrel dogs (10 ± 2 kg) were premedicated with administrations of ketamine hydrochloride (Ketalar: Sankyo pharmaceutical co., Tokyo, Japan) and thiamylal sodium (Isozol: Yositomi pharmaceutical co., Osaka, Japan), then endotracheally intubated. The hearts were exposed by left thoracotomy under general anesthesia monitoring with electrocardiogram (ECG). CO_2 (CO_2 group, n=5) and Ho:YAG (Ho:YAG group, n=5) lasers were irradiated to the anterior wall of normal left ventricle, making 10 channels per a heart. The chest was closed temporarily, then blood samples were collected sequentially and serum CK-MB and TnT were measured. Twenty-four hours after TMLR, the hearts were isolated for pathological study.

Laser equipment

The CO_2 laser (MODEL IRX 104: NIIC Co.Ltd., Kanagawa, Japan) was used with a condition of continuous wave of 100 watts for 0.2 second. The laser was triggered by R wave on ECG, irradiated with a handpiece following a guide beam of Helium-Neon laser. A channel was made by one laser shot and hemorrhaging spouting confirmed attainment of the inside of the left ventricular lumen.

The Ho:YAG laser (Medical Laser System IH102: NIIC Co.Ltd., Kanagawa, Japan) was used with a condition of 10 Hz pulse wave

(2J/pulse) for several seconds. The laser was irradiated without synchronization of ECG, and led to the surgical site with a quartz fiber of 0.4 mm in diameter.

Blood collection and examination

After channels were created, blood was collected with heparin after 0, 6, 12, 18, and 24 hours. Serum was obtained by centrifuging at 3000 rpm for 15 minutes and frozen (-20℃) until use. Serum CK-MB was measured by immunoinhibition and serum TnT by enzyme immunoassay.

Pathological examination

Following injection of 10% formalin into the coronary artery immediately after heart isolation, the left ventricular wall including channels was soaked in formalin buffer and fixed. After 2 or more days, paraffin embedding was carried out, sections were prepared, and pathological study was done with hematoxylin-eosin and Masson's trichrome stains. In 3 dogs from each group, the channel diameter and the width of thermal damage layer were measured, preparing sections vertical to the channel in the middle of myocardium, measuring the distance of the narrowest thermal damage layer and channel lumen.

Statistics

Serum CK-MB and TnT were compared with 2-way analysis of variance (ANOVA). The thermal damage range was compared with a t-test, expressed by mean ± S.D.

RESULTS

Most of laser channels in CO_2 group were penetrated to the left ventricular cavity at the first laser shot, and bleeding was generally controlled by manual compression with gauze. In some cases, suture was needed to control hemorrhage with a 5-0 polypropylene thread. No changes were seen macroscopically around channels. Although arrhythmia did not induced by laser irradiation, ventricular arrhythmias occurred in some cases before the chest closure. These arrhythmias were not fatal, and disappeared with the administration of lidocaine hydrochloride (2% Xylocaine: Hujisawa pharmaceutical Co.,

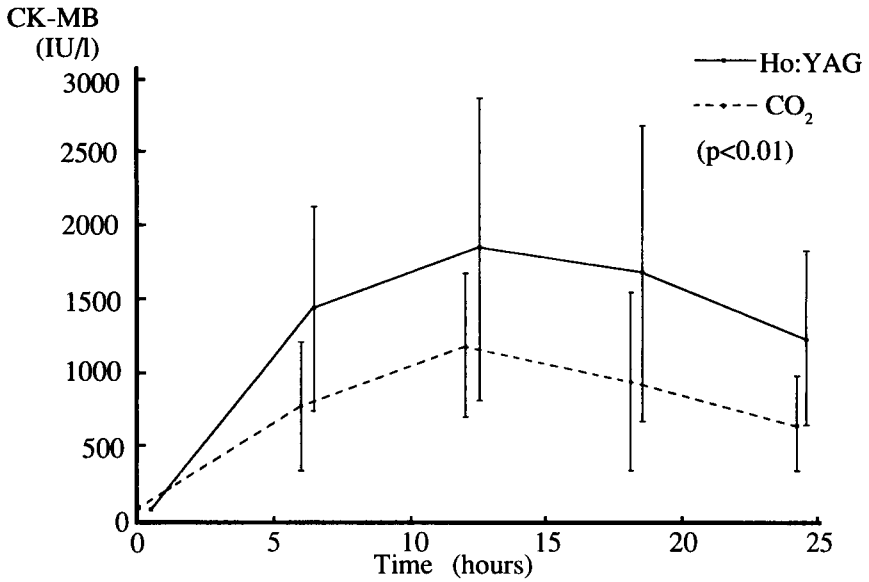

Fig.1. Change of serum MB isozyme of creatinin kinase(CK-MB) after TMLR on the normal myocardium.

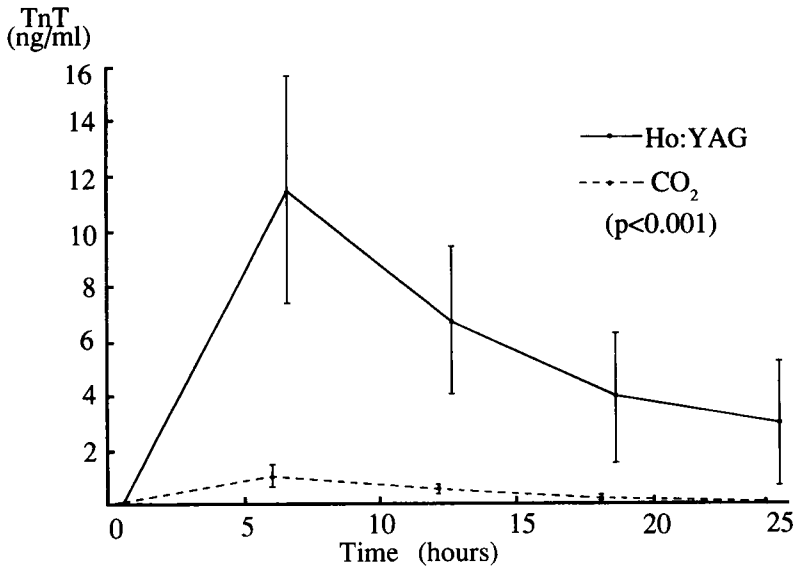

Fig.2. Change of serum TroponinT(TnT) after TMLR on the normal myocardium.

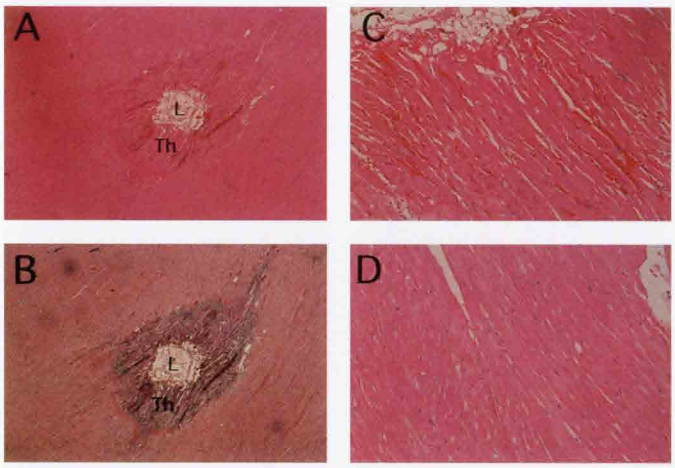

Fig.3. Microscopic findings of the myocardium after TMLR using CO_2 laser.
(L:channel lumen, Th:thermal damage layer)
A) an elliptic layer of thermal damage recognized around the channel. (H-E, x40)
B) an elliptic layer of thermal damage recognized around the channel. (Masson's trichrome, x40)
C) coagulation necrosis recognized in the thermal damage layer. (H-E, x200)
D) normal myocardium outside of the thermal damage layer. (H-E x200)

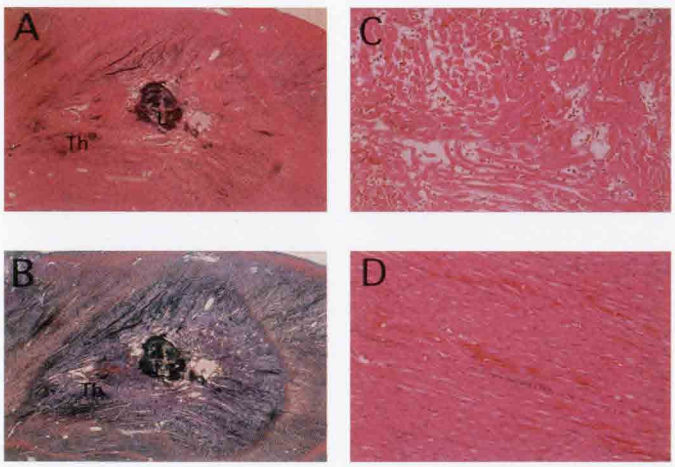

Fig.4. Microscopic findings of the myocardium after TMLR using Ho:YAG laser.
(L:channel lumen, Th:thermal damage layer)
A) an elliptic layer of thermal damage recognized around the channel. (H-E, x40)
B) an elliptic layer of thermal damage recognized around the channel. (Masson's trichrome, x40)
C) coagulation necrosis recognized in the thermal damage layer . (H-E, x200)
D) erythrocytes infiltration in the normal myocardium outside the thermal damage layer.(H-E, x200)

Tokyo, Japan).

In the Ho:YAG group, 8 ± 2 laser shots were needed to create a channel with insular bleeding in adjacent muscle; all hemorrhage was controlled by manual compression. ECG in some cases demonstrated short-run type ventricular tachycardia during laser irradiation and ventricular arrhythmia before chest closure, these arrhythmias disappeared with the administration of lidocaine hydrochloride.

Change of serum CK-MB and TnT

The Ho:YAG group produced a CK-MB peak of 1804.0±992.4 IU/l and the CO_2 group 1162.2±462.2 IU/l after 12 hours, and there was a significant difference between two groups ($p<0.01$, Fig.1). The Ho:YAG group produced a TnT with a peak of 11.6±4.1 ng/ml and the CO_2 group 1.2 ± 0.4 ng/ml after 6 hours, and there was a significant difference between two groups ($p<0.001$, Fig.2).

Pathological examination

Thirty channels in the CO_2 group and 27 in the Ho:YAG group was confirmed. Both showed a thin carbonized layer around the channel formed by myocardial transpiration. Around each channels, the elliptic layer of necrosis due to thermal damage was recognized. Normal myocardium was present on its outer periphery with a distinct border. In the thermal damage layer, coagulation necrosis including irregular myocardial arrangement, partial nucleus disappearance, and neutrophilic infiltration were recognized with hematoxylin-eosin stain. The thermal damage layer was stained dark red by Masson's trichrome stain. Erythrocytes were infiltrated into the normal myocardium adjacent to the thermal damage layer in both groups. In a Ho:YAG group, erythrocytes infiltration could be also recognized in the normal myocardium apart from the channel (Fig. 3, Fig. 4).

Channels were mostly elliptic configuration in the CO_2 group (391 ±212 μm in diameter) and irregular with uneven edges in the Ho:YAG group (470±298 μm in diameter).

The width of thermal damage layer was 249 ± 83 μm in the CO_2 group and 760 ± 288 μm in the Ho:YAG group, and there were significant differences between two groups ($p<0.01$).

DISCUSSION

The indication of TMLR reported by Mirhoseini[7] and Okada[8,9,10] was limited to patients with mild to moderate left ventricular dysfunction. Recently, some reports suggested that the indication of TMLR could be extended to patients whose EF was under 20 - 30%.[12,13] Some of these cases with severe left ventricular dysfunction required reintubation or IABP support due to low output syndrome (LOS) early on postoperatively. TMLR using a Ho:YAG laser had good results similar to using a CO_2 laser for patients with good cardiac function reportedly. However, it is not clear whether a Ho:YAG laser is applicable for patients with severe cardiac failure because tissue damage induced by Ho:YAG laser is generally considered to be greater than CO_2 laser. In this study, we quantitatively compared early postoperative myocardial damage induced by two types of laser.

In our experiment, myocardial damage was greater in the Ho:YAG group than in the CO_2 group apparently due to differences in wave length, focal depth, and output. The wavelength of CO_2 laser is 10.6 μ m, whereas that of Ho:YAG laser is 2.1 μ m. So, most energy of CO_2 laser is absorbed in intracellular liquid and only cells around the channel are affected by the CO_2 laser. On the other hand, the reduction of Ho:YAG laser energy against water is smaller and the energy travels deeper into the tissue far from the channel. Because focal depth is greater with a CO_2 laser, penetrated channels could be made by one laser shot, whereas multiple shots were required in case using Ho:YAG laser. Multiple intramyocardial irradiation appeared to increase myocardial damage and transpired gas did not escape and spreaded in the myocardium, inducing hemorrhage in the myocardium. In addition to thermal damage of individual laser, this gas formation can potentially increase the damage of the myocardium.

Fisher et al. microscopically examined the thermal damage around the channel, and calculated the thermal damage area as an ellipse measuring with long and short axes.[2] However, the channel is not complete ellipse and cutting vertical to the channel is technically difficult and oblique cutting is obtained actually. So we measured the narrowest width of thermal damaged layer for comparison.

The mean value of the narrowest width of thermal damaged layer was 249 μ m in the CO_2 group and 760 μ m in the Ho:YAG group. The

thermal damage in the Ho:YAG group is about 3 times greater than in the CO_2 group, inflicting 9 times greater mycardial damage. Although no report covers the influence of thermal damage versus serum TnT level, there are many reports suggesting that serum TnT well correlates with the size of myocardial infarction.[11] In this study, a quantity of heat-affected myocardium correlated fairly closely with increasing serum TnT. The cause of a smaller difference in serum CK-MB was thought that serum CK-MB was less specific to the myocardium than serum TnT and was easy to increase by other surgical procedures, such as thoracotomy.

A Ho:YAG laser damaged the myocardium more than a CO_2 laser. Although we did not evaluate the change of cardiac function in this study, it conceivably deteriorates at the time of TMLR using a Ho:YAG laser. We suggest that strict care should be paid in TMLR using a Ho:YAG laser, especially for the case of severe left ventricular dysfunction.

CONCLUSION

In TMLR for myocardial ischemia with low left ventricular function, a CO_2 laser is more suitable than a Ho:YAG laser from the aspect of myocardial damage.

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