TMR Mechanism(s) of Action

Physician Training
Proposed Mechanism(s) of Action

- Increased perfusion of myocardium via the channels created
- Increased collateralization via angiogenesis
- Symptom reduction resulting from disruption of pain fiber function
- Possible microinfarcts to the myocardium
- Placebo effect
Channel Patency

Proposed Mechanism of Action
Patent Endocardial Channels

- Laser channels were placed from the endocardium to about ½ way into the myocardium (percutaneously).
- See blood flow into the laser channels acutely.

Image courtesy of Emerson Perin, MD, Texas Heart Institute
Angiogenesis

Proposed Mechanism of Action
3 Week Histology

Longitudinal Channel Remnant-Angiogenesis

Blood vessels that are new since the laser channel has been created

Image courtesy of Daniel Burkhoff, MD, Columbia Medical Center
Induction of angiogenesis after TMR: a comparison of Holmium:YAG, CO$_2$, and Excimer lasers

G. Chad Hughes, MD; Alan P. Kypson, MD; Brian H. Annex, MD; Bangliang Yin, MD; James D. St. Louis, MD; Shankha S. Biswas, MD; R. Edward Coleman, MD; Timothy R. DeGrado, PhD; Carolyn L. Donovan, MD; Kevin P. Landolfo, MD; James E. Lowe, MD

The Annals of Thoracic Surgery, August 2000
Induction of Angiogenesis

A Comparison of Holmium:YAG, CO$_2$, and Excimer Lasers

Study Design:

- Twenty adult male mini swine underwent subtotal (90%) left circumflex coronary stenosis under a chronic ischemia model.
- Baseline positron emission tomography (PET) and dobutamine stress echocardiography were performed to document hibernating myocardium in the left circumflex coronary artery distribution at baseline and six months post TMR.
- Animals were randomized to sham redo-thoracotomy (n=5), TMR with the Holmium:YAG (Ho:YAG) laser (n=5), CO$_2$ laser (n=5) or Excimer laser (n=5).
- Ho:YAG and CO$_2$ TMR significantly improved perfusion and contractile reserve at six months compared to no benefit from Excimer TMR or sham redo thoracotomy.
- Ho:YAG TMR had significantly better angiogenesis than any of the other modalities (which may be a result of the acoustic affect of the laser).

Induction of Angiogenesis

A Comparison of Holmium:YAG, CO₂, and Excimer Lasers

Significant Improvement in Vascular Density and Myocardial Blood Flow

Greatest improvement seen with Ho:YAG

PET Analysis shows significant increase in myocardial blood flow to the lased LCX distribution following TMR

Induction of Angiogenesis

A Comparison of Holmium:YAG, CO$_2$, and Excimer Lasers

Summary of Results:

• Significantly greater vascular density seen with the Ho:YAG laser over the CO$_2$, Excimer, and sham control (p<0.001)
• The Ho:YAG laser exhibited the most “blue staining intensity” – characteristic of endothelial cells
• The degree of thermoacoustic tissue interaction (stimulation, injury, and inflammation) paralleled the amount of neovascularization after six months – greater interaction leads to greater angiogenesis
• Improvement with TMR:
  o the Ho:YAG laser showed a 27% improvement in perfusion at six months (p<0.001)
  o the CO$_2$ laser showed a 19% improvement at six months (p<0.002)
  o the Excimer and sham groups did not show significant improvement.

Conclusion:

- Significant increase in vascular density and myocardial blood flow was seen post TMR.
- Greater neovascularization was produced with the Ho: YAG laser with paralleled the degree of inflammation.
- TMR improves long-term perfusion and stress function, and this functional improvement is associated with a significant neovascularization response.

Angiogenesis

STUDY #2

Angiogenesis is Enhanced in Ischemic Canine Myocardium by Transmyocardial Revascularization

Noriyoshi Yamamoto, MD; Takushi Kohmoto, MD; Anguo Gu, MD; Carolyn DeRosa, BS; Craig R. Smith, MD; Daniel Burkhoff, MD, PhD

Journal of the American College of Cardiology, May 1998
Enhanced Angiogenesis

Angiogenesis is Enhanced in Ischemic Canine Myocardium by TMR

Study Design:
- Chronic ischemia was created in fourteen canine by proximal left anterior descending coronary ameroid constrictors
- TMR was performed with the Ho:YAG laser system in the anterior wall of seven dogs (the others served as the control group)
- Myocardial blood flow was measured at rest and during chemical stress in the acute setting and after two months

Enhanced Angiogenesis

Angiogenesis is Enhanced in Ischemic Canine Myocardium by TMR

Demonstrated Increase in Vessel Density and Myocardial Blood Flow with the Ho:YAG Laser

Angiogenesis is Enhanced in Ischemic Canine Myocardium by TMR

Summary of Results:

- After two months, TMR treated dogs demonstrated a significant increase of ≈ 40% in blood flow capacity during adenosine-induced stress in the ischemic territory compared to untreated dogs (p<0.05)
- Vascular proliferation was ≈ FOUR TIMES GREATER in the TMR treated group (p<0.001)
- Vessel density was ≈ 1.4 TIMES GREATER in the TMR treated group (p<0.001)
- Channels DO NOT remain patent over time

Enhanced Angiogenesis

Angiogenesis is Enhanced in Ischemic Canine Myocardium by TMR

Conclusion:

- Vascular growth is induced by TMR
- TMR with the Ho:YAG laser system induces a significant angiogenic response as evidenced by the:
  - increased number of vessels lined with smooth muscle cells
  - markedly increased vascular proliferation
  - increased blood flow capacity
- The role of myocardial injury and subsequent inflammatory response promote angiogenesis — "These features stimulate budding and growth of small vessels from preexisting blood vessels('true angiogenesis')."
- The authors concluded that the improved blood flow in the TMR treated tissue was the result of angiogenesis

STUDY #3

Histological Evidence of Angiogenesis 9 Months After Transmyocardial Laser Revascularization

Patrick W. Domkowski, MD, PhD; Shankha S. Biswas, MD; Charles Steenbergen, MD, PhD; James E. Lowe, MD
Circulation, January 23, 2001
Angiogenesis

Histological Evidence of Angiogenesis 9 Months after TMR

Study Design:

- Heart transplant candidate received TMR nine months before explant to relieve chronic angina
- The native heart was explanted and examined for evidence of angiogenesis in the TMR treated areas
- Staining with ematoxylin and eosin of the anterolateral wall of the left ventricle was performed and embedded with paraffin (masson trichrome stains were also used)

Histological Evidence of Angiogenesis 9 Months after TMR

Study Results:

- Capillary vascular density in the lased areas of the heart was greater than twice that found in the non-lased areas (p<0.001)
- Improved perfusion in TMR treated areas of the anterior and lateral walls was demonstrated
- Multiple vessels were shown within the channel remnant and adjacent to the channel – red blood cells were present
- These vessels showed positive immunohistochemical staining for CD31 and factor VIII antibody, thus demonstrating the presence of endothelial linings

Histological Evidence of Angiogenesis 9 Months after TMR

Conclusion:
- Capillary vascular density in the lased areas of the heart was greater than twice that found in non-lased areas
- The presence of multiple micro-vessels, red blood cells within the channel remnant lumens, and endothelial linings provide evidence of angiogenesis in the treated ischemic myocardium

STUDY #4

Evidence of Vascular Growth Associated With Laser Treatment of Normal Canine Myocardium

Takushi Kohmoto, MD; Carolyn M. DeRosa, BS; Noriyoshi Yamamoto; Peter E. Fisher, MD; Pedram Failey, BA; Craig R. Smith, MD; Daniel Burkhoff, MD, PhD

Evidence of Vascular Growth Associated with Laser Treatment of Normal Canine Myocardium

Study Design:

- TMR channels were created in eight normal canine hearts
  - Four canines were treated with the Ho:YAG laser
  - Four canines were treated with the CO$_2$ laser
- An average of 12 channels were created
- Animals were sacrificed two to three weeks post TMR
- The myocardium was examined for vascular density and evidence of smooth muscle proliferation using standard immunohistochemical techniques

Evidence of Vascular Growth Associated with Laser Treatment of Normal Canine Myocardium

TMR Significantly Increases Vascular Growth

This indicates the cells in the walls of these vessels are being stimulated to proliferate thus signifying active vascular growth.

A significant increase in vascular density was observed in the TMR treated area.

Evidence of Vascular Growth Associated with Laser Treatment of Normal Canine Myocardium

Summary of Results:

- Increases in Cell Proliferation
  - There was a significant increase in PCNA-positive results in the TMR treated area versus the control (PCNA = Proliferating Cell Nuclear Antigen; a marker)

- Increases in Vascular Density
  - A significant increase in vascular density was observed in the TMR treated areas up to 3 mm from the channel
  - The surrounding areas were subject to a thermoacoustic stimulation which elicits an inflammatory response
  - Evidence demonstrates this inflammatory response liberates cytokines and growth factors and upregulates growth factor receptors

Evidence of Vascular Growth Associated with Laser Treatment of Normal Canine Myocardium

Conclusion:
- The inflammation provided by TMR resulted in significant increases in vascular growth.
- The thermoacoustic interaction (stimulation, injury, and inflammation) surrounding the TMR channel remnants was greater for the Ho:YAG laser than for the CO₂ laser.
- This histologic study provides evidence of active vascular growth in the vicinity of the laser channels two to three weeks after their creation with a high frequency of proliferating smooth muscle cells.
- There has been no reported observations of a chronic patent channel whose internal diameter remained, as seen in the acute setting.

Increases in Perfusion May be Detected Utilizing PET

PET SCAN Example: Individual Patient

Perfusion Improvement – PET scan

Pre TMR

Post TMR (1 month)

TMR Treatment
• 33 channels created
• 21 posterolateral
• 6 anterior
• 6 inferior

Reduced Ischemic Area
Under stress, significantly less ischemia following Ho:YAG TMR

There was also a presentation that showed significant perfusion following Ho:YAG TMR
(Dr. Omar Lattouf, presented by Dr. Robert Guyton, both from Emory University)

Images courtesy of Michael Mack, MD, Medical City Dallas Hospital
Neurogenic

Proposed Mechanism of Action
• The heart is richly innervated
• For every capillary, there is an afferent and efferent sympathetic nerve fiber
  - If laser channels are drilled, there is a disruptive effect on this relationship
  - Sympathetic denervation may explain the acute benefit sometimes seen following Sole Therapy TMR
STUDY #1

Cardiac Sympathetic Denervation After Transmyocardial Laser Revascularization

Thabet Al-Sheikh, MD; Keith B. Allen, MD; Susan P. Straka, RN; David A. Heimansohn, MD; Richard L. Fain, BS; Gary D. Hutchins, PhD; Stephen G. Sawada, MD; Douglas P. Zipes, MD; Erica D. Engelstein, MD

Circulation, July 13, 1999
Sympathetic Denervation

Cardiac Sympathetic Denervation After TMR

Study Design:
- PET imaging of resting and stress myocardial perfusion \left[^{13}\text{N}\right]\text{ammonia} (\text{NH}_3)\right\} and of sympathetic innervation \left[^{11}\text{C}\right]\text{hydroxyephedrine} (\text{HED})\right\} was performed before and after TMR in eight patients.
- Patients were ineligible for CABG or PTCA.
- A mean of 50 channels were created in the left ventricle.
- A semi-automated program was used to determine \text{NH}_3\text{ uptake and HED retention in the left ventricle.}

Sympathetic Denervation

Cardiac Sympathetic Denervation After TMR

Cardiac Sympathetic Denervation After TMR

Conclusion:

- TMR causes decreased myocardial HED uptake in most patients without significant change in resting or stress myocardial perfusion
- This suggests that the improvement in angina may be at least in part due to sympathetic denervation

STUDY #2

Cardiac nociceptive reflexes after transmyocardial laser revascularization: Implications for the neural hypothesis of angina relief

Anthony J. Minisi, MD; On Topaz, MD; M. Susan Quinn; Laxmi B. Mohanty, MD
The Journal of Thoracic and Cardiovascular Surgery, October 2001
Neurogenic Response

Cardiac Nociceptive Reflexes After TMR: Implications For The Neural Hypothesis Of Angina Relief

Study Design:

- Experiments were performed in 13 chloralose-anesthetized canines with sinoaortic denervation and vagotomy.
- Left ventricular receptors with sympathetic afferent fibers were activated by epicardial and intracoronary bradykinin before, and 45 minutes after, TMR.
- Direct recording of efferent renal sympathetic nerve activity quantitated reflex responses elicited by bradykinin.
- TMR was performed using the Ho:YAG laser with fiber optic Sologrip® Delivery System.
- An average of 44.5 ± 1.0 channels were created in the open chest model.

Neurogenic Response

Cardiac Nociceptive Reflexes After TMR: Implications For The Neural Hypothesis Of Angina Relief

Renal Sympathetic Nerve Activity (RSNA) Unchanged Post TMR

RSNA-Epicardial Bradykinin

RSNA-Intracoronary Bradykinin

Neurogenic Response

Cardiac Nociceptive Reflexes After TMR: Implications For The Neural Hypothesis Of Angina Relief

Results:

- Reflex increases in RSNA elicited by epicardial bradykinin – before and after TMR were NOT significantly changed (p=0.19)
- Reflex increases in RSNA elicited by intracoronary injection of bradykinin with fixed and varying doses (1 µg, 10 µg, 100 µg) – before and after TMR were NOT significantly changed (p=0.44)
- Photomicrographs of cardiac nociceptors provide histologic evidence that the receptors remain intact after TMR

Cardiac Nociceptive Reflexes After TMR: Implications For The Neural Hypothesis Of Angina Relief

Conclusion:

- These results provide functional evidence that the neural receptors remain intact after TMR with the Ho:YAG laser and are capable of transmitting.
- Ho:YAG laser does NOT interrupt the neural pathway.

STUDY #3

Transmyocardial Laser Revascularization Remodels the Intrinsic Cardiac Nervous System in a Chronic Setting

R.C. Arora, MD; G.M. Hirsch, MD; K. Hirsch, MD; J.A. Armour, MD, PhD
Circulation, September 18, 2001
Neurogenic Response

Transmyocardial Laser Revascularization Remodels the Intrinsic Cardiac Nervous System in a Chronic Setting

Study Design:

- A Ho:YAG laser created 20 channels through the anterolateral left ventricular free wall of 10 dogs
- Four weeks later, the function of cardiac sensory inputs to the intrinsic cardiac nervous system (ICNS) was studied by applying veratridine to ventricular sensory fields
- Chronotropic and inotropic responses elicited by cardiac sympathetic or parasympathetic efferent neurons stimulated electrically or chemically were also assessed

Neurogenic Response

Transmyocardial Laser Revascularization Remodels the Intrinsic Cardiac Nervous System in a Chronic Setting

Summary of Results:

- Chemical activation of epicardial sensory neurites with veratridine elicited expected ICNS excitatory responses
- Electrical stimulation of sympathetic and parasympathetic efferent neurons induced expected altered cardiac responses
- The responsiveness of the ICNS to systemically administered nicotine was obtunded

Conclusion:

- Although TMR does not affect cardiac afferent or extra cardiac efferent neuronal function, it does remodel the ICNS so that its responsiveness to a known chemical agonist (nicotine) becomes obtunded. Remodeling of the ICNS may account for the acute affect of TMR prior to the long-term benefits seen from the angiogenic cascade.
STUDY #4

Transmyocardial laser revascularization does not denervate the canine heart

Gregory M. Hirsch, MD; Gregory W. Thompson, BSc; Rakesh C. Arora, MD; Kristine J. Hirsch, MD; John A. Sullivan, MD; John A. Armour, MD, PhD

The Annals of Thoracic Surgery, August 1999
**Denervation?**

**TMR Does Not Denervate The Canine Heart**

Study Design:
- A Ho:YAG laser created 20 channels through the anterolateral left ventricular ventral free wall of nine dogs
- Changes in ventricular dynamics and intrinsic cardiac neuronal activity were monitored pre and post TMR in responses to three stimuli:
  1. application of veratridine or bradykinin to the epicardial sensory neurites of intrinsic cardiac afferent neurons
  2. sympathetic or parasympathetic efferent neuronal activation either electrically (4 V, 10 Hz, 5 ms) or chemically (nicotine 5 µg/kg intravenously)
  3. direct cardiomyocyte B-adrenergic receptor stimulation (isoproterenol hydrochloride, 5 µg intravenously)

Denervation?

TMR Does Not Denervate The Canine Heart

Summary of Results:
- Sensory neurites of right atrial afferent neurons in the studied epicardial region responded similarly to chemical stimulation pre and post TMR.
- TMR did not reduce local ventricular contractile responses to direct activation of sympathetic or parasympathetic efferent neurons by electrical or chemical means, nor did it affect cardiomyocyte augmentor responses elicited by exogeneous B-adrenergic receptor challenge.

TMR Does Not Denervate The Canine Heart

Conclusion:
- TMR does not affect afferent or efferent axonal function in the affected ventricle.
- The efficacy of TMR **CANNOT** be ascribed to local denervation.

Placebo

Proposed Mechanism of Action
DMR uses a completely different delivery system, procedural technique, and tissue interaction
- DMR energy was chosen to minimize tissue damage
  - The emphasis was not on channel creation but to trigger endogenous tissue response*
- Direct Trial Conclusion: DMR is Not an Effective Treatment

Six randomized TMR clinical studies prove significant symptomatic relief
Symptomatic benefits persist long-term
Conclusion: An Effective Treatment

Placebo?

Direct Trial: DMR vs Maximal Medical Therapy

Article Reference: Leon M. Presented at Transcatheter Cardiovascular Therapeutics 2000, October 2000 in Washington, DC.
Placebo?

True-Sham, double blind BELIEF Trial and sustained long-term efficacy results demonstrate benefits of TMR is **NOT** from placebo.

So How Does It Work?

Proposed Mechanism of Action
How Does it Work?

• Current theories suggest that the mechanism is a multi-factorial process which occurs in stages:
  o The acute state
    • Neural pathways still transmit
    • ICNS remodeling
    • Local denervation effect
    • No silent ischemia
  o The chronic stage / long-term effect
    • Long-term angiogenic response
      o Produces vascular growth, resulting in increased perfusion, thus leading to long-term symptomatic relief and improved functional clinical benefit

Proven Clinical Benefit

Clinical Trials Have Shown a Clinical Benefit with the Use of TMR

• Primary Outcomes:
  o Relief of Angina by Two or More Classes
  o Increased Exercise Tolerance

• Secondary Outcomes:
  o Reduction in Re-Hospitalizations
  o Reduction in Medication Usage
  o Increased Event Free Survival
  o Increased Perfusion
  o Improved Quality of Life

• Long-Term Efficacy
Proven Clinical Benefit

✓ Proven Symptomatic Relief

✓ Dramatic Improvement in Quality of Life

✓ Significant TMR Reimbursement for Hospital and Physician

• The Blue Cross/Blue Shield TEC States:
  o In 1999: TMR Sole Therapy “Improves Net Health Outcomes”
  o In 2001: TMR+CABG “Improves Net Health Outcomes”

• Advantageous for All Stakeholders
  o Patient, Physician, and Healthcare System