Review

A Proposed Alternative Mechanism of Action for Transmyocardial Revascularization

Prefaced by a Review of the Accepted Explanations

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Laser transmyocardial revascularization, a procedure originally intended to simulate the perfusion mechanism of the reptilian heart, has evolved into an effective but poorly understood treatment for angina when traditional revascularization is not an option. Herein, we review the explanations that have been proposed over the years and suggest a new one. We hypothesize that the long-term mechanism of action of transmyocardial revascularization is the redistribution of stresses on the ventricular wall through the creation of fibrous transmyocardial scars, which penetrate the various layers of muscle that surround the left ventricular cavity. The stress redistribution of a load in an otherwise unchanged ventricular wall reduces the wall stress per unit of wall volume, which in turn decreases the workload for the hyperkinetic compensating areas. This reduces both oxygen demand and local metabolite production, lowering the level of angina. ***(Tex Heart Inst J 2006;33:424-6)***

The law of unintended consequences may have played, in more ways than one, a major role in the success of laser transmyocardial revascularization (TMR). A procedure originally intended to simulate the perfusion mechanism[1] of the reptilian heart has evolved into an effective, albeit poorly understood, treatment for angina when traditional revascularization is not an option.

Randomized trials of laser TMR have demonstrated a beneficial effect on the angina scores of patients who have undergone this treatment,[2-5] yet the science behind the procedure and the true mechanism of action still elude us.

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Currently Accepted Possible Mechanisms of Action

Placebo Effect

Volumes have already been written on placebo effect, both in general and in specific regard to TMR. It is not the objective of this work to speculate further on well-explored topics.

Angiogenesis

The available evidence suggests that TMR-induced angiogenesis is likely to be a nonspecific response of the myocardium to injury, because a laser-specific angiogenesis response has not been identified.[8]

Increased vascular density can be seen in the area immediately surrounding the channel remnants, but this neo-vascularity does not seem to extend appreciably beyond that area.[9,10] Results of post-TMR perfusion scans are mixed. Out of 5 randomized clinical trials of TMR as sole therapy, only 1 shows improvement in perfusion by positron-emission tomographic scan, whereas the results of thallium scans are more favorable.[3,4,11]

New vasculature in the laser-treated area could explain part of the observed clinical improvement, but the vascularization of myocardial scar tissue (that is, after infarct) has very modest oxygen-delivery capacity.[12] Still, it remains to be proved that these new vessels play an active role in improving oxygen delivery beyond the immediate area of the channel remnant.

The calculated volume of tissue with microscopically proven neo-vascularity after the creation of 40 channels[9,10] would range between 17.4% and 31.5% of the treatable myocardium (depending on the number of channels, the sex of the patient, and the body surface). Even in the best-case scenario, blood-flow improvement by any conventional means of revascularization to only 31.5% of the target territory would be considered a marginal result; therefore, angiogenesis is not likely the sole mechanism of action.

Sympathetic Obliteration

Pain as a reflection of brain awareness of myocardial ischemia is dependent on afferent sympathetic fibers and ventricular receptors. Afferent fiber denervation as a possible mechanism of angina relief is controversial and in any event would be temporary, given that heart re-innervation seems to occur within 6 months.[13,14]

Destruction of Ischemic Myocardium

The number of channels drilled on the free surface of the left ventricle (LV) during sole therapy with TMR is approximately 40. By knowing the area of damage (average, 4.5 mm^2 for the holmium:YAG)[6] and the thickness of the LV wall (average, 10 mm), we can calculate the volume of the myocardial cylinder destroyed during the procedure. The total volume of LV myocardium destroyed during a typical TMR procedure would amount to 1.8 cc^3 of tissue, which, given its density, would be equivalent to only 2 grams of muscle. For the CO_2-based laser, the volume of myocardial destruction would be about half that.

If we assume an average LV mass index of 76 ± 13 g/m^2 in men and 66 ± 11 g/m^2 in women[7]—one third of which (the septum) is beyond the reach of the laser—we are left with a mass of treatable ventricular myocardium of 80 to 113 g for men and 62.5 to 88 g for women. The volume of myocardial tissue destroyed by sole therapy with TMR, depending on the patient's sex and body mass, would be between 1.7% and 3.2% of the total treatable myocardium. This percentage of ischemic tissue destruction hardly explains angina relief.

An Alternative Hypothesis

Angina Relief in the Early Postoperative Period. Norepinephrine released by sympathetic activity is perhaps the most important mechanism that regulates myocardial activity. β-Blockers and norepinephrine-depleting drugs interfere with the myocardial response to sympathetic stimulation[15] by successfully controlling the "overdrive" elicited when congestive heart failure is present.

Beek and coworkers,[16] while looking for myocardial denervation, may have unintentionally happened upon an interesting finding. By using a test sensitive for the detection of myocardial postganglionic sympathetic dysfunction (^{123}iodine-labeled metaiodobenzylguanidine cardiac scintigraphy),[17,18] they may have found proof of *efferent* sympathetic denervation. This mechanism of action could provide immediate postoperative angina relief by offering the ultimate efferent surgical β-blockade, allowing for increments in cardiac output through a higher stroke volume rather than a higher heart rate and inotropic status—with an overall improved efficiency and a lower oxygen consumption.[19]

Angina Relief in the Late Postoperative Period. Akinesis and dyskinesis can be readily detected by visual inspection of angiograms or echocardiograms; however, the phenomenon of hypokinesis at the microscopic level cannot. Hearts with diffuse ischemia and preserved function must have, by definition, multiple microscopic areas of undetectable hypokinesis. These areas of hypokinesis are associated with hyperkinesis of other regions as a compensatory mechanism.[15] Hyperkinesis increases oxygen demand and the accumulation of unwanted metabolic products in an area with limited blood flow and oxygen supply. Angina can only be made worse by this local compensatory mechanism.

Interfascicular Tension. Muscle fibers are arranged in different directions as they wrap to form the ventricular cavities. The most superficial fibers are disposed in an oblique fashion, the middle layers are circumferential, and the inner layers are arranged in a longitudinal mode.[20] A simultaneous contraction of the fibers, distributed in different directions, creates extra tension in the fibrous and myocardial connections between the different layers.[21] Furthermore, LV wall thickness increases 25% to 35% during systole, but the relative degree of sarcomere shortening cannot be the same across the ventricular wall. Geometrical considerations dictate that endocardial fibers must shorten relatively more than epicardial ones.[15]

Wall stress is defined as force per unit of cross-sectional area (in dynes/cm^2) of muscle. The ventricular end-diastolic wall stress or resting tension determines the resting length of the sarcomeres,[15] which in turn controls the amount of work that a sarcomere will be subjected to and therefore influences its oxygen demand.

During systole, the minor (transverse) axis of inner wall shortens by 20% to 25% while the major (apex–base) axis shortens by 9%; it is the shortening of the minor axis that accounts for 85% to 90% of the stroke volume.[15] The most internal layers of muscle are the poorest oxygenated and must shorten the greatest distance, but the medial and outer layers are the most effective (more stroke per shortening) and generate the most stroke volume. Incidentally, this may provide a reasonable explanation of why some patients have preserved ventricular function, yet have scores that indicate severe angina.

A Side Note on Stress Distribution. The unquestionable icon of the Middle Ages was the Gothic cathedral.

The use of flying buttresses to distribute and convey the collected pressures at pier intervals enabled the strain and stresses of the walls to be redistributed and ultimately transmitted to the ground.[22] This innovative mechanism allowed medieval architects to design structures, in clear contrast with Romanesque churches, that supported greater loads and pressures despite thinner and taller walls—thus opening large spaces under the vault and permitting vast quantities of light to flood the nave.

Stress redistribution is also used in the construction of retaining walls, wherein the thickness of the wall needed to support the force and movement of retained soil can be reduced by the use of tieback tendons anchored to the bedrock. A good example of this is the "slurry" or diaphragm wall construction at the site of the World Trade Center.[23]

"Revascularization" or Re-Engineering? We could hypothesize that the long-term mechanism of action of TMR is the redistribution of stresses on the ventricular wall through the creation of fibrous transmyocardial scars, which penetrate the various layers of muscle that surround the left ventricular cavity. These well-vascularized scars or mini-tendons, evenly spaced throughout the thickness of the LV, would latch the different layers onto each other, reducing the interfascicular tension by acting as redistribution points. Wall stresses are now scattered to all layers from endocardium to epicardium, through the mini-tendons that act as buttresses or tiebacks.

Unlike architectural design, wherein redistribution of wall stress enables a thinner wall to support a heavier load, TMR does not alter the thickness of the ventricular wall. Nevertheless, the stress redistribution of a load in an otherwise unchanged ventricular wall reduces the wall stress per unit of wall volume, which in turn decreases the workload for the hyperkinetic compensating areas. This reduces both oxygen demand and local metabolite production, lowering the level of angina. Perhaps TMR should be understood in a new light, to mean transmyocardial re-engineering.

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