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Potential Mechanisms of Myocardial Revascularization Techniques: Channels, Functional and Structural Remodeling, Angiogenesis, Denervation, or Placebo

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SUMMARY

Several mechanisms are proposed as possible ways of angina relief after PMR. These include 1) creation of transmyocardial channels, 2) mechanical effects of remodeling, 3) angiogenesis resulting from the thermal and mechanical injury, 4) direct or indirect denervation, 5) remodeling of the intrinsic nervous system, 6) altered myocardial function, and 7) the placebo effect.

PMR/TMR in animals has been found to enhance vascular growth of both large and small arteries in the ischemic myocardium; however, the mechanism responsible for improvement in symptoms and exercise tolerance in humans has yet to be discovered.

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Concern has been raised in the DIRECT Trial regarding "placebo effect" in patients who undergo PMR procedures, but this was offset by recent results of a double blinded placebo study from Norway, the BELIEF Trial, showing significant improvement in symptoms and exercise tolerance with PMR.

Multiple mechanisms are probably at work after PMR. In the early phase denervation may provide symptom relief, whereas in latter stages angiogenesis may have a greater role.

6.1. INTRODUCTION

The premise of laser revascularization is based on the early work of Wearn et al. (1922, 1933), who described arterioluminal and arteriosinusoidal vessels as direct connections between the blood in the ventricular chamber and the myocardium. Thus it seemed obvious to attempt to perfuse the myocardium by creating direct channels with the left ventricular cavity. Several earlier techniques were investigated to achieve that goal, including the insertion of a T-tube implant between the ventricular chamber and the muscle or mechanical boring by needle acupuncture (Goldman et al., 1956; Sen et al., 1965). None of these techniques was found to be successful in perfusing ischemic myocardium. Almost a half-century later, there was a resurgence of the concept of direct myocardial reperfusion, stimulated by an increasing number of patients with coronary artery disease who were not candidates for standard revascularization techniques. Transmyocardial revascularization (TMR) with laser was proposed as a novel technique using this concept to supply oxygenated blood to the ischemic myocardium (Mirhoseini and Cayton, 1981). Numerous animal and human studies have been performed to test this concept. However, despite the clinical relief of angina and improved functional status in the patients treated with TMR, the mechanism of this and related procedures remains unclear. In this chapter we present data supporting and negating various proposed mechanisms including direct channel perfusion, angiogenesis, laser-induced myocardial remodeling, altered mechanical function, denervation, and placebo effects.

6.2. DIRECT MYOCARDIAL PERFUSION BY CHANNELS

The creation of channels by laser or other methods is thought to transect the myocardium and connect with the intramyocardial vascular network. Wearn et al. initially described this network as a sinusoidal system, but other investigators challenged this observation and proposed more of a vascular network that may even involve the lymphatics or just distorted coronary veins (Chiu and Scott, 1973). Thus the attempt to mimic the "reptilian heart" physiology by TMR may be too simplistic.

In the 1960s, Pifarré et al. indicated that it was physiologically impossible for blood to flow from the ventricular chamber to the myocardium during either systole or diastole. Using various animal models, they demonstrated that the pressure within the myocardium was always greater than the pressure within the ventricle; hence, no flow would be possible (Pifarré et al., 1962, 1969). However, several investigators recently postulated that an endocardial-epicardial pressure gradient could allow transmyocardial blood flow. Hardy et al. demonstrated that the endocardial-epicardial gradient increased with progressive rise in left ventricular pressure and that ventricular systolic pressure greater than 207 ± 16.1 mmHg permitted the entry of microspheres into the TMR channels (Hardy et al., 1990). This simulates the conditions often seen in the ischemic myocardium (Kohmoto et al., 1996). Others have observed radiographic contrast as well as ultrasonic medium filling the transmyocardial channels during systole (Berwing et al., 1996; Kim et al., 1999).

Another aspect of this controversy revolved around channel patency. Abela et al. demonstrated patent channels in the myocardium of an acute dog model using an argon laser delivered via an optical fiber extended from a hollow electrode-tipped catheter under fluoroscopic guidance (Abela et al., 1983; Curtis et