CHAPTER 1

Scientific and historic precedents

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Introduction

Transmyocardial laser revascularization (TMR) is based on anatomic and physiologic principles long known and accepted in the history of medicine. The coronary anatomy was first described accurately by Vesalius in his landmark 16th-century text, *De humani corporis fabrica* [1]. The anatomic pathway of the coronary circulation was further elucidated by Vieussens [2], the royal physician to Louis XIV [3]. Vieussens documented the presence of direct vascular communication between coronary arteries and the chambers of the heart [4]. In 1706, he published *Nouvelles découvertes sur le coeur*, which was recognized at the time as the most accurate and detailed account of the structure and function of the heart [5]. This work described the circulation of the heart as inferred from postmortem experiments on the hearts of humans, calves, and sheep [2,3]. In these studies, Vieussens ligated the vena cava and pulmonary veins and injected saffron dye dissolved in alcohol into the coronary arteries. Once injected, the dye solution not only followed the accepted anatomic conduit through the coronary sinus and into the right atrium, but also flowed directly into the right and left ventricular chambers through small channels in the walls of the atria and ventricles [6]. Vieussens labeled these ducts joining the ventricular cavities to the coronary arteries "ducti carnosi" [2,4].

Two years later in Leiden, Holland, Thebesius [7] published *De circulo sanguinis in corde*, also relating to the microanatomy of the myocardium. Thebesius discovered openings in the endocardium by injecting water into the coronary sinus and observing the subsequent arrival of effluent in the atria and ventricles. Further experiments in which air, colored liquids mixed with wax, and glue were injected into the coronary veins provided the same results, confirming the presence of the ducts in the cardiac chambers [4,6]. Thebesius and Vieussens described the same channels, Thebesius by injecting the veins and Vieussens by injecting the arteries. Although Vieussens first reported the existence of these openings, all myocardial vessels that connect to cardiac chambers are now called thebesian vessels. In any case, by the early 18th century, the unique character of the coronary circulation was well established.

The study of comparative anatomy was popularized by the French anatomist Cuvier [8] in the late 18th and early 19th centuries. Cuvier described various ways that nature dealt with the problem of vascularizing the organ responsible

for supplying blood to the rest of the body. As one moves up the evolutionary ladder, the circulation moves from one of direct perfusion from the ventricular cavity through the spongy, non-compacted myocardium as seen in fish and reptiles to one of direct coronary blood flow as seen in mammals. Interestingly, the various steps in this phylogenetic evolution of the coronary circulation are closely recapitulated in the development of the human embryo. Historically, the presence of this retained non-compacted myocardium contributing to a pathologic condition was first noted by Grant [9] in the 1920s. This abnormality, which may be seen in both symptomatic and asymptomatic patients [10,11], is appreciated more today because of the precise diagnostic capabilities of cardiac magnetic resonance imaging (MRI) and echocardiography.

The physiologic potential and possible functional importance of this direct ventriculomyocardial communication was demonstrated by a simple, yet ingenious, experiment by Pratt [12] in 1898. Pratt demonstrated that, by delivering defibrinated blood directly into the ventricular cavity and totally excluding the coronary circulation, it was still possible to maintain cardiac contractility and function, with the only source of oxygenated blood being directly through the ventricular myocardium. In this way, contractility was maintained in a mammalian model for several hours (Figure 1.1).

In 1928, while working in Boston's city morgue, Leary and Wearn [13] detailed the postmortem coronary circulation in two patients who had chronic syphilitic aortitis. Syphilitic aortitis had long been known to selectively invade the ascending aorta. In these two patients, the aortic origin of both coronary arteries had been chronically occluded by this disease. In spite of this, both patients were known to have maintained active lifestyles and gainful employment for a number of years before they died. This finding particularly intrigued Wearn and moved him to question how blood was able to reach the heart despite the obliteration of the coronary access.

After relocating to Western Reserve University in Cleveland, Wearn [6] embarked on a study to further elucidate this question. He studied human hearts by perfusing the coronary arteries with a celloidin mass too thick to enter the capillaries and subsequently observed celloidin plugs in the walls of the heart chambers, indicating that the celloidin had bypassed the capillaries. He detailed his findings in a paper published in 1933 [6]. Dissection and negative casting revealed direct vascular communication between the coronary arteries and the ventricular cavities via two types of vessels, identified as the arterioluminal and arteriosinusoidal vessels. Located near the endocardium, the arterioluminal vessels run directly from the coronary arteries into the lumen of the heart. The arteriosinusoidal vessels are small branches of coronary arteries that eventually lose their arterial character and divide into channels called myocardial sinusoids (Figure 1.2). Myocardial sinusoids vary in diameter from 50 to 250 μm and have thin walls consisting of endothelial tissue.

The study of myocardial circulation became much more pertinent throughout the 1920s and into the 1930s, as angina and coronary artery disease in general became increasingly observed clinically. Nevertheless, the treatment

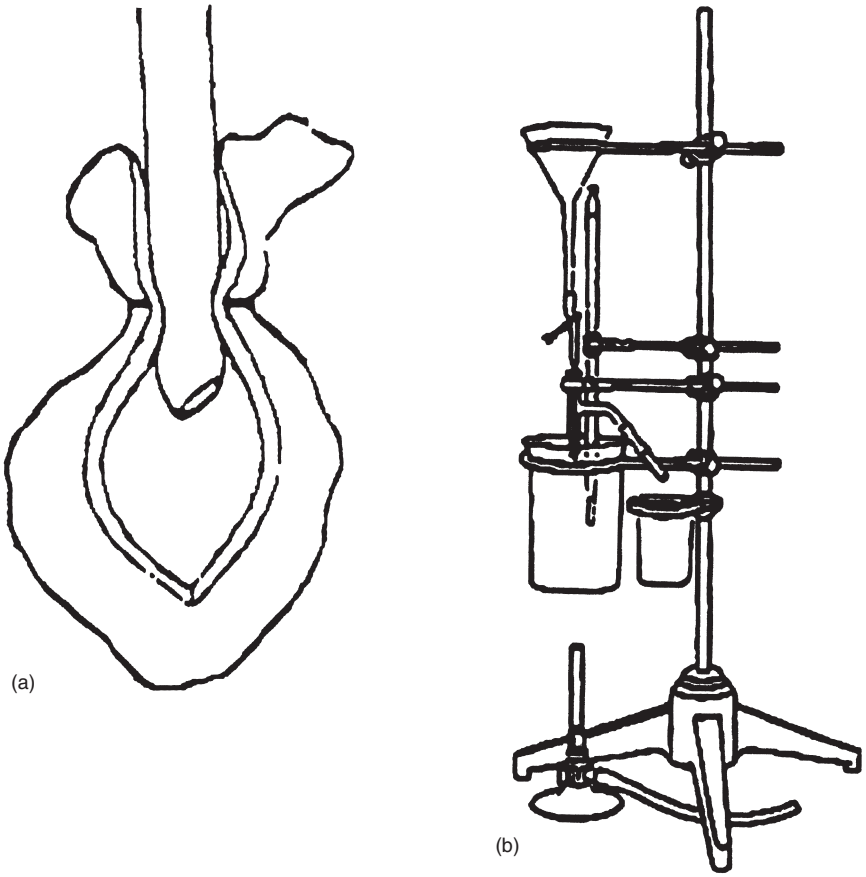


Figure 1.1 (a) Diagram illustrating cannulation of right ventricle of feline heart for perfusion through thebesian veins. (b) This apparatus perfused the feline heart with defibrinated blood through the ventricles and maintained myocardial contractility for several hours. From Pratt [12] with permission.

options for coronary artery disease in this era were limited to symptomatic therapies such as nitroglycerin, which reduced or palliated anginal symptoms.

Claude Beck [14–20], who had been a surgeon in Boston and had also moved to Western Reserve University School of Medicine in Cleveland, was aware of the work of Wearn and was intrigued by his observations regarding the microcirculation of the heart. Beck had also observed extensive collateral blood supply accompanying the restrictive pericarditis frequently associated with tuberculosis. To Beck this seemed to imply that augmentation of blood supply was being induced by an inflammatory response to this infectious process. The possibility implied by Wearn's work was that this augmented blood supply might reach the myocardium directly, thereby bypassing the occluded coronary arteries. Beck attempted to produce this response by irritating the myocardium through abrasion and introduction of foreign bodies (talc) [14,15].

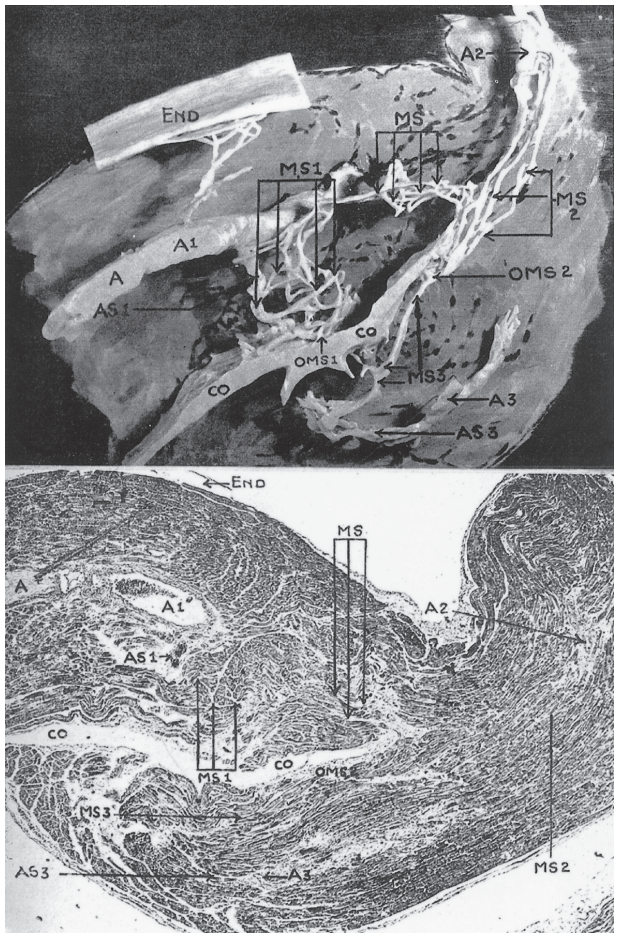


Figure 1.2 (a) Wax reconstruction revealing direct communication between coronary arteries and left ventricle via arterioluminal and arteriosinusoidal vessels. (b) Serial section from block of myocardium used to create the wax reconstruction shown in top panel (magnification ×41). A, artery; AS, arteriosinusoidal vessel; CO, common opening; END, endocardium; MS, myocardial sinusoid; OMS, opening of a myocardial sinusoid into ventricular lumen. From Wearn *et al*. [6] with permission.

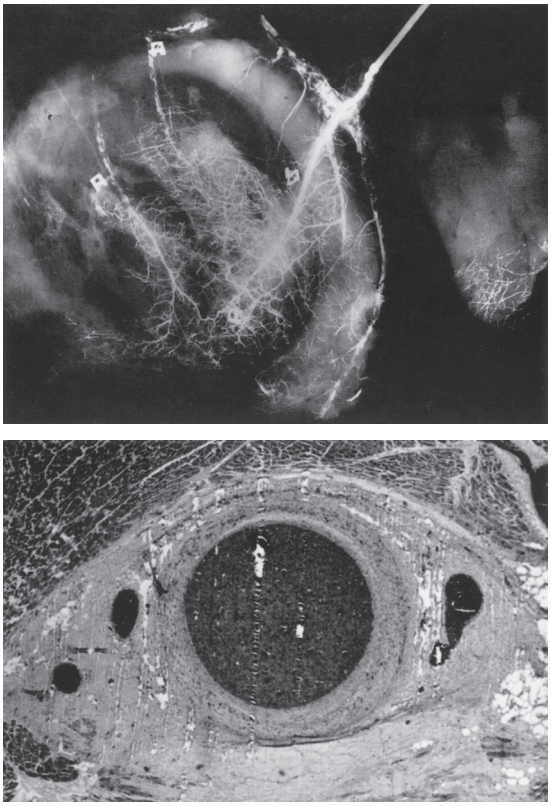
The historic demonstrations of Vieussens and Thebesius implied that direct arterial blood could be brought to the ischemic myocardium by utilizing the venous system. Beck decided to bring arterial blood to the ischemic myocardium in the same way. This approach was once again based on the extensive interconnecting microcirculatory network that proliferated in response to myocardial ischemia. Beck utilized the brachial artery as a graft and the coronary sinus as a conduit from the descending aorta. This operation was researched extensively in the experimental animal and first applied to patients in 1948 [17]. The intrepid Beck performed this milestone operation without benefit of

today's modern vascular instruments or suture materials and, more importantly, without access to cardiopulmonary bypass. This retrograde bypass was performed 20 years before the introduction of antegrade coronary artery bypass procedures. Beck combined various approaches to this indirect revascularization, utilizing chemical and mechanical means to enhance anastomotic channels through adhesions combined, in some cases, with arterialization of the coronary sinus [14–20]. Despite a high mortality rate for these procedures, Beck reported relief of anginal symptoms in the majority of patients [17–20].

Taking an even more direct approach to myocardial revascularization, the Canadian surgeon Vineberg [21,22] began implanting the internal mammary artery (IMA) into the left ventricular wall of canine hearts in 1945. This direct myocardial revascularization technique took advantage of the sponge-like character of the myocardial sinusoids, thus allowing direct communication between the IMA implant and myocardial cells. Postoperative studies confirmed microscopic anastomosis between the open IMA graft and the arteriolar branches of the poorly functioning canine coronary artery. Vineberg performed this procedure for the first time on a patient with coronary insufficiency in 1950 [22]. The majority of patients reported improvement in anginal symptoms as well as increased duration of physical activity. Vineberg's angiographic demonstration of the patency of the open IMA graft, as well as extensive communication to the microcirculation of the heart, enhanced the credibility of these anecdotal reports. The introduction of cardiopulmonary bypass, as well as improvements in vascular instruments and suture materials, allowed coronary artery bypass grafting (CABG) to supplant the Vineberg procedure by the late 1960s. Nevertheless, in 1975, Vineberg [23] demonstrated the long-term effectiveness of the IMA graft procedure when he reported the continued patency of the arteriomyocardial connections and the important symptomatic relief afforded by the procedure after 24 years of follow-up (Figure 1.3). The report included 94 patients, with 84% showing graft patency.

Following Goldman *et al*.'s proposal [24] in 1957 to create a direct communication between the ventricular cavity and coronary circulation using straight and U-shaped arterial grafts, Massimo and Boffi [25] initiated the use of T-shaped polyethylene tubes to offer more protection against obstruction caused by compression during myocardial contractions. That same year, Massimo and Boffi reported that the T-shaped tubes successfully delivered oxygenated blood from the left ventricle directly into the ischemic myocardium of dogs.

In 1964, before CABG had become generally accepted, Sen *et al*. [26–28] reported the use of a unique method of direct revascularization. They based their approach on the accepted corollary, established by Wearn, Pratt, Vineberg, and others, that myocardial viability is preserved by the proliferation of the microcirculation. The aim was to enhance blood flow to the ischemic myocardium by creating small channels with a large-bore needle directly from the left ventricle to the myocardium. Sen noted that Cooley had described to him, in a personal communication, Cooley's use of transmyocardial acupuncture in several desperate cases of insufficient myocardial perfusion in the 1960s [27]. Sen



(a)

(b)

Figure 1.3 Internal mammary artery (IMA) graft after 24-year follow-up. (a) Radiograph of left myocardial network injected with contrast agent to demonstrate graft patency. (b) Histopathologic section of patent IMA graft. From Vineberg [23] with permission.

speculated that the transmyocardial channels would facilitate blood flow to the bed made more receptive of this flow by the proliferation of the microcirculation in response to chronic myocardial ischemia. Creation of this alternate route of blood flow was an attempt to duplicate the reptilian circulation (Figure 1.4). In the reptile, the coronary arteries are small, perfusing less than one-tenth of the myocardial thickness, and most of the myocardium is supplied directly from the ventricular cavity to the myocardial sinusoids during systolic contraction. This attempt by Sen to improve myocardial perfusion through direct ventriculomyocardial communication was an early clinical application of transmyocardial revascularization (TMR) [28].

In 1967, while performing a Vineberg procedure on a 61-year-old man with triple coronary artery disease, Hershey and White [29] employed Sen's acupuncture technique as a last resort to save the patient from refractory ventricular fibrillation. After puncturing the left ventricle approximately 100 times with a 2.5-mm intravenous knobbed cannula and applying prolonged intermit-

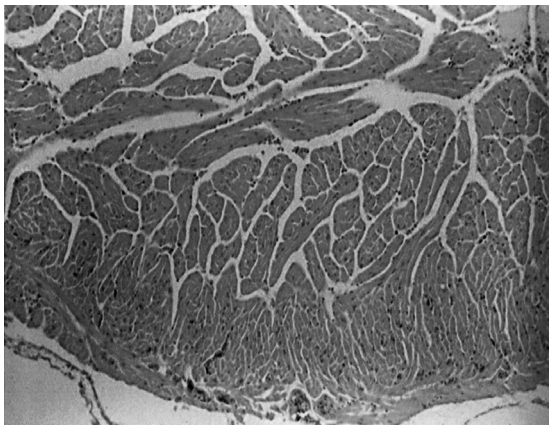


Figure 1.4 Histologic cross-section showing non-compacted myocardium of snake heart.

tent cardiac compressions, revascularization was achieved and normal ventricular rhythm was restored. This allowed the Vineberg procedure to be completed. Angiography almost a year later showed that the Vineberg implants had failed to form anastomoses with the distal coronary vessels, thus suggesting that the patient's recovery may have been due to the transmyocardial acupuncture procedure. In 2000, Hershey [30] reported that the patient remained well and angina free after 14 years of follow-up.

Shortly after Sen and Hershey published their initial reports, Pifarré *et al*. [31] raised questions about the effectiveness of myocardial revascularization by transmyocardial acupuncture. On the basis of their pressure measurements in implanted venous grafts, Pifarré *et al*. believed that no pressure gradient existed between the ventricular cavity and the myocardium. However, later studies by Nematzadeh *et al*. [32] showed not only that Pifarré's indirect pressure measurements were flawed, but also that there was a persistent positive pressure gradient between the ventricular cavity and the myocardium.

Studies at the Texas Heart Institute in Houston using a more exacting and accurate transducer-tipped catheter measurement technique showed that the intramyocardial pressure (IMP) is consistently lower than the left ventricular pressure (LVP) throughout the cardiac cycle (Figure 1.5) [33]. These pressure measurements confirming the persistent positive gradient between the ventricular cavity and myocardium confirmed that unidirectional flow to the myocardium is possible through patent myocardial pathways.

The interest in indirect myocardial revascularization subsided with the successful introduction of direct CABG in the late 1960s. The CABG procedure resulted in the restoration of coronary artery blood flow and significant improvement in the surgical treatment of coronary artery disease. However, by the late 1970s, late occlusion of venous bypass grafts was being observed with increasing frequency. If the occlusion also resulted in deterioration of the clinical status of the patient, then the more arduous and risky coronary redo surgery

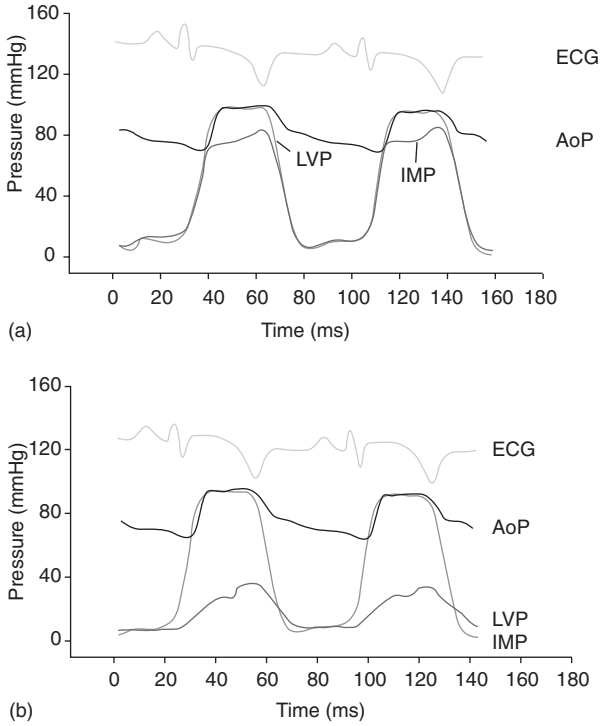


Figure 1.5 Pressure measurements made using a transducer-tipped catheter technique. Intramyocardial pressure at (a) the subendocardial level, (b) the subepicardial level. These pressure measurements demonstrate a persistent positive gradient between ventricle and myocardium and indicate the feasibility of unidirectional flow to the myocardium through patent myocardial pathways. After Frazier and Kadipasaoglu [33] with permission.

became the only alternative. This scenario renewed interest in the indirect myocardial revascularization techniques that had preceded the introduction of CABG surgery.

In 1981, Mirhoseini and Cayton [34] reported their attempt to create patent transmyocardial channels in canine hearts using a CO_2 laser (0–400 W) without producing fibrosis or scarring. In brief, they ligated the left anterior descending (LAD) coronary artery in four experimental groups of dogs and then subjected three of these groups to varying amounts of laser treatment of the myocardium. All dogs in the control group died within 20 minutes of ligation, whereas 100% survival was reported in the dogs that received laser treatment on a large area of their left ventricles perfused by the LAD. Histologic and microscopic examinations of the dogs sacrificed at 6 and 8 months after laser treatment revealed patent transmyocardial channels.

Two years later, Mirhoseini *et al*. [35] presented a clinical case report detailing the results of this laser technique as performed on a 65-year-old male with three-vessel coronary artery disease and LAD obstruction. After implanting four

aortocoronary bypass grafts, this group used the CO_2 laser to create channels in the hypokinetic area of the left ventricle while the patient remained on cardiopulmonary bypass. Evaluation of postoperative technetium-99m stannous pyrophosphate (Tc-PYP) scans showed normalization of perfusion in the area of laser application.

Further experiments with TMR were performed at the Kobe University School of Medicine in Japan by Okada *et al*. [36]. In their experimental model, the researchers utilized the CO_2 laser to create myocardial channels in dogs whose hearts had been rendered ischemic. CO_2 was uniquely suitable for the creation of such channels by virtue of its ability to vaporize small 100-μm sections of the ventricle with minimal lateral injury. In 1985, after achieving promising experimental results, Okada *et al*. performed TMR as sole therapy on a 55-year-old man with severe angina and a history of pericardiectomy. As bypass was not technically possible, a CO_2 laser with an output of 85 W was used to create transmyocardial channels in the left ventricle of the patient's beating heart. The patient survived, and preoperative and postoperative assessments of cardiac catheterization data and electrocardiographic recordings did not demonstrate any abnormal changes. Okada's 12-year postoperative follow-up of the patient confirmed the success of this first reported clinical use of TMR as sole therapy [37].

Mirhoseini *et al*. [38] further assessed the safety and effectiveness of the CO_2 laser by performing TMR in conjunction with CABG on 12 patients with histories of recurrent angina pectoris. Between 10 and 12 laser channels were created in viable myocardial sites where grafting would not have been feasible. The combination therapy resulted in a 100% survival rate, reduced angina, and improved myocardial perfusion as revealed by postoperative left ventriculography and thallium stress testing.

In 1990, PLC Medical Systems, Inc. introduced the 1000-W CO_2 Heart Laser™ [39], which allowed TMR to be performed on a beating heart using a single pulse. In comparison with the 85-W laser, this high-powered laser fires one pulse in synchrony with the *R* wave of the electrocardiogram, at the point of maximal ventricular distention. The distention improves precision and aids in the creation of straight channels; the large amount of blood in the ventricle serves to protect the heart by absorbing the CO_2 laser emission, thereby protecting against injury to the ventricular wall opposite the channel created by the laser.

In the same year, Frazier and Cooley were approached by PLC Medical Systems, Inc. to investigate use of the CO_2 laser for treatment of angina at the Texas Heart Institute. They agreed to embark on this study only if improvement in perfusion could be demonstrated with this technology. The treatment of angina alone is beset with problems related to the placebo effect. This required a clear measurement of improved perfusion to confirm a plausible relationship between the channel creation and relief of anginal symptoms. The first TMR cases enrolled in the Texas Heart Institute study were patients with severe angina related to demonstrated impaired perfusion. These patients were not suitable

candidates for surgical revascularization or interventional cardiology. The laser was applied off-pump and with consistency in regards to the laser energy applied and the number of channels created. Positron emission tomography (PET) scanning was performed to demonstrate a perfusion deficit before intervention was considered. At the time, the PET technology was the most precise scientific means of measuring myocardial perfusion. In addition, it allowed the balance between endocardial and epicardial perfusion to be measured. PET studies were performed before intervention (at baseline) and at 3 and 6 months. There was consistent clinical improvement in the angina but, more importantly, there was statistically significant improvement in endocardial perfusion (Figure 1.6). The scientist who interpreted endocardial perfusion was not involved in applying the therapy [40]. This expensive and time-consuming study provided

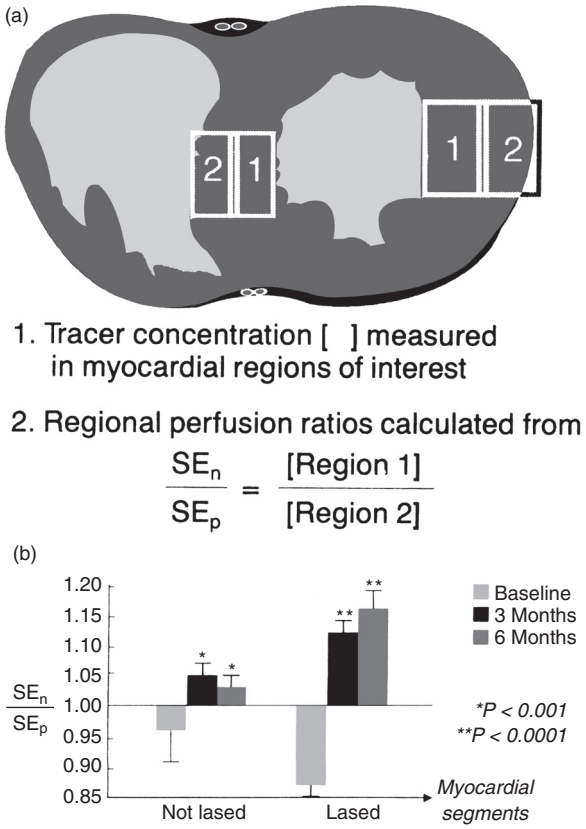


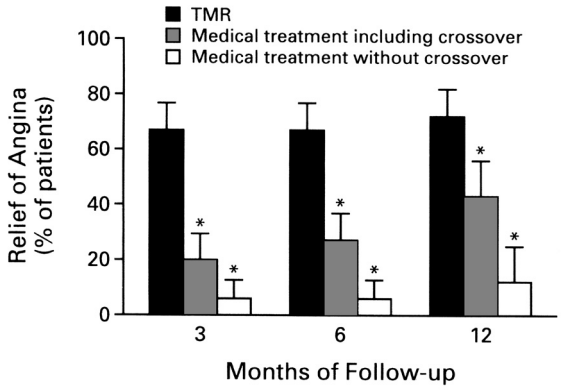
Figure 1.6 (a) Short-axis diagram of myocardium showing subendocardial (SE_n) (1) and subepicardial (SE_p) (2) regions evaluated for perfusion by positron emission tomography (PET). (b) Graph comparing regional radioactive tracer uptake myocardial perfusion in lased and non-lased myocardium during stress at baseline, 3 months, and 6 months. *P* values vs. baseline. From Frazier *et al*. [40] with permission.

convincing evidence of a relationship between improved endocardial perfusion achieved by laser therapy alone.

Between 1992 and 1995, 200 patients underwent TMR as an independent therapy in a non-randomized study at eight different medical centers in the USA [41]. In accordance with the inclusion criteria, the patients had Canadian Cardiovascular Society (CCS) class III or IV angina refractory to medical therapy, had reversible ischemia, and were not candidates for percutaneous transluminal coronary angioplasty, CABG, or cardiac transplantation. Specifically, 20% and 80% of these patients were classified as CCS class III and IV, respectively. Within 12 months after TMR, 13 patients underwent additional procedures, and three of them died as a result. At 1-year follow-up, the overall survival was 83%; postoperative evaluation at 3, 6, and 12 months demonstrated a significant decrease in the patients' CCS angina classifications and improvement of myocardial perfusion. TMR therapy was considered successful if there was a postoperative decrease of two angina classes. By this criterion, statistically significant anginal improvement was achieved. More importantly, blinded, unbiased interpretation of the myocardial perfusion studies (thallium scans) revealed a statistically significant improvement in perfusion in these patients.

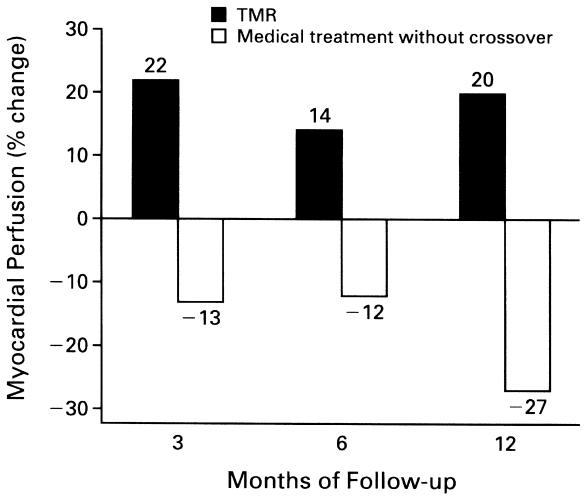
A pivotal trial was initiated in 1995. This study was a prospective, multicenter, randomized trial to compare the safety and efficacy of CO_2-induced TMR versus maximal medical therapy for anginal relief [42,43]. A total of 192 patients were randomized in the study. Patients were evaluated at 3, 6, and 12 months in terms of CCS classification, quality of life, and myocardial perfusion as shown by thallium-201 single photon-emission computed tomography (SPECT) scanning. After 1 year, 72% of the TMR group showed improvement in angina symptoms (i.e., an improvement of two or more CCS classes) compared with only 13% of the medical management group (Figure 1.7) [42]. Experienced interpreters at a leading cardiovascular center who were blinded as to the mode of therapy administered assessed myocardial ischemia. Their interpretations showed a statistically significant improvement in perfusion in the TMR-treated patients and a worsening of perfusion in the patients managed medically (Figure 1.8) [42]. This study led to Food and Drug Administration (FDA) approval of the use of the CO_2 laser as sole therapy on August 20, 1998.

The unique nature of the coronary circulation has been well documented over the last 300 years. The peculiar physiologic status of the heart, which renders it incapable of extracting oxygen when faced with an oxygen debt, makes it singularly dependent on blood supply (Figure 1.9) [44]. Angiogenesis (i.e., proliferation of the microcirculation) is maximized by ischemia [45]. However, the ingress of blood to the ischemic myocardium is limited by the occlusion of epicardially based coronary arteries. As the occlusion of the coronary arteries progresses, the proliferation of the microcirculation becomes increasingly important. The known presence of direct access of blood to the ischemic myocardium is enhanced by the methodologies described here. The clinical importance of these methodologies, including their ability to provide both anginal



No. of Patients			
TMR	78	67	61
Medical treatment including crossover	77	67	54
Medical treatment without crossover	24	24	20

Figure 1.7 Improvement in angina symptoms with transmyocardial laser revascularization at 3, 6, and 12 months of follow-up. Angina relief was indicated by improvement of two or more Canadian Cardiovascular Society (CCS) classes. From Frazier *et al*. [42] with permission.



No. of Patients			
TMR	50	47	38
Medical treatment	38	35	13

Figure 1.8 Effect of transmyocardial revascularization versus medical management (MM) on left-sided myocardial perfusion. The percentage change was calculated by subtracting the number of defects reported at follow-up from the number of defect at baseline, then dividing by the number of defects at baseline. Reprinted from Frazier *et al*. [42] with permission.

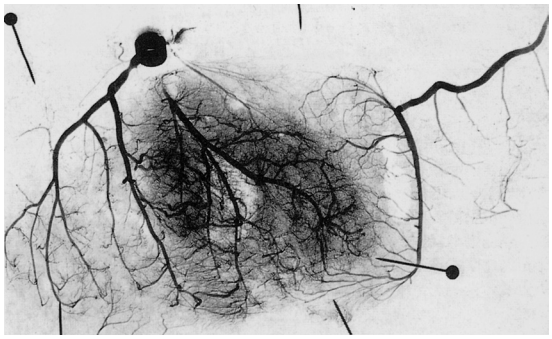


Figure 1.9 Arteriogram of postmortem pig heart injected with barium sulfate contrast dye, dissected, and unrolled. This image illustrates development of anastomoses in response to arterial occlusion by ameroid constriction. Reprinted from Schaper *et al*. [44] with permission.

relief and improved perfusion, has been demonstrated in numerous studies over the past decade. Studies with the CO_2 laser have consistently shown significant improvement in perfusion as assessed by blinded, unbiased interpretation of PET or thallium scans. A number of case reports of perfusion MRI have also demonstrated this [46,47]. TMR appears to confer a significant and consistent benefit on patients meeting the inclusion criteria of the randomized phase III trial of TMR cited above. Follow-up studies lasting up to 5 years have shown an important long-term relief of anginal symptoms in such patients [48]. Substantive improvement in patients suffering from acute myocardial infarction or advanced heart failure has not been shown to date. However, for ambulatory patients with chronic angina and preserved ventricular function, the therapeutic role of TMR has been well documented both clinically and scientifically over the last 30 years.

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