

"Indirect Myocardial Revascularization" Historical Development and Current Progress A Potential Application of Cardiomyoplasty

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Abstract

Indirect revascularization of ischemic myocardium is the procedure of placing extracardiac tissue in contact with the heart and establishing conditions that stimulate the growth of collateral vessels between the tissue and heart. Before the advent of direct revascularization by coronary artery bypass grafting, clinical studies demonstrated that spontaneously developing collaterals from extramyocardial sources could provide a critical amount of blood flow to the diseased heart. Experimental animal studies showed that muscle, lung, or omentum could be used. Animals that underwent indirect revascularization were able to survive the complete obstruction of 2 or 3 coronary arteries. These early experimental studies further showed that the presence of myocardial ischemia enhanced the development of extramyocardial collaterals. More recent studies have identified angiogenic growth factors that are produced by ischemia, and that the administration of exogenous growth factors appears to augment the development of both extramyocardial and intracoronary collaterals.

Key words: angiogenesis, neovascularization, collaterals, growth factors, cardiomyoplasty, Vineberg procedure.

BAM 3 (4): 329-340, 1993

"Two relatively small arteries supply the most vital muscular structure of the body. This muscular organ is in constant motion, and to make its movements free and frictionless it is enclosed in a moist envelope. In providing man with this anatomic pattern, nature has deprived him of an important compensatory mechanism, namely the ability to develop an adequate collateral blood supply to this organ" [4].

What is Indirect Myocardial Revascularization? Why is it Reëmerging as a Possible Treatment of Coronary Disease?

Prior to the development of the coronary artery bypass procedure, surgical attempts at the correction of coronary disease centered around the concept of indirect myocardial revascularization. This idea envisioned that ischemic myocardium would be supplied with a new source of blood flow, which would be the result of the formation of multiple capillary connections between the myocardium and an extramyocardial tissue.

Interest in this method of revascularization has resurfaced with the recognition that extracardiac collaterals can form between skeletal muscle and myocardium after a *latissimus dorsi* cardiomyoplasty is performed. [35] In fact, we have hypothesized that one of the mechanisms for improvement in patient's symptoms after a cardiomyoplasty is indirect myocardial revascularization. In this review, the historical development of indirect myocardial revascularization will be examined, promising new data on angiogenesis which might be used to improve the concept of "bypass at the capillary level" will be presented, and a possible role for the treatment of inoperable coronary disease with a cardiomyoplasty will be reviewed.

Clinical Indications for Indirect Myocardial Revascularization

At present, there are two problems that limit the effectiveness of CABG or PTCA. The first problem is extensive distal coronary disease, which prevents the application of direct revascularization procedures in approximately 5% of patients. [13] A second problem is progression of arteriosclerotic disease, both in the native coronary vessels and

in the vein grafts. Both of these problems could be theoretically overcome by a successful "bypass" at the capillary level. Distal disease would not contraindicate surgery; in addition, surgery might be considered less palliative and more permanent, since the collateral blood flow through collaterals would be expected to improve, rather than deteriorate, with time.

In addition to a possible role for the treatment of patients with ischemic heart disease without failure, revascularization with a cardiomyoplasty should be of benefit to those patients with failure symptoms. The cardiomyoplasty might improve myocardial function from its mechanical effects, in addition to any improvement that results from collateralization from the skeletal muscle.

Intramycocardial and Extramycocardial Collaterals

Potential sources of collateral growth include collaterals derived from the myocardium itself and extra-cardiac collaterals. Enhancement of intramycocardial collaterals seems most appropriate for patients with single or double vessel disease, where distal coronary vessels are not suitable for PTCA or CABG. Extracardiac collateral formation would be most appropriate for patients with severe, distal, triple vessel disease. Advantages of extracardiac collateral formation include an unimpeded blood flow from the extracardiac source and the ability to experimentally manipulate this source [i.e. skeletal muscle] to increase flow, angiogenesis and subsequent collaterals to the myocardium.

A review of the experimental and clinical efforts to revascularize ischemic myocardium at the capillary level will put into perspective possible new developments on the use of a cardiomyoplasty for that purpose.

History of the Development of Indirect Myocardial Revascularization

Early Evidence of Extracardiac Collaterals

Extracardiac collaterals were first demonstrated by the injection of carbon particles into the coronary arteries of human hearts excised at autopsy [27]. In 1880, Langer studied the thebesian vessels through coronary artery injection. He described coronary artery branches anastomosing with adjacent vessels in the mediastinum, parietal pericardium, diaphragm and hilum of the lungs [30]. In 1928, Wearn was able to demonstrate that vessels in the ascending aorta were filled with injections of India Ink from the coronary arteries [66]. In 1930, Robertson discussed the importance and relevance of arteries of the heart's fat pad in the presence of diseased coronary arteries [45]. He was able to ligate both coronary arteries with the myocardium supplied by vessels from the fat pad. When these connections were disrupted, the animals could not survive coronary ligation. At the time, the extent, the mechanism by which these extracardiac anastomoses were formed, and their significance, was not known.

Surgical Approaches to Indirect Revascularization

As early as 1923, while studying the effect of chronic experimental compression of the heart, Claude Beck and

R.A. Griswold noted "small vascular connections" between the heart and its adherent tissues. After inadvertently transecting a compressing scar, Beck noted, "Brisk bleeding occurred from both cut ends" [6]. These direct observations by Beck, that blood may flow bidirectionally from the myocardium to adjacent tissues, started his intense research effort to revascularize patients at the capillary level.

There have been four major historical approaches to indirectly enhancing the coronary circulation. The first technique was cardio-pericardiopexy. This involved the artificial formation of pericardial adhesions to provide a new blood supply to the heart. The second approach to indirect revascularization were extracardiac graft procedures. Skeletal muscle, lung, spleen, small bowel vascular pedicles and omentum were juxtaposed to the heart, so they might serve as potential donor sources of blood supply to the heart. A third technique to increase coronary collateral flow was manipulation of the cardiac venous system. Direct cardiac vein ligation and arteriolization were investigated. Finally, systemic artery-myocardial implantation was developed by Vineberg.

1. Revascularization via Cardiopericardial Adhesions

The idea of heart revascularization by way of cardio-pericardial adhesions was first described by Thorel in 1903 in a case report of a patient whose post mortem examination showed longstanding coronary occlusion [42]. Thorel proposed that intrapericardial adhesions may have provided the heart with an adequate blood supply, rendering the patient asymptomatic.

His observations were tested in the laboratory by several investigators. Robertson induced pericardial adhesions in an animal model of progressive coronary narrowing [45]. He was able to keep the heart functioning with both coronary arteries ligated in the presence of these adhesions. With disruption of these adhesions the animals invariably died. Stanton, Schildt, and Beck used epicardial abrasion in an attempt to increase collateral formation between the coronary arteries [47]. They also experimented with many substances which they believed enhanced development of vascular anastomoses between the coronary arteries. The measurement of the beneficial effects were documented by animal survival after coronary artery ligation. For example, mortality in 50 control animals following ligation was 68%. Mortality in animals after asbestos application prior to coronary ligation was 32% (6 of 19). In addition, the size of the gross infarct area was less in the asbestos treated group. Heindecker and Barton, reported similar findings with myocardial application of an irritating mixture of Aleuronaut, starch and glycerin [26]. All 14 of the control animals died within 3-5 minutes after occlusion of two epicardial arteries. The mortality in animals previously treated with topical irritants was 57%. Thompson reported on a series of 16 dogs which had pericardial adhesions induced by talc [53]. Eight animals survived ligation of all the coronary arteries and 2 animals survived the entire procedure.

These early investigators assumed that they were increasing intercoronary vascular communications through the formation of pericardial adhesions. It is more likely that these adhesions actually provided blood from an extramyocardial source.

2. Revascularization With Epicardial Grafts

Experimental studies

Epicardial grafts were then applied to ischemic myocardium in an effort to provide an extracardiac blood supply to the heart. Tissues such as skeletal muscle, lung, and omentum were all used as an extracardiac source. Initial experiments by Beck used the parietal pericardium and pericardial fat as the collateral vascular bed [6]. In these experiments, a burr was used to abrade the epicardium, since it was believed that the epicardium might act as a barrier to blood vessel growth into the heart. Occlusion of the coronaries was achieved in stages by silver banding. Dye was then injected into the collateral vascular bed and collaterals to areas of ischemic myocardium were demonstrated.

Subsequent operations performed by Beck involved covering the heart with a pectoralis muscle flap [38]. These studies confirmed that anastomoses developed between skeletal muscle and myocardium in areas of chronically ischemic myocardium. In 1958, Beck reviewed his experimental experience with indirect myocardial revascularization with the pectoralis pedicle flap and/or omentum. In the laboratory, over 6000 operations were performed on dogs. The authors reported that, on average, the extramyocardial collaterals provided 5 cc/min of blood flow to the coronary circulation. Although this represents only one seventh of total flow to myocardial risk area, Beck believed this amount of flow afforded physiologic protection in states of decreased coronary flow.

The idea of using the omentum as a source of collateral blood supply was investigated by O'Shaughnessy in 1935 [42]. The omentum was brought up through the diaphragm and sutured to the epicardium. Exercise tolerance was tested on a track following the ligation operation. Animals were then retested after cardioomentopexy and noted to have improved exercise tolerance. Thorotrast injections were used to visualize anastomoses between the omentum and the heart.

In Germany, Lezius used the left lung as a source of extracardiac collaterals [31]. Adhesions were produced between the surface of the heart and lung by bathing them with trypanflavine and suturing them together. Ligation of the left coronary artery was performed and exercise tolerance studies conducted. Lezius reported no objective evidence of functional deficits with systematic running exercises. Carter (1949) described a technique for cardiopneumopexy. He used asbestos to develop adhesions between heart and adherent lung [12]. In most animals 30 days elapsed between the cardiopneumopexy and the coronary artery ligation. Carter reported a decreased mortality and infarct size in animals undergoing left anterior

descending coronary ligation status post protective cardiopneumopexy.

One important conclusion was reached by these early, landmark experiments. Beck noted that myocardial ischemia was needed before collateral blood vessels would form between the heart and extracardiac structures. This observation permitted further subsequent advances, by permitting the development of an appropriate model of myocardial ischemia. The early experimental results were clearly encouraging. However, the results of these early studies must be interpreted in light of the fact that the means used to evaluate the significance of collaterals were not as sophisticated as those available today. The collateral blood flow from the adhesions was not specifically quantified, and the contribution of newly formed intramyocardial collaterals was not separated from extramyocardial collaterals. Nonetheless, these early studies did suggest that significant collaterals could form to ischemic myocardium.

Epicardial grafts - Clinical application

Amidst this exciting experimental background, an attempt at clinical application was made by Beck [4]. This was truly a case of surgical courage and heroics by both surgeon and patient. The patient's life had been incapacitated by angina. He was a gardener who due to his cardiac disease could not even bend down to do his work. With medical therapy unsuccessful and no other treatment options available, the patient opted for surgical intervention. The left pectoralis muscle was grafted around the circumflex distribution of the heart. Postoperatively, the patient had marked improvement of his symptoms and claimed he was cured. He returned to work and resumed a productive life. This was truly a remarkable feat in the history of myocardial revascularization surgery.

3. Coronary Venous Manipulation

Experimental application:

Mercier Fauteux studied the effects of coronary venous ligation on the coronary circulation [17]. In addition, he evaluated the possible benefits of pericoronary neurectomy in reducing anginal pain. In Fauteux's experiment, twenty dogs were used as a control group and their circumflex coronary arteries were ligated. Twenty percent survived this procedure. This protective effect is afforded by the existence of native intramyocardial collaterals. When the circumflex ligation was performed after coronary vein ligation, survival increased to forty percent. When coronary vein ligation was combined with pericoronary neurectomy, survival increased dramatically to over eighty percent. Furthermore, Fauteux concluded that pericoronary neurectomy had a marked decrease in the incidence of ventricular fibrillation and decreased anginal pain. This work combined the ideas of bringing a new blood supply to ischemic myocardium with decreasing pain through neurologic means.

In 1948, Stenstrom asked the question: can ischemic myocardium be perfused directly with systemic arterial blood through the cardiac veins [52]? Since there are no

valves in the coronary venous system, it was hypothesized that arteriolization of the cardiac venous system would result in retrograde perfusion of the myocardium. In animal experiments, arterial supply via the internal mammary artery, subclavian artery, aorta and left atrium were all used to deliver oxygenated arterial blood to the coronary sinus. 356 operations were performed on 240 dogs. These experiments demonstrated that arterial blood can be delivered to the myocardial capillary network by way of the venous circulation. Additionally, the authors report that there was a decrease in the number of infarcts as well as the size of these infarcts following coronary artery ligation.

Clinical application:

In 1948, Beck created an arteriovenous fistula between the aorta and coronary sinus in an elderly man [5]. This was accomplished with the use of a free brachial artery graft. Unfortunately, the patient died on the first post-operative day. Although this procedure and other modifications of the coronary venous system were attempted several additional times, they were later abandoned due to a high operative risk.

4. The Vineberg Procedure

Experimental development:

Arthur Vineberg began to work on the problem of surgically treating coronary artery disease in November of 1945 [65]. At that time, coronary artery disease was believed to be a diffuse, widespread process with great myocardial damage and scarring. The thought of correcting this devastating disease process surgically appeared futile to many skeptics. With the early attempts at indirect revascularization to encourage him, Vineberg sought to optimize myocardial revascularization by implanting the internal mammary artery directly into the myocardium.

This important concept was based on an in depth understanding of the anatomic and pathologic basis of coronary artery disease. Schlesinger and Zoll recognized that coronary arteries are diseased primarily in their epicardial course with the myocardial arteriole and capillary network being disease free [48]. They also demonstrated that the coronary arteries supply specific myocardial zones and have arteriolar-sized branches connecting these zones. Thus, a "bypass" at the capillary level is appealing because of a lack of disease in the distal arteriole and capillary network.

With this as a background, Vineberg's initial experiments were performed to graft a systemic artery into the ventricular myocardium [65]. In one series of experiments, the internal mammary was divided at the sixth intercostal artery and tunnelled into the anterior surface of the left ventricle. In experiment B, the internal mammary was not severed, but rather placed in a trough made in the ventricular surface. In group A, 5 of 10 arteries remained patent and two showed mammary coronary anastomoses. In group B, all arteries remained open but there was no evidence of coronary anastomoses.

After recognizing the importance of a communication between the internal mammary and the myocardial tunnel, Vineberg next concentrated on improving the patency of

the internal mammary artery. The next few years were spent attempting to overcome angulation and scarring of the vessel which Vineberg felt hindered the grafts patency. Internal mammary artery implantation were performed on 104 animals. There were 49 survivors of which 41 had occluded grafts. Discouraged, Vineberg reviewed his protocol and made a critical discovery. He noted that in the animals with mammary to coronary anastomoses, the fifth and sixth intercostal arteries were not tied. In addition, a higher percentage of anastomoses occurred when the internal mammary was only freed from between the fourth to sixth intercostal spaces. The procedure was revised such that the artery was freed between the fourth and sixth intercostal space and the intercostal arteries were left open and bleeding. Patency improved to 63 percent with mammary-coronary anastomoses forming in 46 percent. When this procedure was performed in the presence of chronic myocardial ischemia, the patency rate increased to 76 percent, with a 71 percent incidence of mammary-coronary communications [59, 63, 65].

Vineberg realized that because he had shown that extracardiac collaterals existed it did not necessarily mean that they were functionally significant. Did the newly formed vessels carry nutrient collateral blood flow into the heart? Ligation of the anterior descending artery combined with internal mammary artery implantation resulted in a 70-80 percent survival. Circumflex coronary ligation and internal mammary artery implantation also showed animal survival. When the internal mammary was tied along with the coronary artery, the animals invariably died. It appeared that with sufficient mammary-coronary anastomoses, coronary occlusion could be tolerated. Similarly, Exercise tolerance studies showed improvement in animals following progressive coronary occlusion treated by mammary implantation versus those without implant [59, 64].

Initial attempts at measuring blood flow through the implanted internal mammary artery were first studied by Buller in 1950 [62]. He found that as much as 55cc/min was delivered to the myocardium. 60 percent of this extracardiac collateral flow was recovered from the coronary sinus. Radioopaque dye studies injected into the left subclavian artery demonstrated the direction of flow from the internal mammary, bypassing points of coronary obstruction, and filling the left ventricle.

The Vineberg procedure - Clinical Application

In April 1950, the first "Vineberg Procedure" on a patient was performed [58]. The patient died 62 hours post operatively from a new coronary occlusion. At autopsy, the internal mammary remained widely patent. Thus the operation was technically feasible with the ability to leave an actively bleeding vessel in the myocardial tunnel of the human heart. Glenn modified the implant operation by leaving the end of the artery open in the myocardial tunnel [22, 64]. Glenn believed that the anastomoses were actually granulation tissue which would disappear in time. Through injection cast studies, it was shown that the anastomotic branches were indeed arterioles. Furthermore, the

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internal mammary artery was seen to bud around post operative day 12 with the coronary communications forming at three to six weeks. The idea of these branches being granulation tissue quickly fell into disfavour.

Sewell used the entire pedicle {muscle vein and artery} for myocardial implantation. He performed this operation on 134 patients [51]. The operative mortality was 6.7 percent. More importantly, internal mammary patency was proven by angiography and collateral filling into coronary arteries was noted.

Vineberg treated human coronary artery insufficiency in about 100 patients using internal mammary artery implantation [60]. Results were encouraging in those patients without rest angina. Six to twelve month follow-up revealed that 64 percent of patients showed improvement and 75 percent returned to work. These results as well as a mortality rate of 3.2 percent paralleled the previous experimental data. These results were confirmed by other investigators (Please Refer to Table 1) [8, 16, 19, 24, 51, 60].

Long Term Follow-up: Did the Vineberg Procedure Work?

The clinical significance of the blood flows provided by the Vineberg Procedure has been vigorously debated (Please Refer to Table 2) [9, 18, 23, 25, 41, 50, 61]. Sethi et al reported on 198 patients status post internal mammary artery implantation [50]. Arteriograms via the mammary implant were performed one year later. They could not correlate improvement of symptoms, myocardial infarction or survival with internal mammary artery patency. The authors did agree that collaterals developed between the implant and the coronary arteries. However, the more important question is whether the amount of oxygenated arterial blood delivered to the heart from the implant was functionally significant.

In 1976, Dr. John Ochsner reported on a series of 100 patients who 7-10 years previously had underwent internal mammary artery implantation [41]. Results were reported in terms of symptoms and angiographic findings. 73 implants were studied angiographically. Seventeen (23%) were occluded, 10 (14%) were open, 15 (21%) showed

Table 1. Clinical application of the Vineberg procedure.

Study/Year	# Patients	Mortality	Prelim. Results
Vineberg/1965	103	3.9%	70% marked improvement in symptoms 76% patent implants by arteriography (29 pts)
Sewell/1964	40	10%	31 pts 3/31 little-no relief 28/31 improved symptoms
Gorlin/1966	40	10%	13-31 mos f/up of 20 pts 16/20 improved 3/20 no more angina 1/20 no improvement
Effler/1965	76	5/76 3/76 immed 2/76 late	39 pts 33/39 graft patent 6/39 graft occluded 14/33 lg cor branch fill 6/33 sm cor branch fill 3/33 myo blushing 10/33 no fill
Bigelow/1962	19	0% immed op death 3 late deaths	1- yr. f/up - 11pts 10/11 symptomatic improve 1/11 no change 7/11 good/excellent result by exercise test 5 pts 5/5 patent 2/5 coron comm
Fitzgibbon/1968	21	0% op mort	17 pts 79% improved

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Table 2. Long term follow-up: the Vineberg procedure.

Study/Year	#pts	avg length of f/up	symptoms	angiographic results	mortality
Sethi/1973	198	1-5 yrs	no correlation b/w relief of angina area of infarction w/ angio data	139 pts 11% occluded 61% myo blush 31% cor communications	8.5%
Ochsner/1976	100	7-10 yrs	slight correl of angio data w/ symptomatic improvement	55 pts 23% occ 14% patent w/ no myo filling 21% patent w/ myo blush 42% fill major coronary	11%
Bigelow 1966	44	8mos-13yrs	83%improved	26 pts 6/26 patent no fill 20/26 patent w/ fill	27% of pts w/ rest angina 0% other pts
Favaloro* 1968	150	1-2 yrs	116/150 clinically improved	6 implants studied 5 patent 3 def. coron. communication	9.3%
Gorlin/1969	100	up to 48 months	75% decreased angina 50% low rate reinfarction	39 pts 22/39 patent no cor fill 10/39 patent, myo blush 6/39 patent, no comm coron 1/39 occluded graft	5%
Vineberg/1975	65	3.5yrs. to 17 years avg 9.7 yrs	91% overall improvement	83.7% patent 82% + collats	9%
Gregori/1976	86	avg 3 1/2 yrs	74 pts 92% asympt or improved 69% ventricular improvement	74 pts 82% patent 61% + functional collat circ	immed 7% late 6%

* = double internal mammary implants

myocardial filling of small vessels and finally, 31 (42%) filled a major coronary artery. Ochsner also stated that patency correlated with severity of coronary disease and to a lesser degree with symptomatic improvement. Ochsner concluded that the Vineberg Procedure is technically and physiologically sound but those patients who would benefit are better treated by direct coronary artery bypass grafting.

With these developments the pinnacle of this era of myocardial revascularization had been reached. Indirect

myocardial revascularization was replaced by coronary artery bypass grafting. The herculean efforts of these early investigators, however, were not in vain. They established principles for the development of extramyocardial collaterals which may serve as a building block for further advances. In addition, they clearly demonstrated that indirect revascularization of the heart did work. There are numerous examples of the importance of the internal mammary implant for individual patients. Recent advances in the understanding of the molecular events of collateral

formation, coupled with the identification and purification of proteins that enhance the angiogenic process, may make possible an enhancement of extramyocardial collateral formation.

Indirect Revascularization: Current Developments

"The great potential of collateral development lies in its promise to alter the natural history of coronary artery disease" Wolfgang Schaper.

Myocardial Response to Chronic Ischemia

The natural response of myocardium to ischemia is the development of myocardial collaterals. Collateral formation is the result of two processes. Collateral vessel transformation consists of gradual dilatation of preexisting channels into larger vessels with increased blood carrying capacity. These collaterals are generally located in the subendocardium of humans. This transformation is often insufficient to correct the effects of chronic myocardial ischemia.

Neovascularization, where new capillaries are formed, is another important adaptation to ischemia. Ischemia sets off a sequence of carefully controlled genetic events which lead to DNA synthesis and cellular mitoses. These events involve interactions between cells, mediators of inflammation, growth factors and chemotactic agents [15, 28, 46]. The following has been proposed by Schaper as the steps involved in the myocardial collateral formation that occurs in response to chronic ischemia.

1. Progressive coronary stenosis leads to episodes of ischemia.
2. Ischemic episodes lead to the expression of a yet to be identified "ischemia related-mitogen activator".
3. After binding to a microvascular cell receptor, this activator initiates fibroblastic growth factor (angiogenic factor) transcription.
4. Increased FGF transcription initiates the cell cycle leading to endothelial cell mitoses.
5. Endothelial cell stimulation may produce other growth factors which further induce endothelial cell mitoses.
6. Stimulated endothelial cells can attract monocytes and platelets and cause them to adhere and unload additional growth factors, thus amplifying the process [15, 28, 46].

Angiogenic Factors

Recently, a number of angiogenic factors have been identified which have the ability to stimulate proliferation and growth related changes. These observations have been noted in *in vivo* experiments and raise the possibility that these substances can be infused to clinically stimulate collateralization. Angiogenic factors are a functionally diverse group of substances and have been isolated from a wide variety of tissues and species [15, 20, 28, 46, 67].

Classification of Angiogenic Factors

The classification of angiogenic factors are based on their ability to bind to heparin [15, 20, 28, 46, 67]. Investigations into indirect myocardial revascularization have primarily focused on the group of heparin binding endothelial growth factors. These growth factors have a strong

affinity for the glycosaminoglycan moiety of heparin. Further subclassification divides these angiogenic substances into two distinct groups represented by acidic and basic fibroblast growth factors.

The second group of angiogenic factors are the non-heparin binding growth factors. Angiogenin, tumor derived growth factor, and prostaglandins are examples of this class of growth factors. Angiogenin has been demonstrated to have strong angiogenic activity. The mechanism of this angiogenesis is unknown. Angiogenin is an example of a large molecular weight non-heparin binding angiogenic factor. Prostaglandins, specifically PGE1 and PGE2, have been shown to induce capillary growth in a chick embryo chorioallantoic membrane model. Prostaglandins and tumor derived growth factor are low molecular weight non heparin binding angiogenic factors [15, 20, 28, 46, 67].

Transforming growth factors are another group of polypeptides which can stimulate endothelial cell activity. Two distinct TGF's have been isolated and purified - TGF-beta and TGF-alpha. TGF-beta has been shown to both inhibit and stimulate endothelial cell proliferation. *In vivo* studies performed in the cornea of mice have demonstrated marked angiogenic activity of TGF-beta. In contrast, *in vitro* studies with TGF-beta have shown an inhibition of endothelial cell activity and thus, angiogenesis [15, 20, 26, 46, 57].

Angiogenic Substances Isolated From Cardiac Tissue and Skeletal Muscle

Angiogenic factors have been isolated from cardiac tissue of a wide variety of species. Kumar et al have purified and isolated an angiogenic factor from infarcted myocardium [29]. Endothelial cell growth factor, which is similar to the class of heparin binding growth factors, has been extracted from ischemic rabbit myocardium [21]. Quinckler has purified both acidic and basic fibroblast growth factor from canine, porcine and bovine heart [44]. Casscells has localized fibroblast growth factor from human myocardium [14].

Growth factors have also been isolated in skeletal muscle. Morrow has demonstrated an increased expression of fibroblast growth factor in exercised, conditioned skeletal muscle [40].

Experimental Methods of Enhancing Collateral Development

If growth factors can be infused to enhance angiogenesis in the human heart, either the myocardium itself or an extracardiac tissue may serve as a source of collaterals. The myocardium would be the most likely source for patients with single vessel disease, while an extracardiac tissue would be most suitable for triple vessel disease. Both intramyocardial and extramyocardial collaterals have been enhanced.

Enhancement of Intramyocardial Collaterals Intracoronary injection of growth factors

Enhancement of intramyocardial collaterals may depend upon the type of growth factor infused and its method of administration. Intracoronary injection of growth factors



Figure 1. Gross specimen: Latissimus dorsi cardiomyoplasty in a goat model after growth factor administration. A, Adhered latissimus dorsi; B, Left ventricular myocardium.

have had both beneficial and detrimental effects. Unger administered vascular endothelial growth factor [VEGF] as a daily bolus into the left circumflex coronary artery at a point distal to an ameroid induced coronary occlusion [55]. Radiolabelled microspheres were used to assess blood flow to the myocardium. These authors concluded that VEGF increased intracoronary collateral blood flow in this model of myocardial ischemia. Similarly, Battler et al administered intracoronary basic fibroblastic growth factor in a chronic swine myocardial infarct model [3]. In comparison, a greater degree of collateralization was observed histologically.

The most striking beneficial effects of growth factor infusion on myocardial collateralization have been reported by Miwa et al [39]. They have demonstrated that, in a canine experimental infarct model, intracoronary injection of basic fibroblastic growth factor improved cardiac systolic function and reduced infarct size. In their model, collateral vessel formation occurred within one week of bFGF administration. These results were obtained with a low dose bolus delivery of bFGF via intracoronary injection, with careful attention not to injure the endothelium.

In contrast, Lindner et al have shown that bFGF coronary injections could be a potent mitogen for smooth muscle

cell proliferation *in vivo* and direct administration of bFGF may accelerate intimal thickening [32]. These processes would have a deleterious effect on coronary collateral formation.

In conclusion, the intracoronary injection of growth factors to areas of ischemic myocardium have produced conflicting results. Miwa feels that this inconsistency is due to differences in type of growth factor used, dosing, method of administration and the status of the vascular endothelial cells.

Topical Administration of Growth Factors

Thompson et al produced information that suggested that topical administration of growth factors might induce neovascularization. They noted that acidic fibroblast growth factor, when absorbed in a commercially available gelatin sponge (Gelfoam Upjohn), induced angiogenesis at the site of implantation in the rat neck and abdominal cavity. Angiogenesis was evaluated histochemically. It was determined that the new vessel formation involved cells from tissues immediately next to the gelatin sponge soaked with growth factor, and that the angiogenesis could support a proliferating hepatocyte cell line [54].

These observations stimulated interest in topical administration of growth factors to the myocardium. Using a Vineberg type model, Banai et al directly applied aFGF to

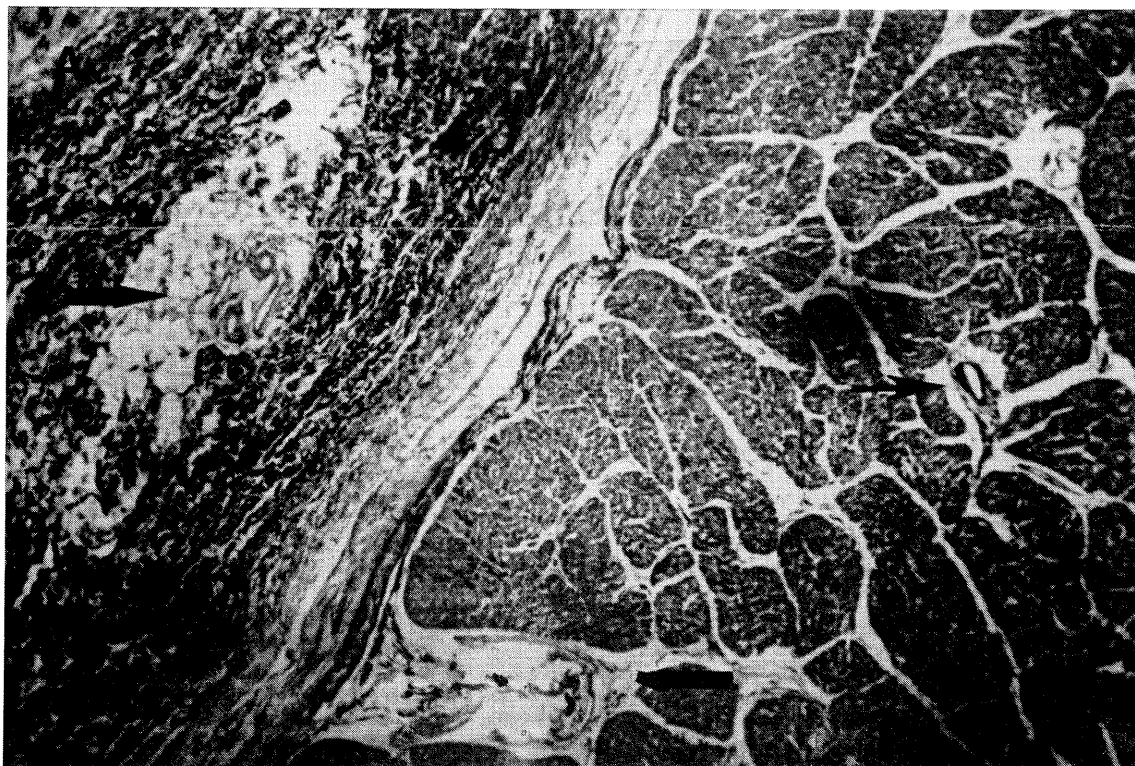


Figure 2. Trichrome stain of a section taken through a latissimus dorsi cardiomyoplasty. A, Adhered latissimus dorsi with scar; B, Ventricular myocardium. Arrows depict sites of angiogenesis in both the latissimus muscle and the myocardium.

ischemic myocardium by absorbing it onto an epicardial sponge composed of either PTFE or collagen [2]. Acidic FGF did not cause an angiogenic response from the internal mammary pedicle. Rather, smooth muscle hyperplasia in arterioles of the risk area was found. Thus, topical administration of this growth factor had a detrimental effect on myocardial blood flow.

Extramycardial Collaterals after a Diaphragmatic Cardiomyoplasty

Several previous investigators have noted that collateral blood vessels form between skeletal muscle and the myocardium after a cardiomyoplasty. Shepherd injected radioopaque fluid into the arterial supply of a pedicled diaphragmatic graft after a cardiomyoplasty. Retrograde filling of the coronary arteries was noted both grossly and microscopically [49]. Macoviak, Stephenson et al injected technetium labelled microspheres into the left atrium after transecting the vascular pedicles of diaphragmatic inlay grafts in the canine model. They demonstrated that microspheres were recovered from the diaphragmatic graft, suggesting that there was a significant collateral circulation between the skeletal muscle and the heart [33, 34]. These experimental observations were also suggested by clinical observations. In the 1960's, Petrovsky performed over 100

cardiomyoplasty procedures with the diaphragm, with or without concomitant ventricular aneurysm resection, and noted a relief of angina in over half of the patients [43].

Myocardial Collaterals after a Latissimus Dorsi Cardiomyoplasty

Mannion et al have studied the collaterals that form between skeletal muscle and the heart after a cardiomyoplasty in a goat model [1, 10, 11, 36, 37]. This species was chosen because it is naturally devoid of significant coronary collaterals [10]. Latissimus dorsi cardiomyoplasties were first performed in goats with normal coronary arteries, and collaterals between the skeletal muscle and the heart could be detected [11]. However, the amount of blood flow between skeletal muscle and normal myocardium was small. Reasoning that a significant collateral blood flow would not be expected to form without chronic myocardial ischemia, a series of cardiomyoplasties was performed after an ameroid constrictor was placed around the circumflex coronary artery [11]. Over a two to three week period, the ameroid constrictor is known to slowly occlude the coronary artery, and subjects the risk area to chronic ischemia. In the presence of myocardial ischemia, collateral blood vessels formed between the muscle and the ischemic myocardium that were sufficient to provide a

flow equivalent to approximately 4% of normal myocardial flow. Thus, after a cardiomyoplasty, significant collaterals between the muscle and the heart appear to form only after the muscle receives a signal from ischemic myocardium.

Enhancement of Latissimus Derived Collaterals

Once collaterals have been established, can the flow through these collaterals be increased? To test this concept, the cardiomyoplasties were acutely stimulated at a rate of 75 beats per minute [36]. The collateral blood flow before and after stimulation was then measured. Since skeletal muscle increases its blood flow with muscle activity, it was hypothesized that collateral blood flow would also increase with muscle activity. In fact, this effect was noted. Stimulation of the cardiomyoplasty at a 1.25 Hz frequency increased the extramyocardial collateral blood flow several fold to approximately 35% of the blood flow to normal myocardium. Chronic stimulation at a 2 Hz frequency for six weeks resulted in a sustained increase in the collateral flow (24% of normal myocardial blood flow), and appeared to lower the risk area infarction that is associated with the ameroid constrictor in this model [1]. Thus, both acute and chronic stimulation increased the extramyocardial collateral blood flow after a cardiomyoplasty [1, 36, 37].

Mannion et al [37] have inferred from blood flow measurements that chronic electrical stimulation of a cardiomyoplasty increases the number of collateral blood vessels. This raises the possibility that growth factors are expressed in chronically stimulated cardiomyoplasties which favour angiogenesis between the muscle and the heart. Morrow et al have reported an increase in FGF expression associated with chronic motor nerve stimulation or exercise in rabbit skeletal muscle [40].

The relationship between growth factor administration and electrical administration of a cardiomyoplasty has not yet been fully investigated. It is within the realm of possibility, however, that the collateral flow can be further enhanced so that it approaches normal myocardial flow.

Beyer et al have performed experimental cardiomyoplasties with a denervated, vascularized free *latissimus dorsi* muscle graft [7]. They have noted a significant collateralization between the atrophied skeletal muscle and the myocardium.

Unger et al have conducted studies to see if growth factors might participate in the collateral development between an epicardially implanted artery and ischemic myocardium [55, 56]. They have shown, in a canine model, that functional anastomotic channels develop between the implanted artery (int. mammary) and a collateral dependent coronary. Furthermore, heparin injection into the internal mammary increased collaterals. This model will allow direct targeting of angiogenic factors to ischemic myocardium by way of an extracardiac artery.

Conclusion

Despite the overall success of bypass surgery and angioplasty, patients with severe distal disease are not candidates for either procedure. Enhancement of collateral formation between skeletal muscle and the heart after a cardiomyoplasty represents a realistic treatment goal for this clinical situation. Previous investigators have laid down an extensive experimental and clinical foundation for the enhancement of collaterals to the heart. It is possible that this early work can be expanded upon. The identification and purification of proteins which have specific angiogenic activity, recent work on the relationship between electrical stimulation of a cardiomyoplasty and collateral blood flow holds promise that an effective treatment may become possible for patients with extensive epicardial disease.

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Supported By NIH HL 19418-5: Claude S. Beck M.D.
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