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Review

Current clinical perspectives on myocardial angiogenesis

Debabrata Mukherjee

Division of Cardiology, The University of Michigan, Ann Arbor, MI, USA

Abstract

Currently accepted modalities of treatment for atherosclerotic coronary artery disease (CAD) include pharmacological therapy, and revascularization with either bypass surgery or percutaneous coronary intervention (PCI). Similarly, conventional treatment of congestive heart failure (HF) is limited to medical therapy, temporary assist devices and in a select few, cardiac transplantation. A significant subset of patients with severe symptomatic CAD and end stage HF is not eligible for these traditional methods of treatment. In spite of maximal medical and revascularization therapy, these patients may not get adequate symptomatic relief. After a decade of investigations, gene therapy is emerging as a promising therapeutic option for this group of patients. This review discusses myocardial angiogenesis as a therapeutic modality in these patients including therapeutic angiogenesis with growth factors and cell transplantation. (Mol Cell Biochem **264:** 157–167, 2004)

Key words: angiogenesis, growth factors, cell transplantation, coronary artery disease

Introduction

There is a growing population of patients with coronary artery disease (CAD) and heart failure (HF) who have refractory symptoms despite maximal medical therapy. A significant proportion of these patients may not be candidates for revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) [1]. These include symptomatic patients with severe diffuse disease in native coronary vessels and not candidates for PCI or CABG; and patients with recurrent narrowing and occlusion of bypass conduits after successful surgery with no further revascularization options. Although gene therapy for HF is still being tested, patients who continue to be limited by severe HF symptoms despite aggressive medical management and who are not eligible for assist devices or cardiac transplantation may potentially benefit from these newer modalities of treatment. We have previously demonstrated that approximately 5% of patients undergoing coronary angiography for angina may not be candidates for traditional methods of revascularization and may be eligible for newer modalities of therapy [1]. Based on 1.4 million cardiac catheterizations performed in the US annually [2] around 70,000 patients per year may be eligible for newer methods of treatment. Moreover, the prognosis of these "no option" patients with refractory angina who are not amenable to traditional modes of revascularization remains poor with a mortality rate up to 17% at 1 year [3].

Maximal pharmacological therapy

The importance of optimum medical therapy in these patients with symptomatic CAD who are not candidates for revascularization cannot be overemphasized. Management includes discontinuation of tobacco use (all forms), lipid reduction with a target low-density lipoprotein <100 mg/dl, and control of hyperglycemia. All patients with symptomatic CAD should receive aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors, nitrates and lipid-lowering agents. And, similarly patients with CHF (depending on the underlying etiology) should receive maximal medical therapy which includes the above-mentioned medications and in addition spironolactone, digoxin and diuretics. Adherence to salt restriction and modification of dietary habits also play a very important role. Angiotensin-converting enzyme

Address for offprints: D. Mukherjee, Division of Cardiology, TC B1-228, The University of Michigan Medical Center, 1500 E Medical Center Drive, Ann Arbor, MI 48109-0311, USA (E-mail: dmukherj@umich.edu)

Table 1. Inclusion and exclusion criteria for candidacy for therapeutic angiogenesis clinical trials

Inclusion criteria
Stable Canadian Cardiovascular Class III–IV angina
Refractory to maximum medical therapy
Area of ischemic myocardium on an imaging stress study
Severe coronary artery disease not amenable to CABG or PCI.
Exclusion criteria
Cancer
Fundoscopic signs of diabetic retinopathy
Severe left ventricular systolic dysfunction with an ejection fraction of less than 20%
Unstable angina
Concurrent severe illness with markedly reduced life-expectancy

inhibitors not only have a salutary effect on left ventricular function but are also anti-ischemic, and may have angiogenic properties [4].

Eligibility for newer modalities

The inclusion and exclusion criteria for patients enrolled in contemporary clinical trials for therapeutic angiogenesis are listed in Table 1 [5]. For most of these trials, patients were considered eligible if they had stable Canadian Cardiovascular Class (CCC) III–IV angina refractory to maximum medical therapy, ischemic myocardium on an imaging stress study, and severe CAD that was not amenable to revascularization with CABG or PCI. Patients have been excluded in most clinical studies if they had evidence of cancer, fundoscopic signs of diabetic retinopathy and severe left ventricular systolic dysfunction with an ejection fraction of less than 20%.

Angiogenesis with growth factors

"Therapeutic angiogenesis" with growth factors involves injection of growth factors capable of generating new blood vessels in an ischemic milieu. This was initially investigated successfully in patients with peripheral vascular occlusive disease. The native biologic response to vascular occlusion is development of collaterals and up-regulation of naturally occurring angiogens. Currently, therapeutic angiogenesis is being investigated in several arenas including myocardial ischemia, restenosis, HF and graft failure [6, 7] with a variety of delivery options (Fig. 1) [8].

A number of gene therapy vectors have been developed, including viral (retro- and adenoviruses) and non-viral vectors (plasmid DNA). Gene transfer with naked plasmid DNA is less efficient and viral vectors significantly increase gene transfer efficiency [9]. Retroviruses integrate with the host genome in a stable fashion, whereas adenoviruses lead to a transient transgene expression [7]. Most of the cardiovascular trials to date have used non-viral vectors [8]. Various methodology for gene delivery have been tried including intravascular, intramyocardial *via* thoracotomy or percutaneous catheter technique and local delivery using microspheres coated with recombinant growth factors [9]. A promising new technique uses ultrasound with ultrasonic contrast agent and has been shown to improve gene transfer efficiency by 15–20-fold [10–12]. This may allow intravenous injection of growth factors and obviate more invasive delivery methods in the future.

Angiogenesis for myocardial ischemia

Vascular endothelial growth factor (VEGF)

VEGF plays a pivotal role in the biology of angiogenesis and consists of several members including VEGFs A, B, C, D, E. The isoforms of VEGF-A have been used in most of the clinical trials (VEGF-121 and -165) [7]. Numerous studies have demonstrated that VEGF is up-regulated in the presence of myocardial ischemia and its expression is mediated through a factor called hypoxia inducible factor-1 (HIF-1). Both VEGF plamid cDNA and protein have been used in clinical trials.

Intramyocardial injection of plasmid DNA encoding 165-amino acid isoform of VEGF (phVEGF) was studied in 30 patients in a Phase I clinical trial [13]. Out of the 30 patients, 29 of them experienced reduced angina, and use of sublingual nitroglycerin. Exercise tolerance improved after gene transfer with complete elimination of angina in 12/20 patients at 6 months and in 7/10 patients followed over 12 months. Overall, at 1 year, CCC functional angina class had improved by at least 2 classes in 27/30 patients and 14/30 patients were free of angina with normal activities [13]. A following trial in 30 patients with chronic stable angina evaluated direct intramyocardial injection of cDNA encoding for VEGF-2 *via* mini-thoracotomy and these patients had similar clinical improvement at 1-year [14]. Overall, at 1 year in these two, Phase I clinical trials, there were two deaths, three acute myocardial infarctions, one transient ischemic attack, and three episodes of HF. None of these adverse events could be attributed to gene transfer. They were likely related to underlying extensive CAD and operative procedure in these high-risk population [9]. Isner *et al.*, demonstrated similar clinical magnitude of clinical improvement at 1 year in 30 patients with class III or IV angina using transepicardial VEGF-2 gene transfer [8]. A total of 13 consecutive patients with chronic stable angina who failed conventional therapy were treated with intramyocardial injection of phVEGF-165 *via* mini-thoracotomy in a study by Vale *et al.* [15]. Objective evidence of improved myocardial perfusion was documented both by dipyridamole SPECT-sestamibi perfusion scans and left ventricular electromechanical mapping (EMM). These modalities were used to distinguish ischemic from infarcted myocardium and demonstrated significant improvement in myocardial ischemia after phVEGF gene transfer ($15.26 \pm 0.98\%$ vs. $9.94 \pm 1.53\%$, p-value 0.004). These results indicated that gene

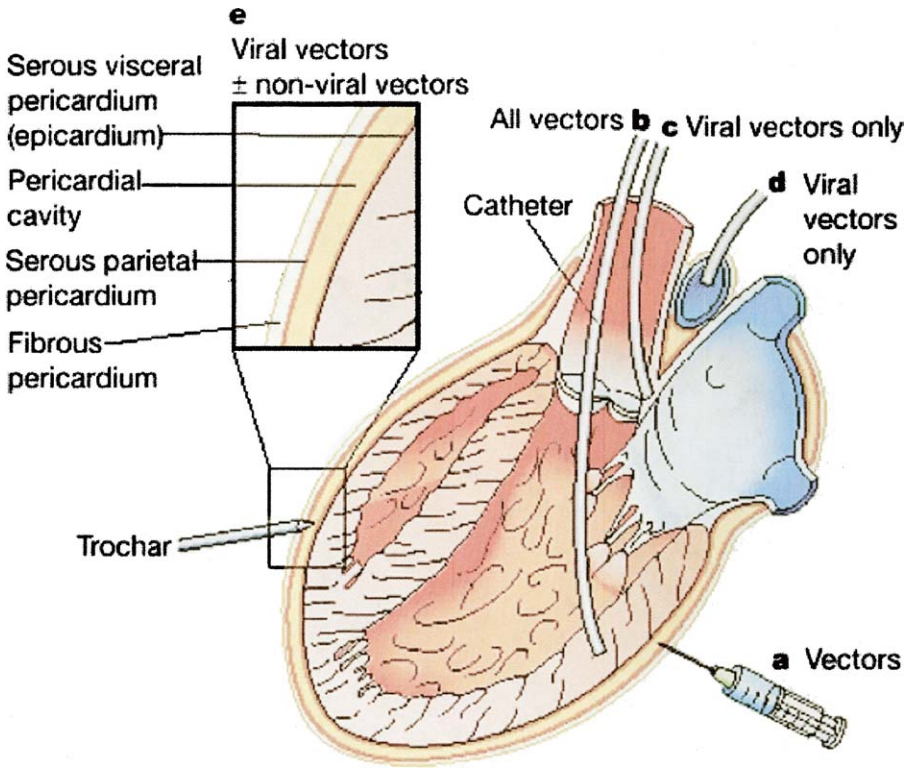

Fig. 1. Delivery options for myocardial gene transfer. (a) Epicardial. After intraoperative intramyocardial injection, the transgene is distributed to local cardiomyocytes and/or myocardial interstitium. (b) Endocardial. After catheter-based intramyocardial injection, the transgene is distributed in a similar way to that described in (a). (c) Intracoronary. Catheter injection directly into coronary arteries delivers the transgene by means of the coronary arterial circulation to a broad sample of cardiomyocytes and/or myocardial interstitium in the area subserved by the injected, source artery. (d) Retroperfusion. Cannulation of a coronary sinus (or subselective vein) with concurrent occlusion of outflow from the coronary sinus distributes the transgene retrograde from coronary venous circulation through the capillary bed to cardiomyocytes and interstitium in potentially all regions of left ventricular myocardium. (e) Intrapericardial. Transthoracic access to pericardium using a specialized catheter permits delivery into the pericardial space with secondary distribution directly to epicardial cardiomyocytes, and indirectly through the circulation shared by the peri- and epicardium. Reproduced from Isner [8].

transfer might successfully rescue hibernating myocardium [15]. In a study by Henry *et al.*, 15 patients with ischemic myocardium who were not suitable for traditional revascularization received intracoronary VEGF during coronary angiography. There was improved myocardial perfusion, angiographic evidence of increased collateral density and symptomatic improvement [16]. Losordo *et al.*, demonstrated that five patients who were given intramyocardial injection of VEGF DNA during minimally invasive surgery showed improvement in angina, nuclear perfusion scans, and angiography [17]. In another study using VEGF DNA, 16 patients with severe angina underwent direct intramyocardial injection of VEGF DNA. There was a significant decrease in anginal episodes, decreased use of nitroglycerin, and a significant improvement in perfusion [18]. A randomized trial of therapeutic angiogenesis with one intracoronary and three intravenous injections of VEGF, the vascular endothelial growth factor in ischemia for vascular angiogenesis (VIVA) demonstrated that VEGF offered no improvement beyond placebo in all measurements by day 60 [19]. By day 120, high-dose VEGF resulted in significant improvement in angina and favorable trends in exercise time and angina frequency [19]. The negative results of this study can be possibly attributed to intravenous as opposed to intracoronary or intramyocardial administration of the growth factor and insufficient local delivery of VEGF after intravenous injections.

Several other clinical studies have evaluated viral vectors for gene transfer. Rosengart *et al.* performed a Phase I clinical trial using intramyocardial injection of adenovirus vector expressing human VEGF. Gene transfer in conjunction with CABG was compared to sole gene transfer *via* a mini-thoracotomy was studied in 21 patients. Both the groups had improvement in clinical angina and ischemic area. Myocardial administration of AdVEGF was well tolerated and had significant benefits at 30-day period [20]. At 6 months, similar results were demonstrated indicating the need for Phase II clinical trials [21]. The same investigators injected 10 patients with adenoviral VEGF transepicardially using video-assisted thoracotomy or thoracoscopy with symptomatic improvement and one late death. Table 2 summarizes the major studies

Table 2. Clinical studies of therapeutic angiogenesis

Author	Angiogen	Type of study	*N*	Delivery method	End points	Comments
Symes *et al.* [13]	$VEGF_{165}$	Observational/ Phase I	30	IM	Ex. Tol angina	Improved
Fortuin *et al.* [14]	VEGF-2	Observational	30	IM *via* MT	Ex. Tol angina	Improved
Isner *et al.* [8]	VEGF-2	Observational	30	IM	Class III/IV angina	Improved
Lathi *et al.* [72]	$VEGF_{165}$	Observational	30	IM *via* MT	Class III/IV angina	Improved
Vale *et al.* [15]	$phVEGF_{165}$	Observational	13	IM *via* MT	Perfusion	Improved
Henry *et al.* [16]	VEGF DNA	Observational	15	IC	Perfusion collaterals angina	Improved
Losordo *et al.* [17]	VEGF DNA	Observational	5	IM	Angina perfusion angiogram	Improved
Losordo *et al.* [18]	VEGF DNA	Observational	16	IM	Angina NTG use perfusion	Improved reduced NTG use
Henry *et al.* [19]	VEGF protein	Randomized	178	IC vs. IV	Angina Perfusion	No improvement at 60 days
Rosengart *et al.* [21]	Adenovirus VEGF	Randomized	21	IM + CABG vs. IM *via* MT	Angina Ischemia	Improved
Rosengart *et al.* [20]	Adenovirus VEGF	Observational	10	Trans-epicardial	Angina	Improved
Grines *et al.* [30]	FGF-4	DB/Randomized	79	IC vs. placebo	Ex. Tol	Improved
Laham *et al.* [25]	FGF-2	Observational	24	Capsules implantation/ CABG	Perfusion	Improved at high dose
Sellke *et al.* [26]	FGF-2	Observational	8	IM beads/CABG	Perfusion	Three out of eight patients improved
Udelson *et al.* [27]	FGF-2	Observational	59	IC	Perfusion	Improved
Schumacher *et al.* [28]	FGF-1	Randomized	20	IM/CABG vs. Placebo	Collaterals	Improved
Simons *et al.* [29]	FGF-2	Randomized	337	IC	Ex. Tol perfusion	Improvement at 90 days but not at 180 days

Ex. Tol: exercise tolerance; IM: intramuscular; IV: intravenous; IC: intracoronary; MT: mini-thoracotomy; CABG: coronary artery bypass graft; NTG: nitroglycerin; DB: double blind; N = number of patients.

evaluating growth factors for therapeutic angiogenesis and Fig. 2 demonstrates new blood vessel formation after intramyocardial injection of $phVEGF_{165}$.

Fibroblast growth factor (FGF)

FGFs have also been studied in various trials with promising results. Acidic FGF (FGF-1) and basic FGF (FGF-2) affect various types of cells in addition to endothelial cells like fibroblasts and smooth muscle cells. FGFs (FGF-1–9) can also induce angiogenesis *in vivo*. FGF-1, FGF-2 and FGF-5 have been the agents used most commonly [22–24]. FGF-2 was implanted *via* heparin alginate capsules near occluded vessels at the time of CABG by Laham *et al.* [25] and improved perfusion was noted in patients receiving FGF-2 in a dose-dependent manner. Eight patients undergoing CABG received intramyocardial injections of FGF-2 in slow release beads in an area of the myocardium not amenable to revascularization in another study [26]. Three patients demonstrated improved perfusion in the non-revascularized region on follow-up nuclear perfusion scans [26]. Intracoronary FGF-2 in patients who are not candidates for CABG has shown improvement in reversible ischemia on SPECT myocardial scan [27]. In a study by Schumacher *et al.* [28], 20 patients undergoing CABG received an intramyocardial injection of FGF-1 near the insertion of the internal mammary graft. Compared with 20 patients treated with placebo injections, the treated patients had evidence of increased collateral growth at follow-up angiography (Fig. 3) [28]. The randomized FGF Initiating RevaScularizationTrial (FIRST) demonstrated that a single intracoronary FGF-2 infusion seems to resultin short-term symptomatic improvement that is most pronouncedin the more symptomatic patient subgroups; however, this didnot translate into improved exercise tolerance [29]. The multicenter, double-blind,placebo-controlled randomized angiogenic gene therapy (AGENT) trial of direct intracoronary administration of adenovirus encoding FGF-4 demonstrated safety and showed a overall trend towards improvement in exercise tolerance [30]. Concordant with the FIRST trial, greatest improvement were noted in patients with baseline ETT $\leq$10 min or in the sicker patients [30].

Other growth factors

Hepatocyte growth factor also has angiogenic activity *via* induction of VEGF. Recombinant HGF was shown to

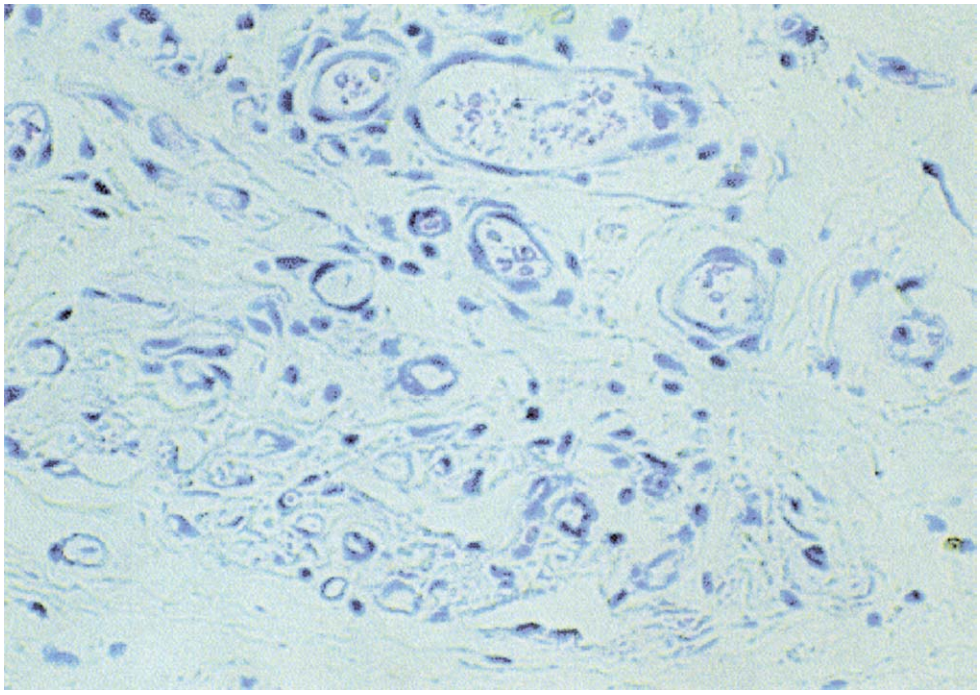

Fig. 2. Typical H + E example of phVEGF$_{165}$-treated heart. New blood vessels are seen within angiomatous structure after intramyocardial injection of phVEGF$_{165}$. The cells are primarily composed of a few endothelial cells forming a ring. Reproduced from Schwarz *et al.* [71].

stimulate angiogenesis in rabbit ischemic limb model [31]. Angiopoietin-1 and angiopoietin-2 modify angiogenesis by causing maturation and stability in the new vessels after VEGF gene therapy [32]. An adenoviral vector was used to achieve gene transfer of active form of hypoxia inducible factor-1 alpha (HIF-1 alpha). HIF-1 alpha has been shown to augment collateral vessels in animal models [33] and clinical results are pending. Other factors like monocyte chemotactic protein-1 and platelet-derived growth factor [34] may mediate angiogenesis *via* VEGF.

In summary, the current weight of evidence favors direct intramyocardial delivery of growth factors, but intracoronary and intravenous delivery has not been consistently successfull. In the future, enhanced local delivery of these growth factors using ultrasound or other techniques may make peripheral intravenous injection feasible by significantly augmenting local delivery.

Combination of bypass surgery and gene therapy

Therapeutic angiogenesis may play an important role in patients who are not candidates for any revascularization and also in the group of patients who require CABG, but complete revascularization may not be feasible in some arterial distributions. These patients might benefit from a combined approach of CABG and angiogenesis. Feasibility of this combined approach has been shown in small preliminary trials [21, 25, 28]. Such an approach may open more avenues such as decreased utilization of saphenous vein grafts with limited patency if indeed gene therapy appears to benefit ungraftable territories.

Risks/concerns with growth–factor-mediated myocardial angiogenesis

The main concern about growth–factor-mediated angiogenesis is pathological angiogenesis. This is thought to play a role in several diseases including tumor growth, diabetic proliferative retinopathy, and progression of atherosclerosis [35]. Growth factors may contribute to the growth of malignant tumors, and because of this patients with a history of cancer has been excluded from the trials. There has been no report of increased new malignancy in the clinical trials to date. Another concern is development/woresing of diabetic retinopathy. At present there are no reports of neovascularization in the retina, despite formal ophthalmological exams in most of the clinical trials. Initially diabetics were excluded, but several trials now include diabetics without retinopathy. In the clinical trials so far there has been no increase in acute ischemic syndromes or progression of atherosclerosis observed on serial angiography. Despite initial concerns, treatment with both VEGF and FGF has been well tolerated in the clinical trials. Both drugs may cause transient hypotension at high doses or with rapid infusion. Slowing the infusion rate may help in these patients. There have been rare reports of proteinuria and thrombocytopenia with FGF, and spider angiomas and peripheral edema with VEGF.

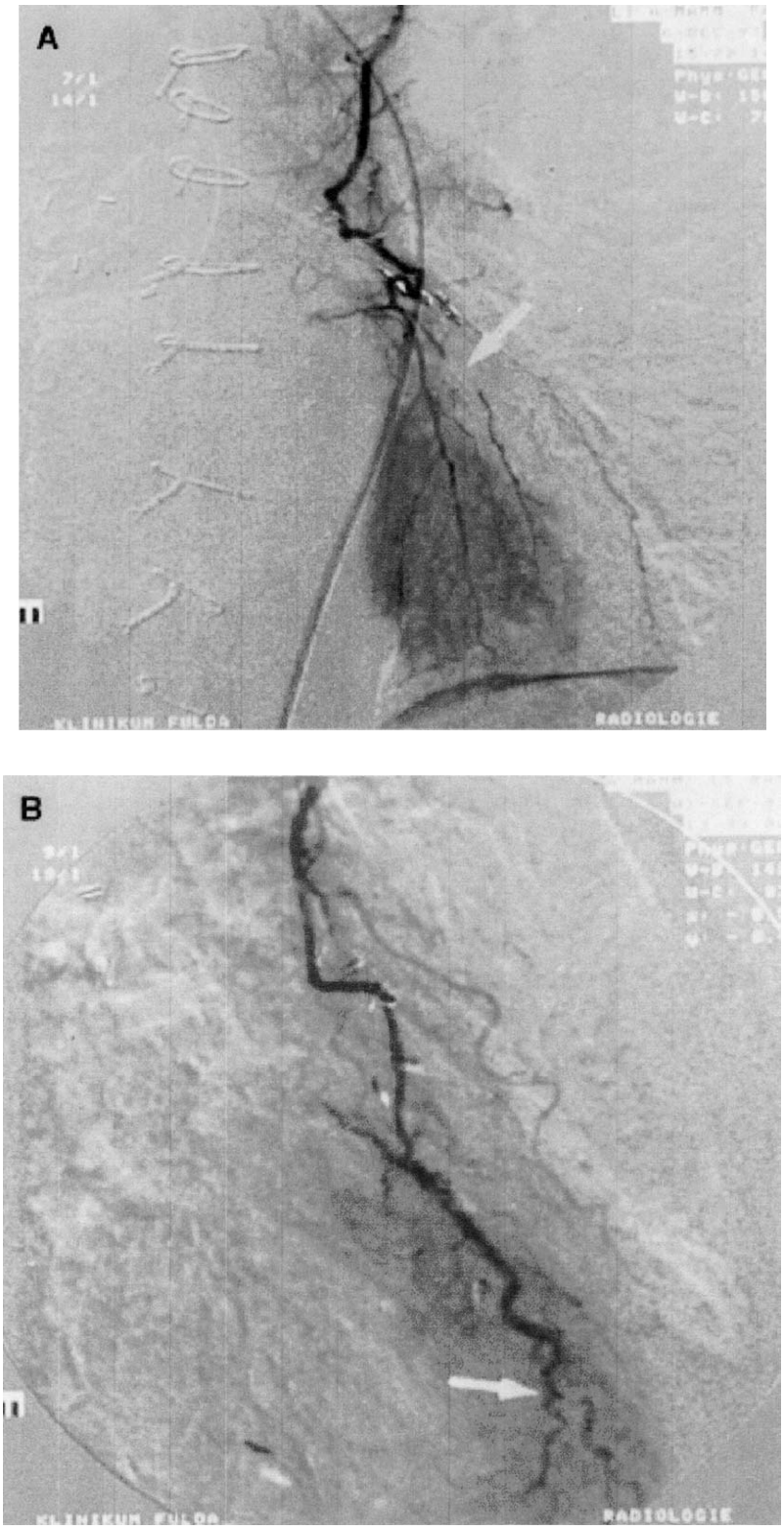

Fig. 3. (A) Collateralization of stenoses (arrow): a diagonal branch occluded just distal to its origin is filled through the newly grown capillaries. At the site of injection of the FGF-I, a capillary network couldbe seen sprouting out from the coronary artery into the myocardium. (B) The peripherally stenosed LAD is filled through newly grown capillaries. Such "neocapillary vessels" can alsoprovide a collateral circulation around additional distal stenosesof the LAD and bring about retrograde filling of ashort segment of the artery distal to the stenosis. Reproduced from Schumacher *et al.* [28].

Coronary artery restenosis and angiogenesis

The incidence of post-PCI restenosis remains approximately 15–20% in native coronary arteries and significantly higher in vein grafts [7]. Current solutions that are being investigated include gene therapy for amelioration of restenosis. Antisense constructs against c-myc, ras, bcl-x, etc. have decreased intimal thickening in experimental models [36, 37]. Smooth muscle cell proliferation can be reduced by blocking PDGF [38]. To be successful, all the above molecules have to be efficiently transfected into host genome. One efficient method could be autologous *in vitro* transfection outside the body and implantation at the needed site. VEGF stimulates nitric oxide [39] and releases prostaglandin-I which prevent smooth muscle cell proliferation. Local delivery of VEGF to prevent re-stenosis may also be potentially useful. The current availability of drug-coated stents with <5% restenosis [40, 41] may however limit the usefulness and affect development of these investigative modalities.

Role of myocardial angiogenesis in heart failure

A strategy of "molecular ventricular assistance" has been proposed for treatment of refractory HF [42]. Prior studies have revealed that reduced expression of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) plays a role in congestive HF [43]. Miyamoto *et al.* [44] showed that adenoviral overexpression of SERCA 2A restored systolic and diastolic function in a rat model and left ventricular size was reduced. SERCA 2a expression decreased Ca^{2+} prevents activation of calcineurin, thus preventing myocyte hypertrophy. Overexpression of SERCA rescues calcium cycling in the failing heart [45].

Beta adrenergic receptors (beta-ARs) play a major role in HF. Down-regulated beta-ARs, can be remedied with intracoronary injection of viral particles encoding beta-AR in rabbits with persistent expression for up to 3 weeks [46]. To circumvent beta receptors, adenoviral gene transfer of vasopressin V2 receptors which increase dp/dt has been performed in rats [47]. Intracoronary injection of adenoviral beta-ARK1 inhibitor lead to improved systolic function in rabbit models with increased dP/dt. A potential problem with this is sustained adrenergic stimulation and arrhythmias. Apoptosis, programmed cell death, seems to play an important role in HF and *in vitro* studies in animal models using adenoviral Bcl-2 to block apoptosis mediated by p53 have been performed.

Cell transplantation

The potential of cell therapy in cardiovascular diseases is rapidly evolving. Two types of cells may be used for this therapy. These are differentiated cells and stem cells. This exciting new approach for the treatment of HF and myocardial ischemia [48] can also be used as compliment to gene therapy. Fetal cardiomyocytes [49], autologous skeletal myoblasts [50–52] and mesenchymal stem cells have shown to improve myocardial function in pre-clinical trials. Initial studies evaluated autologous cell transplantation using cardiac myocytes or skeletal muscle cells into normal hearts [53, 54]. The important observation from these experiments was that ventricular arrhythmias were not induced by cell engraftment.

Subsequently, studies were done looking at injured myocardium in animal models [55–59]. Myocardial injury was induced by ligating artery or by cryoinjury to theepicardium.

Table 3. Pre-clinical and clinical studies of cell transplantation (adapted from [70])

Author	Animal model	Transplantation type	Cell type	Time after infarct	LV* function
Marelli *et al.* [57]	Dog	Differentiated	Skeletal myoblasts	Immediate	N/A
Murry *et al.* [51]	Rat	Differentiated	Skeletal myoblasts	Immediate	N/A
Taylor *et al.* [59]	Rabbit	Differentiated	Skeletal myoblasts	Immediate	Improved
Li *et al.* [55]	Rat	Differentiated	Smooth muscle cell	4 weeks	Improved
Li *et al.* [56]	Porcine	Differentiated	Heart cells	4 weeks	N/A
Rajnoch *et al.* [58]	Sheep	Differentiated	Skeletal myoblasts	3 weeks	Improved
Tomita *et al.* [61]	Rat	Stem cell–direct	Bone marrow	3 weeks	Improved
Kocher *et al.* [60]	Rat	Stem cell–direct	Bone marrow	48 h	Improved
Beltrami *et al.* [63]	Human	Stem cell mobilization	Cardiac myoblasts	4–12 days	Increased muscle mass
Jackson *et al.* [62]	Mouse	Stem cell mobilization	Myocytes, endothelial cells	4 weeks	Endothelial engraftment
Askari *et al.* [66]	Rat	Stem cell mobilization + direct transplantation	Skeletal myoblasts	4 weeks	Increase in left ventricular mass and better cardiac function

*LV: left ventricular function; N/A: not available.

Transplantation of differentiated cells was demonstrated to be successful in several animal models (Table 3). In these studies, fetal myoblasts did not offer improved efficacy when compared to other cells. The mechanism by how these cells help is not yet well understood. Whether it improves contractility of infarcted area or helps with post-infarct remodeling [51] is yet to be delineated but more likely it affects remodeling. If cell transplantation indeed improves contractility, then time to transplantation should not play a major role in efficacy. But, if post-infarct remodeling is the major mechanism, then time to cell transplantation becomes critical. Regeneration of infarcted myocardium using stem cells can be done either by direct injection into myocardium [60, 61] or by mobilizing specific cell population [62, 63] by various stimulating mediators like VEGF [64]. The combination of replacing senescent cells by cell transplantation and deliver gene products *via* gene therapy (VEGF) has led to enhanced capillary density and blood flow in rat hearts [65]. Askari *et al.*, studied the effects of stem-cell mobilization by use of granulocyte colony-stimulating factor with or without transplantation of syngeneic skeletal myoblasts cells and demonstrated that a combined strategy of gene transfer and stem-cell mobilization, results in regeneration of myocardium in a model of ischemic cardiomyopathy [66].

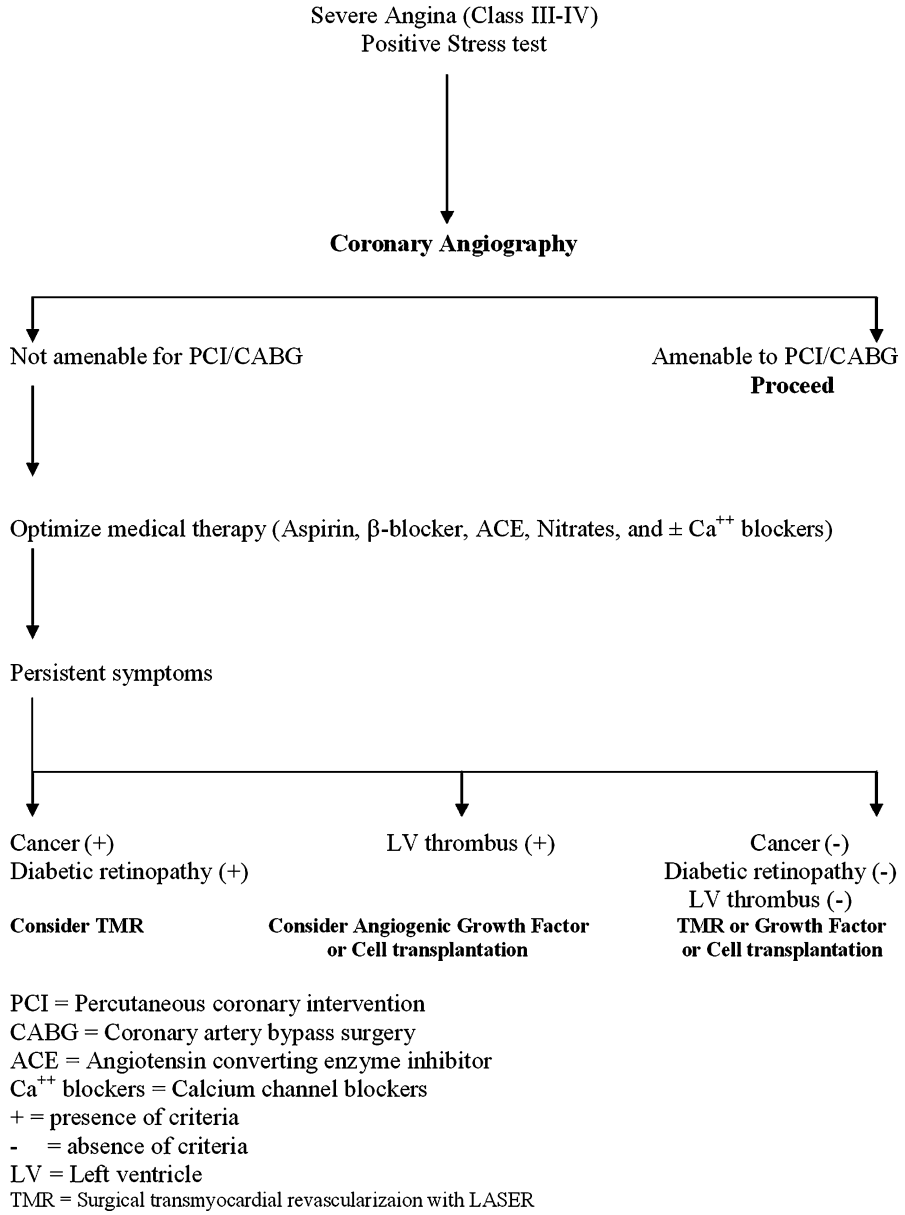

Fig. 4. Treatment algorithm for patients with refractory myocardial ischemia.

This combined modality has a potential to offer a new treatment modality for ischemia and HF. Several studies of stem cell transplantation are summarized in Table 3.

After initial success in animal studies, clinical trials have been initiated. Hamano *et al.*, reported their experience with mononuclear rich autologous cell injection into myocardium along with CABG [67] and demonstrated improved local wall thickening dynamics, presumably due to the angiogenesis induced by the treatment. In patients afflicted with end stage HF, pleuripotent adult stem cell transplantation has lead to some evidence of myocardial regeneration [60–62]. HMG CoA reductase inhibitors which have been shown to be significantly beneficial in patients with CAD have been shown to increase the circulating levels of endothelial progenitor cells [68]. There seems to be significant potential for autologous cell transplantation to heal injured myocardium [69, 70] but needs to be validated in prospective trials.

Conclusions

A significant proportion of patients with symptomatic CAD and end stage HF may not be candidates for conventional therapeutic options like PCI or CABG and heart transplantation. Therapeutic angiogenesis with growth factors, cell transplantation with myoblasts and genetically engineered cells may improve morbidity in these cohort of patients. Current trials have only enrolled patients with severe symptomatic CAD or peripheral vascular disease. In the future, it may also benefit patients with ischemic cardiomyopathy, end-stage HF, post cardiac transplant atherosclerosis, severe restenosis, inherited lipid disorders and patients with microvascular disease. Cell transplantation with differentiated and stem cells have shown significant potential in animal studies and preliminary reports of small case series but needs to be prospectively validated in larger appropriately designed studies. The future may hold many more therapeutic options for patients with advanced ischemic heart disease. Figure 4 is a simplified algorithm for the approach and management of patients with refractory myocardial ischemia not amenable to traditional methods of revascularization.

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