Interventional Cardiology — Promises And Challenges

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In the two decades since Andreas Gruntzig performed the first angioplasty in 1977 [1], great advances have been made in the management of ischemic heart disease. The outcomes of interventional cardiology have much improved since the development of stents. The concept of using an endovascular prosthesis to overcome dissection and recoil was first proposed by Dotter in 1964, although the first implantations in human arteries were performed only 21 years later, by Ulrich Sigwart from Switzerland in 1985 [2]. The explosive growth of coronary stenting has fueled a surge in the number and types of coronary stents. While the number of stents generates a price-competitive market, physicians are now faced with an overwhelming choice of designs.

It is currently thought that while not every coronary intervention should include a stent, 50 to 70% of patients undergoing coronary intervention may benefit greatly from stent placement. Notwithstanding the impressive successes of angioplasty and stenting, many patients remain symptomatic despite maximal medical therapy, in addition to percutaneous and surgical revascularization. This growing population of patients with refractory angina poses a formidable challenge to the developing field of invasive and interventional cardiology.

Current Status of Stents

Ability to Reduce Restenosis and Facilitate PTCA[1]

Randomized trials with STRESS (STent REStenosis Study) and BENESTENT (BElgian NEtherlands STENT study) [3–5] reveal a 30–40% reduction in restenosis compared with PTCA. Stenting allows the interventional cardiologist to treat many vessels with unfavorable anatomy that could not be readily treated with balloon angioplasty alone. In addition, when PTCA is complicated by coronary dissection, stenting may be used to prevent abrupt closure, which in the era prior to stent therapy was the most deleterious acute adverse outcome associated with PTCA.

Stent designs

There are many newer stents being used in the clinical setting or currently being tested for future use [6,7]. "Customized" stents may be used to reach ostial, side-branch and bifurcation lesions, as well as long lesions and lesions in small vessels. Newer stents capable of targeting coronary aneurysms and perforations are also becoming available. In addition to the coated stents — including those treated with agents such as heparin, hirudin, phosphorylcholine, silicium carbide, gold, and diamond-like hard carbon — radioactive stents have been developed to combat restenosis [7]. Yet, despite this plethora of products, there are no clinical data regarding the value of the different designs or coatings in reducing stent restenosis.

Similarity of results

The conservation of similar designs and mechanical compressibility has led to many "equivalence" trials showing comparable efficacy between the newer stents and the previous standard, the Palmaz-Schatz stent [Table 1] [8]. In view of the results of the equivalence trials, focus has been shifted towards new challenges in stenting. These include longer target lesions, smaller culprit vessels, and a more in-depth examination of the lesion subsets that really benefit from coronary stenting [9,10]. For example, the BENESTENT-II study [11] revealed a higher event-free rate at 12 months in patients who underwent stenting of left anterior artery lesions than in patients undergoing angioplasty. Similar results were seen in patients with target vessels larger than 3 mm and in patients with unstable angina. However, there was no significant difference in certain patients undergoing revascularization of the right coronary artery, in patients with small target vessels (<3 mm), or in patients with stable angina. Trials involving BENESTENT-I and II as well as DEBATE (Doppler Endpoints Balloon Angioplasty Trial Europe)-II have demonstrated that patients who experience "stent-like" results with angioplasty (i.e., residual stenosis less than 30–35%) have similar subsequent event rates. This suggests a more pervasive use of stenting in the future.

Contraindicative when risk of diffuse in-stent restenosis is high

Large data define risk factors for diffuse in-stent restenosis [12–16]. In most studies a small post-stent minimal lumen diameter is an independent risk factor for restenosis. Reference vessel diameter of <2.5 mm, lesion length >30 mm, diabetes mellitus, and end-stage renal failure are associated with a high incidence of diffuse in-stent

[1] PTCA = percutaneous transluminal coronary angioplasty

Table 1. Comparison of major studies comparing different stent designs

	Finess II (n=156)	Easi (n=275)	Wellstent (n=105)	MUST (n=260)	Benestent II (n=413)	ROSE (n=120)
Stent used	Nir	Cordis	Wallstent RM	PS 153	PS–heparin coated	BeStent
Male (%)	81	77	84	82	77	80
Angina (%)						
Stable	54	47	52	42	50	48
Unstable	27	28	36	25	32	44
Silent	6	9	4	12	5	8
History (%)						
MI	43	35	46	24	25	36
rePTCA	16	10	15	13	7	26
CABG	4	2	5	2	2	5
Angiographic data						
1 vessel (%)	69	62	62	64	92	71
LAD	46	38	22	45	50	41
LCX	23	22	10	16	19	31
RCA	30	40	68	39	31	28
Lesion length (mm)	9	8	10.4	7.7	8.2	8.4
AHA/ACC B2	69	59	74	–	56	57
C	5	5	14	–	1	3
Quantitative coronary analysis						
Reference diam (mm)	2.96±0.56	2.91±0.44	3.17±0.68	2.92±0.45	2.96±0.48	2.88±0.58
MLD pre-	1.04±0.33	1.07±0.28	1.00±0.50	1.07±0.26	1.03±0.28	0.97±0.28
MLD post-	2.67±0.43	2.93±0.34	2.84±0.47	2.50±0.39	2.69±0.37	2.52±0.40
MLD fup	1.89±0.61	1.99±0.69	1.64±0.75	NA	1.89±0.65	1.86±0.63
Loss Index	0.50±0.36	0.50±0.37	0.68±0.38	NA	0.52±0.37	0.46±0.36
Restenosis rate (%)	17	17	30	–	16	21
Delivery success (%)	99.4	99.6	99	93.8	99	95.8
30-day events						
Death	0	0.4	0	0	0	0
MI	1.3	2.2	3.8	3.1	2.7	4.2
CABG	0.6	0.4	1	0.4	0.7	0
RePTCA	0	0.4	1	0.8	0.5	0
6-month events						
Death	0	1.8	1	0	0.2	0
MI	1.9	3.2	5.7	3.1	3.4	6.6
CABG	1.9	0.7	2.9	1.2	1.5	2.5
re-PTCA	9.6	8.4	16.2	6.2	8.2	10
MACE-free survival (%)	**86.5**	**85.5**	**74.3**	**89.6**	**87**	**80.8**

restenosis. Patients with these characteristics may be considered for balloon angioplasty without stent implantation. Intravascular ultrasound investigation may be considered for arteries with diameter ≤3 mm, to better de-

fine the proper balloon size. A strategy of provisional stenting restricted to poor balloon outcomes may be considered for vessels <3 mm. While in large vessels a strategy of provisional stenting may be considered, it is important to recognize that only a minority of patients will have stent-like results post-PTCA. However, the majority of coronary intervention patients will likely benefit from stent placement.

Restenosis — the Achilles heel of stenting

A potential danger of stenting is diffuse in-stent restenosis [16]. Although the incidence of post-interventional restenosis has been sharply reduced through the use of aggressive plaque-debulking procedures, improved angioplasty strategies and, in particular, the use of coronary stents, the problem has not disappeared [17–19]. Furthermore, in view of the estimated 900,000 coronary stents being placed annually worldwide, and reasonable estimates of in-stent restenosis set at 10–20%, it is clear that up to 200,000 cases of in-stent restenosis will present annually. In-stent restenosis, often diffuse and with a heavy plaque burden, is difficult to treat. Moreover, repeat interventions in the context of in-stent restenosis are themselves associated with a high incidence of restenosis. Although aggressive debulking and repeat stenting have been suggested as superior to balloon angioplasty alone [20], a well-controlled randomized study proving that hypothesis is lacking. Optimal treatment for this problem is still undetermined, especially for the diffuse form of in-stent restenosis which is so difficult to control using "standard" approaches. The most recent studies report rates of second restenosis events ranging from 1 of 5 to more than 1 of 2 treated patients [21–25]. Thus, there is general enthusiasm for an approach that addresses the biology of post-procedure intimal hyperplasia, either to prevent restenosis or to improve the results of its treatment.

The place of other available technologies

The use of intravascular ultrasound as well as the flow-wire pressure wires and their ability to allow the clinician to optimize results shows promise, but their cost-effectiveness remains to be proven in clinical studies. IVUS[2] technology has improved with better image quality and advanced analysis packages, almost on-line, that allows semi-quantitative analysis as to the vessel area. The place of the non-fluoroscopic left ventricular electromagnetic-based mapping system (NOGA™, Biosense, Tirat Hacarmel, Israel) is under investigation.

Many questions are still open; for example, what is the optimal pressure for balloon dilatation before and after stent implantation, and what is the validity of novel dilatation ideas such as the cutting balloon. Should stenting, during treatment of long lesions, be performed only in the diseased lesions (spot stenting) or should it cover the entire lesion? Some registries of patients treated with stenting without pre-dilatation look promising, since this approach has major economic savings although the anti-restenosis benefit is questionable. Some studies are trying to define both the place of rotational atherectomy, directional atherectomy and lazer ablation, and the population that would benefit from these available treatment options.

Platelet IIb/IIIa receptor antagonists

The administration of platelet IIb/IIIa receptor antagonists is associated with reduced adverse coronary events. The one-year results from the EPISTENT trial (n=2,399) showed — for the first time — increased survival in the group treated with prophylactic abciximab (ReoPro™, Eli Lilly, Indianapolis, USA) and stent implantation. The one-year mortality rates were 2.4% in the stent + placebo-treated group, 2.1% in the balloon angioplasty + abciximab group, and 1% in the stent + abciximab group. This 58% reduction in mortality was already observed at the 6-month follow-up. This interesting observation signifies a beneficial effect of abciximab administration in patients receiving catheter-based treatment. The data also suggest that stent-alone treatment may be comparable to balloon angioplasty + abciximab without provisional stenting. In a separate substudy from EPISTENT, abciximab administration and stenting were associated with reduced 6-month target vessel revascularization in both diabetic and nondiabetic patients. The beneficial effect of abciximab on the revascularization rate was found to be more profound in diabetic patients. Despite frequently observed human anti-chimeric antibody titer among abciximab-treated patients, the rate of thrombocytopenia (<50,000 platelets/ml was 2.1% and no anaphylaxis occurred.

Post-stenting antiplatelet therapy

Currrently, a combination of aspirin and ticlopidine is usually used for the prevention of acute thrombosis after stenting. Ticlopidine has a serious side effect — leukopenia — that occurs in about 1–3% of treated patients. Clopidogrel, a new antiplatelet agent, is reported to have fewer side effects. Preliminary results were reported from the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), a prospective double-blind, three-arm, multicenter study involving 1,020 patients undergoing coronary stenting. The two groups (n = 680 each) receiving clopidogrel (75 mg/day with or without 300 mg loading dose) in combination with aspirin demonstrated a significantly better safety and tolerability profile compared with those taking the ticlopidin and aspirin combination treatment (4.6 vs. 9.1%, P=0.005). In addition, the efficacy endpoint of any major adverse cardiac events and/or stent thrombosis (1%) was similar in the three groups. These findings with regard to antiplatelet agents in peri-stenting treatment are certainly encouraging.

[2] IVUS = intravascular ultrasound

Minimally invasive direct coronary artery bypass

It is unclear whether the use of MIDCAB[3] surgery will compete with percutaneous coronary interventions, or complement them. Trials comparing MIDCAB and stenting, as well as comparing standard bypass surgery with combined use of MIDCAB and stenting, are currently underway.

Future Directions

Among the various strategies to improve care for patients with refractory angina, there are three that have raised the most interest: vascular gene therapy, radiation treatment for the prevention of restenosis, and percutaneous myocardial revascularization.

Vascular gene therapy

Strategies for gene transfer therapy in patients with end-stage peripheral vascular disease and myocardial ischemia seem to hold much promise. A wealth of animal data supports the hypothesis that administration of growth factors can stimulate angiogenesis, leading to new blood vessels that grow into the ischemic areas. These animal studies have opened the way for preliminary clinical trials in humans [26–28].

Vascular endothelial growth factor gene therapy for PVD[4]

VEGF[5] stimulates the proliferation and migration of endothelial cells. In unblinded, nonrandomized trials, DNA encoding for human VEGF was administered intramuscularly in patients with nonhealing ulcers or gangrene due to PVD in Buerger's disease; and uncontrolled studies have shown cases of limb salvage in patients with severe nonhealing ulcers and gangrene. Where no other therapy is available, this method has offered patients marked alleviation of severe limb pain.

VEGF gene therapy for myocardial ischemia [26–28]

More recently, intramyocardial administration of VEGF DNA has been performed in patients with severe, disabling angina refractory to maximal medical therapy. These patients were deemed to be unsuitable candidates for further angioplasty or bypass surgery. The VIVA trial was the first randomized, double-blind, placebo-controlled trial to test the safety and efficacy of intracoronary administration of VEGF protein in patients with refractory myocardial ischemia. In this study, VEGF was given by one-time intracoronary injection (low and high dose groups according to results obtained in a phase I study), followed by intravenous injection at days 3, 6 and 9. There were no procedure-related complications. At 60-day follow-up, there were no differences among the three groups in rates of death, myocardial ischemia, hospital admission, or blood analysis. The changes in exercise test and angina class were similar in all three groups. The study therefore failed to meet its primary efficacy endpoints. The safety and tolerability of direct intramyocardial injection of VEGF — plasmid via 'minimal' thoractomy incision — in 24 patients was evaluated in a single-center study without a control group. There were no procedure-related complications, and 96% of the patients experienced significant amelioration of anginal symptoms and significant decreases in their need for anti-anginal medications. Mean treadmill exercise time increased from 240 seconds prior to gene therapy to 410 sec after treatment ($P<0.001$). Scintigraphic evidence of improved myocardial perfusion on single-photon emission computerized tomography-sestamibi imaging was also significant at 60 days.

Future directions for vascular gene therapy

Bioengineering companies are attempting to design catheters that can deliver VEGF DNA to the left ventricular wall in the cardiac catheterization laboratory. Several centers are actively investigating the safety and efficacy of various growth factors in patients with refractory angina. VEGF and fibroblast growth factor are administered via intracoronary, intravenous or intramyocardial routes in blinded placebo-controlled trials. While the early data seem encouraging, we await the results of these randomized trials to determine the potential roles of angiogenic factors in the management of patients with severe coronary disease.

Radiation therapy

Radiation therapy is another strategy under active investigation for the treatment of coronary artery disease. As mentioned above, while coronary stents have lower restenosis rates compared to balloon angioplasty, in-stent restenosis presents a difficult challenge to the interventional cardiologist. Numerous drug compounds have performed poorly in preventing restenosis following coronary intervention [29]. The use of radiation to prevent the intimal hyperplasia that leads to restenosis is an emerging strategy. Radiation has been shown to be highly effective and safe in treating benign vascular malformations and also in preventing keloid formation [30]. Radiation exerts many biological effects. It inhibits smooth muscle proliferation, reduces macrophage infiltration, exerts a beneficial effect on apoptosis, inhibits expression of prostaglandin alpha and beta growth factors, and may lead to a reduction in thrombosis. However, radiation delays normal wound healing. In animal models of coronary restenosis, radiation reduced the intimal hyperplasia associated with restenosis following balloon injury.

[3] MIDCAB = minimally invasive coronary artery bypass
[4] PVD = peripheral vascular disease
[5] VEGF = vascular endothelial growth factor

Table 2. Properties of radioisotypes used for intravascular brachytherapy

Element	Isotope	Emission	T ½	Avg energy (keV)
Iridium	Ir-192	Gamma	74 days	375
Phosphorus	P-32	Beta	4 days	600
Strontium	Sr-90	Beta	28 yr	970
Yttrium	Y-90	Beta	64 h	970
Rhenium	Re-188	Beta	17 h	780
Xenon	Xe-133	Beta	5.3 days	200
Technetium	Tc-99m	Beta & X-ray	6 h	140

Gamma vs. beta emitters

Iridium (Ir-192) is the most commonly used gamma-emitting source. Gamma emitters have a slow rate of decay (half-life of 74 days) and greater penetration, allowing them to infiltrate stent and calcified lesions [30–36]. The drawback of these agents, however, is the high radiation exposure to the operator. Beta emitters include phosphorus (P-32), strontium (Sr-90), yttrium (Y-90), rhenium (Re-188), and xenon (Xe-133). These agents have relatively poor penetration, but they generate substantially less radiation exposure to medical personnel [Table 2].

Clinical restenosis trials using radiation

Native arteries. Three clinical trials (Condado, BERT, and PREVENT) have shown that radiation reduces restenosis following angioplasty in native coronary vessels [Table 3]. PREVENT, a randomized trial, showed that patients treated with P-32 radiation had a 26% restenosis rate compared to 44% for control patients (60% of the study patients received stents). In contrast, neither the Verin nor ARREST trials showed decreased restenosis, yet these trials used lower doses of radiation than PREVENT, which may explain the difference in outcomes [31,37].

In-stent restenosis. Radiation therapy for the treatment of in-stent restenosis has generated a great deal of interest. Three randomized trials (Scripps, WRIST, and ARTISTIC) have shown that patients assigned to the radiation group had restenosis rates of 17–20%, compared to over 50% in control patients [Table 3]. Quantitative angiography and three-dimensional intravascular ultrasound studies have corroborated these results. In each of these studies, there were no adverse effects up to 7 months of follow-up [38]. The multicenter GAMMA-1 randomized clinical trial has enrolled 252 patients with in-stent restenosis and lesions of < 45 mm in length, to radioactive Ir-192 gamma-source ribbon versus placebo ('dummy') source, based on a predefined intravascular, ultrasonic-based calculation of dosimetry. The in-hospital (1.5%) and 30-day adverse clinical outcomes (3.0%) were similar in both groups. The 6-month angiographic follow-up showed that coronary radiation therapy improved percentage diameter stenosis and minimal lumen diameter, resulting in 58% reduction in restenosis within the stent itself and 43% reduction of restenosis in the total lesion segment. This beneficial effect was more pronounced in shorter lesions. Clinical implications included further investigation to optimize the dosimetry parameters in long (>30 mm) lesions.

Table 3. Clinical studies in native coronary lesions and in in-stent restenosis

Study	Isotope	Dose (Gy) at 2 mm	n	Restenosis (%) Treatment	Control
Native lesions					
Condado	Ir-192	20	21	27	–
BERT	Sr-90/Y	12, 14, 16	82	24	–
Verin	Y-90	3	18	50	–
PREVENT	P-32	16, 20, 24	72	26	44
ARREST (Pilot)	Ir-192	12	25	47	–
In-stent restenosis					
Scripps	Ir-192	8–30	55	17	54
WRIST	Ir-192	15	120	19	58
ARTISTIC	Ir-192	12	25	20	–

Radioactive stents. Results from the investigational use of radioactive stents are more disappointing. The IRIS 1A, IRIS 1B, and Milan trials have had restenosis rates in the 30–50% range. These trials have identified the so-called edge (or "candy wrapper") effect with an increased incidence of focal restenosis at the stent edges. It is hypothesized that the decreased radiation dosage at the edges of the stents may in fact stimulate restenosis, while the higher doses emitted in the middle of the stents may inhibit restenosis.

Future directions of radiation therapy for restenosis

Over a dozen ongoing trials are currently using both gamma and beta emitters in the management of native coronary lesions, vein graft disease, small vessel disease, and in-stent restenosis. These trials may help determine whether radiation is effective in reducing restenosis. They will provide valuable information regarding the optimal dose of radiation, which emitter is superior, and whether this strategy is safe. Unanswered questions also include whether centering techniques need to be employed. The issue of preventing focal edge restenosis also needs to be addressed. Many of these questions will be answered by these ongoing trials within the next few years.

Transmyocardial Revascularization and Percutaneous Myocardial Revascularization

In TMR[6] the cardiac surgeon directly accesses the heart via a left-side thoracotomy and, using a laser, cuts a series of channels in the ischemic myocardium. Between 15 and 30 channels, each a millimeter in diameter, are opened. The initial hypothesis is that with the endocardial channels open, oxygen-rich blood may perfuse the myocardium. Although patients undergoing the procedure experienced a significant amelioration in angina symptoms, the 9% perioperative and additional 9% one-year mortality may limit the widespread application of TMR.

[6] TMR = transmyocardial revascularization

PMR[7] may offer an alternative approach to TMR, with a much lower mortality rate. PMR is performed in the cardiac catheterization laboratory using a 9-French femoral arterial approach. A steerable catheter is used to direct the electrocardiogram-timed laser to make 5 mm-deep channels in the left ventricular wall.

The mechanism of TMR and PMR remains controversial. It was originally thought that the channels produced by the laser provide oxygenated blood from the left ventricle to the myocardium. However, histologic studies have shown that these channels scar over within a month. The clinical benefit of laser myocardial revascularization does not appear to be related to long-term, laser-channel patency but rather to a localized injury response, which may directly enhance angiogenesis or possibly affect the function of nerve fibers. Animal studies have showed enhanced expression of angiogenic cytokines in laser-treated areas.

PMR results [39–41]

- *Phase I.* PMR was used in 81 patients with class III–IV angina in a nonrandomized fashion. Investigators opened 10–30 channels per patient (average 19) using the Eclipse Fiberoptic Holmium Laser system (California, USA). The mean age of the patient population was 64±11 years, and 81% were men. The mean angina class was 3.5; 73% had prior angioplasty and 90% had prior bypass surgery. The PMR was successfully completed without major complications in 96.3% of the patients. The average length of stay was 2±3 days. There were three major complications: one patient died of a pulmonary embolus, one had a stroke, and one died due to tamponade. Other complications included ventricular tachycardia requiring cardioversion (3.7%), non-Q-wave myocardial infarction (3.7%), and intraaortic balloon pump placement for hypotension (3.7%). After 6 months of follow-up, another three patients died and four patients had non-Q-wave myocardial infarction. The mean angina class decreased to 1.6 at 3 months, 1.4 at 6 months, and 1.2 at 12 months. Mean treadmill exercise time increased from 482 seconds at baseline to 592 at 6 months follow-up with average improvement of 1 MET (P = 0.03).
- *Phase II.* More recently, 169 patients with severe angina were randomized to PMR, and 166 were assigned to receive maximal medical management. PMR was successfully completed in 95.8% of cases without a major complication. Three-month data show that in 19% of the PMR group and in 49% of the MMM[8] group there was no change or deterioration in angina class, while 31% of the PMR group and 35% of the MMM group improved by one angina class, and 50% of the PMR group and only 17% of the MMM group improved by two or more angina classes. Among patients assigned to the PMR group, mean exercise duration increased from 381 seconds at baseline to 529 sec after 3 months (P=0.0002). Among the MMM patients, there was no significant change in exercise time. Adverse clinical events after 3 months of follow-up are shown in Table 4. These phase II PMR results are very promising. We await the 6- and 12-month clinical follow-up data from this trial.

Table 4. Three-month follow-up data on Phase II PMR Study

Complications	PMR (%)	MMM (%)
No. of patients	169	166
Death	3	1.6
Q-wave MI	0	0
Non-Q-wave MI	7.6	1.6
Angioplasty	0.8	5.6
CABG	0	0.8
Rehospitalization	33.1	36.0

Summary

The current explosion in coronary stent use for the treatment of coronary artery disease has helped to better define who really benefits from coronary stenting. It is clear that plain old balloon angioplasty can be at least as efficacious as stenting in certain patient groups. Patients with reference vessel diameter of <2.5 mm, a small post-stent minimal lumen diameter, lesion length >30 mm, diabetes mellitus and end-stage renal failure — all associated with a high incidence of diffuse in-stent restenosis — should not be stented routinely. The judicious use of stents in percutaneous revascularization will improve patient outcomes and decrease cost.

The progress that has been achieved in coronary stent designs has led to many new questions, such as which patients benefit the most from stenting and whether adjunctive therapies or stent coatings will effectively prevent restenosis. Despite the advances in stent/balloon technology, antiplatelet agents, and interventional operator skill, the problems of in-stent restenosis remain. Novel therapeutic strategies for the management of severe coronary artery disease are evolving rapidly. Radiation therapy shows promise on this front. This therapy may reduce rates of restenosis by inhibiting smooth muscle proliferation and migration. However, important issues regarding the type of radiation and the matter of edge-restenosis are yet to be resolved, and the results of ongoing prospective randomized trials should provide valuable information on the efficacy of this modality. Patients with severe, non-revascularizable coronary artery disease and debilitating symptoms represent another frustrating clinical problem. PMR performed in the cardiac catheterization laboratory may improve symptoms of angina in patients with end-stage coronary artery disease. The early results are propitious. Among patients who have undergone this procedure 80–90% have improved from class IV (the most severe chest pain) to class I or II, enabling them to live relatively normal lives. Most investigators believe that

[7] PMR = percutaneous myocardial revascularization
[8] MMM = maximal medical management

PMR may be used only for those who are unsuitable candidates for percutaneous or surgical revascularization. Finally, gene therapy, by stimulating angiogenesis and improving coronary collateral development, may prove to be the most optimal treatment.

Each of these strategies is currently under active investigation to confirm the results of the pilot studies, identify patient subgroups likely to respond to therapy, and determine long-term safety. Together with its challenges, the future of interventional cardiology is indeed bright.

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Capsule

T cell production — slowed, not exhausted?

Ever since the very early days of the AIDS epidemic, almost two decades ago, researchers have recognized the disease by its signature symptom: a progressive loss of CD4 T lymphocytes. Yet just how HIV causes T cell depletion is still the subject of vigorous debate. Does it destroy T cells so quickly and efficiently that the immune system exhausts itself trying to replace them? Or does it disrupt the immune system's ability to produce T cells in the first place? A team, led by immunologist Joseph McCune of the University of California, San Francisco, and endocrinologist Marc Hellerstein of UC Berkeley, reports results obtained by using a new technique which, for the first time, provides a direct measure of how many new cells are produced over a given time period. The findings, the team claims, support the notion that HIV's most important and insidious talent is to interfere with T cell production

For some researchers, the new paper essentially resolves the controversy. David Ho argues that the results do not necessarily contradict his model. To tackle the question, the UC researchers used an innovative method they first described last year. They intravenously infused subjects with a solution of glucose — a precursor of deoxyribose, in which the glucose molecules contain deuterium, a non-radioactive isotope of hydrogen. They then took blood samples at various times after completion of the infusion. As T cells divided, the deuterium-labeled DNA was progressively replaced by unlabeled DNA, allowing the team to calculate the production rate of new cells as well as their average life span. The team conducted this test on three groups of subjects: uninfected controls, HIV-infected patients undergoing antiviral therapy, and infected patients not yet receiving therapy.

The team found that the average T cell life span in untreated HIV-infected patients was one-third that in controls, consistent with a certain amount of cell killing by HIV. However, the T cell production rate was no higher than that of the controls, as would be expected if the immune system was working overtime to replace these destroyed cells. Moreover, patients taking antiviral drugs had higher T cell production levels than in the control and untreated groups — the opposite of what would be expected if increased production were simply a response to T cell destruction by HIV. Instead, the authors propose that antiviral therapy leads to a "disinhibition" of the production machinery.

But some researchers believe this conclusion is premature. For example, immunologist Angela McLean of Britain's Institute for Animal Health in Compton argues that the new technique may underestimate the actual rate of T cell production in the untreated patients, especially if new cells become infected by HIV and die before they can be counted.

Ho, while lauding the new methodology as "a powerful new technique," says that even if the untreated HIV-positive patients in the UC study did not produce greater numbers of T cells than uninfected controls, this does not necessarily contradict his model of immune exhaustion since these patients had much lower CD4 counts than the HIV-negative group. This means, says Ho, that the same production rate would represent a much faster turnover of their total T cell pool.

McCune argues that if HIV is indeed interfering with the production of new T cells, the findings might point to new strategies for enhancing this production. For example, T cells could be cultured outside the body for reintroduction later in the disease, or patients could be given signaling molecules called cytokines to prompt immune system cells to divide. But whether these measures are warranted depends on discovering what HIV is actually doing to the immune system. The new methods, researchers contend, are an important step in that direction.

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