Revascularization

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It was not until the second half of the 20th century that anything other than palliative treatment could be offered to patients suffering from various pathologies (such as atherosclerosis and myocardial infarction) that resulted in compromised coronary flow and consequent myocardial ischemia. If the ischemia and the affected tissue mass were sufficiently great, then mortality figures were high, usually as a consequence of contractile failure or lethal arrhythmias. However, during the second half of the 20th century, four independent and very different streams of research were initiated and would culminate in the ability, by a variety of means, to reperfuse the ischemic human heart, with the attendant reduction in mortality. These remarkable and differing reperfusion technologies also lead to cardiological “turf wars” aimed in part at winning the hearts and revenue of the millions of patients suffering from ischemic heart disease.

THE PATHOPHYSIOLOGICAL TEAM
The 1960s witnessed a remarkable increase in the systematic study of: (i) the nature of atheroma and thrombosis, and (ii) the metabolic, contractile, ultrastructural, and electrophysiological consequences of myocardial ischemia. Such studies, epitomized by the work of Robert Jennings, Lionel Opie, Richard Bing, and many others, were largely laboratory-based. They used techniques such as coronary artery ligation and tissue analysis to reveal the molecular nature and the spatial and temporal characteristics of myocardial ischemia and evolving infarction. Over the decades, an immense database was established describing the pathophysiology of ischemia and the importance of the critical transition from reversible to irreversible ischemic injury. Somewhat later, due in part to the relative ease of restoring coronary flow in experimental animals, investigators, including the authors of this editorial, turned their attention to the metabolic, structural, electrophysiological, and contractile consequences of reperfusion.
It very soon became clear that severity and adverse consequences of myocardial ischemia were critically dependent on the extent of myocardial flow reduction, the duration of elapsed ischemia and the amount of tissue involved. Put simply, mortality was proportional to infarct size—a notion that led Eugene Braunwald and his colleagues, together with many other laboratories, to seek pharmacological ways of limiting the size of an evolving infarct. In the absence of a means to reperfuse the ischemic human heart, this seemed an obvious way to grapple with the lethal consequences of evolving myocardial infarction. This concept heralded two decades of laboratory investigation in which a veritable cornucopia of compounds such as β-blockers, calcium antagonists, anti-inflammatories, vasodilators, and even enzymes and proteins were administered to animals with myocardial ischemia. Infarct size was estimated by enzymatic, electrophysiological, or morphological means, and the results appeared to be dramatically successful, reducing infarct size even in the absence of reperfusion. The mechanism of protection was presumed to involve “salvaging” the so called “jeopardized” myocardial tissue in the “borderzone” of intermediate flow that was assumed, probably incorrectly, to encapsulate a zone of infarction. While the core of “condemned” tissue would still die, some cells would be saved. The wordsmiths had a field day! Naively, many experimentalists and cardiologists appeared to convince themselves that severely ischemic tissue could be saved from cell death and necrosis without reperfusion and the restoration of blood flow. In the 1970s and 80s, it was appreciated that this approach was flawed—an error that was confirmed by a number of major unsuccessful clinical trials that failed to show benefit with a range of putative infarct-reducing agents. Rather too late, it became apparent that early reperfusion was a prerequisite for the salvage of severely ischemic tissue.

THE SURGICAL TEAM
During the 1950s, 60s, and 70s, cardiac surgery was developing rapidly—largely because of the heroic nature of some adventurous surgeons, the development of the heart-lung machine, and the willingness of surgeons to subject the human heart to ischemic arrest for periods as long as 1 hour. As surgeons became more and more skilled and techniques such as hypothermia and chemical cardioplegia were introduced to protect the heart during elective ischemic arrest, new surgical procedures were developed, including coronary artery bypass grafting in patients with severely occluded coronary arteries. Surgical reperfusion was born, which not only relieved symptoms, but also restored flow to poorly perfused myocardial tissue. Coronary artery bypass surgery became a standard procedure for patients with severe angina that threatened infarction, and, with time, this was extended to emergency surgery during evolving myocardial infarction. The surgeons had a monopoly of the “reperfusion business.”
THE PHARMACOLOGICAL TEAM
In parallel with the pathologists and the surgeons, pharmacologists were looking at other approaches to improving coronary perfusion by combating atheroma or dissolving infarct-initiating thrombi. Disappointingly, early attempts by Sherry and colleagues in the late 1950s to induce fibrinolysis with streptokinase were, for a variety of reasons, largely ignored. However, in the 1970s and 80s, there was a rebirth of interest, with more than 20 clinical trials being carried out, but the results were unconvincing. It was not until the completion of the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI) and Second International Study of Infarct Survival (ISIS 2) trials in the late 1980s that the real benefit of thrombolysis was demonstrated and accepted.

Reperfusion of the ischemic human heart could now be achieved by simple injection, allowing the pharmaceutical industry and the clinical cardiologist to move in on the reperfusion business. This development, along with an increasing knowledge of cardiac risk factors, the importance of lifestyle, and the development of cholesterol-reducing drugs, began to erode the surgical reperfusion business.

THE INTERVENTIONAL TEAM
During the same decades that cardiac surgery and thrombolysis were developing, cardiologists were exploiting the development of cardiac catheterization laboratories, not only for diagnosing and better understanding myocardial ischemia, but also for exploring the possibility of a catheter-based means of dealing with it. The concept of percutaneous coronary intervention, pioneered by Andreas Grüntzig in the 1970s, was slow to catch on, but eventually the flood gates opened and cardiologists with a mechanical bent began to develop a panoply of ingenious mechanical methods for alleviating perfusion deficits and unblocking coronary arteries. The 1980s and 90s witnessed the development of ever more ingenious catheters armed with cameras, lasers, isotopes, balloons, cutters, grinders, stents, and drugs. Less invasive than cardiac surgery and more dramatic than thrombolysis, the mechanical team dug further into the surgeons’ once exclusive business. At the same time they also made the life of surgeons more difficult and sometimes their results less impressive since, increasingly, surgeons only had their “bite of the cherry” after the interventional cardiologists had had a go—and sometimes failed—thereby providing the surgeons with patients suffering from more advanced disease. Coronary artery bypass surgery was in decline due to the success of far less invasive pharmacological and interventional alternatives. While the surgeons fought back with minimally invasive surgical procedures, their market share was irretrievably lost.
CHOICES, CHOICES, CHOICES

At the beginning of the 21st century, we are now armed with a detailed understanding of the nature of ischemia, an appreciation of the importance of early reperfusion, and a wide portfolio of very different procedures for achieving it. The importance and success of research and development are evident from the striking reduction in suffering and cardiac mortality. In this issue of Dialogues, James Willerson and Maximilian Buja explore, in the Lead article, the pathophysiology of ischemia and reperfusion, and in doing so establish the rationale for attempting to reperfuse the ischemic heart by whatever means. Arising from their review is the obvious question that may face the physician confronted with one of a variety of manifestations of coronary heart disease: what is best therapy? Do we employ the surgeon, the interventionalist, or the pharmacologist? The “Expert Answers to Three Key Questions” make it clear that this is a case of “horses for courses”: Raimondo Ascione and Gianni Angelini defend the surgical approach; Gabriel Steg speaks up for the interventional cardiologists; and John Horowitz provides the views of the pharmacologist.

In closing, we might muse on paradigm shifts that have, over the years, characterized the treatment of cardiac disease, a classical example being the abandonment of positive inotropic agents in favor of the use of negative inotropes in the treatment of heart failure. In the context of this issue of Dialogues, it is therefore pertinent to raise the issue of “reperfusion injury”—the paradox that while reperfusion is essential for the salvage of severely ischemic tissue it may not be entirely without danger. Laboratory studies have shown convincingly that reperfusion can increase injury over and above that attributable to the preexisting ischemia, precipitating arrhythmias, suppressing the recovery of contractile function (“stunning”) and possibly even causing cell death in potentially salvable ischemic tissue. The mechanisms of reperfusion injury have been widely studied and a host of often simple procedures have been developed to attenuate this injury in the laboratory. Disappointingly, and for a variety of reasons, this concept and the accompanying therapeutic opportunities have not been widely investigated in the human heart, but, hopefully, as the reperfusion “turf wars” progress, the possibility of reperfusion injury and the prospect of its manipulation will stimulate the competing factions to consider whether their very different weapons have yet been honed to perfection.
Cell death from coronary artery occlusion occurs after approximately 20 minutes of very severe ischemia (Figures 1-8, see pages 268 to 271). Collateral coronary blood flow and partial coronary artery occlusions in humans may allow myocyte survival for longer periods of time. Irreversible ischemic injury, cell death, and subsequent necrosis begin in the subendocardium, and cell death progresses in a wavefront from the subendocardium into the subepicardium of the ischemic bed-at-risk (Figures 7 and 8).

Reperfusion can dramatically affect the outcome, with the timing of reperfusion being a key determinant of the result (Figure 9, page 272).

Reperfusion within 20 minutes of intense ischemia generally saves ischemic myocytes, but recovery from the ischemia is not immediate with reperfusion, probably requiring timely reperfusion by thrombolysis, angioplasty, or bypass. However, full recovery of left ventricular function often takes days to weeks. This is partly the effect of the ischemia, which causes glycogen depletion, cellular acidosis, lactate, free radical and hydrogen ion accumulation, decreased high-energy phosphates and adenine nucleotides, and mild mitochondrial and intracellular edema. However, it is also the effect of the two-faced process of reperfusion itself, which activates an inflammatory cascade manifested as functional impairment (stunning), platelet activation and thrombosis, arrhythmias, calcium loading and apoptosis in critically injured myocytes. A burst of oxygen radicals in the bed-at-risk promotes lipid peroxidation, membrane damage, microvascular obstruction, and no-reflow in the reperfused myocardium. Nevertheless, provided reperfusion is instituted within 2 to 3 hours of ischemia onset, the extent of salvage significantly exceeds the extent of lethal injury. It is hoped that this window can be widened by combining intervention with protective reperfusion cocktails containing hyperosmotic agents, calcium antagonists, and/or free radical inhibitors with the pharmacological recruitment of putative preconditioning mediators, such as the sarcolemmal K_{ATP} channel.

**STUNNED MYOCARDIUM**

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ably because of the marked decrease in high-energy phosphates and the adenine nucleotide pool, glycogen depletion, lactate and H+ ion accumulation, cellular acidosis, and mild mitochondrial and intracellular edema that occur during the ischemia.1,2,6,11 Recovery of myocyte contractile function after brief periods of reversible ischemia may require hours to weeks to occur, depending on the duration and severity of the ischemia and adequacy of reperfusion. Shorter periods of ischemia are followed by more rapid recovery of contractile function (minutes to hours), whereas longer periods of intense, but reversible, ischemia require days to weeks for recovery of contractile function.12-16 This prolonged period to contractile recovery occurs in "stunned myocardium"12-15 as a consequence of the accumulation of free radicals16,17 and increases in cellular calcium concentration,1,2,5,6 as well as the time required to correct the metabolic and structural abnormalities described above.11 It seems likely that the accumulation of free radicals alters cell membrane permeability, contributing to cellular calcium overload in reperfused cells. Alterations in contractile protein structure, eg,
troponin I proteolysis, also occur during reversible myocardial ischemia and reperfusion and may contribute to the prolonged period required for recovery of contractile function. However, there is almost certainly a contribution from the reperfusion itself (ie, “reperfusion injury”) in the functional injury known as “stunned myocardium” as reperfusion enhances cell swelling, calcium entry into cells, and free radical generation (Figures 4, 5, 7, and 8).

**HIBERNATING MYOCARDIUM**

Myocardial hibernation refers to contractile dysfunction associated with reduced coronary blood flow that can be improved with reperfusion and/or by reducing oxygen demand. Studies utilizing myocardial perfusion and metabolic markers (fluorodeoxyglucose) have shown that hibernating myocardium has reduced perfusion, but is metabolically active and can return to normal or near-normal contractile function with reperfusion. It is believed that hibernating myocardium downregulates its metabolism in response to the reduction in coronary blood flow, allowing myocytes to survive.

Therefore, myocardial stunning and myocardial hibernation both refer to contractile dysfunction, but with stunning, the myocardium is not ischemic, but is reperfusion-injured by the accumulation of oxygen-derived free radicals, cellular calcium overload, and alterations in cell volume regulation. Myocardial hibernation refers to ischemic myocardium as a consequence of reduced

![Image](image-url)
coronary blood flow that improves its contractile function with reperfusion, but may also be stunned by the reperfusion itself, thus requiring a prolonged period of hours to weeks to recover some or all of its contractile function.

**MECHANISMS OF ISCHEMIC CELL DEATH**

Acute ischemic myocardial cell death develops by well-established mechanisms involving ATP depletion, cell swelling, and membrane damage (“oncrosis”) as well as by activation of specific pathways involving activation of specific enzymes, the caspases, and double-stranded DNA fragmentation (“apoptosis”).

Reperfusion also influences these processes. Reperfusion also influences these processes. Reperfusion also influences these processes. Reperfusion also influences these processes. Reperfusion also influences these processes.
Myocardial reperfusion: biology, benefits, and consequences - Willerson and Buja

**Figure 7.** Typical histological features of canine left ventricular myocardium subject to temporary severe ischemia and reperfusion (40 minutes coronary occlusion and 20 minutes of reflow) showing a spectrum of cytopathological changes. 

A: The interstitial space is expanded by fluid accumulation, ie, interstitial edema (E). Some myocytes (lower right) exhibit hypercontraction injury ×475. 

B: Pleomorphic population of cardiomyocytes. Some myocytes are normal with compact cytoplasm and relaxed myofibrils. One myocyte is pale and swollen (swollen muscle cell, SMC); a second myocyte is contracted and densely stained (dense muscle cells, DMC). Other myocytes show severe contraction band injury (arrow). Interstitial hemorrhage (extravasated erythrocytes) is also present ×450. 

C: This region contains several pale and swollen SMCs and interstitial edema (E) ×400. 

D: This area exhibits interstitial edema (E), cardiomyocytes with contraction band injury (arrows), and myocytes with palely stained zonal lesions (ZL) adjacent to intercalated discs ×400. 


**Figure 8.** Ultrastructural features of canine left ventricular myocardium subject to temporary severe ischemia and reperfusion (40 minutes coronary occlusion and 20 minutes of reperfusion). 

A: Two swollen cardiomyocytes (swollen muscle cells, SMC) exhibit prominent intracellular edema and swelling with marked separation of organelles, glycogen depletion, and focal mitochondrial damage. Adjacent cardiomyocytes do not exhibit swelling and contain glycogen deposits. The interstitial space is widened and contains precystated edema fluid. The capillary (C) and adjacent mast cell (MC) are normal ×6400. 

B: An area of severe mitochondrial injury contains cardiomyocytes with hypercontracted myofibrils, damaged mitochondria, and subsarcolemmal areas of edematous cytoplasm containing either mitochondria (M) or numerous vacuoles (V). The adjacent capillary exhibits numerous projections of endothelial cytoplasm (arrows) and a membranous bleb (B) ×8300. Such changes along with sequestration of neutrophils contribute to the no-reflow phenomenon, a component of reperfusion injury. 

REPERFUSION INJURY

Reperfusion can be a powerful intervention to limit the extent of ischemic myocardial irreversible injury and subsequent necrosis. However, the effects of reperfusion are complex and include some deleterious effects on ischemically injured myocardium; these deleterious effects are collectively referred to as reperfusion injury (Figures 6 to 8). This reperfusion injury involves activation of an inflammatory cascade and is manifest as functional impairment (stunning), platelet activation and thrombosis, arrhythmias, and accelerated progression of cell death in certain critically injured myocytes. Reperfusion also produces a spike in apoptosis, likely involving a population of predisposed cardiomyocytes that undergo explosive cell swelling and calcium overloading upon reperfusion. The major mediators of reperfusion injury are oxygen radicals, calcium loading, and neutrophils. The burst of oxygen radicals on reperfusion is produced by myocytes, endothelial cells, and neutrophils in the bed-at-risk. The oxygen radicals promote lipid peroxidation and membrane damage, which leads to calcium loading. The activated neutrophils accumulate in the microcirculation, produce inflammatory mediators, and contribute to microvascular obstruction and the no-reflow phenomenon in the core of the reperfused myocardium. Nevertheless, if reperfusion is instituted promptly and within 2 to 3 hours of the onset of ischemia, the extent of salvage significantly exceeds the extent of lethal reperfusion injury. Thus, these observations form the basis of the concept of reperfusion as a two-faced (“Janus-like”) process (Figure 9).

PROTECTIVE INTERVENTIONS

Bolli et al have shown that the accumulation of short-lived oxygen-derived free radicals, including superoxide anion and hydroxyl radicals derived from superoxide, occurs in stunned and/or reperfusion injured myocardium (Figure 10). Nitric oxide (NO) released during reperfusion may react with superoxide to form peroxynitrite, another free radical that may also contribute to stunning. Bolli et al have shown that there was substantial reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion. In animal models, pretreatment with intravenous infusions of superoxide dismutase (SOD) and catalase, enzymes that scavenge oxygen-derived free radicals, may also attenuate or prevent myocardial stunning. Iron chelators, such as desferrioxamine and iron-catalyzed oxidants may also attenuate myocardial stunning in experimental

Figure 9. Temporal evolution of myocardial infarction, reperfusion injury, and salvage of myocardium by reperfusion. A: When reperfusion is achieved within 30 minutes of coronary occlusion, minimal irreversible injury occurs and most of the ischemic myocardium is salvaged, but the salvaged myocardium exhibits transient dysfunction (stunning). B: When reperfusion occurs within 2 hours of coronary occlusion, a significant amount of subendocardial myocardium develops irreversible injury, including some myocytes that become irreversibly injured at the time of reperfusion (reperfusion-induced cell death). Nevertheless, reperfusion also results in significant salvage of subepicardial myocardium that would otherwise have developed irreversible injury with permanent coronary occlusion. However, after 2 hours of coronary occlusion, the previously ischemic myocardium will exhibit prolonged impairment of contraction (prolonged stunning) with slow recovery toward baseline function.

animal models. With the recognition that oncotic and apoptotic pathways contribute to ischemic cell death, new opportunities for therapeutic intervention, including the use of caspase inhibitors, mitochondrial stabilizers, and Na+/H+ exchange inhibitors, have been recognized.

Pretreatment with trimetazidine has recently been found to be associated with an increase in endogenous antioxidants during cardiac surgery, while an earlier report had observed a significant reduction in troponin-T levels during CABG. These findings suggest this agent may play a role in protecting against ischemia-reperfusion injury.

**PRECONDITIONING**

Repetitive periods of transient and brief myocardial ischemia can protect against extensive myocardial necrosis by a phenomenon known as “ischemic preconditioning.” Murry et al. reported that anesthetized dogs subjected to 40 minutes of transient coronary artery occlusion and reperfusion had substantial reductions in myocardial infarct size when the animals received four brief episodes of ischemia followed by 5 minutes of reperfusion just before the 40-minute occlusion. In Murry et al.’s study, even in animals with reduced coronary collateral flow, the extent of myocardial necrosis was markedly reduced with preconditioning. Preconditioning can be induced by periods of ischemia as short as 3 to 5 minutes followed by 5 minutes of reperfusion. Kloner and Jennings have emphasized that a single episode of transient ischemia is all that is needed to induce preconditioning; however, the subsequent period of intense and prolonged ischemia needs to follow the brief period of ischemia within several minutes. If several hours elapse between preconditioning and a more prolonged coronary artery occlusion, the preconditioning effect is lost. Cohen et al. have also shown that myocardium may be chronically preconditioned by repetitive brief occlusions, but if the occlusions are too frequent and too close together,
the preconditioning protection is lost.40 Cohen and Downey,41,42 Murray et al,43 and other investigators43 have shown the involvement of a second messenger system in preconditioned myocardium. Preconditioned myocardium has a relatively small adenine nucleotide pool, excess intracellular glucose, a creatine phosphate overshoot, and stunning 38 The preconditioned myocardium reacts differently to a second episode of ischemia by utilizing ATP and accumulating lactate and H+ ion relatively slowly41-43 Thus, it appears that energy demand is reduced in ischemic preconditioned tissue42-44 and that preconditioned tissue dies more slowly because of the reduction in energy demand.38 The protective effect associated with transient ischemia is possibly caused by a mediator as yet undefined, but candidates include the KATP channels in the sarclemma and the mitochondria,1,2,41,42,45 and specific isoforms of protein kinase C (PKC).46,47

A KATP Channel is found in high concentration in the sarclemma, and it opens whenever intracellular ATP is markedly reduced.43 Such reductions occur in conditioned myocardium in experimental animal models and the KATP channel opening can be blocked by glibenclamide and 5-hydroxydecanoate (5-HD).1,2 Available data suggest the sarclemmal KATP channel may help mediate the preconditioning effect. There is also a KATP channel in mitochondria that may be opened specifically by diazoxide and blocked by 5-HD.41,43 Jennings et al have shown that pretreatment with diazoxide pharmacologically preconditioned the canine heart and reduces subsequent infarct size with more prolonged myocardial ischemia similar to that occurring with ischemic preconditioning.2 Downey and Cohen have suggested that the mitochondrial KATP channel is a trigger rather than mediator of preconditioning.41,43 The epsilon isoform of PKC has also been mentioned as a mediator of preconditioning.46 The isoform of this kinase is translocated during ischemia. When activated, it phosphorylates serine and threonine groups in enzymes and channel proteins. Inhibitors of this PKC isoform (such as chelerythrine) block the preconditioning effect in perfused rabbit and rat hearts.2 Other kinases may also be involved in the preconditioning effect.47 Vahlhaus et al have shown that inhibition of both PKC and troponin kinase prevents ischemic preconditioning in the pig heart, but inhibition of PKC alone has no effect.48

There is also evidence that adenosine may play a role in the preconditioning effect.43,49 Adenosine and A1 agonists pharmacologically precondition canine and rabbit hearts against a brief period of myocardial ischema. These effects are blocked by inhibitors of adenosine and by glibenclamide, the KATP channel inhibitor.2 The A1 receptor appears to mediate the effects of adenosine and this receptor stimulates PKC isoform translocation.43,49 These data suggest that adenosine plays a role in preconditioning with ischemia and that the potassium channel mediates adenosine’s effects.

**DELAYED PRECONDITIONING**

Preconditioning ischemia results in the synthesis of new enzymes, including inducible NO synthase, SOD, and heat-shock proteins.30 Yellon et al have shown that protection against cell death for hearts preconditioned with transient ischemia returns after 24 hours of reperfusion. This is referred to as “delayed” or “late preconditioning,” and also as a “second window of protection.” Others have shown that this form of preconditioning protects against stunning and cell death.2,50 The delayed preconditioning effect appears to be mediated by inducible nitric oxide synthase (iNOS).2,50 The beneficial effects of iNOS are prevented by free radical scavengers implicating free radicals as contributing to iNOS formation.

**CLINICAL APPLICATIONS**

Presently, reperfusion may be provided to patients with coronary heart disease by thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA)/stenting, or by coronary artery bypass surgery (CABG). There are a number of clinical conditions that are influenced by reperfusion (Table I). Patients with unstable angina and non-ST-segment–elevation myocardial infarction (NSTEMI) generally have ulcerated...
or fissured atherosclerotic plaques in one or more coronary arteries with transient coronary artery occlusions caused by thrombosis and dynamic vasoconstriction at site(s) of coronary artery injury. At sites of atherosclerotic plaque ulceration or fissuring (more common in women) platelets adhere, aggregate, and release potent promoters of platelet aggregation and dynamic vasoconstriction, including thromboxane A2, serotonin, platelet-activating factor (PAF), and adenosine diphosphate (ADP). Other mediators of thrombosis accumulating at the same sites are thrombin, ADP, and oxygen-derived free radicals. Endothelin, a potent vasoconstrictor, is also released locally from injured endothelial cells. Sites of endothelial injury are also missing, relatively or absolutely, the normally protective substances that prevent thrombosis, inflammation, and constriction, ie, prostacyclin, NO, and tissue plasminogen activator (t-PA). Thus, at sites of vascular injury associated with inflammation and plaque ulceration or fissuring, a potent prothrombotic and vasoconstrictor environment develops.

The clinical syndromes of unstable angina and NSTEMI are associated with transient coronary artery occlusion and reperfusion. Unstable angina typically has periods of transient coronary artery occlusion lasting 5 to 20 minutes followed by reperfusion associated with platelet-initiated transient thrombosis and vasoconstriction followed by reperfusion. This condition has been modeled in experimental animal models with coronary artery endothelial injury and applied external constriction that leads to cyclic flow variations (CFVs) as shown initially by Uchida et al and Folts et al. These CFVs are caused by local accumulation of the prothrombotic and vasoconstrictor mediators described above. The clinical syndrome of NSTEMI is associated with myocardial necrosis occurring in the subendocardium and caused by slightly more prolonged periods of coronary artery occlusion, ie, 30 minutes to 1 to 2 hours associated either with CFVs or incomplete coronary artery occlusion. In both cases, reperfusion occurs either spontaneously or as a result of protective antithrombotic medications the patient receives, including aspirin (thromboxane A2 inhibitor and anti-inflammatory medication), clopidogrel, an inhibitor of ADP, and nitrates (NO donors and coronary vasodilators), and thrombin inhibitors (heparins, unfractionated or low-molecular-weight heparin).

With coronary artery spasm (variant angina or Prinzmetal angina), total occlusion of a coronary artery occurs in susceptible patients usually for periods of 5 to 15 minutes. This is associated with severe chest pain and ST-segment elevation on the ECG. This condition often occurs in the early morning hours, awakening the patient from sleep; the coronary artery spasm is usually relieved by nitrates and/or a calcium antagonist.

ST-segment–elevation myocardial infarction (STEMI) is associated with prolonged coronary artery occlusion by thrombosis and vasoconstriction, and reperfusion is achieved with either PTCA/stent, or when the percutaneous interventional approach (PCI) is not available, by thrombolytic therapy. The coronary artery occlusion has usually lasted from 1 to 4 hours (and sometimes even longer) prior to reperfusion in these patients. Thus, there is a greater possibility of more marked cell swelling and extracellular edema, including hemorrhage with reperfusion. PCI (PTCA/stents) and coronary artery revascularization surgery allow reperfusion of chronically ischemic myocardium; therefore, these interventions may treat hibernating myocardium, but should be associated with reperfusion injury and stunning at the same time.

It has also been shown that an open infarct-related artery, especially the left anterior descending coronary artery (LAD) after STEMI is associated with improved survival in patients. It should be noted, however, that these findings have recently been challenged.

**SUMMARY**

Thus, reperfusion provided at an early time period for severely ischemic myocardium may limit or prevent myocardial necrosis; early reperfusion is the only practical way to salvage this tissue. In the setting of chronic myocardial ischemia, reperfusion may enhance segmental and global myocardial function by reversing left ventricular segmental contraction abnormalities in hibernating myocardium. Repetitive brief episodes of myocardial ischemia followed by reperfusion may limit myocardial necrosis with a more prolonged period of severe ischemia. However, full recovery of segmental and global left ventricular function with reperfusion in patients often requires days to weeks to occur. Therefore, assessments of segmental and global left ventricular function by imaging techniques must take this into account in order to identify the full extent of functional recovery.

It seems advisable that the physician be able to utilize some of the biological information about each of the cellular phenomena associated with ischemia/reperfusion to develop improved therapeutic strategies for
enhancing the beneficial effects of reperfusion in patients. Cardiovascular surgeons have attempted to do this with various reperfusion "cocktails" that are administered either before and/or with surgical reperfusion, including hyperosmotic agents, inhibitors of free radicals, calcium antagonists, etc.\textsuperscript{54} The development of intracellular edema with ischemia, and intracellular and extracellular edema and sometimes hemorrhage with reperfusion after more prolonged periods of ischemia, as well as cardiomyocyte metabolic and membrane changes, should allow physician-scientists enhanced ability to detect ischemia and reperfusion using noninvasive imaging methods in the future. Clinical translational research devoted to the development of new methods of cellular protection during ischemia and with ischemia/reperfusion should have a rebirth as more sophisticated and sensitive noninvasive imaging methods are developed for tissue characterization within the heart.

One of the most important concerns related to providing reperfusion in patients with coronary heart disease is the selection of the most appropriate form of therapy, ie, thrombolytic therapy, PTCA/stenting, or CABG, and within these different interventions, the most effective and safe procedure. These issues are discussed in this issue of \textit{Dialogues} in three subsequent papers by active experts who themselves use CABG, PTCA/stenting, and thrombolytic therapy to achieve reperfusion in patients.

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Revascularization

Expert Answers to Three Key Questions

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When and why should we employ the surgeon? Biological and clinical rationale for early reperfusion

R. Ascione, G. Angelini

2

When and why should we employ the interventional cardiologist?

P. G. Steg

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When and why should we employ the pharmacologist?

J. D. Horowitz
Revascularization in patients with coronary artery disease (CAD) has changed over the last two decades, favoring the use of percutaneous coronary intervention (PCI) over coronary artery bypass grafting (CABG), even though there is no available hard evidence to support this change. Nevertheless, PCI stenting has been progressively expanding its indications to include multivessel coronary disease, diabetes mellitus, and left main stem coronary artery disease. Proponents of PCI justify its expansion with the improvement in restenosis achieved with drug-eluting stents. However, the established treatment of CAD is CABG, with proven long-term life expectancy benefit. The ongoing replacement of CABG with PCI would be therefore justified only if a critical scrutiny of the evidence clearly demonstrates similar or better life expectancy benefits.

When and why should we employ the surgeon?
Biological and clinical rationale for early reperfusion

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Revascularization in patients with coronary artery disease (CAD) has been increasingly taking center stage with respect to coronary artery bypass grafting (CABG) as a therapeutic option to revascularize patients with coronary artery disease (CAD) and is steadily gaining new indications, such as multivessel coronary (artery) disease (MVD), diabetes mellitus, and left main stem (LMS) coronary artery disease. This article looks at whether current evidence is strong enough to justify this growing trend in the face of the well-established benefits of CABG, and asks whether the ultimate decision should, as is now the case, continue to rest overwhelmingly in the hands of the cardiologist or—excluding other factors, like the clinician’s experience, financial considerations, and even political reasons, which should not be allowed to skew the debate—whether it is now time to give more weight to the surgeon’s point of view.

“A surgeon should be employed in all those cases where the available evidence, critically scrutinized, suggests so; because only evidence-based medicine is what matters to patients and their life expectancy.”

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AVAILABLE EVIDENCE: TRIALS AND REGISTRY DATA

According to the 2005 guidelines published by the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology, PCI can be considered a valuable initial mode of revascularization in all patients with stable CAD with objective large ischemia in the presence of almost every lesion subset, with the exception of chronic total occlusions that cannot be crossed.

However, the guidelines do not specify the meaning of “valuable initial mode of revascularization,” a statement open to many interpretations. Despite lack of direct supporting evidence, the guidelines suggest that the availability of drug-eluting stents and the improved technical approach to chronic total occlusions will reduce the indications of surgery for the treatment of multivessel coronary disease…

but then go on to conclude that… until proved otherwise, PCI should be used only with reservation in diabetics with multivessel disease and in patients with unprotected left main stenosis.

Valuable evidence may be derived from either prospective controlled randomized trials or from data entered in large registries. Trials have the advantage of scientific accuracy. However, their results cannot be generalized and can only be applied to populations similar to that of the study. As for the data from large registries, though they cannot claim identical accuracy, they are nevertheless also very useful, since they reflect how guidelines and recommendations are interpreted by clinicians and applied in real practice, and do not exclude any patients, as opposed to trials. Critical appraisal of data concerning primary outcomes supposes a prospective setting, bearing in mind that the only meaningful outcome that matters to patients is the duration and quality of their life expectancy. Any other outcome has “academic” value only. Yet, surprisingly, most available trials comparing PCI and CABG have been powered only for “academic” end points (eg, recurrence of restenosis), or short-term clinical and/or cost-efficacy end points.

Evidence from randomized controlled trials

CABG vs PCI

Several trials of PCI vs CABG were carried out during the 1980s, the findings of which we briefly discuss. In the following we liken the patients undergoing PCI or CABG to “teams of runners” competing to win the race of “best treatment,” and point out that one team may occasionally have been given an “unfair advantage” over the other, depending on the design of the studies, thus biasing the conclusions.

The Emory Angioplasty Surgery Trial (EAST), involved 392 patients with MVD who were randomly assigned to PCI or CABG. The randomization rate was only 7.7% (out of a total of 5188 patients screened), mostly because of patients who were not suitable for PCI treatment. Thus, although the 8-year mortality was 17.3% and 21.7% in the CABG and PCI groups, respectively, this relative mortality difference of 20% in favor of CABG did not reach statistical significance because of the small size of the study population. In this trial, both “teams of runners” were therefore equally “hamstrung.”

The Bypass Angioplasty Revascularization Investigation (BARI) trial was conducted in 18 centers from 1988 to 1991. Of the 25,200 patients initially screened with MVD, about 50% were excluded for clinical or administrative reasons, or presence of left main stem coronary artery disease. Of the remaining 12,530 patients who met the clinical eligibility criteria, more than 60% were subsequently excluded because of unsuitability for percutaneous transluminal coronary angioplasty (PTCA). The randomization rate was only 7.3% (1829 patients). In this trial, the selection process was tailored to PCI requirements, so that the “PCI runner” was given a little advantage over the adverse team. Despite this, there was a significant survival benefit for CABG vs PCI at 7 years (absolute survival difference 2.5%, relative survival difference 15%; P<0.043).13

A meta-analysis of nine subsequent trials of CABG vs PCI in MVD patients revealed that although survival was equivalent in these highly selected low-risk patients at 1 and 3 years, the 8-year mortality rate was 13.7% with CABG vs 17.1% with PCI (P<0.03), and the relative mortality with PCI was 25% higher.2

CABG vs PCI with stents

The first Arterial Revascularization Therapies Study (ARTS I) included 1205 patients with MVD. The randomization rate was only 5%. There was a long list of exclusion criteria including previous revascularization, congestive heart failure, recent myocardial infarction, and cerebrovascular accident. Mean age was only 61 years. Once again, most of the patients were excluded because they were not suitable for PCI with stents. The “PCI runners” were therefore given the most “even” track of the stadium. What’s more, they even received a “little additional push,” as, following randomization, patients undergoing CABG had to wait on average 16 days longer before...
surgery than their PCI/stent counterparts. Unfortunately, while waiting, 3 of them died, 4 suffered myocardial infarctions, and 1 suffered a stroke. The “little push” to the “PCI runner” consisted in considering these preoperative events as CABG outcomes. Despite all, the number of deaths after the procedure was the same (15 in the stent group, 14 in CABG group) at 1 year, but the need for repeat revascularization was 16.8% and 3.5% for the PCI and CABG groups, respectively. Also, patients undergoing CABG had a higher rate of complete revascularization (84.1% vs 70.5%, \( P<0.001 \)). Among diabetic patients, those treated by stenting showed the lowest 1-year event-free survival rate (63.4%) compared both with diabetic patients treated by CABG (84.4%, \( P<0.001 \)) and with nondiabetic patients treated by stenting (76.2%, \( P<0.04 \)). Similar results were present at 3 years follow-up, the event-free survival rate being lower in stented diabetic patients compared with the surgery arm (52.7% vs 81.3%, \( P<0.001 \)). Furthermore, the “CABG runner” clearly won the life expectancy race with a 5-year combined death, myocardial infarction, and stroke rate of 13.5% vs 18% for PCI/stents (relative risk approximately 1.33), and a repeat revascularization rate of 8.8% vs 30% for PCI/stents (relative risk approximately 3.46). However, the authors didn’t see these CABG-related benefits, and did not include these results in their conclusions. In fact, they drew a PCI-supporting conclusion stating that there was no difference in 5-year mortality between the groups (even though the study was not powered to detect a difference in mortality!). As a finale, they pulled out the rabbit from the hat and stated “the difference in outcomes seen between bare metal stents (BMS) vs CABG is likely to narrow substantially with the advent of drug-eluting stents (DES).” This was pure unsubstantiated “wishful thinking.”

The obvious outcome of the trial—ie, CABG is superior to PCI with stent—was not mentioned. Sadly, there is no further follow-up scheduled for the SoS trial since funding has been stopped, with a consequent censoring effect on data not favorable to PCI with stents. In this way, the “PCI runner,” is getting a bonus, since any future meta-analysis will not include mid- to long-term data from SoS.

The Stent or Surgery (SoS) trial was carried out in 53 centers across Europe and Canada and totaled 988 MVD patients, including those with low left ventricular ejection fraction. The need for repeat revascularization at 2 years was dramatically higher in the PCI group—21% vs 6% in the CABG group, a 15% absolute difference rather than the 5% difference that had been assumed, ie, 3 times as high (hazard ratio 3.85, \( P<0.0001 \)). Two-year mortality was 2% with CABG vs 5% with PCI (hazard ratio 2.91, \( P=0.01 \)), and this difference was even more marked in the subgroup of 142 diabetic patients, mortality in the PCI group being 2.9 times that in the CABG group (\( P<0.01 \)). In spite of the “CABG runner” having so very clearly won the race here, the authors concluded that the use of coronary stents has reduced the need for repeat revascularization compared with previous studies that used balloon angioplasty, though the rate remains significantly higher than in patients managed with CABG. The apparent reduction in mortality with CABG requires further investigation.
and 3% for age >70 years. Interestingly, these differences were all heaped on the shoulders of the "CABG runner." This "CABG runner" also had a blister on one of his feet since the average use of arterial conduit during surgery was below average, at only 70%. To compound matters, there was also some confusion in study design since 10 patients allocated to the CABG group were actually treated by PCI only, while 8 patients allocated to the PCI group were also treated by CABG. One wonders what kind of evidence can arise from such a trial. For the sake of completeness, there was no difference in survival at 3 years follow up, and the same survival outcomes were found in the subgroups of diabetic patients, but nevertheless there was a higher rate of repeat revascularization in the PCI arm.

**CABG vs PCI with DES**

The advent of DES, with its potential to reduce restenosis, has been sufficient to move most of MVD into the PCI field. Although a large meta-analysis of 11 trials of DES vs BMS showed a reduced incidence of restenosis favoring DES, not a single trial demonstrated a mortality benefit for DES and, in fact, pooled mortality outcomes appeared to be identical. Similarly, DES did not reduce the occurrence of myocardial infarction. These trials were conducted in patients who received only single-lesion treatment and with a good ejection fraction. A recent meta-analysis of 17 randomized controlled trials comparing DES and BMS over an extended follow-up of up to 4 years found a trend toward an increased overall mortality risk in patients treated with DES. Sensitivity analyses showed that sirolimus-eluting stents were associated with an increase in noncardiac mortality at 2 and 3 years of follow-up. These findings confirm the crucial importance of long-term monitoring and of the precise disclosure of causes of death in patients treated with DES, in order to assess the long-term safety of these devices.

To date, no randomized clinical trial comparing DES-assisted PCI and CABG has been published. Nevertheless, more and more MVD patients with or without diabetes mellitus, and even those with LMS disease are treated by PCI with DES. It is all happening without supporting evidence.

ARTS II was a single-arm, 45-center, European study in which 607 patients with inclusion criteria matching those of the ARTS I trial were treated by sirolimus-eluting stents. Outcome was compared with that of ARTS I. The primary end point of this study was the freedom from MACCE at 1 year compared with the ARTS I CABG arm. The results of this trial were considered more satisfactory in the ARTS II arm compared with ARTS I CABG and ARTS I PCI (MACCE rate 10.4% vs 12.2% vs. 26.2%, respectively). The first comment that comes to mind when examining ARTS I and II is that "Errare humanum est, perseverare diabolicum." Having concluded the report of ARTS I with the statement one wonders why the authors avoided a fair race by choosing a single-arm design for ARTS II. Scrutinizing ARTS I and II, one cannot resist being malicious and thinking that this was yet another convenient choice for the lucky "PCI runner." It is very suspicious to observe that the primary end point of ARTS II was set to be the freedom from MACCE. This is because "CABG runners" in ARTS I had already been handicapped before starting the race with the burden of 3 deaths, 4 myocardial infarctions, and 1 stroke (ie, MACCE events)! These events occurred during the waiting time and there-

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**Table I.** Bare metal stents (BMS) in selected left main stem (LMS) patients.

**Abbreviations:** PCI, percutaneous coronary intervention; revasc, revascularization.
before surgery. This is simply an abuse of intention-to-treat analysis. On the other hand, ARTS II follow-up was scheduled at 1 year, but not at 5 years. Again, this is suspicious when considering that in ARTS I the most obvious CABG-related long-term life expectancy benefit were observed at 5 years. Finally, one should not forget that the randomization rate for ARTS I was only 5%.

Evidence from clinical practice (registry data)

The evidence from trials is of course of high scientific accuracy. However, it can only be applied to the type of population selected in the trials. The major limitation of all trials comparing CABG and PCI is their very low randomization rate due to their strict enrolment criteria. Therefore, their clinical applicability should be restricted to those 5% to 7% of patients selected from the entire screened population. For the remaining 93% to 95% of the population, it is simply unethical to apply these results.

In a study evaluating to what extent patients in clinical practice were similar to those who participated in trials comparing PCI and CABG, 4713 patients enrolled in the Euro Heart Survey on Coronary Revascularization were compared with 8647 patients who participated in 14 major trials of PCI vs CABG. Patients in clinical practice were indeed at higher risk, being older, more often with comorbid conditions, single-vessel disease, and LMS disease when compared with trial participants. Despite this, in clinical practice, PCI was the treatment of choice, even in ineligible patients (46% PCI, 26% CABG, 28% medical). There is no logical justification for this. PCI also remained the preferred treatment option in patients with MVD (57% in eligible and 40% in ineligible patients, respectively, \( P < 0.001 \))

What then is the outcome of PCI as based on data registries? Hannan et al.28 compared results of PCI vs CABG in New York State residents from 1993 to 1995. Late mortality outcome was adjusted for baseline imbalances and differences in comorbidities. In MVD patients, 3-year adjusted mortality was 43% higher with primary PCI relative to primary CABG (absolute 3-year mortality 13.9% with PCI, 9.7% with CABG). Furthermore, 3-year need for repeat revascularization was 11 times higher in the PCI group (37% PCI, 3.3% CABG). Based on these results, one wonders why on earth MVD patients were treated by PCI in New York State from 1993 to 1995!

The New York State Registry has been also used recently to open a window on the impact of PCI with stent on clinical practice.29 This study compared the results of PCI with stents and CABG in 60 000 MVD patients (CABG = 37 212; PCI with stents = 22 102) treated between 1997 and 2000. This time, both “teams of runners” started off on equal footing (hospital mortality: CABG = 1.75%, PTCA = 0.68%). But what about life expectancy? With regard to duration of life, adjusted 3-year mortality was 7.9% with CABG vs 10.2% with stents in patients with two-vessel disease, including proximal left anterior descending (LAD) coronary artery (relative risk 29% higher in PCI); and it was 10.7% with CABG vs 15.6% with PCI stents in patients with three-vessel disease including proximal LAD coronary artery (relative risk 46% higher in PCI stents) (Figures 1 and 2).

With regard to quality of life, the relative risk of 3-years repeat revascularization after PCI and
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Stents in MVD patients was 7 times higher compared with CABG. Such an impressive poor impact on patient life expectancy, both in terms of duration and quality, is in our opinion the reflection of the uncritical use of PCI in the entire population despite lack of supporting evidence.

The last frontier: PCI with stent for patients with LMS disease

The American College of Cardiology/American Heart Association guidelines currently recommend surgical revascularization for patients with LMS disease. The use of PCI for the treatment of unprotected LMS stenosis is supported by a Class III indication in virtually all patients. It is worth noting that Class III is recommended for those conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Despite this, over the last decade there has been a progressing trend in treating LMS disease patients by PCI. The long-term Coronary Artery Surgery Study (CASS) experience (32 studies including 3 trials carried out between 1975 and 1990) demonstrated a clear life expectancy advantage for CABG compared with medical therapy. The reported median survival for surgically treated patients is 13.3 years vs 6.6 years for medically treated patients. Meanwhile, advances in surgical and anesthetic technique have allowed a further improvement in clinical outcome of LMS disease patients undergoing surgery. At our institution, we have recently reviewed our LMS disease patients series (n=1225) compared with non-LMS disease patients (n=5456). In-hospital myocardial infarction, stroke, and mortality for the LMS disease group was 3.3%, 0.8%, and 2.5%, respectively. Eight-year survival and freedom from cardiac-related events in LMS disease patients were 76.6% and 83.6%, respectively (Figures 3 and 4).

To date, there are several reports on the use of PCI with BMS in patients with LMS disease (Table I). However, even in anatomically favorable LMS lesions, PCI with BMS was associated with a 6% in-hospital mortality and a 4% need for repeat revascularization. By 1-year follow-up, the overall mortality was 17% with a need for repeat revascularization of 29%. More recently, several reports have also been published on the efficacy of DES vs BMS in patients with LMS disease. Chieffo et al. did a retrospective analysis on the use of PCI with stent for patients with LMS disease.

Figure 3. Eight-year post-surgery survival: review of left main stem (LMS) coronary artery disease patients (n=1225) vs non-LMS patients (n=5456) at the Bristol Heart Institute between 1996 and 2005.

Figure 4. Eight-year post-surgery freedom from cardiac-related events. Review of left main stem (LMS) coronary artery disease patients (n=1225) vs non-LMS patients (n=5456) at the Bristol Heart Institute between 1996 and 2005.
of 64 LMS disease patients treated by BMS compared with 85 treated by DES. During hospitalization, 2 patients in the BMS group underwent CABG. The incidence of in-hospital myocardial infarction was 8% vs 5.9%, respectively, with no hospital deaths. However, at the 6-month clinical follow-up, the incidence of cumulative main adverse coronary events (MACE) was 24.7% vs 42.1%, in the DES and BMS groups, respectively, \( P=0.03 \). Six-month mortality was 14.1% and 3.5% in the BMS and DES groups, respectively. In a similar retrospective study, Valgimigli et al\(^9\) reported on 182 LMS disease patients treated by BMS (n=86) and DES (n=96). In-hospital mortality was 7% and 11% and MACE rate was 19% and 15% in the BMS and DES groups, respectively. By 18 months post treatment, mortality was 16% and 14% and the rate of MACE was 45% and 24% in the BMS and DES groups, respectively. Rightly, these authors concluded that DES are superior to BMS in reducing MACE, but not 18-month mortality. Until new evidence is provided by randomized controlled trials (RCT) directly comparing the surgical and percutaneous approaches, CABG should remain the preferred revascularization treatment in good surgical candidates with left main coronary artery (LMCA) disease.\(^9\)

### The Biological Rationale for Employing the Surgeon

There are strong indications in the literature that the deployment of coronary stents is associated with endothelial injury, local and systemic inflammatory responses, and myocardial injury.

Endothelial injury triggers an acute inflammatory response (neutrophil recruitment, followed by macrophage accumulation) within 0 to 3 days.\(^31\) By 2 to 4 weeks, acute inflammation subsides and is replaced by chronic inflammatory cells, along with proliferating smooth muscle cells associated with organizing thrombus and a thin provisional extracellular matrix. Beyond 30 days, fibrin and chronic inflammation persist, and smooth muscle cells and extracellular matrix further enrich the expanding neointima.\(^32\) The initial inflammatory reaction is more accentuated at the points of greatest strain of the stent on the endothelium.\(^33\) Inflammatory and proliferative reactions also extend from the injured vessel throughout the surrounding tissues, including adjacent myocardium.\(^34,35\)

Navarro-Lopez et al\(^36\) demonstrated that at 6 months follow-up patients with stent restenosis presented marked inflammatory activity expressed by a rise in the cytokotic T lymphocytes CD3+/CD56+ and activated monocytes CD11b. Plasma concentrations of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-\(\alpha\)) increased significantly after the intervention, and TNF-\(\alpha\) concentrations remained high at 6 months.\(^36\) PCI with stent results in leukocyte and platelet activation and increases the expression of adhesion molecules, and formation of platelet-leukocyte complexes.\(^37\) Although significant stent restenosis occurs in about one third of patients with BMS, varied grades of restenosis are observed in all stented arteries.\(^38\)

Endothelial damage is a major cause of postangioplasty restenosis.\(^31\) The harm to endothelial function affects the availability of vasculoprotective molecules such as nitric oxide (NO) and prostacyclin as well as antioxidant systems, with a concomitant increment in the production of growth-promoting substances.\(^39\) Stenting seems to enhance endothelial dysfunction more than balloon angioplasty,\(^40\) to inhibit synthesis of vasodilatory mediators (particularly NO),\(^41\) and to increase the release of endothelin-1, a potent vasoconstrictor.\(^42,43\) Stents are usually deployed in the area of the so-called culprit lesion, which is generally the area of most intense inflammation.\(^44\) It has been suggested that stent deployment acts in synergy with the atherosclerotic plaque and the ongoing inflammatory response.\(^45\)

Periprocedural PCI myocardial injury may play an important role in the cascade of inflammatory events. The incidence of troponin I release is higher in patients undergoing stent implantation than in those treated by angioplasty alone.\(^46\) Release of cardiac troponin I after PCI has been reported in roughly 50% of stented patients.\(^46,47\) The emergence of DES has introduced a further variable interacting with the arterial wall. Despite the antiproliferative effect of sirolimus (rapamycin) resulting in reduction of restenosis, the inflammatory response seems to be aggravated at the stent extremities (edge effect).\(^48\) Sirolimus delays endothelialization,\(^48\) increases the effect of some platelet agonists, and thus may promote thrombus formation.\(^49\) In addition, it decreases NO production,\(^50\) which plays a significant role in promoting vasodilation and preventing platelet aggregation. These effects may explain the similar late stent thrombosis rates in BMS and DES. In clinical trials, the cumulative incidence of DES thrombosis at 9 to 12 months ranged from 0.4% to 0.6%, depending on the type of DES. By contrast, new findings suggest that this rate is at least twice as high, about 1.3%, in the real world. On multivariate analysis, premature discontinuation of antiplatelet therapy, renal failure, bifurcation lesions, diabetes, and lower...
ejection fraction were identified as predictors of stent thrombosis. The observed mortality among these patients was 45%.

One of the limitations of PCI with stent is that it is used to treat the culprit lesion only. This is particularly the case in patients with multiple vulnerable plaques. An intravascular ultrasound study by Rioufol and coworkers found that 79% of the patients presenting with acute coronary syndrome had multiple ruptured plaques at sites other than the culprit lesion that caused the clinical symptoms. Only 37.5% of plaque ruptures were on the culprit lesion.

Ruptured plaques appear to develop within the nonstenotic reference segments, away from the culprit lesion and therefore remote from the site of stent deployment.

CONCLUDING REMARKS

When deciding "what, who, when, and why" in the race between CABG and PCI, critical, objective, and genuine scrutiny of the available evidence is of key importance. The UK National Health Service Health Technology Assessment Programme (NHSHTAP) has already carried out this exercise in a systematic review. They demonstrated that in MDC patients from 18 months post treatment onward, CABG is progressively more beneficial, with an accumulated extension of life of 6 months by the 10th year. An economic model was created for a low-risk patient with two-vessel disease corrected for bias including delay in treatment. This demonstrated that CABG had cost-effectiveness in simple two-vessel disease of £52 411 compared with DES, and this marked saving was to be much larger in subsequent years. When this modelling was applied to high-risk MVD patients, including poor ejection fraction, three-vessel disease, diabetes mellitus, etc, CABG was much more cost-effective. The conclusion of this systematic review was as follows:

In the case of multiple-vessel disease the accumulated trial evidence comparing CABG with PTCA with bare metal stents is sufficient to project over 5 years an important and substantial survival advantage for CABG. Given that CABG is the standard therapy for most patients with multiple-vessel disease, it is difficult to justify substitution by a less effective treatment simply on the grounds that it is cheaper. This argument remains valid also in the case of DES, since the apparent additional benefits from fewer interventions and consequent quality of life gains are balanced by the extra costs of the new stents. Hence we find no grounds for the substitution of CABG by DES in multiple-vessel disease. Indeed we find that higher-risk individuals gain greater relative benefit from CABG, not less.

The ideal way of answering these questions is through the multidisciplinary exchange between cardiologists, surgeons, radiologists, etc, where the available evidence is critically scrutinized and applied, without misinterpretation, pulling, and/or stretching. Ultimately, the patient should be informed fully on all aspects of the available procedures and all related early and long-term implications. His opinion could then be valued appropriately. Is this dreaming? At present, the decision of what to do, and therefore also of when and why, is entirely up to the cardiologist—the "gatekeeper." The surgeon has very little say in this life expectancy-affecting decision-making process. The patient is provided with one-sided, biased information, and therefore his consent cannot be considered genuine. Is this ethical?

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When and why should we employ the interventional cardiologist?

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Interventional cardiology has undergone a major growth in the past decade from adjunctive therapy for revascularization of selected patients to being the crux of treatment of coronary artery disease.

In many respects, percutaneous coronary interventions (PCI) today are the keystone of management of coronary artery disease, not only because these interventions have become more effective and safe, but also because decisions regarding their use now govern almost all aspects of cardiac care, upstream and downstream of the procedure, from the type of hospital patients should be admitted to, to the type of antithrombotic therapy that should be used before, during, and after the procedure, and the duration of antiplatelet therapy.

WHY SHOULD WE EMPLOY THE INTERVENTIONAL CARDIOLOGIST?

Interventional cardiology has now “come of age,” with increasing procedural success, safety, and durability of its results. With the advent of stents, improvements in adjunctive antithrombotic therapy, and, lately, the availability of drug-eluting stents to tackle the problem of restenosis, it is now possible to provide effective and reliable relief of anginal symptoms and myocardial ischemia.

Percutaneous coronary intervention (PCI) represents a “success story” of modern cardiology. In the wake of its enormous growth, large-scale registries and trials have established that PCI is effective in relieving ischemia and symptoms, safe, and “comfortable.” Its best indications are the severe forms of ischemia, in particular high-risk acute coronary syndromes and stable angina pectoris with severe ischemia. Its efficacy is highly dependent on the skill of the interventional clinician and the center’s experience, both in terms of the technical requirements of the procedure itself, as well as of the highly sophisticated adjunctive antithrombotic therapies used before, during, and after the procedure. However, this success should not detract from the need for careful selection of indications and assessment of outcomes.

Keywords: acute coronary syndrome; angina-pectoris; outcomes research; primary angioplasty; reperfusion

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SELECTED ABBREVIATIONS AND ACRONYMS

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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>ENACT</td>
<td>European Network for Acute Coronary Treatment</td>
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<td>FRISC II</td>
<td>Fragmin and/or Revascularization during InStability in Coronary artery disease-II</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<td>NSTEMI</td>
<td>non-ST-segment–elevation myocardial infarction</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>PRAIS-UK</td>
<td>Prospective Registry of Acute Ischaemic Syndromes in the UK</td>
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<td>PTCA</td>
<td>percutaneous transluminal coronary angioplasty</td>
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<td>REPLACE-2</td>
<td>Randomized Evaluation in PCI Linking Angioplast to Reduced Clinical Events–2</td>
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<td>RITA-2</td>
<td>Second Randomized Intervention Treatment of Angina</td>
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<td>STEMI</td>
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<td>TACTICS–TIMI 18</td>
<td>Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival–Thrombolysis in Myocardial Infarction–18</td>
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and protection from acute coronary syndromes (ACS), using a simple percutaneous technique, under local anesthesia, often in an ambulatory setting, and with a low risk of complications. This success largely accounts for the expanding use of PCI. It is estimated that more than 1 million PCI procedures were performed in the United States in 2004.

**PCI is effective**

Stent-based PCI has proven remarkably effective in relieving myocardial ischemia and anginal symptoms, with postprocedural success rates exceeding 95%. Assessing its long-term efficacy is more difficult because outcomes vary with definitions and methods of assessment, few long-term studies are available, and outcomes appear to improve steadily with the improvement of techniques. The second Randomized Intervention Treatment for Angina (RITA-2) clinical trial compared medical therapy and percutaneous transluminal coronary angioplasty (PTCA) in 1018 patients considered suitable for either treatment option. Long-term outcomes from that trial indicated that both strategies were equally effective in preventing major cardiac events (such as death or myocardial infarction, which occurred in 14.5% vs 12.3% of the patients in the PTCA and medical arms, respectively, P=0.21).\(^1\) Reinterventions for additional restenosis were required in 27.2% of the patients in the PTCA arm vs 35.4% in the medical arm. An initial policy of PTCA was more effective than medical therapy in relieving anginal symptoms and improving exercise times, although the difference tended to narrow over time (after 5 years, the prevalence of grade 2 or worse angina was 19.0% in the PTCA group compared with 21.4% in the medical group, P=0.011). Patients in the PTCA group also had to use less antianginal medications than patients in the medical arm, even at long-term follow-up. Up to the late 1990s, the main limitation of interventional cardiology was restenosis, which occurred in roughly 30% of patients treated by balloon angioplasty and approximately 15% of patients fitted with stents, although it is important to stress that the frequency of restenosis is highly dependent on the definition used.\(^2\) It is probably clinically relevant to use the need for new target lesion revascularization as an indicator of clinically meaningful restenosis (although even this criterion will be influenced by the rate of repeat angiography within 6 to 9 months of the procedure). Based on this criterion, approximately 5% to 15% of patients undergoing stenting require further revascularization of the target lesion, usually within 6 months of the initial procedure. The durability of PCI results has been tremendously improved by the advent of drug-eluting stents.\(^3,4\) Clearly, restenosis rates are now below the 5% mark with drug-eluting stents, although this may be partially offset by the requirement for protracted dual antiplatelet therapy with aspirin and clopidogrel to avoid subacute or late thrombosis of drug-eluting stents, which may occur beyond the traditional 1-month time window that had been observed with bare metal stents.\(^4\)

**PCI is safe**

In-hospital mortality rates after PCI vary according to the indications, from virtually 0% in young patients undergoing elective PCI for single-vessel disease to very high rates (as high as 70%) in patients undergoing emergency PCI for cardiogenic shock in the setting of acute myocardial infarction. Overall, they have remained fairly stable over time because improvements in procedure outcomes were offset by the expansion of indications to patients at increasingly baseline risk. In the Dynamic Registry collected by the National Heart, Lung, and Blood Institute (NHLBI) in 1997-98, mortality was 1.9%.\(^5\) Although it is likely that mortality rates in the current era are somewhat lower, few large-scale data are available so far. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, mortality was 0.3%. The rate of Q-wave periprocedural myocardial infarction is nowadays in the range of 1%.\(^6\) The frequency of non-Q-wave myocardial infarctions after PCI is very dependent on the definition used. When a threshold of more than three times the upper limit of normal of CK-MB is used, periprocedural myocardial infarction is found to occur in approximately 8% of elective procedures. There is considerable debate as to the significance of asymptomatic rises in biochemical markers after “angiographically successful” procedures, although larger studies tend to indicate a stepwise increase in long-term mortality with stepwise increases in rises in markers.\(^7\) Other complications include coronary perforation or rupture. However, although such complications are severe, they are exceptional.

Bleeding is a more frequent complication, which is favored by the use of “cocktails” of adjunctive antithrombotic therapies, including antithrombin and antiplatelet drugs. Bleeding most frequently occurs at the access site (roughly half of all bleeds), but may also be gastrointestinal, genitourinary, retroperitoneal, or related to cardiac surgery in patients who require it. In the REPLACE-2 study of elective or urgent percutaneous intervention (a large-scale study using contemporary antithrombotic therapy), major bleeding rates ranged from 2.4% to 4.1% (lower if Thrombolysis In Myocardial Infarc-
WHEN SHOULD WE USE THE INTERVENTIONAL CARDIOLOGIST?

Several observations should be made when debating the optimal indications for interventional cardiology: first, as with any highly technical and sophisticated procedure, “practice makes perfect” and there tends to be a strong relationship between volume and experience on the one hand and outcomes on the other, regarding both the interventional cardiologist and the institution in which the procedures are being performed. Although the actual statistical demonstration of this observation is not entirely consistent and may be in part confounded by a variety of factors, it is my personal opinion that it is wise to use an experienced interventional cardiologist from a high-volume institution.

Another important topic is that interventional cardiology nowadays involves an array of sophisticated adju nctive therapies, chiefly anticoagulant and antiplatelet therapy. The ideal indications, dosage, duration, and monitoring of these treatments is complex and requires detailed knowledge. Yet, these treatments are essential to the outcome of interventions, firstly because their absence may lead to catastrophic thrombotic events, but also because their use may be linked to bleeding, a frequent and potentially severe complication of interventions. Therefore, proficiency in the use of antithrombotic therapies, and particularly their dosage and the management of their complications, is essential for the interventional cardiologist.

Acute coronary syndromes

Acute ST-segment–elevation myocardial infarction

In the setting of acute ST-segment–elevation myocardial infarction (STEMI), randomized clinical trials have consistently demonstrated that emergency primary PCI is the most effective and safest method for recanalizing the infarct-related artery and that its use is associated with the lowest mortality and morbidity. There are, however, two important factors that are a key to good outcomes in this setting:

- Timely implementation of primary PCI. It is especially important for patients to be treated within the first 2 to 3 hours after symptom onset, as recanalization of the infarct-related artery beyond this time window will adversely impact infarct size and survival. Ultimately, for patients diagnosed within the first 2 to 3 hours after symptom onset who cannot have access to a catheterization laboratory within 90 min, immediate implementation of thrombolysis may be preferable to delayed primary PCI and may in fact not necessarily contraindicate subsequent PCI (the so-called facilitated PCI strategy).

- Proficiency of the interventionalist and interventional cardiology team, as a higher volume of STEMI and primary PCI is associated with improved outcomes.

Provided these two requirements are met, primary PCI is widely recommended as the state-of-the-art therapy for acute STEMI. However, real-life data from registries have not confirmed the clear superiority of primary PCI over intravenous thrombolysis, and this appears to be largely related to the longer delays for implementation of primary PCI compared with the ideal setting of trials (Figures 1 and 2).

Non-ST-segment–elevation acute coronary syndromes

The use of PCI in ACS has been evaluated in several randomized clinical trials. The most recent trials (frag-
min and/or Revascularization during InStability in Coronary artery disease [FRISC II]; Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival–Thrombolysis in Myocardial Infarction–18 [TACTICS–TIMI 18], and RITA-3) were consistent in their findings that a strategy of early revascularization was superior to an initially conservative strategy. However, the magnitude of the benefit was variable across trials and hinged in a large part on the definitions used for periprocedural acute myocardial infarctions. Analyses consistently showed that the benefit of early invasive strategy was greatest in patients at highest risk and nil in those at low risk. Therefore, both European and US guidelines recommend the use of early angiography with a view to revascularization in high-risk patients. However, there are very wide variations in the use of interventions in non-ST-segment–elevation myocardial infarction (NSTEMI) and the optimal rate of usage of revascularization is still debated. Interestingly, some data suggest that gender differences may exist and that the benefit of an interventional strategy may be greater in men than in women.

Stable angina: the elective indication

Several studies have compared PCI with either medical therapy or surgical revascularization and have found that PCI is an effective and valuable method of revascularization. Patients with objective demonstration of large ischemia and clear and severe symptoms are the most likely to benefit from revascularization. Compared with surgery, contemporary PCI (using stents) appears to provide similar symptom relief and survival, albeit at the expense of more frequent repeat procedures, largely related to restenosis. The interpretation of these findings should, however, not be that PCI is superior to surgical revascularization, since survival is similar and PCI is “simpler”: as recently highlighted, most trials have been carried out in patients with single- and two-vessel disease, are of relatively modest size, and have limited follow-up.

The long-term effectiveness of PCI for complex multivessel disease compared with surgery remains still somewhat uncertain. In the drug-eluting stent era, it is likely that the rate of late reinterventions will
When and why should we employ the interventional cardiologist? - Steg

dwindle, but formal comparisons between PCI using drug-eluting stents and surgical revascularization is only starting in two studies (SYNTAX and Future Revascularization Evaluation in Diabetes Optimal Management with surgery versus drug-eluting stents [FREEDOM]). In the interim, there is general agreement that there are at least two patient subsets in which surgery should remain the default strategy and PCI should be used parsimoniously, because surgery is still the established strategy for management: diabetics with multivessel disease and patients with left main coronary artery stenosis.

ARE WE AFFLICTED WITH “INTERVENTIONAL FRENZY?” THE EXAMPLE OF PCI IN ACUTE CORONARY SYNDROMES

The tremendous growth in the use of interventional procedures in the past years has several explanations: refinements in imaging and technical aspects of the procedures have made them simpler, shorter, more effective, less risky and uncomfortable for the patients. Examples of such improvements are the increasing use of the radial approach, which allows early ambulation and reduces bleeding complications, the use of ever-decreasing doses of antithrombin therapy and smaller bore catheters to reduce bleeding and discomfort, the use of direct stenting to minimize trauma to the vessel, procedure duration, restenosis rates, and costs, improvements in contrast media type and use, and in the preparation of the patients. Yet, these procedural and periprocedural improvements of PCI are not the sole reason why interventional cardiology has experienced such a phenomenal growth. It is important to recognize other and less pleasant aspects that have played a role in the growth of PCI. Among these, one can list the desire to use “expensive and new” interventional equipment in hospitals, the need to achieve targeted hospital and operator yearly volumes to maintain proficiency and achieve quality goals, self-selection of indications for revascularization by interventional cardiologists, the financial incentives related to the use of fee-for-service, and, finally, a factor that exists in all fields of life and to which cardiology is not immune: fashion. The case of the use of PCI in the management of patients with ACS is particularly telling. Clinical guidelines on both sides of the Atlantic recommend high-risk patients with ACS as the best target for PCI, yet there is strong evidence from observational registries that PCI is not targeted at these patients at all.

The Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) collected simple information regarding major determinants of risk such as age and ECG abnormalities in ACS patients. In the same registry, the use of PCI was examined as a function of these factors. The results of this analysis (Figure 3 A and B) are particularly striking: the use of PCI is not related to increasing risk characteristics, in fact, PCI was more frequently used in younger, lower-risk patients, implying that the current selection process for interventional cardiology is geared towards patients in whom PCI will provide good results rather than patients who will actually benefit from PCI.

Figure 3. (A) Six-month risk of death or myocardial infarction stratified by age and baseline ECG in the PRAIS-UK Registry. (B) Six-month angiography rates according to the same stratification. There is an almost inverse correlation between risk and use of angiography.

Abbreviations: BBB, bundle-branch block; MI, myocardial infarction; PRAIS-UK, Prospective Registry of Acute Ischaemic Syndromes in the UK.

Other evidence comes from the European Network for Acute Coronary Treatment (ENACT) study performed in 1999-2000, which reported major international variations in the use of PCI in ACS patients. However, use of PCI was not found to correlate with risk markers. One of the strongest correlates was the national rate of use of PCI according to country: patients in “interventional” countries such as France or Germany were 4 to 5 times more likely to undergo PCI compared to similar patients from “noninterventional” countries such as the UK, Scandinavia, Italy, or Greece. Interestingly, hospital outcomes were no better in “interventional” compared with noninterventional countries. More recently, a similar analysis was performed in ACS patients participating in the international Global Registry of Acute Coronary Events (GRACE). This analysis found that, across the whole spectrum of ACS, one of the most important determinants of the use of PCI in ACS was the availability of a catheterization laboratory in the hospital. patients in hospitals with a catheterization laboratory were 8 to 10 times more likely to undergo PCI than patients from hospitals not equipped with interventional facilities. Again, in this analysis, patients treated in interventional hospitals fared no better, but in fact worse (at hospital discharge) compared with patients admitted and treated in hospitals without interventional facilities.

These data are not presented to imply that PCI is not an effective therapy for the management of ACS patients, nor are they intended to show that conservative management of ACS patients is superior to the routine use of revascularization. Rather, they underline the need for a concerted effort to improve risk stratification and selection of indications in order to concentrate the efforts, risks, and costs of revascularization on those patients who are most likely to benefit (ie, high-risk patients).

**CONCLUSION**

PCI is today usually a safe, simple, and very effective procedure to revascularize the ischemic myocardium in coronary artery disease. The incremental advances in technique and adjunctive pharmacotherapy observed in the last 15 years are largely responsible for this success. However, interventional cardiologists need to devote more efforts to quality control of the interventions as well as to careful outcomes research. The success of PCI in coronary artery disease has sparked enormous interest in spreading the applications of PCI to many other fields in cardiology, such as stenotic and regurgitant valvular disease, hypertrophic cardiomyopathy, congenital heart disease, and even prevention of arterial thromboembolism. The future of cardiology is largely interventional!

**REFERENCES**


When and why should we employ the pharmacologist?

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The need for coronary revascularization, whether emergency or elective, arises to a large extent from the limitations of currently available pharmacotherapy. This review addresses the roles for drug therapy in patients with stable angina and acute coronary syndromes (the latter including acute ST-segment–elevation myocardial infarction [STEMI]; thrombolysis vs percutaneous coronary intervention [PCI]; and unstable angina pectoris [UAP] and non–Q-wave myocardial infarction [NQAMI]; antiaggregatory agents / anticoagulants / antianginals). Special consideration is given to therapies for severe or refractory angina (PCI vs traditional antianginals vs the newer metabolic anti-ischemic agents) as well as to the need to improve pharmacotherapy in conjunction with high-risk coronary angioplasty/stenting procedures to minimize early or late failure of these interventions.

**Keywords:** stable angina; ST-segment–elevation myocardial infarction; non-Q-wave coronary acute myocardial infarction; coronary artery disease; acute coronary syndrome; refractory angina; revascularization; pharmacotherapy; thrombolysis; antiplatelet therapy; anticoagulant therapy; anti-anginal therapy; ACE inhibitor; statin; metabolic agent

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**SELECTED ABBREVIATIONS AND ACRONYMS**

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<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
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<td>ESSENCE</td>
<td>Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events</td>
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<td>GISSI-I</td>
<td>Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico</td>
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<tr>
<td>IRA</td>
<td>Infarct-related artery</td>
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<td>ISIS-2</td>
<td>Second International Study of Infarct Survival</td>
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<tr>
<td>NQAMI</td>
<td>Non–Q-wave acute myocardial infarction</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>STEMI</td>
<td>ST-segment–elevation myocardial infarction</td>
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<td>UAP</td>
<td>Unstable angina pectoris</td>
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Revascularization of ischemic myocardium represents the critical management decision for both patients with acute and chronic myocardial ischemia. In many circumstances, mechanical or surgical revascularization is seen as an alternative to pharmacotherapy, and indeed as rather a more attractive alternative from a number of fundamental points of view.

First and foremost, restoration of “normal” coronary perfusion has psychological connotations, both to patient and practitioner: it more closely approximates to a “cure,” despite evidence to the contrary (“if I were an ischemic myocardial cell, and someone offered me drugs or blood, I think I would take blood” [W. Paulus, 1992]). Secondly, there is a scientifically based perception that is increasingly widespread, that pharmacotherapy for the clinical spectrum of myocardial ischemic syndromes is often ineffective compared with mechanical intervention. Finally, the concept that pharmacotherapy is critical to the success of mechanical intervention is often given insufficient emphasis.

The need for myocardial revascularization in acute or chronic ischemic syndromes could theoretically be based upon symptomatic efficacy and/or on prognostic considerations. From a cost-effectiveness point of view, it must be recognized that in most Western European countries, the United States, and Australia, there has been a considerable decline in age-adjusted incidence of symptomatic myocardial ischemia and in coronary disease-related mortality for approximately the last 30 years. However, the prevalence of symptomatic coronary disease in these communities has not fallen, and neither has the incidence of disease on a whole-of-life basis. Thus, there is an increasing probability that patients with symptomatic myocardial ischemia will have had prior ischemic “crises,” be elderly,
and have multiple extracardiac medical problems that may compromise the safety both of pharmacotherapy and of mechanical interventions, and may also mean that the potential prognostic advantages of interventions are less important than their benefits from a symptomatic/quality-of-life point of view.

Two other emerging considerations are of great importance here. First, coronary artery disease incidence and mortality exhibit marked socioeconomic gradients in most Western societies, and the increasing incidence of mortality through acute coronary syndromes in eastern Europe and many parts of Asia potentially will also exhibit a similar socioeconomic gradient, although this is not as clearly established. Secondly, the increasing importance of myocardial ischemia as a process superimposed, whether acutely or chronically, on prior myocardial damage, complicates the management of ischemia: for example, it is necessary for decisions regarding potential mechanical revascularization and/or pharmacotherapy to take into account concomitant processes, such as hypertensive heart disease, with left ventricular hypertrophy and associated diastolic dysfunction, or prior myocardial infarction with associated impairment of systolic dysfunction. Hence, the management chosen must both be affordable by the patient and beneficial in the context of possible prior myocardial injury.

Some major roles of the pharmacologist in decision-making in patients with acute and chronic myocardial ischemia are summarized in Table 1. This review will therefore address pharmacotherapy both as an alternative to mechanical intervention, as adjunctive therapy before, during, or after surgery or percutaneous coronary revascularization, and as primary therapy in patients in whom mechanical revascularization is impracticable.

**MEDICAL THERAPY IN ACUTE AND CHRONIC MYOCARDIAL ISCHEMIA: CURRENT STATUS**

The role of medical therapy as primary modality of treatment varies considerably with the specific coronary syndrome, as well as with the precise patient group. Acute ST-segment–elevation myocardial infarction (STEMI), unstable angina pectoris (UAP)/non-Q-wave myocardial infarction (NQAMI), and stable angina pectoris will be considered separately, as they represent considerably differing therapeutic challenges.

**Acute ST-segment–elevation myocardial infarction: how bad is thrombolysis?**

The development of effective regimens for intravenous thrombolysis utilizing streptokinase, beginning about 25 years ago, revolutionized the management of acute STEMI. The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI-1)² and Second International Study of Infarct Survival (ISIS-2)³ studies, in particular, demonstrated that streptokinase is considerably more effective than placebo in reducing short-term mortality in patients presenting within the first 12 hours after onset of symptoms. Furthermore, the ISIS-2 study demonstrated that concomitant therapy with low-dose aspirin was associated with further reductions in 35-day mortality (although the precise interaction between aspirin and thrombolytic therapy has never been explored adequately).

Thrombolytic therapy with streptokinase and aspirin was cheap and could be utilized in the majority of patients with STEMI. However, it was clear that there was an appreciable risk of development of hemorrhagic complications in some patient subgroups. Specifically, thrombolysis was contraindicated in patients with...
potentially active major bleeding sites (eg, recent surgery, active peptic ulceration). Furthermore, the risk of intracerebral hemorrhage, a potentially disastrous complication of thrombolysis, increased markedly with systolic blood pressure and (presumably in part for the same reason) with patients’ ages. This is increasingly problematic with recent trends for aging of patient groups presenting with acute STEMI.

There were also obvious concerns from the start as regards the efficacy of thrombolysis in reducing infarct size. Essentially, these reflected data that suggested that only in about 40% to 50% of patients treated with streptokinase, was there full restoration of patency in the infarct-related artery (IRA) within 90 minutes of inception of therapy, and that the probability of achieving full IRA patency with thrombolysis decreased markedly as duration of ischemia increased. For example, in many patients, post-thrombolytic angiography suggested occurrence of the “no-reflow” phenomenon: reduced coronary flow rate despite absence of residual IRA stenosis. Similarly, in many patients, resolution of ST-segment elevation (indicating tissue reperfusion) lagged considerably behind restoration of IRA patency.

The potential to improve efficacy of thrombolysis with streptokinase by rapid infusion of the drug was partially limited by the risk of hypotensive reactions. A number of alternative thrombolytic agents were developed, with emphasis on lower antigenicity and greater ease of administration. However, it is likely that none of these agents has more than marginal advantages over streptokinase with regard to effects on mortality of acute STEMI, while there may be an associated increase in risk of hemorrhagic complications. A number of studies have now compared efficacy of thrombolytic therapy and that of primary angioplasty ± stenting in STEMI. In general, results suggest that mortality is somewhat lower in patients treated with percutaneous coronary interventions (PCI). However, this difference in outcomes tends to reflect superiority of PCI in patients treated beyond the first 1 to 2 hours post onset of STEMI. Indeed, results of thrombolysis in the first hour post onset of symptoms are generally remarkably good. Given the lack of access to PCI for some patients in rural areas, and the doubts about benefit vs risk of thrombolysis in some elderly patients, we may arrive at a schema for preferred reperfusion strategies as outlined in Table II. It should particularly be noted that PCI provides the optimal therapeutic modality for patients with pulmonary edema or cardiogenic shock associated with STEMI.

The UAP/NQAMI continuum: suppression of ischemia as an end point

Probably no central area of cardiology currently is the subject of as much controversy as the case for routine vs selective revascularization therapy for patients presenting with threatened myocardial infarction, but in whom at the time of hospital admission there is minor, or no, myocardial necrosis. It is clear that in the majority of such patients there is a risk of ongoing ischemia and/or recurrent myocardial infarction, essentially based upon the precipitation of acute ischemia by platelet aggregation, thrombus formation, and coronary vasoconstriction superimposed upon rupture or fissure of an atheromatous plaque.

However, the 1-year mortality rate in most series is less than 3%, and therefore the primary aims of treatment are the suppression of ischemia and reduction of risk of further infarction.

Optimal pharmacotherapy in patients with UAP or NQAMI remains extremely controversial. Indeed, the...
The definition of NQAMI has recently been broadened to include all cases where there is transient release of cardiac-specific biomarkers (whether troponins or creatine kinase), but this definition has not been applied rigorously in all studies involving PCI, on the (probably mistaken) grounds that the “infarctlets” induced by PCI procedures are relatively harmless.

The range of pharmacological agents commonly postulated to be of potential therapeutic value in the treatment of UAP/NQAMI is summarized in Table III. While the majority of patients received immediate treatment that includes antiaggregatory, anticoagulant, and antimicrobial drugs, the precise value of individual treatment components and their additive/synergistic impact remains controversial.

While it is generally agreed that low-dose (50-150 mg/day) aspirin is likely to be useful in such patients, relevant clinical trial data in the context of background modern pharmacotherapy with angiotensin-converting enzyme (ACE) inhibitors and statins are somewhat fragmentary. Furthermore, if aspirin is to be prescribed routinely, it is unclear which medically treated patients are most likely to benefit from short-term treatment with additional antiaggregatory therapy, for example with ADP receptor antagonists (eg clopidogrel) or in the short term, with intravenously infused glycoprotein IIb/IIIa inhibitors. The lack of convenient methods for monitoring of extent of inhibition of platelet aggregation in individual cases, together with widely variable responsiveness to all these agents, makes the choice of treatment difficult. However, it is likely that, in the context of multiple pharmacotherapy, there is little advantage in combining aspirin with other antiaggregatory agents for routine therapy (as distinct from patients with ongoing ischemia, or patients undergoing stent insertion). The choice of optimal anticoagulant treatment in UAP/NQAMI also remains uncertain, as does the appropriate duration of therapy. Unfractionated heparin exerts anti-ischemic effects that vary with partial thromboplastin time, but the majority of patients treated with intravenous unfractionated heparin many series have subtherapeutic monitoring results. Therefore, while the results of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial suggest that the low-molecular-weight heparin enoxaparin is more effective than unfractionated heparin in the management of patients with UAP/NQAMI, it is not clear to what extent this difference may result from suboptimal algorithms for achievement of therapeutic effects in the case of unfractionated heparin.

As regards the utility of antianginal agents in this group of patients, it has generally been considered in the past that β-adrenergic antagonists may improve outcomes. Despite their known effectiveness in improving long-term outcomes after (substantial) myocardial infarction, there is little evidence that β-adrenergic antagonists reduce frequency of angina or prevent (re-)infarction. The negative findings of available studies in UAP/NQAMI, combined with recent evidence of increased risk of cardiogenic shock with β-adrenergic agents in STEMI should prompt a reexamination of their therapeutic roles in this context.

Nitrate therapy in UAP/NQAMI also remains problematic because of recent findings that (i) many patients are relatively unresponsive to nitrates, a phenomenon termed nitric oxide resistance, (ii) progressive attenuation of nitrate effects (nitrate tolerance) develops within 24 hours of continuous low-dose infusion of nitroglycerin, resulting from progressive impairment of nitrate bioconversion to release nitric oxide. To date, no completely effective therapy to circumvent these two problems has been developed, although considerable progress is now being made.

As regards the L-channel (nondihydropyridine) calcium antagonists verapamil and diltiazem, there is considerable evidence that they suppress anginal symptoms, and some evidence that they reduce risk of

### Table III

<table>
<thead>
<tr>
<th>Category of agents postulated to improve short-term outcomes in patients with unstable angina pectoris/non-Q-wave acute myocardial infarction (UAP/NQAMI)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiaggregatory agents</td>
<td>Aspirin, Clopidogrel, Glycoprotein IIb/IIIa antagonists</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Unfractionated heparin, Low-molecular-weight heparins</td>
</tr>
<tr>
<td>Antianginals</td>
<td>β-Adrenergic antagonists, L-Calcium channel antagonists, Organic nitrates</td>
</tr>
</tbody>
</table>
Factors militating against further revascularization
• Previous coronary surgery ± PCI
• Lack of a single clear-cut primary ischemic zone
• Advanced age
• Extracardiac comorbidities: eg, lung disease, cerebrovascular disease, diabetes, renal insufficiency
• Impaired left ventricular systolic function (eg, due to prior myocardial infarction)

Factors limiting utilization of anti-ischemic agents
• Left ventricular systolic failure (contraindication to use of verapamil or diltiazem)
• Asthma (contraindication to use of β-adrenoceptor antagonists)

Table IV. Common clinical characteristics of “end-stage” patients with exertional angina pectoris. PCI, percutaneous coronary intervention.

When and why should we employ the pharmacologist? - Horowitz

The patient with severe/refractory angina: emerging therapeutic options

One of the central criteria for consideration of mechanical revascularization is “failure of optimal medical therapy.”

Essentially, there is considerable doubt that PCI improves survival in any subgroup of patients with stable angina pectoris, and indeed the evidence in favor of improved survival with surgery is essentially limited to patients with extensive coronary artery disease and impaired left ventricular systolic function. However, it must also be admitted that none of the three major classes of “traditional” prophylactic antianginal agents are startlingly effective in improving exercise tolerance or reducing frequency of angina in daily life. Furthermore, combined use of these agents (long-acting nitrates, β-adrenoceptor antagonists, L-channel calcium antagonists) produces little incremental effect. Therefore, it is increasingly common for patients to be revascularized relatively early “on symptomatic grounds.”

Increasingly, the problem comes later. Together with improved survival of patients with ischemic heart disease, the practitioner more and more often faces the prospect of management of angina pectoris in “end-stage” patients, with clinical characteristics similar to those outlined in Table IV. While there is a tendency to subject these patients to “desperation” PCI procedures, evidence is lacking that this form of therapy is likely to improve symptomatic status markedly.

The management of this group of patients has been facilitated by gradual improvements in understanding of the “metabolic” anti-ischemic agents: drugs that reduce the frequency of angina by improving the efficiency of myocardial oxygen utilization. In general, such agents effect a shift from predominant long chain fatty acid to carbohydrate utilization by the myocardium (for review, see reference 24), either by inhibiting the “carnitine shuttle” (whereby long-chain fatty acids traverse the myocardial membrane—eg, perhexiline, amiodarone) or by partially inhibiting intramitochondrial fatty acid metabolism (trimebutidine, ranolazine). There are considerable advantages associated with these agents, as indicated in Table V.
PHARMACOTHERAPY IN ASSOCIATION WITH EMERGENCY OR ELECTIVE REVASCULARIZATION

The process of coronary revascularization, whether surgical or via PCI, should not be considered as being completely distinct from pharmacotherapy. There are considerable challenges therapeutically both in association with the intervention procedure(s) and during follow-up, in order to minimize procedural risk (both cardiac and extracardiac) and to reduce the risk of subsequent recurrence of ischemia.

The greatest challenges therapeutically are associated with emergency/high-risk PCI, for example, in elderly patients presenting with evolving STEMI. In such patients, there are a number of major therapeutic considerations as summarized in Table VI.

However, there is evidence that optimal therapeutic activities peri-PCI should be much more extensive than this. For example, it may be possible to achieve restoration of antegrade coronary flow by methods other than prior thrombolysis, which probably carries little advantage. Furthermore, there is good evidence that rapid correction of hyperglycemia in diabetics, whether with STEMI or UAP/NQAMI, is likely to be of benefit, not only by limiting myocardial redox stress, but also by limiting platelet aggregation.

Furthermore, deterioration of renal function post PCI, largely reflecting contrast-induced nephropathy, is a concern in some fragile patients. The recent demonstration that N-acetylcysteine, which has previously been shown to limit redox stress in evolving STEMI, improves outcomes in patients undergoing primary PCI, suggests that this is an important area.

The limitation of myocardial infarct size via pharmacological cardio-protection and prevention of reperfusion injury deserves specific comment as an area where pharmacotherapy has thus far failed to deliver, despite theoretical promise. As recently summarized, this is an area of current focus for translational research.

Table VI. Therapeutic challenges associated with management of patients with evolving ST-segment-elevation myocardial infarction (STEMI), where reperfusion is to be attempted by primary percutaneous coronary intervention (PCI).

Table V. Considerations regarding the utility of anti-ischemic agents with primary effects on efficiency of myocardial oxygen utilization in the management of patients with “end-stage” angina pectoris.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of effect</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perhexiline</td>
<td>CPT inhibition</td>
<td>+++</td>
<td>Hepatitis* Peripheral neuropathy* Hypoglycemia</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>CPT&lt;sub&gt;1&lt;/sub&gt; inhibition</td>
<td>++</td>
<td>Thyroid disease Pulmonary fibrosis Photosensitization Hepatitis</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>pFAox inhibition (3-ketoacyl-CoA thiolase inhibitor)</td>
<td>+</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>pFAox inhibition</td>
<td>+</td>
<td>? QT prolongation</td>
</tr>
</tbody>
</table>

*Side-effects closely linked to plasma drug concentrations.
Post PCI, the specific focus of pharmacotherapy should be optimization of long-term patency/lumen size in the stented area. It is now clear that here are substantial potential problems with both ‘bare-metal’ and drug-eluting stents (DES); the relatively low risk of in-stent stenosis with DES is counterbalanced by increased risk of late stent thrombosis, a potentially lethal complication. A major priority for pharmacotherapy should be prevention of these complications.

A FUTURE WISH LIST FOR PHARMACOTHERAPY

A major priority of drug therapy of ischemic heart disease should be the extension of the end points of therapy beyond palliation of symptoms toward reversal of the underlying disease process. There is evidence that some currently available agents, notably statins and ACE inhibitors, achieve some of these objectives in reducing the incidence of ischemic events. We need effective agents not only to stabilize atheromatous plaques, but also to reverse endothelial dysfunction, inflammation, and lipid deposition. Emerging therapies, aimed primarily at stimulation of endothelial repair and formation of new blood vessels in ischemic zones of myocardium, may represent some of the first steps toward this appropriate goal of effective pharmacoreperfusion.

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recurring theme in the previous articles in this series has been the challenges posed to hunters of novel drugs by conflicting experimental and clinical observations as well as controversy over competing scientific hypotheses. The story of the discovery of \( \beta \)-hydroxy-\( \beta \)-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors illustrates yet again the pivotal importance of academic/industrial collaboration in cardiovascular drug discovery.\(^1\)-\(^3\) There are three interwoven themes in this article, which are: (i) mechanisms of cholesterol homeostasis; (ii) controversies over hyperlipidemia/hypercholesterolemia and atherosclerosis; and (iii) the discovery of a first HMG-CoA reductase inhibitor.

**CHOLESTEROL HOMEOSTASIS**

Cholesterol is synthesized from acetyl-CoA in a linked series of 20 enzymatic steps (Figure 1). It had been demonstrated by Schoenheimer in 1933\(^4\) that feeding cholesterol to mice reduced the endogenous production of cholesterol. This observation was confirmed 20 years later in analogous studies in rats using \(^{14}\)C-labeled acetate.\(^5\),\(^6\) These observations suggested that there was an end-product negative feedback mechanism, which had not previously been observed in mammalian systems, but was known in fungal species. Numerous studies were undertaken in the 10 years from 1955 in attempts to identify the nature of the negative feedback system, much of the work being pioneered by Siperstein’s group in the University of Texas. In a brilliant series of experiments, his group showed that the site of the negative feedback system was specifically located at the point of conversion of \( \beta \)-hydroxy-\( \beta \)-methyl glutaric acid to mevalonic acid. The physical location of the site was identified as being the membranous portion of the microsome.\(^7\),\(^8\) In the discussion section of this paper Siperstein and Fagan state: This membrane-bound \( \beta \)-hydroxy-\( \beta \)-methyl glutaryl reductase is under sensitive negative feedback control... It is primarily at this site that the feedback control of cholesterol synthesis is carried out.\(^8\)

**Figure 1.** Abbreviated illustration of the cholesterol biosynthetic pathway.

Abbreviation: HMG-CoA, \( \beta \)-hydroxy-\( \beta \)-methyl glutaryl coenzyme A.
They also remark on the existence of a similar feedback system in bacteria.

The existence of this mechanism in bacteria provided the rationale for Endo’s study of fungal metabolites as potential inhibitors of HMG-CoA reductase (vide infra). Furthermore, Goldstein and Brown in 1970 showed that in order for cholesterol to exert its negative feedback effects, it must first enter the cell as low-density lipoprotein (LDL) via a specific LDL receptor-mediated endocytosis.

# CHOLESTEROL AND ATHEROSCLEROSIS

In the current era, it is now difficult to realize that for many years controversy raged among clinical scientists as to the relative importance, if any, of elevated circulating levels of cholesterol and atherosclerotic arterial disease. The background and evolution of this controversy has been elegantly portrayed by Steinberg. The persistence of the cholesterol-atherosclerosis controversy over more than 30 years is relevant in the context of research designed to identify effective hypocholesterolemic agents, since many drug research directors in pharmaceutical companies might reasonably conclude that seeking such agents might be mis-directed or even foolhardy. The evidence available to support the case for seeking such agents is summarized in Table I. However, such considerations were refuted by eminent cardiologists, especially Mann in the USA and Oliver in the United Kingdom. The latter wrote in 1981:

> It is probably of little value to reduce raised serum cholesterol concentrations in patients with overt coronary artery disease.

The unexplained paradox is that Oliver initiated the World Health Organization multicenter study of clofibrate in hypercholesterolemic subjects in 1968, maintaining a 13-year follow-up of the trial. Despite the negative opinions about the cholesterol/atherosclerosis hypothesis of many practicing physicians and scientists, many drug research programs to find hypocholesterolemic compounds were initiated from the 1950s onwards.

## TREATMENT OF HYPERLIPIDEMIA PRIOR TO 1982/4

Between 1950 and 1980 several chemotherapeutic agents for the treatment of hyperlipidemia had been introduced (Table II). The basic approaches were either to reduce intestinal absorption of cholesterol or reduce its endogenous formation by one means or another. The desired serum cholesterol level was about 200 mg/100 mL, but none of the available agents consistently achieved this goal. This was due either to low intrinsic efficacy (plant sterols, fibrates) or dose limitation due to a dose-dependent adverse effect (nicotinic acid, D-thyroxin, neomycin, cholestyramine).

The evaluation of candidate compounds both in vitro and in vivo at that time had many shortcomings, perhaps the most important being species difference in lipoprotein physiology. It was not appreciated at that time that the rat transported cholesterol mainly in the high-density lipoprotein (HDL) fraction with very low levels of endogenous LDL. This is in marked contrast to primates and humans. Numerous approaches to inhibition of cholesterol biosynthesis somewhere along the 20 enzymatic steps were studied. It soon became clear that blocking synthesis of cholesterol beyond the HMG-CoA-mevalonate step (Figure 1) could lead to unacceptable adverse effects either in animals (SKF-7997) or man (MER-29). Several research groups demonstrated inhibition of cholesterol formation from mevalonic acid in rat liver homogenate studies, but compounds active in this test were not active in the same species in vivo. A major hurdle at this time was lack of technology to understand if inactivity in vivo was due either to poor intestinal absorption, rapid excretion/conjugation, or failure of the compound to penetrate the intact hepatic cell. Many companies appreciated the rationale for inhibiting HMG-CoA reductase, but the standard test of reducing 14C acetate incorporation in liver homogenates was not sufficiently specific to pinpoint a major effect on HMG-CoA reductase.

## DISCOVERY OF FIRST-GENERATION HMG-CoA REDUCTASE INHIBITORS

Between 1969 and 1974, at least three different research groups reported studies on small molecule inhibitors of HMG-CoA reductase. Porcellati et al. reported that β-benzyl butyric acid inhibited cholesterol biosynthesis prior to mevalonate formation, suggesting inhibition of either acetyl-CoA ligase or transferase. About the same time, Boots et al. in the Department of Chemistry, Pharmaceutical Chemistry and Biochemistry, Virginia, Commonwealth University, USA refuted Porcel-
lati’s findings showing that 3-isomers of 3-methyl-4-phenyl butenoic acid did not inhibit HMG-CoA reductase, which had been prepared by this group from bakers’ yeast. In 1973, the same group published a study of the structure function inhibitory properties of 45 arylalkyl hydrogen succinates and glutarates. One compound (5S) showed 80% to 90% inhibition of HMG-CoA reductase at 1.5 to 2.5 mM concentration. It is noteworthy that their paper was entitled “Hypocholesterolemic agents,” but it is unclear as to what happened subsequently to the active compounds.

The third group, working in the Beecham Pharmaceutical Company UK, reported the isolation and chemical characterization of a molecule isolated from Penicillium brevicompactum, which had antifungal activity. This compound was named compactin. The publication in the Journal of the Chemical Society described in considerable detail the structural characteristics of compactin, including x-ray crystallographic data relying on collaboration with the universities of Nottingham and Aberdeen. Notably, the paper contains no biological data. The research target of the Beecham scientists was to find improved agents for treating gonorrhea, but compactin was not sufficiently potent for this purpose. A compound identical in structure to compactin was also isolated from Penicillium citrinum by Endo and coworkers in the fermentation research laboratories of Sankyo Company.

Professor Akira Endo (Figure 2) joined the Sankyo Company in 1938 as a research fellow working on antifungal agents. In 1966, he was seconded to the Albert Einstein College, NY, to work on lipopolysaccharide synthase in the cell wall of bacteria. While there he learned also about the importance of high serum cholesterol in possibly causing coronary artery disease. Upon his return to Sankyo in 1968, his research target became a search for inhibitors of HMG-CoA reductase, which he started in 1971 in collaboration with Dr Kuroda.

He devised an economical 2-stage in vitro testing system of microbial culture broths. Extracts were first tested for inhibition of [14C]acetate nondetected. The HMG-CoA reductase inhibitors (statins) - Fitzgerald

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption inhibitor</td>
<td>Cholestyramine</td>
<td>Anion-exchange resins binding bile acids in gut lumen. Effective, but dose limited by GI side effects</td>
</tr>
<tr>
<td></td>
<td>Colestipol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neomycin (antibiotic)</td>
<td>Precipitates cholesterol in the GI tract. Nausea and diarrhea limit long-term treatment</td>
</tr>
<tr>
<td>Modulation of lipoprotein and cholesterol metabolism</td>
<td>d-Thyroxin</td>
<td>Reduces plasma cholesterol by about 20%. May induce angina pectoris in coronary artery disease patients, tachyphylaxis observed on prolonged exposure.</td>
</tr>
<tr>
<td></td>
<td>Triparanol (MER-29)</td>
<td>Blocks conversion of desmosterol to cholesterol. Serious adverse effects on long-term exposure, so drug was withdrawn</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
<td>PPARx agonists that stimulate reverse cholesterol transport and reduce TG by inhibiting DGAT, but lack potent effects in reducing LDL</td>
</tr>
<tr>
<td></td>
<td>Niacin (nicotinic acid)</td>
<td>Decreases hepatic uptake of APO-AI and reduces adipose tissue lipolysis. Flushing and occasional hepatotoxicity may limit exposure, but it has proven beneficial effects in atherosclerosis</td>
</tr>
</tbody>
</table>

**Table II.**

Hypolipidemic drugs available in the 1970s.

**Abbreviations:**

- APO-AI, apolipoprotein-AI
- DGAT, diacylglycerol acyltransferase
- GI, gastrointestinal
- LDL, low-density lipoprotein
- PPARx, peroxisome proliferator activated receptor α
- TG, triglycerides

**Figure 2.** Professor Akira Endo, BA, PhD. 1957-1978: Research Fellow, then Senior Research Fellow, Sankyo Co Lt. Tokyo, Japan, 1979-1997: Associate Professor and then Full Professor, Tokyo University of Agriculture & Technology, 1997-present: Director, Biopharm Research Laboratories Inc, Tokyo. © The Science and Technology Foundation of Japan.
saponifiable lipids. Broth extracts were then tested for inhibition of lipid synthesis from [1H]mevalonate. In a subsequent paper, he commented that the preferred test of measuring the incorporation of radioactivity from [14C]HMG-CoA into mevalonate was too expensive to use for studying thousands of broth samples. Over 6000 broth extracts were tested for their effects on lipid and synthesis. The first active inhibitor, citrinin, which they identified, was isolated from the Pythium ultimum mold. It irreversibly inhibited HMG-CoA reductase. Its metabolite, mevastatin was the identical compound isolated by the Beecham Group, which they had named compactin and was a very potent (K_i: 1x10^-9) reversible inhibitor (Figure 3).

In acute studies in rats, mevastatin (20 mg/kg) reduced plasma cholesterol by 30%, but prolonged dosing did not consistently reduce plasma cholesterol. Also, mevastatin was ineffective in mice. Numerous analogs also failed to work on rodents.29 Pilot studies in chickens showed a 50% reduction in plasma cholesterol and, subsequently, consistent hypocholesterolemic effects were seen in dogs and monkeys (Figure 4).30 During the same period, the Beecham Group, now led by Fears, also studied the effects of their compactin on serum cholesterol in rats and chickens. In their discussion they concluded:

What is clear, however, is that direct inhibition of HMG-CoA reductase is futile as a means of reducing cholesterogenesis, if it is not accompanied by a repression of new enzyme synthesis, as is claimed for regulation of cholesterol itself.

HURDLES AND COINCIDENCES

Common characteristics of successful drug hunters are both persistence in the face of failure, and a problem-solving attitude. Endo overcame the negative rodent data by studying compactin in dogs and monkeys. In monkeys, compactin (50 mg/kg) reduced plasma cholesterol by 36% with no change plasma triglyceride levels (Figure 4).30

Two apparently major problems arose in the preclinical toxicology studies. The compactin-treated rats showed deposition of cholesteryl ester crystals and, in the dog, very high doses of compactin (100 to 200 mg/kg over 12 to 24 months) appeared to cause intestinal lymphoma. During the same period, pilot clinical trials were started in Japan in patients with severe familial hypercholesterolemia (FH). The compound had only modest effects in FH homozygous patients, but in FH heterozygotes treated for 8 weeks a reduction of 22% to 28% in total cholesterol was observed with doses of 50 to 150 mg/day.32 Despite these encouraging results, the toxicological findings led to a decision by senior Sankyo management to stop the clinical development of compactin in December 1980. While these exciting studies were taking place in Japan, it happened that Brown and Goldstein, of the University of Texas, chose to study the molecular mechanism of defects in patients with FH by examining the effects on cholesterol synthesis of adding cholesterol to cultured human fibroblasts. They showed that FH was due to a genetic defect in cell surface receptors transporting plasma cholesterol into the cell.33 Endo referred to this publication when reviewing lipid research for a Japanese publication. By chance, Brown and Goldstein found the Japanese paper only because they subscribed to the Institute of Scientific Information (ISI) database, which they used to identify articles referring to their own work. Subsequently, they monitored for any publications by Endo and discovered his work on ML-236B (mevastatin). They asked Endo for a sample in order to examine its effects on cholesterol metabolism in their cultured human fibroblast system. They favored this compound because it was a potent reversible inhibitor with a structure resembling mevalonate. Endo, after attending a conference in the USA, visited their laboratories on
September 22, 1977. During the visit he was shown a draft paper proving that his compound not only reduced cholesterol, but stimulated HMG-CoA reductase synthesis. Since Endo had already made similar observations they published a joint paper.  

An even stranger coincidence is related by Endo in that when he sought a fellowship in the USA in December 1965, he first wrote to Professor Roy Vagelos wishing to study lipid metabolism in his laboratories. Vagelos replied rather late, offering him a post in his new laboratory in Washington School of Medicine (1966). By this time Endo had already accepted the job in the Albert Einstein University.  

Vagelos became head of research at Merck Sharp & Dohme (MSD) in 1975 where he continued studies on lipid metabolism with his colleague Dr Alberts who also moved to MSD from the University of Washington. Brown and Goldstein were consultants to MSD and sent their joint paper with Endo to Vagelos, proposing research collaboration in the clinical development of statins. They proposed that compactin (mevastatin) might become the penicillin for cholesterol! No formal collaboration was agreed, but they were retained as consultants.

Nevertheless, Alberts’ group at MSD initiated a program to discover HMG-CoA reductase inhibitors. They isolated a potent inhibitor, mevinolin, which was isolated from Aspergillus terreus. This compound, subsequently named lovastatin, had a methyl substitution instead of a hydrogen in the bicyclic decalin ring (Figure 3). Clinical trials with lovastatin were started in 1980, but were suspended when Sankyo’s compactin clinical studies were stopped due to the toxicological observations in dogs. Compassionate-use trials of lovastatin in high-risk FH were continued while MSD expanded its toxicological evaluation program. After much internal deliberation, clinical trials were restarted in patients who were at high risk of myocardial infarction in 1983. As confidence in the risk/benefit profile of lovastatin increased, more extensive studies took place from 1984 onwards. The period 1980-1984 in regard to statins was characterized by major concerns about their comparative safety. Endo, who left Sankyo in 1978, was convinced that the intestinal abnormalities observed in the Sankyo toxicological studies in dogs given extremely high doses of compactin were due to a toxic reaction caused by large deposits of the undigested drug in the intestinal lumen.

Goldstein visited Endo in Japan in 1980 and suggested an alternative reason for the toxicological observations. This was that the high rise in cellular reductase concentrations secondary to compactin resulted in a large increase in the endoplasmic reticulum whose crystalloid membrane tubules stained abnormally in histological slides. Brown and Goldstein proposed to MSD that if their hypothesis was correct, coadministration of mevalcone should prevent the abnormal toxicological signs. Great uncertainty remained among the Merck management and it was the new R&D director, Dr Ed Scolnick, who finally decided to restore lovastatin development after he visited the laboratories of Brown and Goldstein in Dallas on March 18, 1984. Subsequently, lovastatin was approved for sale in March 1987.

**REPRISE**

After an initial roller coaster in early discovery and development, statins are now firmly established as effective therapy for risk reduction in cardiovascular diseases. Sankyo, having abandoned compactin for, with hindsight, the wrong reasons, developed pravastatin in collaboration with the Squibb Company (US). It was identified as a urinary metabolite of compactin in dog urine and subsequently commercialized. Merck also developed an additional statin, simvastatin, which had a different substitution to mevinolin (MK803). It is a semisynthetic derivative of lovastatin and is twice as potent.

The benefits of statin treatment on the morbidity and mortality in cardiovascular diseases and diabetes mellitus are definitely established. Extensive clinical trials have finally refuted the skeptical views on the cholesterol atherosclerosis hypothesis. There remains much to be done to explain fully the molecular mechanisms by which these clinical benefits are achieved.
While the end-product feedback inhibition of cholesterol synthesis is firmly established, the complexity of the system continues to unfold. The genetic control of the cholesterol biosynthetic pathway is determined by the activity of sterol regulatory element-binding proteins (SREBPs), which activate all the genes required for the synthesis of cholesterol, a process involving twenty separate enzymatic steps. The intracellular concentration of cholesterol is monitored by proteins embedded in the membranes of the endoplasmic reticulum, namely Scap and HMG-CoA reductase. These two proteins possess sterol-sensing domains, which bind two other proteins in the endoplasmic reticulum, termed Insig I and II. Binding of these elements results in an inhibition of cholesterol synthesis by increasing the rate of HMG-CoA reductase degradation (Figure 4). Thus, the unique sterol regulation of reductase degradation determines subsequent cholesterol synthesis and the most potent endogenous sterol regulator is lanosterol, which is four synthetic steps down the pathway from mevalonate.

Clinical studies have also shown that treating patients with coronary artery disease associated with a reduction of 15% to 30% of the inflammatory marker, high-sensitive C-reactive protein (CRP). Based on extensive studies on the cellular action of statins, it is now postulated that they modulate endothelial cell, immune cell, and platelet cell function independent of their hypolipidemic actions. It is suggested that reduction of mevalonate biosynthesis secondarily reduces the intermediate isoprenoids, which consequently leads to a reduction in Rho, which then reduces the activity of the key inflammatory mediator nuclear factor kappa B (NF-κB). Undoubtedly, much has yet to be learned concerning the mechanisms of this unanticipated anti-inflammatory action of statins.

This account of the discovery and development of statins illustrates yet again the intellectual challenges and protracted timeframes involved in innovative cardiovascular drug research.

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Survival and procreation determine our existence. Sublimation of these biological drives is responsible for artistic and scientific pursuits and the search for meaning of the past and present. The past is the guidepost for the future. The lives, tribulations, and triumphs of men and women who preceded us are a most important part of history. From them, we learn that our ancestors faced many of the difficulties which confront us today.

The career of Raymond Ahlquist is an example of life made difficult because of ignorance and prejudice. Ahlquist was the antithesis of venture capitalist scientists whose motivation is not the search for the unknown, but financial and social reward. Raymond P. Ahlquist was born in Missulah, Montana in 1914. He received his PhD degree in pharmacology from the University of Washington. After being affiliated with South Dakota State College, he moved to the Medical College of Georgia where he became Professor and Chairman of the Department of Pharmacology. In 1977 he was appointed the Charbonnier Professor of Pharmacology. He died in 1983. In 1948, he published an article in the *American Journal of Physiology*, which was to revolutionize cardiology and pharmacology, entitled “A study of the adrenotropic receptors.” This paper had a curious history. It was undertaken to find a remedy for dysmenorrhea. A uterine muscle relaxant was therefore needed. Ahlquist had difficulty in publishing this paper, and once published, it remained unnoticed for several years. In this paper, Ahlquist graded the reaction of a series of six sympathomimetic amines on vasoconstriction, the pupil, heart, gut, and uterus. He found that their action, inhibitory or excitatory, depended on the site of action. He concluded...
that the relative density and distribution of two types of receptors (alpha and beta) determines the opposing responses at different locations. This idea challenged the then current opinion of the scientific establishment led by Walter Cannon of Harvard, who had postulated the role of two transmitter substances for adrenergic impulses, sympathetic E and sympathetic I. I remember a lecture which Dr Cannon gave at the College of Physicians and Surgeons at Columbia University in 1936 in which he stressed the relationship between adrenaline to sympathins. Unquestionably, the reviewers judging Ahlquist’s paper belonged to this establishment, and encouraged the editorial rejection slip that followed the first submission of this report to the Journal of Pharmacology and Experimental Therapeutics. The paper was also a loser in the Able Award competition, and only could be published in the American Journal of Physiology due to Ahlquist’s personal friendship with W. H. Hamilton, the editor. Ahlquist himself compared his fate to that of other pioneers of science, for example, that of Avery, who in 1944, proved that DNA, not protein, was the genetic carrier.

Although Ahlquist’s 1948 paper was first ignored, a time came when it was finally noticed, primarily because of the confirmation and extension of his work by Powell and Slater, and by Black. Powell and Slater’s discovery in 1958 provided the turning point in the acceptance of the idea of dual receptor mechanism. They found that the
dichloro analog of isoproterenol selectively blocked some inhibitory effects of epinephrine and isoproterenol. In 1964, Black, working with the Imperial Chemical Industry at the medical unit of St George's Hospital in London, synthesized a new adrenergic β-receptor antagonist, Inderal (propranolol), which satisfies most of the criteria of a β-blocker. A. C. Witham, from the Medical College of Georgia, wrote that Ahlquist estimated the maximum cost of his experiments to be $3500. This included about $3200 for his annual salary, which also provided instruction in pharmacology for the entire class of 65 medical students. About $300 for supplies, animals, etc, was scraped from the department budget. Student laboratory equipment was used in the experiments. Witham concludes, “No external meddling, no technicians, no research grants, no administrative overhead!”

What does Ahlquist’s scientific history teach? Let us speculate on the answer he might have received if he had submitted a research grant. It is not difficult to guess the contents of the comments returned to him by the reviewers. Some of the remarks: “this is mere speculation,” “goes against the established facts,” “conclusions are based on insufficient experimental evidence.” All this proves the well-known fact that our judgment is often biased against the new and the unusual. Great discoveries can be relatively simple, and need not necessarily involve complicated techniques, although these may be needed. Peer reviewers can separate the very good from the mediocre and bad, but they have often failed to recognize the new, unusual, and outstanding, particularly when it is presented without the frills of scientific grantsmanship.

Ahlquist’s struggle also teaches us how research has changed. Like medicine, it has undergone a revolution. In Ahlquist’s time, the motivating force in research was the search for the unknown. Now, the dance around the golden calf of financial success is the driving force. Treatment with α- and β-blockers or agonists has been introduced for coronary heart disease, hypertension, urological dysfunction, and ophthalmological disorders, among others. While Ahlquist’s expenditure for his experiments was a few thousand dollars, the pharmacological industry has spent millions on his ideas and has earned billions. Admittedly, these efforts of the industry have had advantages, particularly because of the development of new compounds. Ahlquist himself derived little monetary gain from his discovery, although he received the Lasker Award. Ahlquist’s fate is that of many original artists and scientists, yes, of all who present new ideas. As George Bernard Shaw wrote in his Saint Joan, “Oh God that madest this beautiful earth, when will it be ready to receive thy saints? How long, oh Lord, how long?”

Oswald Theodore Avery (1877-1955), a Canadian-born American, Avery was the first to prove, in an experiment published in 1944, that DNA controlled the development of a cellular feature, and was implicated as the basic genetic material of cells. This discovery stimulated James Watson and Francis Crick to later establish the structure of DNA and how it replicated. Photo taken ca 1944, courtesy of the Tennessee State Library and Archives, Oswald T Avery Papers.
Revascularization

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2006;11:319-329

1. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog
   R. B. Jennings and others. Arch Pathol. 1960

2. Depression of regional blood flow and wall thickening after brief coronary occlusions
   G. R. Heyndrickx and others. Am J Physiol. 1978

3. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow

4. The stunned myocardium: prolonged, postischemic ventricular dysfunction

5. Effects of the selective thromboxane synthetase inhibitor dazoxiben on variations in cyclic blood flow in stenosed canine coronary arteries
   L. R. Bush and others. Circulation. 1984

6. Myocardial reperfusion: a double-edged sword?
   E. Braunwald and R. A. Klener.
   J Clin Invest. 1985

7. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction
   Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI).
   Lancet. 1986

8. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium
   C. E. Murry and others. Circulation. 1986

9. Demonstration of free radical generation in “stunned” myocardium of intact dogs with the use of the spin trap alpha-phenyl N-tert-butyl nitrate

10. Medical and cellular implications of stunning, hibernation, and preconditioning: an NHLBI workshop

Selection of seminal papers by James T. Willerson, MD;
Maximilian Buja MD - University of Texas Health Science Center
Texas Heart Institute - Houston Tex - USA

Highlights of the years by Ian Mudway, MD
Cardiovascular Research - The Rayne Institute
St Thomas’ Hospital - London SE1 7EH - UK
In 1960, Robert Jennings and colleagues asked the very simple question, “When does tissue actually die after a coronary artery occlusion?” There were much anecdotal data indicating hearts could survive short periods of coronary occlusion. For example, attacks of angina were known to be caused by transient ischemic episodes and certainly caused no permanent injury. Jennings reasoned that the duration of ischemia required to kill myocardium could be determined by making hearts ischemic for a variable length of time and then measuring necrosis after they had been reperfused. Twenty minutes of ischemia was the threshold for cardiomyocyte death, which was much longer than anyone had anticipated. It is interesting that no one had thought of making such a fundamental measurement before, but it must be remembered that in those days no one ever dreamed that it would become possible to reperfuse a patient’s heart.

The Jennings lab concluded the ischemic core following a circumflex coronary artery occlusion must be centered in the posterior papillary muscle. Past experience had shown them that necrosis would appear there if nowhere else in the heart. As a result they simply reported the percentage of the posterior papillary muscle that became necrotic. A decade later it would be demonstrated that the borders between adjacent coronary branches are in fact razor sharp and those borders could be used to determine the amount of tissue at risk. But of course these investigators had no way of knowing that at the time.

They reported data from 115 dogs. Because Jennings and colleagues were the first to reperfuse such a large number of animals, they were first to make some very surprising observations. The first was that reperfusion was very arrhythmogenic. Of the 115 dogs, only 36 contributed data since most died from intractable ventricular fibrillation. Fibrillation usually occurred at reperfusion, typically after an occlusion of only 20 to 24 minutes. After longer periods of ischemia hearts seemed to cool off despite greater injury.

Another fundamental observation they made was that reperfusion hastens the appearance of necrosis in the ischemic heart. They had plenty of experience with autopsy material from patients who had died within a few hours of a coronary thrombus. Those hearts appeared surprisingly normal, but the infarct was clearly delineated in hearts from patients succumbing several days after an occlusion. Thus, they allowed the dogs to recover from surgery for 4 days to facilitate demarcation of the infarcts. A few of the reperfused dogs died from complications well before the 4-day target, and they were surprised to see that infarcts were grossly visible within hours of reperfusion. Their position was that reperfusion hastened the appearance of necrosis in lethally injured cells. This was of course only an educated guess and could not be proved. Others would later interpret these same findings as evidence of a reperfusion injury and as discussed on page 325 this would eventually become a very contentious issue 15 years later. They were also puzzled by the marked striations in the reperfused ventricular muscle seen under the light microscope. They were observing contraction band necrosis for the first time.

They got one point very wrong, however. They concluded that killing was complete after just 60 min of ischemia. A methodological error derived from just measuring infarction in the papillary muscle led them to this conclusion. In their wavefront paper (see page 322) Dr Jennings and Keith Reimer would later show that some myocardium can survive up to 6 hours of ischemia, and that has become the guideline for reperfusion therapy today.
s more and more investigators became interested in protecting the heart against ischemic injury in the 1970s, the isolated rat heart in which postischemic recovery of mechanical function was the end point became popular. It was assumed that the deficit in function following an ischemic insult was simply the result of infarction of myocytes. While accurate function measurements were relatively easy to make in an isolated heart that contracted on a fluid-filled balloon, the model had one serious flaw: the heart was viable for only a few hours, making long-term studies impossible.

There had always been a great interest in measuring cardiac function in vivo. The first attempts were with mechanical devices like the Walton-Brodie strain gauge that was sewn onto the heart’s surface. While the gauge gave a crude estimate of isometric force, it was insensitive to loading conditions. Moreover, the gauges did not do well when chronically implanted. Robert Rushmer in Seattle was a pioneer in the in situ measurement of cardiac function using electronic instrumentation to measure cardiac dimensions in real time. In the early 1950s, he hired Dean Franklin, an engineering technician, to help design new instrumentation. Dean was a radar technician in the military, and at the time Rushmer’s lab had been experimenting with piezoelectric crystals, which had recently become available. Their initial attempts were plagued with problems, but Dean used his knowledge of radar to redesign the sonomicrometer. Two crystals were sewn on opposite sides of the heart. One crystal was excited by a signal causing it to mechanically vibrate and send out sound waves that could then be sensed by the second crystal. The distance between the two crystals could be calculated by multiplying the time elapsed between transmission and reception of the pulses by the speed of sound in tissue. The device worked and allowed continuous measurement of ventricular diameter in these dogs (Circ Res 1954;2:14-21).

Robert Van Citters, one of Rushmer’s students, took a position at the Scripps Clinic and Research Foundation in La Jolla and fortuitously brought Dean Franklin with him. There, Dean developed a version that used much smaller crystals that could be implanted in the cardiac wall and measure either segment shortening or wall thickening in chronically instrumented dogs. Unlike the strain gauges, the crystals survived well when implanted chronically in canine hearts and this soon became a standard model. While in La Jolla, Stephen Vatner became very adept with this model and in the early 1970s moved to Boston and began working on ischemia. Guy Heyndrickx was working in Vatner’s lab with chronically instrumented dogs in which a balloon occluder had been implanted on a coronary branch. He found that 15 minutes or less of ischemia followed by reperfusion caused a marked reduction in the strength of myocardial contraction that persisted for up to 24 hours, but without infarction as determined by postmortem tetrazolium staining. The defect was transient and after just 1 day contractility had returned to normal. Because of the temporary nature of the defect in contractility, the myocardium was considered to be “stunned.” Stunning was a new kind of injury that had not been appreciated prior to this study.

This observation was an important milestone in our understanding of the many faces of myocardial ischemia. It became clear that infarction was not the only mechanism by which ischemia weakened the heart and that the return-of-function and infarct-size models did not measure the same thing. Postischemic recovery of function was influenced by both stunned and infarcted myocardium, while infarct size measures only the amount of necrosis. Stunning is very important for the heart’s short-term survival, while infarct size determines long-term prognosis for the heart.

Depression of regional blood flow and wall thickening after brief coronary occlusions

G. R. Heyndrickx, H. Baig, P. Nellens, M. C. Fishbein, S. F. Vatner


A copy of the Gutenberg Bible sells for $2.4 million at auction in London;
James Christy’s discovery of Pluto’s moon Charon is announced; and Argentina beats the Netherlands 3-1 in the 11th World Cup finals in Buenos Aires
The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow

K. A. Reimer, R. B. Jennings

Lab Invest. 1979;40:633-644

In 1971, Maroko and colleagues (Circulation 1971; 43:67-82) reported β-blockade limited necrosis in dogs with coronary occlusions. They concluded cardiologists could improve long-term survival in their patients with an intervention that limited necrosis. The rationale for suggesting β-blockers could protect myocardium was based on a supply-demand concept of infarction. In their studies, protection was evaluated by examining epicardial ST-segment tracings during 20-minute coronary occlusions rather than infarct size. They assumed any intervention lowering the summed current of injury at myocardial sites would reduce the size of resulting infarction if reperfusion didn’t ensue. We now know the method and theory were both flawed. Nevertheless, those studies established limitation of infarct size as an important direction of research for the next three decades. Those visionary and seminal studies from Braunwald’s lab encouraged investigators to look for interventions that would attenuate consequences of acute coronary occlusions.

Today we take the various models of ischemic injury for granted, but we must remember each had to be conceived, evaluated, and validated. Many animal models such as those using ST-segment maps to assess effectiveness of interventions lacked sensitivity or specificity and were eventually discarded. However, two models were perfected in the 1970s are still used. The first is the recovery-of-function model in which an isolated heart is subjected to global ischemia and then reperfused. Strength of contraction after reperfusion was expressed as a percentage of the preischemic value. Anything raising this value was considered to be protective. The second model was primarily developed by Keith Reimer and Robert Jennings. Regional ischemia was created in open-chest dogs and resulting infarct size measured directly. While others had tried direct measurement of infarcts in dogs, variability between animals made it difficult to determine whether or not an intervention modified infarction. This paper solved the problem by identifying the determinants of infarct size so they could be either controlled or accounted for. Reimer and Jennings observed that infarction following coronary occlusions of increasing duration advanced across the ventricle as a wavefront. Infarction always started at the subendocardium where collateral flow was least and spread outward toward the epicardium. They also showed infarct size is determined by three factors. The first is the size of the ischemic zone or “region at risk.” Infarct size is obviously proportional to the amount of tissue rendered ischemic (the risk region). Reimer normalized for differing risk zone sizes by expressing infarction as a percentage of the risk zone. This simple and intuitive practice of normalization, revolutionary at the time, is now universally applied and has made it possible to compare infarct sizes in different animals from different laboratories. The second factor is duration of ischemia. Myocardial cells in these dogs started to die about 20 minutes after onset of ischemia and by 6 hours the killing was complete. This factor is fundamental to the concept of reperfusion therapy. The last factor is collateral flow. Some dogs naturally have very well developed collateral vessels that contribute to viability. They found an inverse relationship between collateral flow and infarct size. This observation launched a massive effort to induce collateral vessel development in cardiac patients.

This study set the standard for infarct size analysis in experimental animals. Infarct size for each heart was expressed as a percentage of region at risk and plotted against collateral flow. For any duration of ischemia a straight line resulted. This so-called “Reimer-gram” fully characterized the heart’s vulnerability to ischemia. Anything shifting this relationship downward was considered cardioprotective. By accounting for all of these determinants it was possible to conclude with certainty in a relatively small number of animals whether an intervention could limit infarct size.

1979

US movie star John Wayne dies of stomach cancer; Pope John Paul II pays his first visit to his communist homeland, Poland; and Bryan Allan flies the man-powered Gossamer Albatross across the English Channel in 2 hours and 49 minutes
he physician-scientist has always been needed for the critical job of translating basic findings into clinical practice, and a prime example of this is reflected in the editorial/review on myocardial stunning by Braunwald and Kloner in 1982. That paper, which was prominently featured in the widely-read clinical journal *Circulation*, explained the ramifications of stunning to the clinical community. They took the observation from the animal lab that brief coronary occlusions would only transiently disturb myocardial contractility without permanent damage (see page 321) and suggested that the same was occurring in patients with coronary artery disease.

The evidence for stunning had been hiding from cardiologists in plain sight. Braunwald and Kloner pointed out that many common observations could now be explained on the basis of stunning, such as how a patient’s contractility could mysteriously recover in the days after a myocardial infarction. More importantly, it explained why patients undergoing newfangled reperfusion therapy showed surprisingly little increase in contractile performance when coronary blood flow was restored. They urged that evaluation of cardiac function in patients with reperfused myocardium be delayed for up to 2 weeks to allow ample time for stunned myocardium to recover.

Additionally, they pointed out stunning might be a more important entity following surgical myocardial revascularization where the left ventricle can be so depressed from stunning that it may be unable to support the circulation, making it impossible to wean patients from the bypass pump. In practice, balloon pumps or inotropic agents were often used to tide patients over in such circumstances, and Braunwald and Kloner pointed out that stunning explained why these patients eventually recovered left ventricular function. Interestingly, there were already observations in animals that stunned myocardium responded to inotropes such as catecholamines. Later, Schaper et al (*Circ Res* 1987, 61:834-846) and others would demonstrate that inotropes could in fact completely restore function of stunned myocardium, which not only made the surgeons much more comfortable, but also indicated that the problem was one of calcium handling rather than defects in contractile filaments.

One of the most prophetic observations of the editorial was the suggestion that repeated myocardial ischemia as might occur in a patient with angina could lead to chronically stunned myocardium. They were still years away from the concept of “hibernating” myocardium, which Rahimtoola would introduce in 1989 (*Am Heart J* 1989;117:211-221). He proposed that hibernating hearts downregulate their function and metabolism to survive a prolonged period of ischemia. In 1982, Braunwald and Kloner proposed that patients having chronically depressed, but viable segments, might simply have repetitive stunning. Interestingly, the repetitive stunning hypothesis would be revived in the 1990s as an alternative explanation of the hibernation phenomenon.

The last thing that caught our eye in their editorial was the discussion of mechanisms of stunning. The concept of free radical injury had not yet become popular, but rather attention was focused on prolonged deficits of ATP in stunned hearts. They proposed that washout of adenosine from these hearts could deplete the purine pool leaving too little adenosine substrate to rephosphorylate back into ATP. That was later disproven when Schaper’s lab showed that rapid repletion of purines by AICAR had little effect on stunning (*Basic Res Cardiol* 1985;80:445-458). It would be left to Roberto Bolli to sort out the mechanism (see page 328).

### 1982

Polish pianist Arthur Rubinstein dies in Geneva, aged 95; Michael Jackson releases “Thriller,” best-selling album of all time; and the first permanent artificial heart is successfully implanted at the University of Utah into retired dentist Barney Clark, who survives 112 days.
Although intracoronary thrombosis at the site of a ruptured plaque is now recognized to be the culprit in myocardial infarction, platelet aggregation is also considered to play a pathophysiologic role in acute coronary syndromes. This was elegantly demonstrated by John Folts et al in a groundbreaking experimental study (Circulation 1976; 54:365-370) and amplified by Bush et al. These investigators constricted the coronary artery of a dog and then followed sequential changes in flow in the narrowed vessel. With a surprising periodicity, flow would gradually decline to a nadir that was close to zero and then abruptly recover with a reactive hyperemia, only to be followed again by another cycle of progressive decrease and then sudden recovery. Morphologic analysis of coronary arteries at the site of constriction revealed platelet thrombi with blood erythrocytic and leukocytic involvement. It was reasoned that rheologic disturbances at the site of arterial narrowing led to endothelial denudation, which in turn encouraged platelet accumulation and aggregation with trapping of other formed blood elements. As the platelet mass increased, the obstruction to flow worsened until near-total occlusion of the lumen ensued. Then, suddenly, the platelet mass would give way allowing restoration of flow. Presumably, small platelet aggregates would embolize to smaller vessels downstream. This cyclic flow reduction was repetitive.

Platelet plugs may indeed be a contributing cause of angina and other acute coronary syndromes. The difference between a friable platelet plug and a longer-lasting thrombus is the deposition of fibrinogen with subsequent conversion to fibrin in the latter. A thrombus in the coronary artery generally forms after a plaque ruptures and the very thrombogenic collagen and lipid core are exposed to circulating blood elements. So the platelet plug is a part of a pathologic continuum, which can result in only minor anginal pains or devastating myocardial infarction.

Once it was established that platelet plugs would repeatedly form at the site of coronary constrictions, it was reasoned that prevention of platelet aggregation might abolish the observed cyclic flow reductions. Thus the antiaggregatory aspirin as well the thromboxane synthetase inhibitor dazoxiben, which interfered with thromboxane A2 production by platelets, both attenuated formation of platelet plugs and nearly eliminated the cyclic changes in coronary flow in animal models with critical coronary constrictions. Experimental studies such as these have resulted in important changes in clinical care of patients with coronary artery disease. Numerous clinical studies in patients with angina and myocardial infarction have clearly demonstrated the efficacy of aspirin and a host of other agents targeting specific platelet receptors participating in a cascade of interactions resulting in aggregation. Thus, nearly every individual with proven or even suspected coronary artery disease consumes daily aspirin and/or other antiplatelet agents to prevent thromboxane synthesis and platelet aggregation. This clinical treatment is a wonderful example of how observations in animal models can be extrapolated to the clinical arena, and how basic scientists, clinical researchers, and clinicians are all partners in a complex process seeking to improve patient care.

Effects of the selective thromboxane synthetase inhibitor dazoxiben on variations in cyclic blood flow in stenosed canine coronary arteries


Circulation. 1984;69:1161-1170

Bruce Springsteen releases the album “Born in the USA”; Ivan Lendl wins the French Open, his first grand slam title; and US 400-meter hurdler Edwin Moss wins his 100th consecutive race
Myocardial reperfusion: a double-edged sword

E. Braunwald; R. A. Kloner

J Clin Invest. 1985;76:1713-1719

One of the most contentious issues in ischemia has been the proposed existence of reperfusion injury. By 1985, reperfusion therapy for acute myocardial infarction was in full swing. While early reperfusion may reduce infarct size, it certainly did not eliminate it. Patients seldom could be reperfused before a significant amount of myocardium had already infarcted. It was believed some additional intervention might further reduce infarction in these patients. But what would it be? Having already introduced the clinical community to the vicissitudes of stunned myocardium, Braunwald and Kloner turned their attention to the thorny issue of reperfusion injury. In their classic editorial in 1985, they posed the question whether reperfusion itself actually kills some heart tissue. Answering that question has been surprisingly difficult. The difficulty arises because of uncertainty as to how one assesses myocardial viability.

If tissue is not reperfused, it will certainly starve to death from ischemia, so the best test of viability is to see if cells survive after reperfusion. But how can one tell if reperfusion itself might be killing some potentially viable living cells? There was evidence that free radical production and calcium flooding occurring at reperfusion were injurious, and there was no doubt that much of stunning occurs at reperfusion. Jennings had noted reperfusion hastens the morphological changes associated with cell death (see page 320), but the irrefutable evidence suggesting that reperfusion injury was real came when David Hearse demonstrated that reoxygenation of hypoxic rat hearts was associated with sudden and explosive cell death. He termed this the oxygen paradox (J Mol Cell Cardiol 1975;7:315-324).

Jennings had proposed that the dramatic morphological changes associated with reperfusion were simply related to osmotic swelling from the sudden availability of water, but that could not be the case for the oxygen paradox. Oxygen seemed to be the culprit. Hearse and colleagues speculated that perhaps some of the oxygen had been converted to toxic free radicals. It was agreed by all that the best proof of lethal reperfusion injury would require finding a way to remove the reperfusion injury and then demonstrating that there was increased viability in that reperfused tissue. Although Ben Lucchesi and others had reported just that with free radical scavengers, many other competent investigators were unable to reproduce those results and so the issue of reperfusion injury remained controversial.

And so the argument raged as to when heart cells experiencing ischemia/reperfusion were actually killed. Was it during ischemia or was it at reperfusion? We recall the famous “dead cat” debate one evening at the scientific sessions of the American Heart Association in which Robert Jennings argued that reperfusion only causes morphological changes in tissue that has already been killed by ischemia. If swelling occurs in already dead tissue, is it still reperfusion injury? To dramatize the point he posed the rhetorical question, “How many times can you kill a dead cat?” and showed some black-humor cartoons from a popular book, 101 Uses for a Dead Cat. Despite the impassioned position, others believed that events at reperfusion were capable of further damaging and killing cells injured or at least metabolically challenged during the preceding ischemia. But the techniques were not yet available to enable one to conclude which position was right. The review by Braunwald and Kloner summarized the available evidence in 1985, focused the arguments, and demonstrated to clinicians the implications of the existence of a reperfusion injury. If reperfusion injury were killing reperfused myocardium, then preventing reperfusion injury would result in smaller infarcts in patients with successful revascularization. The answer to the question of the existence of reperfusion injury would have to wait several years until a phenomenon called “preconditioning” came along (see page 327).

US comedian Phil Silvers (Sergeant Bilko) dies, aged 73; General Jaruzelski is elected Poland’s head of state; and Gary Kasparov becomes the World Chess Champion at the age of 22 when he defeats Anatoly Karpov
Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction

Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI)

Lancet. 1986;1:397-402

One of the obvious ramifications of the wave-front study by Reimer and Jennings (see page 322) was that if myocardium were to be salvaged, it had to be reperfused, and the sooner the better. Despite fears of possible reperfusion injury (see page 325), Reimer and Jennings never identified a duration of ischemia after which reperfusion caused infarct size to be bigger than would have occurred with permanent occlusion. Thus, there seemed to be no contraindication to reperfusion and this then became the basis for reperfusion therapy.

The technical challenge was the means by which this could be accomplished. Patients undergoing acute myocardial infarction were probably not the best surgical candidates and, accordingly, attempts at emergency coronary artery bypass were at best disappointing. However, at the same time there was emerging evidence that most acute occlusions were caused by thrombi, and that revelation drove the development of thrombolytic agents, streptokinase and tissue plasminogen activator (t-PA). With the availability of effective thrombolytics in the 1980s, clinical trials of reperfusion therapy began in earnest. The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) study was the first to document that early reperfusion in the course of coronary occlusion causes a significant improvement in mortality. This was a large study by the standards of the day, with over 11 000 patients recruited. It was a controlled, multicenter, randomized, unblinded trial of intravenous streptokinase in patients hospitalized within 12 hours of onset of the pain of a myocardial infarction. Patients who had either ST-segment depression or elevation in at least one limb or precordial lead were accepted for study. Only mortality during the 14-to-21-day hospitalization period was evaluated, but the overall statistics were striking: there was a highly significant 18% decrease in mortality in those patients treated with streptokinase. This dramatic decrease in mortality was identified in only those patients admitted within 6 hours of onset of pain, and ranged from 23.3% in those presenting within 3 hours and 16.7% in those arriving from 3 to 6 hours after pain onset. Later arrivals were not helped by thrombolysis. Perhaps not surprisingly, benefits were confined to those individuals with ST-segment–elevation myocardial infarctions, ie, those with likely coronary thrombi. Those with ST-segment depression were not helped, and this is understandable because of the multiplicity of etiologic factors in non-ST-segment–elevation myocardial infarctions. Thus, this landmark study established the efficacy of early thrombolysis in patients with ST-segment–elevation myocardial infarctions, and thrombolysis continues to be performed extensively today.

Unfortunately, these investigators used streptokinase, which future Thrombolysis In Myocardial Infarction (TIMI) trials would later show to be inferior to t-PA. Nevertheless, it was good enough. In the past 20 years, many refinements to the thrombolysis protocol have been made to make it more effective and less dangerous. It is noteworthy that the results of the trial were pretty much as the experience in animal models had predicted: rapid thrombolysis leading to smaller infarcts translated to improved prognosis. Hence, reperfusion therapy became the standard of care. Today, virtually all patients with ongoing myocardial infarction are evaluated for reperfusion. Although mechanical revascularization with angioplasty techniques has to a certain extent supplanted pharmacologic reperfusion, thrombolysis still remains as the reliable procedure that can be performed in hospitals without access to cardiac catheterization laboratories within the recognized critical window of the first few hours after symptom onset.

1986

Haiti’s President Jean-Claude Duvalier flees to France and Henri Namphy takes over the presidency; President Marcos flees the Philippines after newly elected Corazon Aquino succeeds him; and Swedish Prime Minister Olof Palme is assassinated in Stockholm
Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

C. E Murry, R. B. Jennings, K. A. Reimer

Circulation. 1986;74:1124-1136

Through 1985 no strong candidate for a cardio-protective intervention other than early reperfusion itself had been introduced. Many investigators began to suspect that it might even be theoretically impossible to alter a heart’s vulnerability to infarction. That all changed in 1986 when a paper on “ischemic preconditioning” by Murry et al from the well-respected laboratory of Reimer and Jennings was published. We can still remember vividly Charles Murry presenting this paper at an abstract session of the American Heart Association meeting. One would think it would have caused quite a stir, but in actuality it was met with only mild enthusiasm. We heard one fellow comment afterwards, “It probably just opens collateral vessels—nothing important.” Most in attendance were either skeptical or didn’t realize the importance of what had just been reported.

Murry and colleagues had applied four 5-minute periods of coronary occlusion, each followed by 5 minutes of reperfusion, prior to a 40-minute coronary occlusion in dogs. Rather than making a bigger infarct, the sublethal ischemic insults caused the heart to rapidly adapt itself to become very resistant to infarction from the 40-minute ischemic insult. Amazingly, 4 years followed before the next 2 papers confirming ischemic preconditioning appeared, one by Wolfgang Schaper et al (Circ Res 1990;66:1133-1142) and the other by Ben Lucchesi et al (Circulation 1990;82:609-619). As others tried preconditioning, they realized this was indeed a powerful antinfarct intervention. Before preconditioning, anything that caused 5% to 10% reduction in infarction was considered highly protective. Ischemic preconditioning typically reduced infarct size by 50% to 70%. The word quickly spread and a research industry for the 1990s was launched.

On page 325, we indicated that ischemic preconditioning held the key to the reperfusion injury debate. The question of when heart muscle is killed was an important one, because patients present with myocardial infarction after ischemia has begun. Thus, ischemic preconditioning was not an option since it had to be invoked prior to onset of ischemia. If, however, cell killing occurred at reperfusion, then it would not be too late to treat these patients and salvage myocardium. In the 1980s, reperfusion injury was considered to be synonymous with free radical attack. Since no free radical scavenger had been shown to unambiguously limit infarct size, the free radical hypothesis of cell death was seriously questioned. Then, Derek Yellon’s lab showed ischemic preconditioning exerts its protective effect early in reperfusion via the protective kinases ERK and PI3-kinase (Am J Physiol 2005;288:H971-H976), which inhibit formation of mitochondrial permeability transition pores. Transition pores kill viable cells by uncoupling mitochondria, thus blocking ATP production. Interestingly, both free radicals and calcium induce transition pores, although it is not known how much either contributes to pore opening in the reperfused heart. Many interventions have now been identified that cause large-scale salvage when given just prior to reperfusion, and virtually all do so through a PI3-kinase/ERK-dependent mechanism. If an intervention given at reperfusion can salvage myocardium, then it must have done so by preventing a reperfusion injury.

The World Health Organization announces the first global effort to combat AIDS; the Iran-Contra affair erupts in the USA when arms sales to Iran are shown to have funded the anticomunist Contras in Nicaragua; and a factory near Basel, Switzerland, goes up in flames, spewing tons of chemicals in the river Rhine, turning it red.
After the description of myocardial stunning, it made perfect sense that short periods of ischemia stunned the heart and longer periods killed it. But, unfortunately, it was wrongly assumed that both stunning and infarction had the same etiology and that any intervention that protected against one would also protect against the other. In the 1980s, Roberto Bolli became very interested in determining the mechanism of stunning and in a series of important papers showed that free radicals contribute to stunning. It was at this time that free radicals were generally considered to have deleterious effects on tissue viability, structural and morphologic elements, intracellular proteins and enzymes, and nucleotides. In this particular publication, he and his colleagues showed that reperfusion was associated with free radical production as assessed by a spin trap, the gold standard for detecting a radical species. Actually, one of us (JMD) reviewed this paper when it was submitted for publication, and anyone who has reviewed a Bolli paper knows that his papers are submitted as close to perfect as is humanly possible. Out of desperation for something to contribute, I pointed out that if his theory were correct excess spin trap in the coronary perfusate should act as a free radical scavenger and should actually protect against stunning. Bolli was asked to please provide functional data for those hearts. In the submitted revision of the manuscript, these additional data were provided, and the results supported the prediction. It should be pointed out that it was not a single paper that made the case for free radicals being the pathogenetic cause of stunning, but rather a series of publications from the Bolli lab over a period of several years that resulted in evolution of this concept. These studies established a direct link between production of free radicals upon reperfusion of ischemic myocardium and functional, transient deterioration of left ventricular contractility.

Bolli and colleagues found that conventional scavengers such as superoxide dismutase and catalase could blunt stunning (Circulation 1985;72:915-921), but had no effect against infarction (Am J Physiol 1990;258:H369-H380). That led to the now accepted concept that the two forms of injury, stunning and infarction, probably have very different etiologies. Thus, an intervention that preserves postischemic function and therefore minimizes stunning cannot be assumed to limit infarct size, and vice versa. Hence, animal models using postischemic function as the end point are strongly influenced by stunning and measure a different process than models using infarct size as the end point. Surgeons who are primarily concerned with weaning their patients from bypass following revascularization surgery during which the heart experiences some degree of obligate myocardial ischemia are mostly concerned with stunning. They still heavily rely on recovery of function models when designing cardioplegic solutions or cardioprotective interventions. On the other hand, cardiologists who deal with patients with acute myocardial infarction are more concerned with infarct size. If the patient survived the trip to the hospital with akinesis of the ischemic segments, then any potential additional stunning after recanalization will obviously be tolerated and the focus will be on long-term survival of the ischemic tissue. In this case the prognosis of the patient is determined by the amount of surviving myocardium that can effectively contract. In this setting, an anti-infarct intervention (such as early reperfusion) would be most desirable.

Demonstration of free radical generation in “stunned” myocardium of intact dogs with the use of the spin trap alpha-phenyl N-tert-butyl nitrone

R. Bolli, B. S. Patel, M. O. Jeroudi, E. K. Lai, P. B. McCay


Enzo Ferrari, the Italian sports car manufacturer, dies, aged 90; a plane blast kills Pakistani president Mohammed Zia ul-Haq; and a cease-fire begins in the 8-year Iran-Iraq war
Medical and cellular implications of stunning, hibernation, and preconditioning: an NHLBI workshop

R. A. Kloner, R. Bolli, E. Marban, L. Reinlib, E. Braunwald

_Circulation_. 1998;97:1848-1867

In 1996, a group of highly talented investigators were invited to Columbia, Maryland, just outside Bethesda, where the current state of cardioprotection was assessed and future directions contemplated. In those days, ischemia session programmers for scientific meetings always concentrated on the “Big 3”: stunning, preconditioning, and hibernation. There was seldom enough material to fill a program with any single subject, so all three were usually lumped together. So it was with the workshop. Although the summary report by Kloner and colleagues is now almost a decade old and much of it may be irrelevant today, it beautifully summarized the state of the art at the time. For example, Figure 4 of the report gave an amazingly perceptive insight into preconditioning. We say that in jest, of course, because it was the contribution of our lab to the workshop. In retrospect, Figure 4 presented the simplest of flowcharts; but, thank goodness, for the most part it turned out to be correct.

Stunning was a case where excellent clinical and animal models existed. While the molecular mechanisms of stunning are still poorly understood, free radicals clearly play a role. Oddly, hibernation is a rare case where a good clinical model exists, but the available animal models are amazingly divergent and it is still difficult to get a clear demonstration or definition of hibernating myocardium in an animal model. The final entity, ischemic preconditioning, has been well studied and there is a wealth of published information on it. Interestingly, it has only been in the past few years that the underlying mechanism of protection—prevention of permeability transition pores by the survival kinases—has been appreciated, however.

There are three known avenues that can be utilized to protect a patient’s heart against infarction. The first, early reperfusion, is now a clinical reality. The second, stimulating angiogenesis to grow collateral coronary vessels, has so far met with frustration at both the experimental and clinical levels. The third avenue, invoking the preconditioning mechanism as an adjunct to early reperfusion, is currently available for clinical trials. A number of pharmacological agents can turn on the survival kinases and unambiguously salvage myocardium when given at reperfusion in animal models, but there has been surprisingly little interest in the pharmaceutical industry for pursuing their development. This regrettable decision has been very annoying to clinical cardiologists as well as research scientists. The rationale from industry for not testing these agents has been that the required clinical trials would be too expensive and the resulting market would be too small to be profitable. Also, industry has to be a little gun-shy after three decades of failed trials of cardioprotectants. Finally, the community has been looking ahead to stem cell therapy with a “who cares if patients infarct, we will just grow new muscle” attitude. Problems with getting seeded cells to proliferate are now tempering some of that enthusiasm, however, and perhaps tissue salvage before the myocardial cells die may come back into vogue and receive renewed attention from either the clinical community or the pharmaceutical industry.

Former Rwandan president Jean Kambanda pleads guilty to genocide charges before a UN tribunal; art thieves in Rome steal two paintings by Van Gogh and one by Cézanne from the National Gallery of Modern Art; astronomers detect a giant explosion in space second in magnitude only to the “Big Bang.”
Revascularization

Bibliography of One Hundred Key Papers

selected by James T. Willerson*, MD; L. Maximilian Buja†, MD

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President-Elect and Medical Director - Texas Heart Institute - Houston, Tex
† Executive Vice President for Academic Affairs - Professor of Pathology and Laboratory Medicine at the
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