

Revascularization

Summaries of Ten Seminal Papers

James M. Downey, PhD; Michael Cohen, MD

Department of Physiology - College of Medicine - MSB 3024 - University of South Alabama
Mobile, Ala - USA (jdowney@usamail.usouthal.edu)

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

K. A. Reimer and R. B. Jennings. *Lab Invest.* 1979

4

The stunned myocardium: prolonged, postischemic ventricular dysfunction

E. Braunwald and R. A. Kloner. *Circulation.* 1982

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

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

6

Myocardial reperfusion: a double-edged sword?

E. Braunwald and R. A. Kloner.

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 nitron

R. Bolli and others. *J Clin Invest.* 1988

10

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

R. A. Kloner and others. *Circulation.* 1998

Highlights of the years by **Ian Mudway, MD**
Cardiovascular Research - The Rayne Institute
St Thomas' Hospital - London SE1 7EH - UK

Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog

R. B. Jennings, H. M. Sommers, G. A. Smyth, H. A. Flack, H. Linn

Arch Pathol. 1960;70:68-78

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 is-

chemic 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.

1960

The Beatles start playing at the
Kaiserkeller Club in Hamburg, Germany;
The USSR's Sputnik 5 is launched, carrying
two dogs, Belka and Strelka, and returns to earth
the next day with both animals still alive;
and America's new 50-star flag honoring
Hawaiian statehood is unfurled



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

Am J Physiol. 1978;234:H653-H659

As 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 receipt 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 deficit 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.

1978

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 that 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 pre-ischemic 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



The stunned myocardium: prolonged, postischemic ventricular dysfunction

E. Braunwald and R. A. Kloner

Circulation. 1982;66:1146-1149

The 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

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

L. R. Bush, W. B. Campbell, L. M. Buja, G. D. Tilton, J. T. Willerson

Circulation. 1984;69:1161-1170

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.

1984

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).

1985

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 antiinfarct 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.

For the first time it was clear infarct size modification was indeed scientifically possible. The heart had a built-in ability to protect itself. We just hadn't known which buttons to push. Many investigators dissected ischemic preconditioning to learn its secrets and a PubMed search at the time of this writing for "ischemic preconditioning" and "heart" uncovered more than 2200 papers.

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.

1986

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
anticommunist Contras in Nicaragua;
and a factory near Basel, Switzerland, goes up
in flames, spewing tons of chemicals in
the river Rhine, turning it red

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

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

J Clin Invest. 1988;82:476-485

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 obligatory 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.

1988

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.

1998

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”