Basic and Clinical Aspects of Ischemic Preconditioning

Karin Przyklenk, PhD

Heart Institute, Good Samaritan Hospital and University of Southern California, Los Angeles, California, USA

There is no question that myocardial ischemia has profound and deleterious effects on the metabolism and contractile performance of the heart, and ultimately, on myocyte viability. However, in 1986, Murry and colleagues revealed an intriguing paradox: i.e., that one or more brief episodes of ischemia - too brief in themselves to cause myocyte death - render the heart *resistant* to a later more prolonged period of coronary artery occlusion [1]. This concept of "preconditioning with ischemia" has, since its first description, captured the interest of researchers world-wide, as evidenced by the ~200 published papers per year currently devoted to this topic (Figure 1). My aim in this review is to provide a synopsis of the insights gained from this substantial body of work, with particular emphasis on: (i) the definition and fundamental properties of so-called 'classic' ischemic preconditioning; (ii) the potential clinical relevance of this phenomenon; and (iii) the cellular mediators thought to participate in eliciting this increased resistance to ischemia.

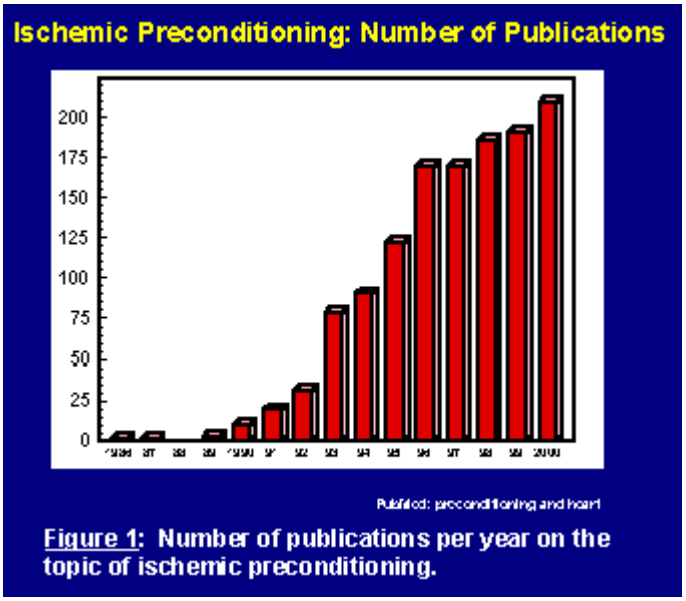

Figure 1

WHAT IS ISCHEMIC PRECONDITIONING? DEFINITION AND CHARACTERISTICS

The "gold standard": reduction of infarct size

We began our investigations of "preconditioning with ischemia" in the anesthetized canine model with what has become a "typical" preconditioning protocol. As a preconditioning stimulus, we utilized 4 5-minute periods of coronary artery occlusion interspersed with 5 minutes of intervening reflow, while control animals received a matched, 40 minute period of uninterrupted perfusion. In the control group, infarct size produced by a subsequent 1 hour sustained test occlusion averaged 20% of the myocardium at risk, while, in marked contrast, mean infarct size in the preconditioned cohort occupied only 5% of the risk region (Figure 2). Similar profound reductions in infarct size have been described in virtually all species and experimental models tested to date (Figure 2), both in the in vivo setting and in isolated buffer-perfused heart preparations [2]. This consensus is remarkable, particularly when viewed in the context of the

countless cardioprotective strategies and interventions that have failed to withstand the rigors of repeated investigation. Indeed, reduction of infarct size has been firmly established as the "gold standard" of ischemic preconditioning.

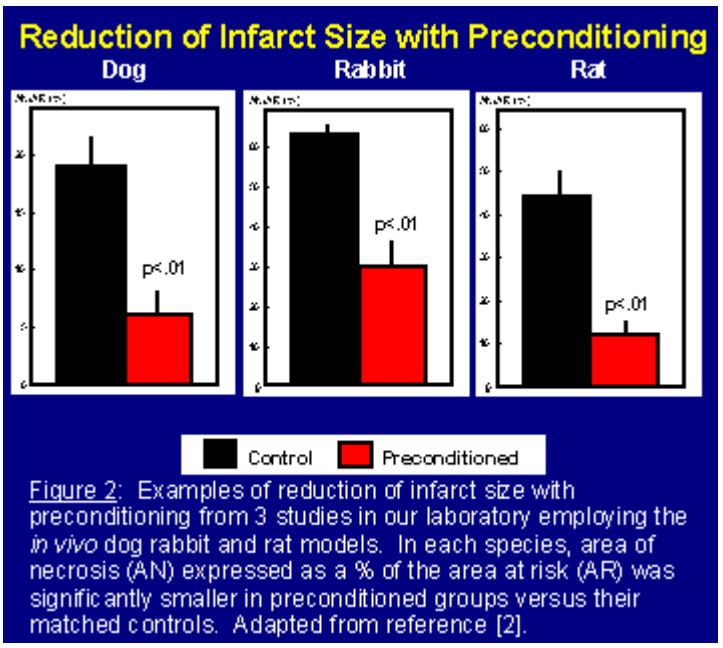

Figure 2

Preconditioning "at a distance"

In the initial in vivo experiments documenting infarct size reduction with preconditioning, both the antecedent ischemia and the sustained test occlusion were imposed in the same vascular bed: i.e., brief occlusions of the left anterior descending (LAD) coronary artery protected the LAD bed; while brief occlusions of the circumflex (Cx) artery similarly preconditioned the Cx bed. Interestingly, however, brief ischemia in one vascular bed appears to elicit widespread protection, a phenomenon termed preconditioning at a distance

The first evidence of remote, preconditioning-induced protection was obtained using the canine model: experiments from our laboratory showed that infarct size produced by 1 hour of LAD occlusion was significantly reduced in dogs randomly assigned to receive 4 5-minute episodes of antecedent Cx occlusion when compared with time-matched control animals that received LAD occlusion alone [3]. Subsequent studies have expanded upon this concept and demonstrated that brief episodes of ischemia in peripheral sites (i.e., kidney, skeletal muscle) can protect the heart against infarction [4]. Moreover, emerging evidence indicates that isolated buffer-perfused hearts release cardioprotective factor(s) during brief ischemia/reperfusion that, when administered to virgin acceptor hearts via transfer of coronary effluent, elicit a reduction in infarct size comparable to that achieved with ischemic preconditioning per se [5]. These findings give rise to the obvious question: what is the identity of the protective factor(s), apparently released from the heart and other organs, that initiate protection at remote sites? The mechanisms that participate in 'preconditioning at a distance' - and, indeed (and as discussed later in this review), the mechanisms of conventional ischemic preconditioning -- remain to be elucidated.

Preconditioning the diseased and aging heart?

Although reduction of infarct size with preconditioning has been reported in virtually all experimental preparations, the vast majority of studies have employed juvenile or adult animals devoid of underlying cardiovascular disease. Surprisingly, few investigators have focused on an issue of paramount importance - whether preconditioning is manifest in the diseased or aging heart.

There is an emerging consensus among most (but not all) of the small number of published studies that

the benefits of preconditioning are maintained in rat and mouse models of hypertension, hypertrophy, diabetes, hypercholesterolemia and atherosclerosis [6,7]. In contrast, concern has been raised that the aging heart may be an exception to the paradigm of preconditioning-induced cardioprotection [8]. This concept is, however, based exclusively on data from isolated buffer-perfused rat hearts; indeed, recent evidence obtained by our laboratory in the *in vivo* rabbit model revealed that preconditioning was equally effective in limiting necrosis in both middle-aged and senescent animals as compared with the standard adult population [9]. Whether this discrepancy represents a difference between the species and/or preparation used (rat versus rabbit; *in vitro* versus *in vivo*; buffer- versus blood-perfused) is a fundamental question that, at present, remains unresolved.

EXPANDING THE PARADIGM: ANCILLARY EFFECTS OF PRECONDITIONING

The profound reduction of infarct size seen with brief antecedent ischemia prompted many investigators to ask: do the protective effects of preconditioning extend beyond myocyte viability and encompass one or more of the other deleterious sequelae of prolonged myocardial ischemia? In contrast to the consensus among studies with regard to infarct size reduction, there is confusion and controversy concerning the effect of preconditioning on other ancillary endpoints (Table 1).

Table 1.

Endpoints and Indices of Preconditioning

Gold standard:

- reduction of infarct size

Ancillary effects:

- improved recovery of contractile function following relief of sustained ischemia: *secondary consequence of infarct size reduction.*
- reduction in the incidence of ischemia- and reperfusion-induced arrhythmias: *observed in some, but not all, models.*
- reduction of myocyte apoptosis; preservation of endothelial and smooth muscle function in the coronary vasculature; attenuation of platelet-mediated thrombosis: *require confirmation in multiple models and species.*

Table 1

Perhaps the most widely employed surrogate endpoint of cardioprotection with preconditioning is the recovery of left ventricular (LV) contractile function during the initial minutes-hours following relief of sustained ischemia. There is general (but not complete) agreement that, in isolated rat, rabbit and mouse heart models of global ischemia, recovery of LV developed pressure may indeed be improved in preconditioned hearts versus controls. However, it is now well-recognized that this improvement in function is a secondary consequence of infarct size reduction, rather than a direct, beneficial effect of preconditioning on the contractile performance of the remaining viable but "stunned" myocardium (reviewed in [2,10]. A second surrogate endpoint in many preconditioning protocols has been the assessment of electrocardiographic alterations and rhythm disturbances. There is overwhelming evidence that, in the rat, preconditioning is associated with a marked reduction in the incidence of ischemia- and reperfusion-induced ventricular fibrillation (VF) and tachycardia (VT). This is not, however, a consistent feature among models and species: i.e., in the pig, preconditioning reportedly favors (rather than attenuates) the development of VF while, in the dog, the presence versus or absence of an "anti-arrhythmic" effect of preconditioning is apparently dependent upon the anesthetic agent that is used [2,10]. Finally, a growing number of studies further suggest that, in addition to limiting myocyte necrosis,

brief antecedent preconditioning ischemia may reduce myocyte apoptosis, preserve endothelial and smooth muscle function in the coronary vasculature, and, interestingly, attenuate platelet-mediated thrombosis in damaged and stenotic coronary arteries [2]. Extensive and conclusive documentation of these latter three endpoints in multiple models and species is, however, still lacking. As a result, reduction of infarct size remains the sole, established hallmark of ischemic preconditioning.

TEMPORAL LIMITATIONS OF ISCHEMIC PRECONDIITONING

It must be emphasized that, even with regard to infarct size reduction, preconditioning is not a panacea. Rather, there are three important temporal criteria that must be met in order to achieve preconditioning-induced cardioprotection.

The preconditioning stimulus

Although initial studies employed multiple cycles of antecedent ischemia as the preconditioning stimulus, it has since been established (with some variations among models), that a single ~90 second ischemic insult represents the lower threshold needed to initiate protection. At the opposite extreme - and as logic would dictate -- episodes of 'brief' ischemia that, in themselves, result in myocyte death (~10-20 minutes, depending on the model employed) do not elicit significant cardioprotection, and, indeed, may increase infarct size versus time-matched controls (reviewed in [2,10]. Moreover, numerous repeated episodes of brief ischemia do not augment the preconditioning response; rather, there is evidence for a loss in efficacy with multiple (~45-60) repeated preconditioning stimuli [2,10,11].

Duration of intervening reperfusion

There is a complex, biphasic temporal relationship between cardioprotection and the duration of reflow separating the preconditioning stimulus from the onset of the prolonged test occlusion (Figure 3). Maximum protection - i.e., 'classic' ischemic preconditioning, the focus of the current review -- is achieved when the sustained ischemic challenge is initiated soon (within ~5-30 minutes) after the final bout of preconditioning ischemia, and, if the duration of intervening reflow is extended to ~1 hour, protection rapidly wanes [2]. Interestingly, however, if the period of intervening reperfusion is further protracted to 24-72 hours, a delayed or 'second window' of protection emerges (reviewed in [12]. Although there are fundamental differences between the two temporal components (i.e., delayed preconditioning, in contrast to 'classic' preconditioning, protects against myocardial stunning [12]), both the 'first' and 'second' windows are characterized by an increased resistance to infarction. The reduction of infarct size evoked in the 'second window' is, however, more modest in magnitude (albeit longer in duration) than the 'first window' of cardioprotection.

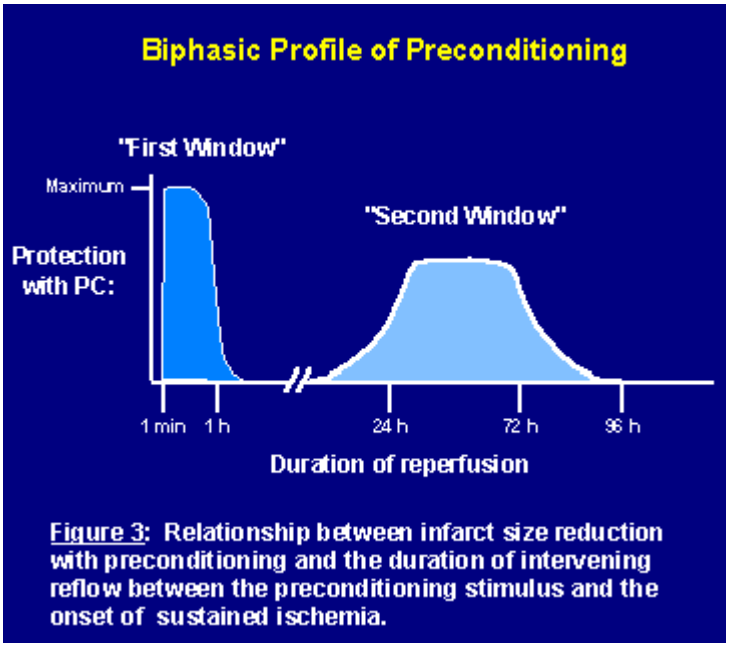

Figure 3: Relationship between infarct size reduction with preconditioning and the duration of intervening reflow between the preconditioning stimulus and the onset of sustained ischemia.

Figure 3

Duration of sustained ischemia

A host of studies have demonstrated that preconditioning is highly effective in limiting infarct size caused by a sustained ischemic insult lasting ~30-90 minutes. However, it has been appreciated since the seminal observations of Murry et al [1] that preconditioning fails to elicit protection when the sustained test ischemia is extended to 3 hours. This temporal limitation underscores a crucial caveat: preconditioning does not prevent or preclude the development of myocardial necrosis, but rather protects the heart by slowing or delaying myocyte death. If preconditioning is not coupled with timely reperfusion, no benefit is achieved [2,10].

IS PRECONDITIONING A CLINICALLY RELEVANT PHENOMENON?

Is preconditioning a laboratory curiosity manifest only in experimental models, or can the human heart be similarly protected by brief ischemia? This is a deceptively difficult question, as carefully timed protocols and definitive histopathologic measurement of our gold standard -- infarct size - are clearly not feasible in patients. As a result, conclusions regarding the clinical relevance of ischemic preconditioning are largely dependent upon the use of surrogate (and, in some cases, sub-optimal) endpoints. Nonetheless, evidence of adaptation or enhanced tolerance to ischemia has been described in at least 5 clinical settings: with repeated balloon inflations during coronary angioplasty; with repeated bouts of exercise (the "walk-through" or "warm-up" phenomenon); with preinfarct angina; and with brief ischemia intentionally imposed before coronary artery bypass grafting or before harvesting donor hearts destined for transplant (Table 2); reviewed in [2,13,14].

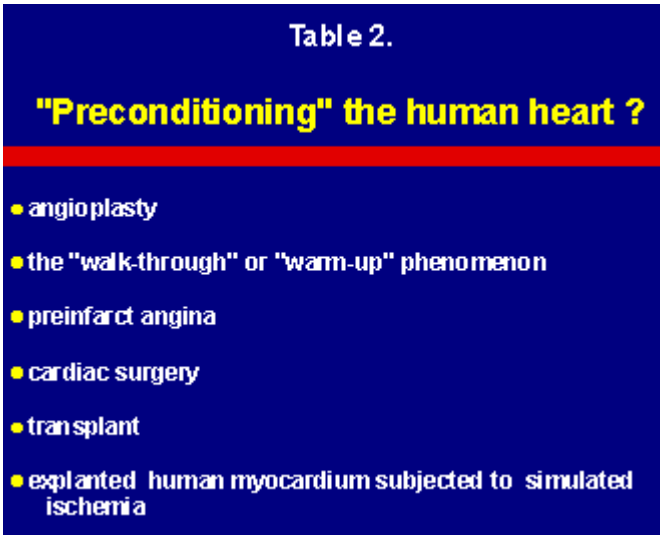

Table 2

Protection with preinfarct angina: a clinical correlate to preconditioning?

If brief antecedent ischemia can protect the human heart against infarction, then preinfarct angina should, in theory, represent a clinical correlate of ischemic preconditioning. Indeed, in support of this concept, a retrospective analysis conducted by our group of in-hospital outcome in the TIMI-4 trial revealed that patients with a history of angina at any time before acute myocardial infarction (MI) had a lower incidence of in-hospital death, congestive heart failure and/or shock, as well as smaller infarct sizes (determined by creatine kinase release) when compared to the cohort without preinfarct angina (Figure 4A) [15]. Moreover, this protection could not simply be ascribed to differences between groups in either the use of antianginal mediations or the presence of angiographically visible collateral vessels [15]. We further reasoned, based on experimental studies, that if angina truly preconditions the human heart, then the greatest protection should be seen in patients experiencing anginal episodes closest to the time of MI. In this regard, prospective temporal analysis of data from the TIMI-9B study demonstrated that the incidence of death, recurrent MI, heart failure and/or shock during the initial 30 days post-infarction was lower in

patients exhibiting angina within < (less than) 24 hours of their MI versus those with either no angina or angina at earlier time points [16].

While these data suggest that brief antecedent ischemia may effectively precondition the human heart, not all studies are consistent with this theory. For example, in the International Tissue Plasminogen Activator/Streptokinase Mortality Trial, antecedent angina was a predictor of a worse (rather than improved) clinical outcome: i.e., mortality in-hospital and at 6 months post-MI was significantly higher in patients with versus without preinfarct angina [17] (Figure 4B). Indeed, disagreement among studies is not limited to the setting of preinfarct angina: for each of the 5 clinical scenarios cited as clinical evidence of ischemic preconditioning, conflicting results have been obtained [2].

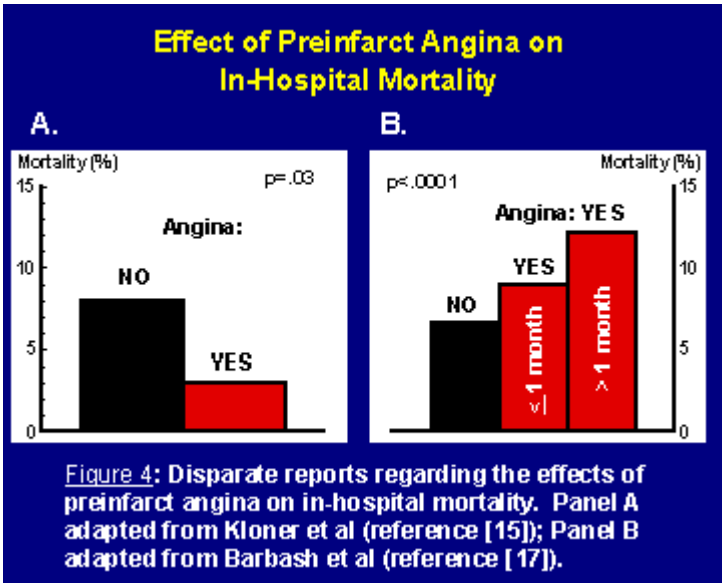

Figure 4: Disparate reports regarding the effects of preinfarct angina on in-hospital mortality. Panel A adapted from Kloner et al (reference [15]); Panel B adapted from Barbash et al (reference [17]).

Figure 4

Exploring the discrepancies: insights from isolated human tissue samples

How can these discrepancies be explained? There is speculation that differences in baseline demographic characteristics - most notably, the age of the patients, as well as the incidence of hypertension, heart failure, diabetes etc - may play a confounding role. Perhaps most notably, recent data have raised concern that the myocardium of diabetics may not be amenable to preconditioning-induced protection [18]. However, there is, at present, no definitive evidence from either experimental or clinical studies that increased age (reviewed in [19] or concomitant disease alters the efficacy of preconditioning.

A second obvious possibility, given the inherent limitations of all clinical protocols, is that the favorable outcome seen in some studies with "preconditioning" was due to other spurious factors (i.e., baseline differences in collateral perfusion between groups; progressive recruitment of collateral flow with repeated ischemia [20], rather than an increased tolerance of the heart to ischemia. However, a growing number of studies have demonstrated, using explanted human myocardial samples subjected to simulated ischemia, that myocyte viability is significantly improved in preconditioned groups versus controls [21,22] (Table 2). These data provide perhaps the most promising grounds for optimism that, at least in some instances, ischemic preconditioning can elicit protection in the human heart.

CELLULAR MECHANISMS OF ISCHEMIC PRECONDITIONING

While the ability of preconditioning to limit infarct size has been exhaustively documented, the obvious question that continues to beg for resolution is: what are the cellular mechanisms, triggered by brief ischemia, that result in cardioprotection?

Fifteen years of intensive investigation has yielded compelling evidence that preconditioning is a

receptor-mediated phenomenon. In the simplest of terms, brief antecedent ischemia is thought to stimulate one or more receptors on the myocyte membranes, thereby initiating one or more signal transduction pathways that culminate in the phosphorylation of a membrane-bound effector protein and ultimately render the myocytes resistant to sustained ischemia (Figure 5); reviewed in [2]. Considerable progress has been made in elucidating both the proximal and distal components of this paradigm. First, a wealth of data has established the specific involvement of G-protein coupled receptors: although the first insight into this concept was obtained from observations that adenosine released from myocytes during brief antecedent ischemia/reperfusion, and resultant stimulation of A_1 and/or A_3 receptors, can initiate cardioprotection, it is now recognized that this pathway can be triggered by multiple receptors (including the M2 muscarinic, α (alpha)-adrenergic, δ (delta)-opioid, etc) in this family [2]. In addition, as discussed in detail in the lecture by Gross and reviewed in [23], considerable interest has focused on the mitochondrial and/or sarcolemmal ATP-sensitive potassium channel as the purported end-effector. In contrast, efforts to identify the central component(s) of the paradigm - the signal transduction pathway(s) - have yielded discrepant and controversial results.

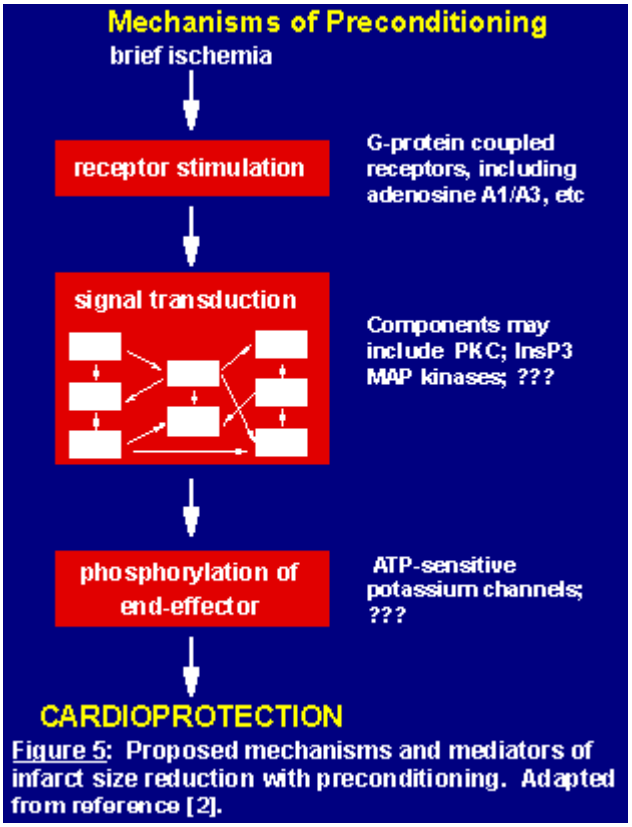

Figure 5

The PKC hypothesis

The first - and, indeed, most popular - integrative cellular hypothesis, pioneered by Downey and colleagues in 1994, is that infarct size reduction with preconditioning is critically mediated by the enzyme protein kinase C (PKC) [24]. In brief: stimulation of G-protein coupled receptors during the preconditioning stimulus is proposed initiate production of the second messenger diacylglycerol and result in the activation and subcellular redistribution of one or more of the 12 isoforms of PKC from the cytosol to the myocyte membranes. This then presumably places active PKC in the correct position, early at the start of the sustained test occlusion, to phosphorylate the membrane-bound end-effector and elicit the reduction in infarct size.

A host of studies, largely conducted in rabbit and rat models and for the most part employing pharmacologic agonists and antagonists of PKC, have provided corroborative evidence in support of this concept (reviewed in [2,25]. Moreover, direct and quantitative isoform-specific immunoblotting has

identified PKCε (epsilon) as the isoform involved in preconditioning-induced cardioprotection [26]. However, evidence in support of the PKC hypothesis is not equivocal, particularly in large animal models [2,25]. For example, we have found that PKC inhibitors fail to block the reduction in infarct size obtained with preconditioning in the canine model [27]. Moreover, neither brief episodes of increased oxygen demand (tachycardia: an effective preconditioning stimulus in dogs [28], nor, in preliminary studies from our group, brief preconditioning ischemia per se, elicit translocation of PKCε (epsilon) to the membrane-containing particulate fraction in this species. Similarly, in the pig, investigators have reported that combined inhibition of PKC and protein tyrosine kinases is required to block the benefits of preconditioning [29], while others have concluded, in marked contrast to the PKC hypothesis, that PKC antagonists protect the heart and reduce infarct size [30].

Beyond PKC: multiple pathways and kinase cascades

Although these seemingly discrepant results might pessimistically be viewed with disappointment, they nonetheless underscore a critical point: i.e., that infarct size reduction with preconditioning undoubtedly involves complex multi-factorial, integrated and/or redundant signaling pathways. For example, we have found that myocardial concentrations of inositol 1,4,5-trisphosphate, (InsP3) the second messenger generated 'in parallel' with diacylglycerol (the substrate for PKC activation), are doubled in response to brief preconditioning ischemia in both rabbit and dog heart (reviewed in [31]). This latter observation may be especially noteworthy, given the lack of support for the 'PKC hypothesis' in the dog model. Perhaps more importantly, there is evidence to suggest that this increase in InsP3 content with brief ischemia contributes importantly to infarct size reduction with preconditioning in the rabbit [32].

In addition to the contribution(s) of diacylglycerol-InsP3-PKC, it has been hypothesized that multiple kinases, either 'in parallel' or 'in series' with PKC, mediate the increased resistance to ischemia seen with preconditioning. Although numerous kinases are under investigation, the candidate that has most recently gained favor is p38 mitogen-activated protein kinase (MAPK). Indeed, a dual role for p38 MAPK has been proposed: activation of p38 MAPK during brief antecedent ischemia has been suggested to participate in triggering the benefits of ischemic preconditioning [33], while a further augmentation of p38 MAPK activity during sustained occlusion in preconditioned hearts versus controls may serve to mediate cardioprotection [34,35].

There is general agreement that, in rat and rabbit hearts, brief episodes of ischemia typically used as preconditioning stimuli elicit a robust, ~5-fold increase in myocardial p38 MAPK activity [36,37]. In addition, several (but not all) studies have concluded, via the use of the pharmacologic inhibitor SB 203580, that this activation of p38 MAPK signaling during antecedent ischemia may indeed play a role in initiating the benefits of preconditioning [33]. In contrast, the second component of this 'dual hypothesis' has been disputed by recent evidence from our laboratory and others showing that the ischemia-induced increase in p38 MAPK activity during the sustained test occlusion is attenuated, rather than augmented, in preconditioned hearts versus controls [36,37]. This observation may be of physiologic relevance, as 'loading' of the heart with SB 203580, such that p38 MAPK activity is phamacologically inhibited during the early minutes of sustained ischemia, is, in itself, capable of eliciting a modest but significant reduction of infarct size [37].

As with the 'PKC hypothesis', efforts to resolve the role of p38 MAPK in infarct size reduction with preconditioning have cle arly resulted in controversy. These discrepancies may reflect the fact that, as with PKC, there are at least 4 isoforms of p38 MAPK and, most notably, the emerging evidence that the major isoforms present in heart - p38 α(alpha) and β(beta) - may have divergent effects on myocyte viability (reviewed in [38]. Development of isoform-selective antibodies and inhibitors will in all likelihood be required in order to resolve this issue.

The 'signaling module' approach

Efforts to date to identify the mechanisms involved in ischemic preconditioning have largely employed a 'linear' strategy to sequentially investigate (through the use of selective pharmacologic tools, biochemical

assays, etc) the potential involvement of individual signaling elements. However, recent advances in proteomic and bioinformatic technologies have prompted the emergence of a comprehensive, complementary approach - termed the integrated 'signaling module' concept - in which the subcellular location and dynamic, co-ordinated interactions of multiple proteins are probed [39,40]. The first test of this contemporary, technology-driven approach, pioneered by Ping and colleagues [39], has identified 36 structural, signaling and stress-responsive proteins physically allied with PKCε (epsilon), which may thus, by association, contribute to preconditioning-induced cardioprotection or other functions governed by PKCε (epsilon) in heart. Although the potential power of the 'signaling module' concept cannot be disputed, the requisite validation that these candidate proteins are, indeed, involved in preconditioning may prove to be a daunting task. As a result, the practical utility of the 'signaling module' approach in resolving the complexities of ischemic preconditioning remains to be established.

SUMMARY

Ischemic preconditioning stands virtually alone in its unquestionable ability to limit infarct size in the controlled setting of the experimental laboratory. Moreover, there is grounds for cautious optimism that brief antecedent ischemia may similarly protect or 'precondition' the human heart. The current challenges are to elucidate - using 'traditional' assays and pharmacologic tools coupled with contemporary technologies - the elaborate web of cellular mediators and signal transduction pathways that effect the reduction in infarct size achieved with preconditioning and, ultimately, translate this information to the intelligent design of novel and benign strategies to prophylactically render the human heart resistant to sustained ischemia.

REFERENCES

For purposes of brevity, only a limited number of key references are cited. A comprehensive reference list is published in: Przyklenk, K. Ischemic preconditioning. J Thrombosis Thrombolysis 2000;9:99-103.

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124-1136.

2. Przyklenk K, Kloner RA. Ischemic preconditioning: exploring the paradox. Prog Cardiovasc Dis 1998;40:517-547.

3. Przyklenk K, Bauer B, Ovize M et al. Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 1993;87:893-899.

4. Pell TG, Baxter GF, Yellon DM, Drew GM. Renal ischemia preconditions myocardium: role of adenosine receptors and ATP-sensitive potassium channels. Am J Physiol 1998;275:H1542-H1547.

5. Dickson EW, Lorbar M, Porcaro et al. Rabbit heart can be 'preconditioned' via transfer of coronary effluent. Am J Physiol 1999;277:H2451-H2457.

6. Speechly-Dick ME, Baxter GF, Yellon DM. Ischemic preconditioning protects hypertrophied myocardium. Cardiovasc Res 1994;28:1025-1029.

7. Li G, Tokuno S, Tahepold P et al. Preconditioning protects the severely atherosclerotic mouse heart. Ann Thorac Surg 2001;71:1296-1302.

8. Fenton RA, Dickson EW, Meyer TE et al. Aging reduces the cardioprotective effect of ischemic preconditioning in rat heart. J Mol Cell Cardiol 2000;32:1371-1375.

9. Przyklenk K, Li G, Whittaker P. No loss in the in vivo efficacy of ischemic preconditioning in middle-aged and old rabbits. J Am Coll Cardiol 2001: in press.

10. Przyklenk K, Kloner RA. Preconditioning: a balanced perspective. British Heart J 1995;74:575-577.

11. Cohen MV, Yang XM, Downey JM. Conscious rabbits become tolerant to multiple episodes of ischemic preconditioning. Circ Res 1994;74:998-1004.

12. Bolli R. The late phase of preconditioning. Circ Res 2000;87:972-983.

13. Verdouw PD, Gho BCG, Duncker DJ. Ischemic preconditioning: is it clinically relevant? Eur Heart J 1995;16:1169-1176.

14. Yellon DM, Dana A. The preconditioning phenomenon: a tool for the scientist or a clinical reality? Circ Res 2000;87:543-550.

15. Kloner RA, Shook T, Przyklenk K et al. Previous angina alters in-hospital outcome in TIMI-4: a clinical correlate to preconditioning? Circulation 1995;91:37-47.

16. Kloner RA, Shook T, Antman EM et al. Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. Circulation 1998;97:1042-1045.

17. Barbash GI, White HD, Modan M et al. Antecedent angina pectoris predicts worse outcome after myocardial

infarction in patients receiving thrombolytic therapy: experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. J Am Coll Cardiol 1992;20:36-41.

18. Ghosh S, Standen NB, Galinanes M. Failure to precondition pathologic human myocardium. J Am Coll Cardiol 2001;37:711-718.

19. Kloner RA, Shook T, Cannon CP, Przyklenk K. Ischemic preconditioning: implications for the geriatric heart. Am J Geriatric Cardiol 2001;10:145-148.

20. Billinger M, Fleisch M, Eberli FR et al. Is the development of myocardial tolerance to repeated ischemia in humans due to preconditioning or to collateral recruitment? J Am Coll Cardiol 1999;33:1027-1035.

21. Ikonomidis JS, Tumiati LC, Weisel RD et al. Preconditioning human ventricular cardiomyocytes with brief periods of simulated ischemia. Cardiovasc Res 1994;28:1285-1291.

22. Ghosh S, Standen NB, Galinanes M. Preconditioning the human myocardium by simulated ischemia: studies on the early and delayed protection. Cardiovasc Res 2000;45:339-350.

23. Gross GJ, Fryer RM. Sarcolemmal versus mitochondrial ATP-sensitive K+ channels and myocardial preconditioning. Circ Res 1999;84:973-979.

24. Ytrehus K, Liu Y, Downey JM. Preconditioning protects ischemic rabbit hearts by protein kinase C activation. Am J Physiol 1994;266:H1145-H1152.

25. Simkhovich BZ, Przyklenk K, Kloner RA. Role of protein kinase C as a cellular mediator of ischemic preconditioning: a critical review. Cardiovasc Res 1998;40:9-22.

26. Ping P, Zhang J, Qiu Y et al. Ischemic preconditioning induces selective translocation of protein kinase C isoforms e and h in the heart of conscious rabbits without subcellular redistribution of total protein kinase C activity. Circ Res 1997;81:404-414.

27. Przyklenk K, Sussman MA, Simkhovich BZ, Kloner RA. Does ischemic preconditioning trigger translocation of protein kinase C in the canine model? Circulation 1995;92:1546-1557.

28. Domenech RJ, Macho P, Velez D et al. Tachycardia preconditions infarct size in dogs: role of adenosine and protein kinase C. Circulation 1998;97:786-794.

29. Vahlhaus C, Schulz R, Post H et al. Prevention of ischemic preconditioning only by the combined inhibition of protein kinase C and protein tyrosine kinase in pigs. J Mol Cell Cardiol 1998;30:197-209.

30. Vogt AM, Htun P, Arras M et al. Intramyocardial infusion of tool drugs for the study of molecular mechanisms in ischemic preconditioning. Basic Res Cardiol 1996;91:389-340.

31. Przyklenk K, Simkhovich BZ, Bauer B et al. Cellular mechanisms of infarct size reduction with preconditioning: role of calcium? Ann NY Acad Sci 1999;874:192-210.

32. Gysembergh A, Lemaire S, Piot C et al. Pharmacological manipulation of Ins(1,4,5)P3 signaling mimics preconditioning in rabbit heart. Am J Physiol 1999;277:H2458-H2469.

33. Maulik N, Yoshida T, Zu YL et al. Ischemic preconditioning triggers tyrosine kinase signaling: a potential role for MAPKAP kinase 2. Am J Physiol 1998;275:H1857-H1864.

34. Weinbrenner C, Liu GS, Cohen MV et al. Phosphorylation of tyrosine 182 of p38 mitogen-activated protein kinase correlates with the protection of preconditioning in the rabbit heart. J Mol Cell Cardiol 1997;29:2382-2391.

35. Nakano A, Baines CP, Kim SO et al. Ischemic preconditioning activates MAPKAPK2 in the isolated rabbit heart: evidence for the involvement of p38 MAPK. Circ Res 2000;86:144-151.

36. Marias E, Genade S, Huisamen B et al. Activation of p38 MAPK induced by a multi-cycle ischemic preconditioning protocol is associated with attenuated p38 MAPK activity during sustained ischemia and reperfusion. J Mol Cell Cardiol 2001;33:769-778.

37. Gysembergh A, Simkhovich BZ, Kloner RA, Przyklenk. p38 MAPK is not increased early during sustained coronary artery occlusion in preconditioned versus control rabbit hearts. J Mol Cell Cardiol 2001;33:681-690.

38. Ping P, Murphy E. Role of p39 mitogen-activated protein kinase in preconditioning: a detrimental factor or a protective kinase? Circ Res 2000;86:921-922.

39. Ping P, Zhang J, Pierce WM et al. Functional proteomic analysis of protein kinase C e signaling complexes in the normal heart and during cardioprotection. Circ Res 2001;88:59-62.

40. Vondriska TM, Klein JB, Ping P. Use of functional proteomics to investigate PKCe-mediated cardioprotection: the signaling module hypothesis. Am J Physiol 2001;280:H1434-H1441.

Top

by the lecturer or experts on the subject in the Basic Research list.
Please fill in the form (in Spanish, Portuguese or English) and press the "Send" button.

Question, contribution or commentary:

Name and Surname:

Country: Argentina

E-Mail address: @

Send Erase

Top

2nd Virtual Congress of Cardiology

Dr. Florencio Garófalo
Steering Committee
President
fgaro@fac.org.ar
fgaro@satlink.com

Dr. Raúl Bretal
Scientific Committee
President
rbretal@fac.org.ar
rbretal@netverk.com.ar

Dr. Armando Pacher
Technical Committee - CETIFAC
President
apacher@fac.org.ar
apacher@satlink.com

This company contributed to the Congress