ischemia-reperfusion postconditioning maneuver per se causes some extent of ischemia-induced damage, and the injury made by relatively short-index ischemia was too small to be substantially rescued by ischemic postconditioning. Second, a short time period of <1 min after the onset of reperfusion/reoxygenation before the onset of the brief ischemia postconditioning might protect the myocardium (230), whereas a longer time period invalidates cardioprotection from the following brief ischemia (88, 230). While time periods longer than 1 min fail to exert cardioprotection in small rodent models (88), it is still effective after 3 min in large animal models (189), whereas a 5-min interval seems to be beyond the cardioprotective limit (218) even in the human. Third, the duration and number of ischemic postconditioning procedures that could affect the strength of stimulus might also be critical (143). In vivo, the predominant findings across the species are that at least three cycles of brief occlusion and reperfusion are needed to elicit substantial cardioprotection as measured by reduced myocardial cell death (71, 118, 143), but additional cycles did not seem to provide further protection (88, 230). Also, a 10-s to 1-min period appears to be the optimal duration for an ischemic postconditioning mechanism to limit infarct injury (88, 143), and this tends to be shorter in small animals (26, 230).

Role of brief ischemia in putative mechanisms of postconditioning. Taken together, the postconditioning procedure should start within a few minutes after index ischemia, and periods of ischemia, <1 min, should be repeated at least several times within the total duration of several minutes (230). Because preconditioning ischemia and reperfusion periods do not require such strict time windows as postconditioning, preconditioning and postconditioning transient ischemia might use different mechanisms and conditions: postconditioning brief ischemia at the moment of reperfusion injury activates triggers or mediators that cause "instant" cardioprotection, whereas the brief preconditioning ischemia has additional time before the final effectors are activated, either during index ischemia or upon reperfusion. Therefore, limited signals and events, which are caused by brief ischemia and altered within seconds or a few minutes, could actually confer the same cardioprotection as postconditioning.

Indeed, transient acidosis, which may result from the brief ischemic period, might directly confer cardioprotection by attenuating intracellular Ca^{2+} levels, regional ROS generation (88, 118), and mPTP opening (29), independent of subcellular kinase signaling pathways (135). However, accumulating evidence shows that postconditioning strictly requires a brief ischemic/anoxic phase to activate the RISK pathways (ERK and Akt) (118, 230), produce NO, and open mitochondrial K_{ATP} channels (230), thereby preserving mitochondrial function (143) and preventing apoptotic changes (149). This requirement implies a common cardioprotective mechanism for ischemic preconditioning and postconditioning because postischemic activation of RISK pathways is also important for preconditioning, as we described in *p38 MAPK, ERK, and phosphatidylinositol 3-kinase/Akt.* Prompt activation of the RISK pathways (63) could also subsequently inhibit mediators, such as GSK-3β, prevent mPTP opening, or induce NO synthesis, and most of these are common to ischemic preconditioning (242) and reduce ROS production and Ca^{2+} overload (197).

Role of transient reperfusion in the postconditioning mechanism. Meanwhile, Cohen et al. (29) reported that the restoration of oxygenation is necessary to activate PKC and cardioprotective cascades, while maintaining an acidic myocardial pH for several minutes until RISK cascades can be activated. Other reports also showed that the paradoxical effects of postconditioning might be related to the divergent effects of postconditioning on Akt phosphorylation and ROS production (118). Such mechanisms are recognized as the reason why brief ischemia and reperfusion should be frequently repeated upon reperfusion to obtain the unique protection of postconditioning. Accordingly, cotreatment with the ROS scavenger *N*-(2-mercaptopropionyl)glycine is reported to blunt cardioprotection by ischemic postconditioning (29).

Subsequent cardioprotective mechanisms of postconditioning. Furthermore, Garcia-Dorado and colleagues (76) reported that the activation of the cGMP/PKG pathway is upstream of delayed normalization of intracellular pH upon reperfusion via PKG-dependent inhibition of Na^+/H^+-exchange. This indicates that the pre- and postconditioning mechanisms differ substantially because the Na^+/H^+ exchange inhibition seems distant from cardioprotection that is induced by ischemic preconditioning (55).

In addition, the contribution of some endogenous autacoids, such as adenosine and opioids as well as their receptors (mostly GPCR), on postconditioning-induced cardioprotection is also expected (143). Adenosine is increasingly released or focally accumulated upon reperfusion (90), and it is recognized to cause cardioprotection before index ischemia as a trigger of preconditioning, as well as at reperfusion as an effector of both preconditioning (95) and postconditioning (143). In a rodent model, the nonselective opioid receptor antagonist naloxone, as well as the selective antagonists of specific (δ, κ, or μ) opioid receptors, blunted cardioprotective postconditioning; however, the nonselective agonist morphine exerted pharmacological postconditioning (239). There are other possible mediators of postconditioning-induced cardioprotection such as bradykinin or tyrosine kinase receptors (143), but their mechanisms of action are still under discussion.

Clinical Translational Trials Based on Cardioprotection of Pre- and Postconditioning

It would be extremely beneficial if direct or mimicking procedures of cardioprotection by preconditioning and postconditioning in the clinical fields are successful. Confirmation of a clinical presence of cardioprotection induced by ischemic preconditioning (78) and postconditioning (58) against ischemia-reperfusion injury has warranted recent clinical investigations.

Preconditioning procedures for elective ischemia-reperfusion. Yellon et al. initially found in open-heart surgery that intermittent cross clamping preserved cardiac ATP levels (231) and protected the myocardium (81). Accordingly, unstable angina during the last 48 h before surgery mimicked preconditioning in the early postoperative period (224). Furthermore, ischemic preconditioning significantly reduced lethal postoperative ventricular arrhythmia (225) as well as postoperative atrial fibrillation (226). However, because scheduled cardiac surgeries usually employ cardioplegia and anesthesia, which have the potential to provide cardioprotection (42), the added benefit of

additional treatments seems controversial even after prospective clinical trials (216). Even in the case of elective percutaneous coronary intervention, the preceding use of some drugs such as statins was reported to reduce myocardial injury (132), but the application of its putative downstream mediator by nitroglycerin before ischemic insult failed to exert any significant cardioprotection (82). One of the reasons it may be difficult to identify preischemic pharmacological strategies mimicking "triggers of preconditioning" could be the critical timing and intensity required for procedures in clinical situations.

By contrast, in a procedure called "remote preconditioning," promising results have been obtained in recent trials where cardioprotection was successfully achieved by applying repeated cycles of transient ischemia on distant organ(s), such as limb muscles (23, 220).

Postconditioning mimetics for predictable or unexpected ischemia-reperfusion. Because cardioprotection by both preconditioning and postconditioning mainly focuses on the reduction of ischemia-reperfusion injury and because the accessibility of sudden unexpected ischemia-reperfusion, such as acute coronary syndrome, is usually quite convenient after the onset of ischemic insult, most of the recent translational therapeutic strategies are applied at the time of reperfusion. This protocol is followed because of findings of "final effectors of preconditioning" and "contributors of postconditioning" at reperfusion, which share some common pathways (64). Unfortunately, very few large clinical trials to date have successfully shown sufficient cardioprotection (129). As the initial translational application in the clinical field, the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial (116a) proposed cardioprotection by adenosine, which is considered to be a final effector of preconditioning at reperfusion. It revealed that patients with acute myocardial infarction who underwent continuous intravenous adenosine infusion together with percutaneous transluminal coronary recanalization had a smaller infarct size and a better functional recovery than those without adenosine infusion, especially in the instances of anterior wall infarction. However, a following AMISTAD-II trial (162), which specifically evaluated anterior wall infarction, found no difference in the primary end point of new congestive heart failure, rehospitalization for CHF, or death from any cause within 6 mo, although the infarct size tended to decrease in a dose-dependent manner. Cohen and Downey (31) addressed an important limitation in the AMISTAD-II study regarding the method for calculating the infarct size and the different measurements of infarction in the placebo group (45 and 27% in AMISTAD-I and -II, respectively). Similarly, the Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage (J-WIND) trial (89a) successfully found cardioprotection when recombinant human atrial natriuretic peptides (ANP) were administered at reperfusion as adjunctive therapy just after successful percutaneous coronary intervention in acute phase, which reduced myocardial creatine kinase (CK) release and increased left ventricular (LV) ejection fraction at 6–12 mo. In another portion of this study, a hybrid of the K_{ATP} channel opener and the NO donor nicorandil failed to show any infarct limitation in the acute phase, although oral administration during follow-up increased LV ejection fraction. Differences in the results among these studies might be due to differences in the details of the protocols used, but the favorable outcome, especially in chronic phase, is also supported by other clinical trials (79, 89a), as well as the preceding Impact of Nicorandil in Angina (IONA) study (77), demonstrating chronic cardioprotection due to nicorandil by reducing coronary heart disease death, nonfatal myocardial infarction, or unplanned hospital admission for anginal heart attack. Therefore, at least the chronic use of nicorandil as well as the adjunctive use of ANP might be recognized as evidence-based medicine in the clinical field, originated in the knowledge of pre- and postconditioning-induced cardioprotection. On the other hand, following the initial success in protecting the myocardium in both the acute (195) and chronic phase (206) in patients suffering from left anterior descending coronary artery or right coronary artery infarction within 6 h of the onset with four cycles of 60 min ischemia-reperfusion, the direct application of postconditioning brief ischemia-reperfusion is also intensively evaluated. Actually, the salvage impact varies among the studies, probably depending on critical requirements in postconditioning maneuvers, and it seems less protective by the protocols that have fewer cycles or longer intermission (143).

Among recent studies using the cardioprotective signaling of postconditioning, the use of 3-hydroxy-3-methylglutaryl-CoA inhibitors (statins) is reported as a readily available, safe, and hopeful option to date. The immediate use of statins either before the onset of ischemia (72, 215) or around the reperfusion period (173) reduced infarct size regardless of hyperlipidemia. This result was also shown in humans (125); in addition, immediately using statins at these time point also reduced adverse outcomes when used as late as 24 h after reperfusion (182). This evidence strongly suggests that cardioprotection induced by statins goes beyond lipid lowering and involves the signaling cascades of postconditioning, such as Akt activation (173) and oxidative stress reduction (72).

Another emerging target is the use of the mPTP inhibitor cyclosporine A, a noteworthy and quite reasonable pharmacological intervention to date, which exhibited cardioprotection in acute phase (153) by infarct-limitation, measured in terms of CK release and MRI image on *day 5* after infarction, as well as in chronic phase (126) by restoring LV function. The findings of protection by cyclosporine are now expanded in endothelial function upon reperfusion in humans (140) but seem still immature and need further confirmation in large-scale clinical trials to establish evidence-based medicine.

Comorbidities and Cardioprotection: Prevailing Knowledge into Real-World Clinical Medicine

The most important issue is to bridge the results of basic research with clinical medications or therapeutic procedures. It is unfortunately true that there is an inevitable gap in the scientific approaches used in basic science and in clinical medicine. Clinical science largely relies on statistics because of heterogeneity of disease conditions and individuals, such as age, sex, background diseases, and their comorbidities (45).

Hypertension and cardiac hypertrophy. Hypertrophied myocardium is at greater risk of exacerbating myocardial injury after ischemia-reperfusion through the development of rigor contracture during ischemia, resulting in reduced contractile function and increased CK release (45). Also, epidemiologic (165) and experimental studies (17) show that ventricular

tachyarrhythmias are highly associated with hypertensive LV hypertrophy (LVH), probably via abnormalities in ectopic ion channel currents (45) and increased dispersion of action potential duration through reentrant mechanisms induced by increased interstitial fibrosis (221). Accordingly, the preconditioning effect of prodromal angina is reportedly attenuated in acute myocardial infarction patients with hypertensive LVH (203). It also seems to be the case with cardioprotection by ischemic (150) and pharmacological (151) postconditioning, although few studies have been published on this point.

It is important to distinguish between the primary benefits of regression of LVH or the reduction of blood pressure from those of acute treatments during ischemia-reperfusion when considering the effects of cardioprotective interventions. The regression of LVH by lowering blood pressure leads to a reduction in the susceptibility to negative outcomes, especially arrhythmias. In fact, the pharmacological reduction of acute blood pressure with LVH reduced mortality and infarct size to control levels (74), supporting the contribution of perfusion pressure rather than LVH to potentiating irreversible injury in hypertensive animals. Also, classic ischemic preconditioning preserved cardioprotection in the isolated model (40) of rats with pressure-overloaded LVH. On the other hand, there is evidence that normalization of myocardial action potential duration is related to a restoration of transient outward current density after LVH regression (235), and pharmacological cardioprotection by bradykinin was attenuated in the isolated pressure-overloaded hypertrophied hearts (40), even though the isolated effects of either high blood pressure or LVH are still arguable.

Although the influence of acutely applied cardioprotective procedures on reducing injury in established LVH has been immature to date, Rajesh et al. (156) propose the effectiveness of opening K_{ATP} channels in the protection of preconditioning.

Heart failure. The unfavorable situations are quite similar in long-duration hypertension in the status of cardiac remodeling and in heart failure. Studies in isolated hearts of aged rats showed that preconditioning is protective in control hearts collected from normotensive animals, but in hearts collected from age-matched hypertensive animals, it neither enhanced postischemic functional recovery nor attenuated creatine phosphate release during global ischemia-reperfusion (41, 131). This finding highly suggests a reduced efficacy of preconditioning in chronic hypertension or in the presence of aging and hypertension. In rabbits, ischemic preconditioning failed to reduce infarct size in postinfarction remodeled hearts, whereas cardioprotection by pharmacological preconditioning with diazoxide was not affected (127). Accordingly, in right atrial appendages obtained from patients, ischemic preconditioning reduced myocardial injury in the myocardium in the presence of mild LV failure but failed to rescue those with severe LV failure. By contrast, diazoxide treatment resulted in similar protection for all groups (51).

These data are consistent with a defect within the upstream cardioprotective signal transduction pathway of failing hearts that does not interfere with direct activation of the downstream cardioprotective signaling cascade of preconditioning. In this way, an insufficiency in the signal transduction cascade in failing hearts might occur upstream of mitochondrial K_{ATP} channels. Ferdinandy et al. (45) have described an important potential modification of upstream cardioprotective signaling in diseased hearts at the level of adenosine metabolism. These authors found that in patients with heart failure, increased ecto-5′-nucleotidase activity results in an increased serum adenosine level (90) and leads to the loss of cardioprotection by ischemic preconditioning due to tachyphylaxis (60). These observations could potentially explain the failure of the adenosine A_1/A_{2A} receptor agonist, AMP579, to reduce the infarct size in patients with impaired LV function in the AMP579 Delivery for Myocardial Infarction Reduction (ADMIRE) study. In line with this, pharmacological postconditioning with isoflurane reduced infarct size (112) and activated the salvage kinase pathway (44) in the post-myocardial infarction-remodeled heart.

Another possible explanation could be found in mitochondrial malfunction (161), such as decreased electron transport chain activity in the status of cardiac remodeling and the failing heart. Recent studies reveal that mPTP can modulate mitochondrial function in the heart (37) and that ischemic pre- and postconditioning effects might be impaired under mitochondrial insufficiency (62) but that the direct pharmacological restoration of mitochondrial function by inhibiting cyclophilin D might protect against the failing heart (108).

Hyperlipidemia. It was initially reported that protection conferred by classic preconditioning against myocardial stunning and electrophysiological changes was lost when rabbits developed hypercholesterolemia, irrespective of atherosclerosis, which was restored by normalization of serum lipid levels (46) or the administration of statins (215). Other more recent reports (83) have shown that increasing the number of preconditioning cycles can aggravate infarct size in isolated rabbit hearts that are subjected to ischemia-reperfusion after 8 wk of experimental hypercholesterolemia. However, a number of recent studies have shown a limited impact of hypercholesterolemia on the cardioprotective effects of ischemic preconditioning (38). Taken together, it is likely that hyperlipidemia modifies the effect of preconditioning to some extent but that the net result of this effect is critically dependent on the strength of the cardioprotective signals. This also applies to late preconditioning (199) and postconditioning (73). In fact, the same rabbit in the ischemia-reperfusion model was used to show the loss of the infarct limitation in response to late preconditioning (204).

The use of statins has been reported to reduce myocardial injury regardless of hyperlipidemia both before the onset of ischemia (72, 215) and around the reperfusion period (173), suggesting that the cardioprotection induced by statins is not merely the result of a lipid-lowering effect.

Diabetes and hyperglycemia. The reduced protective effect of classic preconditioning in vivo on infarct size, ischemia-reperfusion-induced arrhythmias, and contractile dysfunction in experimental streptozotocin-induced diabetic hearts have been shown in a variety of species including rats, dogs, and sheep (45). Resistance to the protective effect of preconditioning in this experimental model has also been described for late preconditioning (39), isoflurane-induced pharmacological preconditioning (240), and postconditioning (243). Some clinical observations also suggest that patients with diabetes and ischemic heart disease might present a reduced response to preconditioning-like events, such as prodromal angina (78) and brief ischemic events, which can produce infarct limitation and increase survival after coronary angioplasty (104) in normal

hearts. Furthermore, hyperglycemia per se has been shown to be a significant risk factor for mortality in a very large cohort of hospitalized patients with acute myocardial infarction (100), as well as a determinant of infarct size, irrespective of the presence of diabetes (86).

Mitochondrial dysfunction (6) or rather mitochondrial K_{ATP} dysfunction (51) has been proposed to be the mechanism underlying this characteristic behavior of diabetic or hyperglycemic hearts. This might entail an impaired integrity of mitochondrial DNA (124), impaired Akt phosphorylation in response to ischemic preconditioning (213), increased oxidative or nitrosative stress (47) caused by impairment of mitochondrial respiratory capacity (114), as well as enhanced susceptibility to mPTP opening, caspase activation, and apoptosis (223).

In the experimental conditions described above, PKC or p38 MAPK activation were still protective, suggesting that insufficiency in the cardioprotective signaling cascade arises upstream of PKC and p38 MAPK (61). Accordingly, treatment of diabetes with insulin or pioglitazone has been suggested as a way to overcome the negative effects on cardioprotection by activating ERK and Akt, the downstream effectors and central mediators of the RISK pathway (227).

Antidiabetic drugs might have an effect on cardioprotection, beyond their direct effect on diabetes and hyperglycemia. Insulin-secreting drugs such as sulfonylureas and glinides increase insulin secretion by blocking K_{ATP} channel on the pancreatic β-cell (SUR1/Kir6.2). However, in coronary smooth muscle cells (SUR2b/Kir6.1), the K_{ATP} channel modulates coronary blood flow at rest and in hypoxia, and myocardial sarcolemmal K_{ATP} channels (SUR2a/Kir6.2) contribute to the adaptation of the myocardium to stress. Interestingly, the inhibition of cardiovascular K_{ATP} channels by sulfonylureas increases mortality in diabetic patients after coronary angioplasty (50, 104). In particular, despite the absence of structural information, mitochondrial K_{ATP} channels have been suggested to play an important role in cardioprotective mechanisms. This is thought to occur because nonselective K_{ATP} channel blocker glibenclamide and the selective mitochondrial K_{ATP} channel blocker 5-hydroxydeaconate block, at least in part (172), the cardioprotection of classic as well as late preconditioning. This has been shown in several species including humans (45). Interestingly, the selective pancreatic K_{ATP} channel blocker glimepiride does not appear to have any negative effect on cardioprotection, even when clinical data were analyzed (104).

Aging. The morbidity and mortality due to ischemic cardiovascular diseases are significantly higher in the elderly than in young adults (99). It is also generally recognized that aged hearts are resistant to cardioprotection from various kinds of preconditioning procedures (18), although there is still some controversy about the specific effects of classical, late-phase, and pharmacological preconditioning in certain animal models (34, 184).

Besides changes in structural components of the myocardium, such as increased fibrosis (174), the aged myocardium displays functional alteration of the cardiomyocytes (18). Intriguingly, telomere dysfunction even in quiescent cells, such as cardiomyocytes, produces aging-induced impaired mitochondrial biogenesis and function that lead to reduced respiratory capacity (114). This produces insufficient gluconeogenesis, cardiomyopathy, and increased ROS through the p53-PGC axis (166). The aging-induced increase in ROS generation is also the product of NADPH oxidases (116) and increased cardiac monoamine oxidase-A activity (18), as well as of reduced antioxidant capacity (187). In addition, in the aged myocardium the expression of several genes is altered (19). Among these, the decreased expression of IGF-IGF receptor, PKC-ϵ, ERK, Akt, MnSOD, and catalase might not only weaken the impact of the protective effect of preconditioning or postconditioning but also increase susceptibility to ROS. Furthermore, increased inducible NOS and decreased connexin-43 expressions (19) might be considered as an adaptation to continuous stress. Finally, aged myocardium shows a reduced tolerance to ischemic injury (1).

Ischemic preconditioning reduces infarct size and LV remodeling and therefore potentially improves the prognosis of patients with an acute myocardial infarction (78, 232). However, these benefits seem diminished in patients older than 65 yr (2). Ischemic postconditioning failed to reduce infarct size (154), but a longer and more intense postconditioning procedure restored protection (20). In accordance with this, chronic opioid treatment confers cardioprotection in both the young and senescent mouse heart via PKA activation, independently of acquisition of analgesic tolerance (145), whereas protection with acute morphine treatment, which is PKC dependent (146), is lost in aged hearts (147). Therefore, prolonged or stronger preconditioning stimuli might provide a powerful cardioprotection for the aging heart.

Regular exercise, especially endurance exercise, protects against ischemia-reperfusion injury in both young and old animals through the induction of myocardial HSPs and endothelial NOS, and either improves cardiac antioxidant capacity or restores mitochondrial function (10). Aging-induced increases in LV cardiomyocyte apoptosis and subsequent remodeling are improved by exercise, which also normalizes the Bax-to-Bcl-2 ratio in the LV of the aged rat heart (103). In the clinical setting, the protective effect of prodromal angina against subsequent acute myocardial infarction was reported to be preserved in aged patients with a high level of physical activity (3).

Sex difference. Premenopausal women have a reduced risk for cardiovascular disease, but this risk arises after menopause (65). However, a large clinical trial unexpectedly showed that hormone replacement therapy increases cardiovascular events in healthy postmenopausal women (163).

In most animal studies, no sex difference in ischemia-reperfusion injury has been observed, except in the rat model where injury was smaller in female than in male hearts (148). Furthermore, estrogen administration, at least for short duration, has been shown to reduce ischemia-reperfusion injury via acute nongenomic responses that involve the activation of Akt pathway (192). Also, nuclear estrogen receptor activation has been shown to result in an altered expression of a number of cardioprotective genes, such as NOS and HSPs, and a number of genes involved in metabolism, such as lipoprotein lipase, PGD2 synthase, and PGC-1α (133). Recently, the third category of G protein-coupled estrogen receptors has been shown to protect the myocardium regardless of sex (36), allowing us to reconsider sex-induced differences in ischemia-reperfusion injury as well as in preconditioning-induced cardioprotection.

Summary and Future Directions

In this review, we first discussed the original hypotheses and current findings regarding the nature of ischemia-reperfusion injury. Based on both basic and clinical findings, ischemic pre- and postconditioning with a cardioprotective potential has been discovered and established. We summarized here the ongoing investigation on the protective mechanisms of ischemic pre- and postconditioning as well as its potential application for molecular, pharmacological, or mechanical treatments against ischemia-reperfusion injury and subsequent adverse outcomes. Among various factors, Ca^{2+} overload and ROS generation are recognized as the key players of injury, whereas modulation on mitochondrial homeostasis as well as activation of intracellular salvaging kinase signaling (such as RISK pathway) is thought to be the emerging target of therapeutic interventions. We also reviewed major previous and upcoming translational clinical trials upon such basic findings, but we still need to further optimize such trials along with clinical comorbidities to make these trials more applicable and adaptive in clinical medicine.

Although further work is needed to understand the mechanism of cardioprotection and to make it fully applicable in the clinical setting, the connection between the bench and the bedside can be achieved by additional translational studies and established by large-scale clinical trials. We need to facilitate the creation of large clinical trials in variable situations to bring the results obtained by basic research into the real world.

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