Protection of the Myocardium During Ischemia and Reperfusion
Na\(^+\)/H\(^+\) Exchange Inhibition Versus Ischemic Preconditioning

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The hypothesis that sarcolemmal Na\(^+\)/H\(^+\) exchanger activity may contribute to myocardial injury during ischemia and reperfusion was first published in 1985, preceding by 1 year the first description of the ischemic preconditioning phenomenon. Initial pharmacological evidence in support of the Na\(^+\)/H\(^+\) exchanger hypothesis was subsequently provided by Karmazyn, who showed that amiloride (an inhibitor of the exchanger) enhanced the postischemic recovery of contractile function and reduced creatine kinase leakage in rat hearts subjected to global ischemia and reperfusion. Since then, a number of Na\(^+\)/H\(^+\) exchange inhibitors, including highly specific novel inhibitors such as HOE-694, HOE-642 (cariporide), and EMD-85131, have been shown to afford cardioprotective benefit in a variety of animal models of ischemia and reperfusion. Nevertheless, as an innovative approach to the protection of ischemic myocardium, Na\(^+\)/H\(^+\) exchange inhibition has failed to capture the imagination of cardiologists (experimental and clinical alike) to quite the same extent as ischemic preconditioning. Indeed, a survey of articles published in Circulation and Circulation Research over the past decade reveals only 14 articles whose title or abstract contains the keywords “Na\(^+\)/H\(^+\) exchange(r) and ischemia,” whereas 115 articles are identified when the combination “preconditioning and ischemia” is used. Is this a fair reflection of the relative cardioprotective efficacy, and perhaps the therapeutic potential, of these interventions?

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In this issue of Circulation, Gumina and colleagues report a comparison of the efficacy of Na\(^+\)/H\(^+\) exchange inhibition (achieved with BIIB-513, the latest addition to the family of novel Na\(^+\)/H\(^+\) exchange inhibitors) versus ischemic preconditioning in limiting infarct size in dog hearts subjected to regional ischemia and reperfusion in vivo. This is the first such comparison in a large animal, and the findings carry additional weight because they originate from a laboratory that has made a major contribution to the characterization of the powerful preconditioning phenomenon. The most striking result of the study is that extending the duration of index ischemia from 60 to 90 minutes abolishes the protective effect of ischemic preconditioning but does not affect the protection afforded by Na\(^+\)/H\(^+\) exchange inhibition. This indicates that at least in dog myocardium, Na\(^+\)/H\(^+\) exchange inhibition may afford greater protection against ischemia and reperfusion-induced injury than does ischemic preconditioning.

Does Ischemic Preconditioning Alter Na\(^+\)/H\(^+\) Exchanger Activity?

Some of the issues raised in the study by Gumina et al warrant a brief overview of the potential effects of ischemic preconditioning on Na\(^+\)/H\(^+\) exchanger activity. Intracellular acidosis occurs even during the brief periods of ischemia that are used to trigger preconditioning and is a potent stimulus for sarcolemmal Na\(^+\)/H\(^+\) exchanger activity. In addition to such allosteric activation of the exchanger by intracellular acidosis, ischemic preconditioning may also initiate post-translational regulatory mechanisms (eg, phosphorylation of the exchanger and/or its regulatory proteins) that increase Na\(^+\)/H\(^+\) exchanger activity by altering its sensitivity to intracellular H\(^+\). In this regard, it is notable that stimuli that can mimic ischemic preconditioning, such as \(\alpha_1\)-adrenergic receptor stimulation, also increase sarcolemmal Na\(^+\)/H\(^+\) exchanger activity, through an enhancement of its sensitivity to intracellular H\(^+\).7 Nevertheless, it has been shown recently that, after the induction of an intracellular acid load of comparable severity, the rate of recovery of intracellular pH is identical in preconditioned and nonpreconditioned myocardium under aerobic conditions.8 From this, it appears that any stimulation of sarcolemmal Na\(^+\)/H\(^+\) exchanger activity in preconditioned myocardium may not persist beyond the triggering ischemic episodes.

During index ischemia, a commonly observed consequence of ischemic preconditioning is a reduction in the severity of intracellular acidosis. Although other potential mechanisms for this "antiacidotic" effect exist (eg, reduced metabolic H\(^+\) production), the pertinent question within the context of this editorial is whether this effect arises from increased cellular H\(^+\) extrusion via the sarcolemmal Na\(^+\)/H\(^+\) exchanger. Al-
though the evidence outlined above would argue against such a possibility, 2 recent studies have addressed this question by determining the effects of Na⁺/H⁺ exchange inhibitors on intracellular pH. Unfortunately, the results have been contradictory, with Na⁺/H⁺ exchange inhibition shown both not to alter and to significantly attenuate the antiischemic effect of ischemic preconditioning. Furthermore, it has been suggested that this effect may arise from increased H⁺ extrusion through an alternative pathway. Therefore, from the available data, it is not possible to deduce that ischemic preconditioning increases Na⁺/H⁺ exchanger activity during index ischemia. Conversely, unless ischemic preconditioning increases the exchanger’s sensitivity to intracellular H⁺, attenuated intracellular acidosis during index ischemia in preconditioned hearts would be expected to reduce Na⁺/H⁺ exchanger activity.

**Na⁺/H⁺ Exchanger Inhibition and Ischemic Preconditioning: Counteractive or Additive?**

Regardless of whether ischemic preconditioning alters sarcolemmal Na⁺/H⁺ exchanger activity, an important question is whether an active exchanger is necessary to achieve cardioprotective benefit from this intervention. A number of studies have addressed this issue, again by using pharmacological inhibitors to suppress Na⁺/H⁺ exchanger activity at various times during the experimental protocol: during the cycles of triggering ischemia, during index ischemia, or during both periods. Although contradictory findings have also been reported, the majority of these studies have shown that the cardioprotective benefit of ischemic preconditioning is not attenuated by Na⁺/H⁺ exchange inhibition, indicating that an active exchanger is not necessary to achieve such benefit. To the contrary, in some studies, the combination of Na⁺/H⁺ exchange inhibition with ischemic preconditioning has been shown to provide an additive benefit, with the limitation of infarct size or the improvement in the recovery of contractile function appearing to be significantly greater with the combined intervention relative to either intervention alone. Provided that the Na⁺/H⁺ exchange inhibitor doses and ischemic preconditioning protocols used in these studies were those that each afforded the maximum attainable protection, then the additive effects observed may indicate independent mechanisms of action.

It is notable that both of the previous studies that have shown additive benefit with the combination of Na⁺/H⁺ exchange inhibition and ischemic preconditioning were carried out in rat hearts and that no similar additive effect has been observed in the rabbit. At first consideration, this might appear to indicate species-specific responses, with Na⁺/H⁺ exchange inhibition and ischemic preconditioning possessing distinct mechanisms of action in the rat but sharing a common mechanism of action in the rabbit. This scenario is unlikely, however, because in the rabbit heart, interventions that abolish the cardioprotective benefit of ischemic preconditioning (such as protein kinase C inhibition and ATP-sensitive K⁺ channel blockade) do not seem to affect the cardioprotective efficacy of Na⁺/H⁺ exchange inhibition. Furthermore, the study by Gumina et al. in this issue provides evidence that, in the dog heart also, the combination of Na⁺/H⁺ exchange inhibition and ischemic preconditioning affords greater cardioprotective benefit than either intervention alone, with an index ischemia of 90 minutes’ duration. A unique feature of this study is that a marked reduction in infarct size was afforded by the combination of Na⁺/H⁺ exchange inhibition by low-dose BIIB-513 and ischemic preconditioning, even though either intervention alone did not produce a statistically significant effect. The authors describe this effect of the combined intervention as “greater than additive,” which is akin to the textbook definition of synergism. However, the data may not reflect a true synergistic interaction between Na⁺/H⁺ exchange inhibition and ischemic preconditioning, because each intervention alone tended to reduce infarct size by ≈25% (Figure 3 in Reference 5) and the effect of the combined intervention was not substantially greater than the sum of the individual effects. Instead, the apparent greater-than-additive effect could have arisen by chance, in view of the intragroup variability in infarct size, which most likely reflected a variable collateral flow. Another potential confounding factor is that low-dose BIIB-513 is unlikely to have produced a complete suppression of Na⁺/H⁺ exchange activity (as evidenced by the enhanced protection afforded by a 4-fold greater dose), which makes it difficult to interpret mechanistically the effects of combining this intervention with ischemic preconditioning. Regardless of these issues, however, the important new data provided by Gumina et al. considered together with other pertinent evidence in the literature, strongly suggest that Na⁺/H⁺ exchange inhibition and ischemic preconditioning can each afford significant cardioprotective action in ischemia and reperfusion (most likely through independent mechanisms) and that the former intervention does not counteract (but may add to) the protection afforded by the latter.

**Na⁺/H⁺ Exchange Inhibition Versus Ischemic Preconditioning: Is One Superior to the Other?**

A recent Special Report in *Circulation* stated that “...other than early reperfusion, preconditioning is the strongest form of in vivo protection against myocardial ischemic injury.” While there can be no argument that reperfusion is an absolute prerequisite for the salvage of ischemic myocardium and that ischemic preconditioning is a powerful cardioprotective intervention, the new evidence provided by Gumina et al. and other published data do not wholly support this statement. The Table summarizes the protocols and main findings of 5 studies, 2 of them in vivo, which (to the best of the author’s knowledge) constitute all of the studies in the literature that have directly compared the cardioprotective efficacy of Na⁺/H⁺ exchange inhibition versus ischemic preconditioning. In these studies, ischemic preconditioning was shown to afford marked protection against ischemia-and reperfusion–induced injury, which was manifest as an attenuation of contractile dysfunction and creatine kinase leakage or a limitation of infarct size. The earlier studies all showed that Na⁺/H⁺ exchange inhibition is equally as effective as ischemic preconditioning in protecting...
the myocardium during ischemia and reperfusion. The current findings of Gumina and colleagues\textsuperscript{5} similarly demonstrate comparable efficacies with both interventions in dog hearts subjected to 60 minutes of index ischemia, but they suggest that Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition may afford superior protection when this is extended to 90 minutes.

In discussing the relative efficacy of Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition and ischemic preconditioning, Gumina et al\textsuperscript{5} coined the phrase “ceiling of protection” to describe the minimum duration of index ischemia against which a particular intervention cannot afford significant protection. Their data suggest that in the dog in vivo and with infarct size as the index of injury, this ceiling is between 60 and 90 minutes for ischemic preconditioning but >90 minutes for Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition. Although it may not be entirely helpful to extend the architectural analogy, it is probable that the higher ceiling for Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition simply reflects a further extension of the time window during which myocardial salvage can be achieved by reperfusion. The figure illustrates this concept by showing hypothetical “injury curves” that describe the relationship between ischemia duration and infarct size in 3 groups of hearts: untreated controls, hearts subjected to ischemic preconditioning, and hearts pretreated with the maximally effective dose of a Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibitor. It should be stressed that although the early sections of these curves have been drawn with the guidance of data from Gumina et al,\textsuperscript{5} the sections beyond 90 minutes (shaded area) are speculative. Nevertheless, the figure illustrates that the greater limitation of infarct size afforded by Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition versus ischemic preconditioning after extended ischemia may arise from a greater delay in the progression of ischemic injury, depicted as a further shift to the right of the injury curve. By increasing the amount of viable tissue remaining at the time of reperfusion, this would then allow significant myocardial salvage to be achieved even after extended ischemia.

The scheme proposed above does not take into account any potential contribution of reperfusion injury to the infarct size measured after ischemia and reperfusion. Recent work by Matsumura and colleagues\textsuperscript{20} suggests that in dog hearts subjected to 90 minutes of ischemia followed by reperfusion (as in the study by Gumina et al\textsuperscript{5} ), a substantial proportion of the infarcted myocardium is viable at the end of the ischemic period but loses viability after 180 minutes of reperfusion. In this context, it is important to highlight earlier evidence from Gumina and colleagues,\textsuperscript{21} also in the dog, that has shown that administration of a Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibitor cariporide shortly before reperfusion can produce a significant limitation of infarct size. Interestingly, preliminary evidence for this mode of action has been obtained in humans as well, in a recent study in which patients with anterior myocardial infarction received the Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibitor cariporide shortly before undergoing primary percutaneous transluminal coronary angioplasty.\textsuperscript{22} Therefore, it is reasonable to suggest that Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition may provide superior protection by limiting the loss of myocardial viability not only during ischemia but also during reperfusion.\textsuperscript{5}

The preclinical evidence\textsuperscript{4} that Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibition represents an effective approach to the limitation of myocardial injury during ischemia and reperfusion has been strengthened substantially by the work reported by Gumina and colleagues,\textsuperscript{5} whose data suggest that, at least in the dog, the
protection afforded by this intervention may be superior to that provided by ischemic preconditioning. Because specific and apparently well-tolerated inhibitors of the Na\(^+\)/H\(^+\) exchanger are now available, a further advantage of Na\(^+\)/H\(^+\) exchange inhibition over ischemic preconditioning may arise from the greater practicability of assessing its therapeutic potential. Indeed, a multicenter clinical trial, designed with the objective of assessing the potential benefits of cariporide in patients with acute coronary syndromes, was recently completed. Although the preliminary results of this trial (as presented at the American College of Cardiology Scientific Session in March 1999) have not shown a significant overall benefit, subgroup differences suggest that cariporide treatment may have provided benefit when ischemia was terminated by reperfusion. This finding, if confirmed by detailed analysis, would be wholly consistent with the established evidence for selective mediation by the \(\alpha_1\)-adrenergic subtype. Circ Res. 1998;82:1078–1085.


Acknowledgments
The author is supported by a British Heart Foundation Senior Lectureship Award (BR/93002). Helpful discussions with Professor David J. Hearse and Dr Michael S. Marber are gratefully acknowledged.

References


4. Avkiran M. Rational basis for use of sodium-hydrogen exchange inhibitors in animal models. 4 The challenge now is to design and perform further trials that reflect the knowledge that has been accumulated from such recent clinical experience and through extensive preclinical investigation; ultimately, only these can provide the acid test in preconditioning in hearts.


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Circulation. 1999;100:2469-2472
doi: 10.1161/01.CIR.100.25.2469
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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