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No Pain, No Gain:

The Useful Function of Angina

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Myocardial ischemia, the major cause of mortality and morbidity in the United States, accounts for nearly 20% of all deaths.[1] The prognosis of patients with acute myocardial infarction is strongly related to the amount of tissue destroyed during ischemia/reperfusion; hence, limiting this injury is of paramount importance for reducing the morbidity and mortality associated with ischemic heart disease.[2, 3] Over the past 40 years, several hundred pharmacological or nonpharmacological therapies have been reported to alleviate ischemia/reperfusion injury in experimental animal models; unfortunately, few of these results have been reproducible, and, with the exception of early reperfusion, none have been translated into clinical therapies. [4] These sobering facts provide a cogent rationale for a reassessment of the models and methodologies that have been used heretofore to test the efficacy of putative cardioprotective interventions. The obvious translational failure in this field calls for a new paradigm in which preclinical studies must be done as rigorously as their clinical counterparts, that is, using clinically relevant animal models, appropriate statistical methods, and a multicenter, randomized, blinded design using centralized core laboratories for data analysis.[4] This paradigm would also improve our understanding of the mechanism of cardiomyocyte death during ischemia/reperfusion.

One facet of ischemic biology that has received relatively little attention is the role of cardiac sensory nerves. Myocardial ischemia/reperfusion is known to cause the release of bradykinin and protons, both of which activate the vanilloid receptor 1 (VR1, also known as transient receptor potential vanilloid type 1 [TRPV1]) on the capsaicin-sensitive cardiac sensory nerves (unmyelinated [type C] or thinly myelinated [A-δ] fibers).[5] The VR1 is a nonselective cation channel that plays an important role in the polymodal detection of noxious stimuli such as low pH and heat.[6] It can also be activated by chemicals such as capsaicin (the main pungent ingredient in chili peppers), anandamide (an endocannabinoid), and lipoxygenase products.[6] VR1s are widely expressed in primary afferent fibers throughout the cardiovascular system, including the epicardium and the kidney and around central and peripheral blood vessels.[7] Recent evidence suggests that VR1s on the sensory fiber ending of the heart function as transducers responsible for sensing tissue ischemia and initiating cardiac nociception.[6, 8] Thus, activation of VR1s by ischemia results in activation

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of the sympathetic system, which leads to the cardiac sympathoexcitatory reflex and to the sensation of cardiac pain.[8, 9] In addition to initiating central autonomic reflexes, cardiac sensory nerves release neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P (SP), neurokinin A (NKA), and other neurokinins, which have been proposed to act in a paracrine manner to mitigate myocardial ischemia/reperfusion injury.[10] These neuropeptides produce coronary vasodilation and negative inotropic and chronotropic effects, which would be expected to limit the deleterious consequences of ischemia on the myocardium.[10] In support of this concept, depletion of endogenous CGRP exacerbates ischemia-reperfusion injury in pigs,[11] and there is evidence that CGRP plays a role in both the early and the late phases of preconditioning (PC), although the mechanisms are still unclear.[12–14] In addition to its own protective actions, CGRP has been shown to potentiate the effects of SP by competing for the same catabolic enzyme (neutral endopeptidase [NEP]) and thus prolonging the duration of action of SP.[15] SP increases the synthesis of NO, a major cardioprotectant that exerts a panoply of beneficial actions during ischemia/reperfusion and also induces cardiac PC.[16] Thus, activation of cardiac sensory endings has been proposed to exert salubrious effects on the ischemic/reperfused myocardium that are mediated, at least in part, by enhanced NO availability.

In this issue of *Circulation*, Wang and Wang[17] report the results of a study in which they used $VR1^{-/-}$ mice to explore the potential cardioprotective role of VR1s. Isolated hearts from $VR1^{-/-}$ and wild-type mice were subjected to 40 minutes of ischemia followed by 30 minutes of reperfusion in the presence and absence of agonists and antagonists of VR1, CGRP receptors, and SP receptors. The postischemic recovery of left ventricular end-diastolic pressure, left ventricular developed pressure, and coronary flow was impaired in $VR1^{-/-}$ compared with wild-type mice, and this coincided with a decreased release of SP in response to ischemia, which indicates that ischemic activation of VR1s initiates cardioprotective mechanisms that are mediated, at least in part, by enhanced release of SP. Interestingly, baseline SP release was similar in $VR1^{-/-}$ and wild-type mice, which suggests the existence of VR1-independent mechanisms for its release.

The investigation by Wang and Wang[17] is comprehensive and well-designed. Although previous pharmacological experiments had suggested a possible cardioprotective role of VR1s,[8, 10, 12–14, 18–20] the present study is important because it is the first to use a genetic approach (targeted deletion of VR1) to establish a modulatory function of these nociceptors on the severity of myocardial ischemia. In addition, this study is the first to suggest that VR1s are necessary for the ischemia-induced (but not basal) release of SP and that the salubrious effects of VR1s in myocardial ischemia/reperfusion are mainly due to SP. There are, however, a number of limitations that must be considered when one interprets these data. First and foremost, because all studies were conducted in isolated buffer-perfused hearts, it is unclear whether the protective effects of SP (and thus of VR1) occur in vivo. SP has been shown to activate macrophages and neutrophils, releasing inflammatory cytokines and generating free radicals,[21] effects that may negate its cardioprotective actions. The model used by Wang et al[17] is a first step toward understanding the role of VR1s and SP in modulating ischemia/reperfusion injury, but it does not reproduce the complex in vivo situation, particularly with respect to the systemic consequences of activation of sensory nerve fibers. It is therefore essential that the role of VR1 be studied in conscious animal models in which VR1 activation in the ischemic tissue may induce not only paracrine protective effects such as those observed by Wang et al[17] but also proinflammatory actions and autonomic reflexes (sympathetic activation), which may negate the local effects by increasing myocardial oxygen demands.

Another weakness is the exclusive reliance on cardiac function and coronary flow without assessment of cell death (by cardiac enzyme release or macrohistochemistry). Hemodynamic

and functional parameters, although important, do not enable a full assessment of myocardial protection because they do not distinguish between myocardial stunning (reversible injury) and myocardial infarction. For example, an improvement in the postischemic recovery of cardiac function may merely reflect attenuation of stunning, without a limitation of infarct size; this would represent a transient beneficial effect, less important than a permanent effect such as reduction of cell death.

The study by Wang and Wang[17] is important because it focuses interest on the possible protective role of nociception; however, the results must be viewed with caution. As discussed in the report of the National Heart, Lung, and Blood Institute's working group on translation of therapies for protecting the heart from ischemia,[4] randomized, blinded studies in clinically relevant animal models (including conscious models) are needed to definitively establish the presence or absence of true cardioprotection. Although admittedly demanding, this approach will greatly enhance the accuracy of experimental evaluation of potential cardioprotective drugs, which will prevent premature clinical trials. Other issues that remain to be explored in the future are the nature of the VR1-independent mechanism(s) of SP release, the molecular mechanism whereby SP limits ischemia/reperfusion injury, and the contribution of CGRP to VR1-mediated cardioprotection.

If the results in the study by Wang et al[17] are confirmed in vivo in conscious animal models, they would also have interesting clinical implications. Diabetes mellitus is known to be associated with a greater propensity to myocardial ischemia and a worse outcome after myocardial infarction and other acute coronary syndromes. Do diabetics and other patients with neuropathy experience more severe ischemic events because of impaired VR1 and SP activity and consequent loss of cardioprotection? Moreover, the results of the study by Wang et al raise the possibility of using SP or, more specifically, NK1 agonists to achieve protection against ischemia/reperfusion injury. Another implication is that blockade of VR1 receptors could be used to alleviate angina; however, this may not be desirable, because the loss of the potential cardioprotective effects of VR1 receptors may offset the analgesic effects of VR1 blockade (in addition to the fact that angina is important for alerting the patient to the presence of acute ischemia). Finally, it has been known for many years that patients with preinfarction angina have a better prognosis after acute infarction than those without preinfarction angina, a phenomenon ascribed to ischemic PC.[22–24] Evidence of ischemic PC has also been observed in other clinical settings, such as exercise-induced ischemia, open heart surgery, and coronary angioplasty.[22–24] Is this phenomenon due, at least in part, to activation of VR1 nociceptors and the attendant release of neuropeptides with PC-mimetic actions?

In summary, our understanding of the role of cardiac sensory nerves and VR1 receptors in myocardial ischemia is evolving rapidly, in light of increasing evidence that suggests that these nociceptors may play a protective role by various mechanisms. First, they serve as transducers that sense ischemia and initiate the signals that result in angina. This enables patients to discontinue ischemia-inducing activities and seek prompt medical attention. At the same time, the hypothesis has been proposed that ischemia-induced activation of VR1 receptors elicits multifarious cardioprotective signals via the release of SP, CGRP, NKA, and possibly other neuropeptides, which results in enhanced NO availability, lleviation of ischemia/reperfusion injury, and a shift to a preconditioned phenotype. Considerable additional work (including studies in conscious models) will be necessary to confirm or refute this hypothesis. If this scenario proves to be correct, angina would be useful not only because it alerts the patient to the impending cardiac injury but also because the very mechanisms that create pain would also limit the severity of the injury. Although the goal of physicians is obviously to prevent myocardial ischemia in the first place, painful ischemia

may be preferable to painless ischemia. Life has taught all of us the wisdom of the adage, "no pain, no gain." Could this truism apply to angina as well?

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