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A novel path of improving heart function after infarction

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When nitric oxide was first discovered, it was considered a toxic radical. However, through continued research, it was learned that nitric oxide was essential for health and that toxicity depended on rates of production and the oxidative character of the local environment [1]. As early as 1991, it was reported that nitric oxide reduced the necrotic area as well as myeloperoxidase in infarcted hearts suggesting that nitric oxide protected against ischemic injury by reducing neutrophil recruitment [2] Likewise, eicosanoids and hydroxylated arachidonates were considered mediators of inflammation. Yet, as eicosanoid research continued, it became clear that not only were proinflammatory eicosanoids generated after injury but also anti-inflammatory eicosanoids. Importantly, just as was shown for nitric oxide, taprostene, a stable analogue of prostacyclin, was reported to be cardioprotective [3].

Almost 15 years ago, Charles Serhan reported that first-phase eicosanoids promoted a shift in the production of anti-inflammatory lipids and that lipoxins represented a new class of lipid mediators that promoted resolution of inflammation [4]. Since that time, resolvins have been reported to decrease inflammation and promote repair in a variety of disease states by a number of laboratories. As was the case with nitric oxide and eicosanoids, continued research helped set the stage for using resolvins to treat the heart after myocardial infarction (MI).

The current study Kain et al. [5] furthers our understanding of resolvins in the injured heart by showing how resolvin D1 (RvD1) reprograms the myocardium post-MI. Their studies help define five main functions of RvD1 that appear critical for reducing inflammation and remodeling in the heart after infarction. They show that RvD1: 1) prevents splenic depletion of neutrophils; 2) regulates B cell activation; 3) does not alter neutrophil priming post-MI but decreases neutrophil density in the myocardium after 5 days; 4) promotes macrophage clearing as well as increases the M2 phenotype of macrophages; and 5) speeds up resolution of inflammation, which actually promotes changes in the extracellular matrix that decrease fibrosis and improve remodeling. What this means is that RvD1 holds great potential for not only reducing myocardial injury after MI but also for reprogramming the injured myocardium to promote effective healing. Fibrosis is limited and remodeling takes on a repair and

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Disclosure statement

None.

restores character rather than the fateful, downward, inflammatory response that leads to heart failure.

The current study adds to an increasing number of publications showing how important resolving inflammation is to healing in many different diseases. Resolvins have been administered in vivo and in vitro in a number of different disease states and injury models where results have consistently led to the singular conclusion that resolvins play important roles in resolving inflammation and promoting repair [6–13]. Accordingly, such reports provide strong support for the idea that resolvins hold great promise as therapeutic agents for treating inflammation in a wide variety of settings ranging from cognitive impairment, atherosclerosis, hyperplasia, and dermal wound healing to obesity [6,7,9–12,14]. The report by Kain et al. now demonstrates that resolvins even reduce inflammation and promote repair in the ischemic heart and as such may be effective agents for preventing myocardial scar formation after MI and maybe even heart failure.

Members of the resolvin family are metabolites of ω -3-polyunsaturated fatty acids. They are named after their precursors' docosahexaenoic and eicosapentaenoic acid. Resolvin Ds are metabolites of docosahexaenoic acid. Resolvin Es are metabolites of eicosapentaenoic acid. The report by Kain and colleagues stimulates new ideas for the continued investigation into how members of the resolvin family can improve myocardial function after MI. Such information may be important for developing more specific therapeutic resolvin-based strategies for treating the heart after MI. For example, although a single dose improved myocardial function after ischemia additional studies are needed to determine whether RvD1 therapy should be extended beyond a single treatment after MI. Will extending therapy induce even greater improvements in myocardial function?

In diseases characterized by abnormal essential fatty acid metabolism, plasma phospholipid concentrations of eicosapentaenoic acid and docosahexaenoic acid are low [15,16]. Lower concentrations of resolvins have been shown to prolong inflammation and delay recovery [15,17]. Such observations provide the rationale for using resolvins as therapeutic agents to limit inflammation. At the present time, two clinical trials are ongoing; a Phase 1 clinical trial targeting asthma, and a phase 2 clinical trial to treat chronic dry eye. The observations by Kain et al. should encourage additional investigations into how resolvins can be used to treat the myocardium after MI. Hopefully, positive results will lead to new clinical trials to determine if liposomal-delivered resolvins can improve myocardial remodeling and heart failure in humans who have had an MI just as effectively, as it did in mice.

Potential areas of future research could be studies to determine whether inhibiting myeloperoxidase increases endogenous production of resolvins and protectins [18] or whether resolvin therapy can be combined with agents designed to inhibit apoptosis and necrosis of the injured myocyte to prevent the myocytes from transitioning into chronically inflamed myocytes that are believed to mediate the progression of remodeling and heart failure [19].

We should all be encouraged by the findings of Kain et al. [5], because their work shows that endogenous repair systems can be effectively exploited to resolve inflammation and prevent

the fibrosis and improve remodeling the injured heart. Armed with this knowledge, we can ask new questions and when we do, findings should breathe new life into myocardial ischemia research as well as spur the development of new and novel therapeutic strategies for preventing fibrosis, remodeling and hopefully even heart failure after MI.

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