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Inflammatory responses in the atria: Should they stay or should they go?

Heather S. Duffy, PhD

Center for Life Sciences 913, Beth Israel Deaconess Medical Center, Harvard Medical School, 3 Blackfan Circle, Boston, MA 02115, 617 735-4250, 617 735-4207, fax

Heather S. Duffy: hduffy@bidmc.harvard.edu

It is estimated that more than 2 million Americans are afflicted with atrial fibrillation (AF) and that this number is growing rapidly,¹ making it the number one cardiovascular disease in this country. Risk factors for AF include other cardiovascular illness such as myocardial infarction or heart failure along with aging, inflammatory response to disease or injury, genetic abnormalities, obesity or no known obvious cause¹. Risk of death increases two-fold in patients with AF² and quality of life for patients with symptomatic AF has been reported to be lower than patients without AF². The most devastating potential consequence of AF is stroke which has been reported to increase by over 5 fold³. Additionally, AF is associated with increased ventricular tachycardiac and arrhythmic heart failure². Recently an association of atrial fibrillation with the development of Alzheimer's disease also has been suggested⁴. These negative clinical outcomes make it critical to identify therapeutic treatments. While some risk factors are not possible to affect, such as genetic load and aging, others are more easily addressed. For example, addressing obesity in the patient populations may be helpful in decreasing the AF burden. Another easily addressed issue could be inflammation. A new article by Kume et al⁵ in this issue of *Heart Rhythm* focuses on inflammation and lends support to the idea that decreasing the inflammatory response that occurs in cardiovascular disease may decrease the risk for development of atrial fibrillation in this at-risk population⁵.

One of the more interesting molecular biology findings in terms of inflammation is the role of one of the Peroxisome Proliferation-Activated Receptors (PPARs) family members, PPAR γ . PPARs were originally described as ligand-dependent transcription factors important in cellular metabolism lipid transport⁶. Further studies identified the role of this key activator of gene expression in the regulation of brown fat differentiation⁷ but its role in cardiac tissue is less clear. PPAR- γ activation has been shown to limit the inflammatory response,⁶ thus is an interesting potential target for altering inflammation in the atria. The first studies to examine this possibility showed that indeed, activation of PPAR- γ by the drug pioglitazone is associated with attenuation of atrial fibrosis and subsequent fibrillation⁸ in a tachypacing model of induced heart failure and atrial fibrillation. These authors determined that pioglitazone treatment inhibited the formation of heart failure-induced atrial fibrillation by activation of the ERK/MAPK pathways primarily affecting the cardiomyocytes. This new study by Kume et al⁵ suggests that pressure overload induced fibrosis, as would be found in hypertensive patients, may also be attenuated by activation of PPAR- γ in part by affecting the formation of myofibroblasts.

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Many cardiovascular diseases such as heart failure and myocardial infarction are associated with an ongoing inflammatory response which includes infiltration of immune cells such as monocytes and macrophages into the atrial tissue where they produce and secrete inflammatory cytokines which then act upon the resident cells of the atria including both myocytes and fibroblasts. In biopsies from AF patients, inflammatory infiltrates such as monocytes and macrophages are commonly seen⁹. They appear to migrate from the endocardial surface into the subendocardial region with fewer immune cells found in the midmyocardium⁹. These cells then produce and secrete a number of cytokines that alter the delicate balance of Matrix Metalloproteinases (MMPs) and their endogenous inhibitors, the Tissue Inhibitors of MMPs (TIMPs)¹⁰. This imbalance leads to expansion of the extracellular matrix. Additionally, many of these cytokines help to initiate and support the transformation of resident fibroblasts into reactive myofibroblasts¹¹, an event which then augments the systemic inflammatory response. Myocytes respond to cytokines by activating the hypertrophic signaling cascades¹² and initiating inside out signaling via the integrins¹² which stimulates collagen production and deposition. Activation of TNF- α , IL-1 β , IL-6 and TGF- β receptors all lead to activation of gene programs that upregulate the formation and deposition of collagen via the myofibroblasts. Thus inflammation in the atria leads to increased fibrosis via the increased deposition of collagen and cellular hypertrophy both of which correlate with formation of the arrhythmogenic substrate. In some ways, fibrosis can be beneficial by filling in areas where the myocytes may have died out and helping scaffold the remaining cells. This event is far outweighed by the negative effects of fibrosis which include widening of the extracellular space that leads to decreased connectivity between the myocytes which helps maintain the fibrillatory events in the atria¹³.

Pioglitazone belongs to a family of drugs first described as insulin-enhancers, the Thiazolidinediones¹⁴. They were found to increase the reactivity to insulin in cases of insulin-resistance by activating PPAR- γ . This novel mechanism for increasing insulin sensitivity revolutionized the treatment of Type II Diabetes although cautionary notes were very quickly added to the literature due to the potential for increased liver disease¹⁵. Other studies found no hepatotoxicity with pioglitazone specifically¹⁶ suggesting that this family member may be the safest option in treatment. The first inklings that these drugs could have beneficial off target effects was suggested by Ricote et al.¹⁷ in a paper that showed that activation of PPAR- γ inhibited the production of inflammatory cytokines by monocytes. From there, studies began to crop up showing that pioglitazone decreased atherosclerosis¹⁸, attenuated Parkinson's Disease¹⁹ and a number of other inflammatory based diseases (for review see reference²⁰). Thus it appears that the general effect of pioglitazone, outside of its role in increasing insulin sensitivity, causes an overall immune suppression.

Due to the fact that the myocardial tissue has somewhat limited regeneration capabilities, the response to injury is critical to minimizing damage. This includes a tightly orchestrated inflammatory response. The body's primary response to injury, including cardiac injury, is activation of the inflammatory response. The associated release of cytokines and chemokines mediates increases in blood flow, capillary permeability and aids in the increase of inflammatory cells to perform "clean up" duties in the injured heart²¹. These processes, when well controlled, help heal the heart and if they are completely eliminated may increase overall injury. On the other hand, this response cannot be too long or scar formation and fibrosis dominate the tissue. Thus, while the studies of Kume et al, described here are suggestive of a positive effect of immune suppression in pressure overload heart failure,⁵ this should be tempered with a modicum of caution. Before we dive headlong into pioglitazone treatment for heart disease, it might be important to understand more about the positive roles of the inflammatory response so that we do not accidentally throw out the baby (healing) with the bathwater (fibrosis).

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