IL-6 Rapidly Induces Reversible Atrial Electrical Remodeling by Downregulation of Cardiac Connexins

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Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and is associated with an increased morbidity and mortality because of contributing to an increase in the risk of stroke and heart failure. AF affects >30 million individuals worldwide, and its management accounts for 1% of the National Health Service budget in the United Kingdom[1] and between $6 and $26 billion of annual healthcare spending in the United States. AF has been reported to complicate 33% of patients undergoing coronary artery bypass grafting,[1] and multiple studies have shown its association to infectious or inflammatory disorders.[2,3] AF is associated with mortality, with an odds ratio of 1.5 and 1.9 in men and women, respectively,[4] and an estimated additional cost of ≈$6400 in patients who developed AF after coronary artery bypass grafting in the United States.[1]

Cells influence their microenvironment either through a paracrine mechanism or direct cell-cell interaction that may involve both adhesion-mediated communication and gap junction–mediated homocellular and heterocellular communication. Proinflammatory (IL-1, IL-6, IL-7, IL-8, IL-12, IL-17, IL-18, tumor necrosis factor-α, and interferon-γ) and anti-inflammatory (IL-4, IL-10, IL-13, interferon-α, and transforming growth factor-ß) cytokines and chemokines provide molecular signals for paracrine communication between cells, and play significant roles in sustaining and regulating inflammatory reactions. The paracrine interaction represents only a facet of the potential mechanisms by which the 2 cell types influence each other's function. In fact, many signaling molecules are membrane impermeable, are produced in low concentration, or may have a short half-life. Hence, the direct transfer between 2 cells, through gap junctions, represents an efficient conduit to deliver such molecules to certain cells specifically. Gap junctions are clusters of transmembranous channels composed of structurally related proteins known as connexins, which mediate the intercellular transfer of small molecules and ions between adjacent cells: These include regulatory molecules up to 1 kDa, cell metabolites, and second messengers, such as cyclic nucleotides, inositol triphosphate, and calcium. The connexon, also known as a connexin hemichannel, is an assembly of 6 proteins called connexins that form the pore for a gap junction between the cytoplasm of 2 adjacent cells. Gap junctions are ubiquitous in multicellular organisms, and they are an integral part not only of solid tissues but also of the lymphoreticular system, secondary lymphoid organs, and peripheral blood mononuclear cells. Connexins 40 and 43 are expressed in the atria and contribute to atrial conduction velocity and refractoriness heterogeneity, which are determinants of reentry mechanisms maintaining AF.

The increased transient risk of AF during infection/inflammation can be explained by structural atrial remodeling attributable to myocardial injury and fibrosis or by electrical remodeling attributable to direct effects of cytokines on atrial ion channels (inflammatory channelopathy). In this issue of the *Journal of the American Heart Association* (*JAHA*), Lazzerini et al[5] studied the association between patients with systemic inflammation and atrial electrical remodeling by assessing electrophysiological parameters and circulating gap junction proteins (connexins 40 and 43) from peripheral blood mononuclear cells. Although the working hypothesis is not novel, the cohort used and the study findings shed the light on the downregulation of cardiac connexins 43 and 40 by IL-6. The authors establish the importance of P-wave indexes (including P-wave duration, P-wave dispersion, and P-wave SD [P-wave index]) as markers of atrial electrical remodeling that transiently change during various inflammatory conditions, thus putting the patients at risk of developing AF; and these P-wave indexes return to normal when the inflammation resolves. Lazzerini et al[5] also found a positive correlation

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between CRP (C-reactive protein) and these P-wave indexes during systemic inflammation, allowing use of CRP as a marker of AF risk. This is supported by a previous study that demonstrated that high-sensitivity CRP and P-wave dispersion indexes are independent predictors of AF.[6] The authors investigated various proinflammatory cytokines' (tumor necrosis factor-α, IL-1, and IL-6) and the anti-inflammatory cytokine's (IL-10) relationship with P-wave indexes. IL-6 was associated with the P-wave indexes that were transiently elevated during inflammation and then the P-wave indexes normalized as soon as inflammation was controlled. The authors showed a positive correlation of mRNA expression of connexins 40 and 43 in atrial tissue with mRNA expression of connexins 40 and 43 in peripheral blood mononuclear cells. After showing that connexin 43 expression does change during inflammatory states, Lazzerini et al[5] showed the negative association of IL-6 with connexin 43, with this association becoming stronger in patients who experienced a greater change in P-wave indexes (high-P Δ group with reduction of P-wave dispersion and/or P-wave SD values >25% from active disease [PRE] after therapeutic interventions resulting in a CRP decrease >75% compared with the baseline [POST]). Lazzerini et al[5] showed a causal downregulation of connexin 40 and 43 expression by IL-6: IL-6 supplementation induced reduction of connexin expression in mouse atrial myocytes, and the addition of an IL-6 antibody reversed it.[5]

The article had few limitations, which included a lack of 1:1 matched controls (only 25 controls were included). It would have been of interest checking the effect of IL-1 and tumor necrosis factor-α stimulation in HL-1 (mouse atrial cardiomyocyte) cells to correlate the results with the in vivo part of the study. A more specific experiment is recommended in the future, where HL-1 cells are stimulated with serum collected from peripheral blood mononuclear cells of patients having systemic inflammation and from control subjects.

The findings from this study add to our understanding of the underlying mechanisms of atrial electrical remodeling during systemic inflammation besides the previously stabled "inflammatory channelopathy" as a cause ultimately leading to AF.[3] Previous studies investigated nonselective interventions (dexamethasone[7] and ISIS-CRP[8]) on AF and have documented the role of anti-inflammatory agents, such as colchicine[9] and methylprednisolone,[10] as well as the role of agents typically used to treat or prevent cardiovascular disease, such as metoprolol[11] and atorvastatin,[12] in reducing inflammatory markers and in reducing AF burden. Multiple studies have linked CRP to developing AF for the first time,[13,14] its recurrence,[10,15–17] and even developing permanent AF,[10] with the level of CRP correlating with the AF burden.[18] CRP has also been linked to developing AF postoperatively.[19,20] In addition, IL-6 was linked to recurrence[17] as well as developing AF postoperatively.[20] Lower IL-6 and CRP levels have been associated with sinus rhythm maintenance after pharmacologic cardioversion,[21] in addition to their role in cardiovascular morbidity and mortality, independent of cardiac, renal, and clinical risk factors.[22] Further research in the IL-6 pathway may have clinical implications in AF management in the future, with studies comparing targeted interventions with previously studied nonselective interventions.

Disclosures

None.

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