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EDITORIAL COMMENT

Fishing CHIPs to Predict Postoperative Atrial Fibrillation*

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Postoperative atrial fibrillation (POAF) is a frequent complication of thoracic surgery and is associated with immediate adverse outcomes, including increased risk for stroke and hemodynamic instability, prolonged hospital stay, and increased hospital costs.[1] In addition to the classical pre-existing risk factors for atrial fibrillation (AF), peri- and postoperative events such as neurohormonal activation, ischemia-reperfusion injury, and inflammation are thought to play an important role in the occurrence of POAF.[1] Beta-blockers reduce the risk for sympathetic activation and ischemic injury and are the most established prophylactic therapy.[1] However, targeting inflammation using corticosteroids[2] or colchicine[3] failed to reduce the risk for POAF, highlighting the need for a better understanding of the underlying causal inflammatory pathways.

Clonal hematopoiesis (CH) refers to the clonal expansion of a hematopoietic stem cell and its progeny because of the presence of somatic mutations that provide a selective growth advantage to the mutated cells. CH of indeterminate potential (CHIP) is increasingly prevalent with age and refers to cancer-associated somatic mutations, without any diagnosed hematologic or clonal disorder. Recently, CHIP sparked interest in the cardiovascular community after it was found to be associated with an increased risk for atherosclerotic cardiovascular disease.[4] Inflammation, and more particularly activation of the NLRP3 inflammasome/interleukin (IL)-1β/IL-6 pathway, was proposed as a major causal molecular mechanism.[4,5] Subsequent studies reported significant associations of CHIP with a number of additional cardiovascular conditions, including heart failure,[6,7] and increased mortality after transcatheter aortic valve replacement (AVR).[8] The proposed underlying mechanisms were still attributed to NLRP3 (or AIM2) inflammasome/IL-1β-dependent pathways.[9-11] Intriguingly, some of the most recent studies applying Mendelian randomization analyses did not support a significant causal association of CHIP with atherosclerotic cardiovascular disease.[12,13] Age was identified as a strong confounder,[12] which is in line with the finding that CHIP is associated with accelerated epigenetic aging[14] and that the presence of the latter may explain the association of CHIP with coronary artery disease.[14] Importantly, however, the largest studies confirmed an independent association of CHIP with chronic heart failure[12] and identified a new significant association with AF.[12] The results of the study by Ninni et al[15] in this issue of the *Journal of the American College of Cardiology* are therefore assessed and interpreted in light of this background knowledge.

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CHIP IS ASSOCIATED WITH INCREASED RISK FOR POAF

Ninni et al[15] studied 52 elderly patients with POAF and compared them with 52 patients who maintained sinus rhythm during the 7 days after surgical AVR. They found that CHIP prevalence was higher in patients who experienced POAF compared with control patients, after adjustment for age and several relevant confounders. Most mutations were in *DNMT3A* and *TET2* genes, with one-third of CHIP carriers

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having mutations in multiple genes. CHIP carriers displayed preoperative alterations in peripheral blood monocytes and myocardial macrophages, and the presence of CHIP was associated with an exacerbated inflammatory response following AVR. The investigators concluded that CHIP is frequent in elderly candidates for AVR and that CHIP-associated inflammation predisposes patients to POAF. The results are important and deserve close inspection and scrutiny.

A major issue relates to the various definitions of CHIP used by the investigators. The definition used for sample size calculation was the conventional CHIP definition, restricted to a list of 97 candidate genes, with variant allele fraction (VAF) of ≥2%, as in the first report of CHIP association with cardiovascular disease.[4] Using this definition, the association of CHIP with POAF was not statistically significant. The investigators explored additional less stringent definitions of CHIP on the basis of various VAF thresholds and on screening for somatic mutations in an extended list of 576 candidate genes and found associations between those CHIP definitions and the occurrence of POAF. However, only 1 CHIP definition (HemePACT panel, VAF ≥1%) would remain significant after correction for multiple testing. Therefore, although the association between CHIP and POAF is scientifically plausible, reproducing the results in other larger independent cohorts will be necessary to strengthen the validity of the association, and potentially extend it to POAF occurring after other cardiac and noncardiac surgical procedures.

WHAT ARE THE MECHANISMS?

Ninni et al[15] put effort into studying the inflammatory mechanisms that could account for the link between CHIP and POAF. They performed preoperative and postoperative measures of immunoinflammation in a subset of patients undergoing AVR. CHIP (HemePACT panel, VAF ≥1%) was associated with a higher systemic inflammatory response post-AVR, but interestingly, the most important difference between CHIP carriers and noncarriers was found already at the preoperative stage, supporting the concept of a primed inflammatory status, ready to (over)respond to subsequent stimulations.

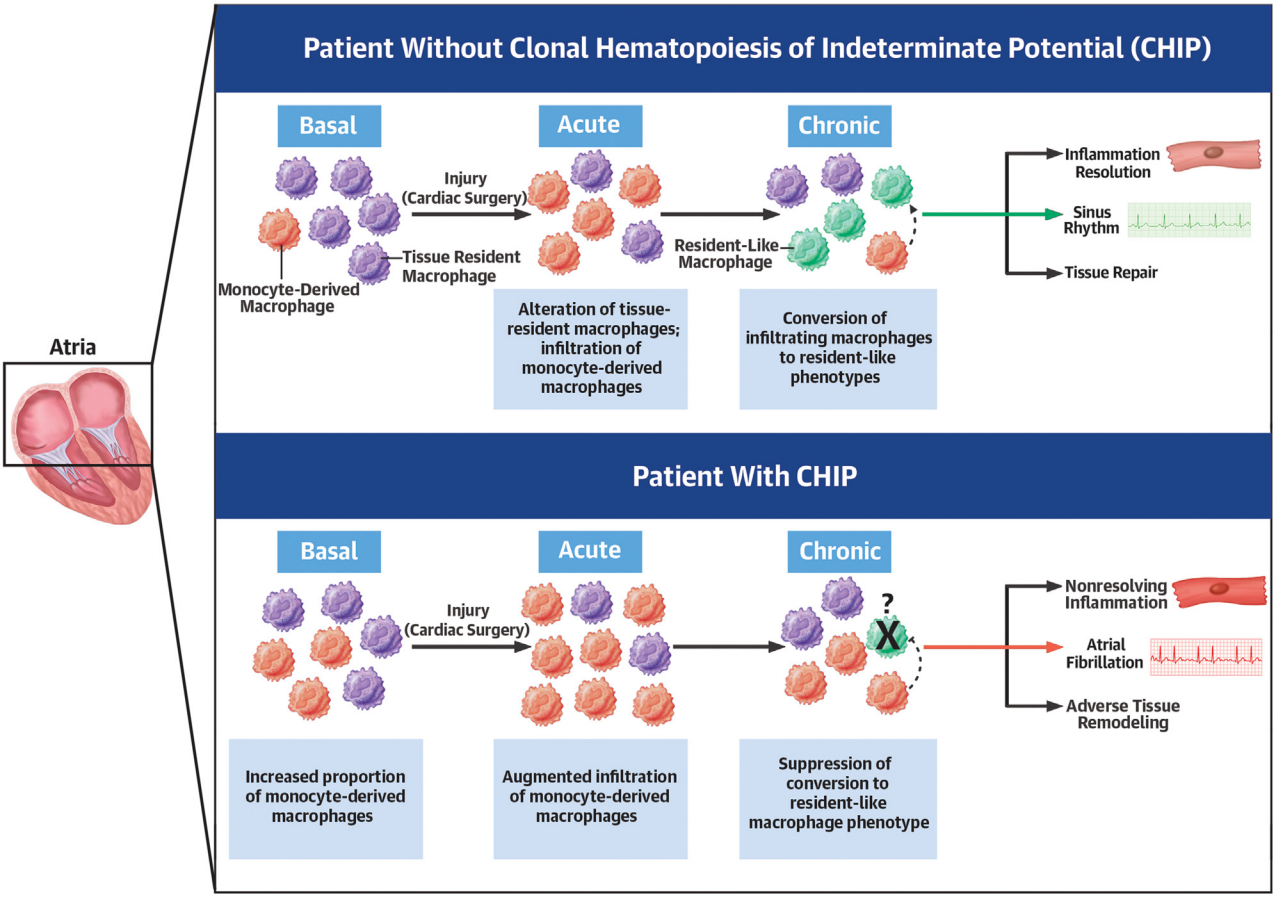
The primed preoperative state was seen in circulating $CD64^{+}CD14^{+}CD16^{-}$ monocytes, which were increased in CHIP carriers compared with noncarriers. Gene expression analysis of these monocytes revealed enrichment for "myeloid leukocyte activation," with up-regulation of genes involved in monocyte proliferation, differentiation, chemotaxis, adhesion, and polarization. Surprisingly, none of the differentially expressed pathways were related to NLRP3, IL-1β, or IL-6. These results differ from previous work that reported increased levels of circulating $CD14^{dim}CD16^{++}$ monocytes in a similar setting of patients with TET2 somatic mutations and severe degenerative aortic valve stenosis[8] and that attributed the primed status of circulating monocytes to increased activation of the NLRP3/IL-1β/IL-6 pathway.[10] These differences in the underlying CHIP-dependent inflammatory mechanisms highlight the need for mechanistic studies that include a larger number of patients and account for the various types of somatic mutations. Nevertheless, the absence of an IL-1β signal in the study by Ninni et al[15] may explain in part the lack of efficacy of colchicine, an inhibitor of NLRP3 inflammasome, in preventing POAF.[3]

Another interesting finding by Ninni et al[15] was the enrichment of a $CD64^{+}HLA\text{-}DR^{+}CCR2^{+}CD11c^{+}CD206^{+}$ monocyte-derived cardiac macrophage population in CHIP carriers, which correlated with the enrichment in circulating classical monocytes, further suggesting that the primed inflammatory state was also present locally within the atrial tissue. The investigators speculated that these macrophages could promote cardiac fibrosis through their expression of CD206. However, the latter is much highly expressed in resident cardiac macrophages at the steady state in the absence of pathologic fibrosis. Nevertheless, macrophages with CHIP mutations could be responsible for cardiac fibrosis through paracrine activation of fibroblasts, as recently proposed.[16]

HOW WILL THE FINDINGS AFFECT OUR VIEW OF THE INFLAMMATORY MECHANISMS OF (PO)AF?

The results of Ninni et al[15] support the hypothesis that monocytes and macrophages are involved in POAF, and potentially AF in general, and that these immune cells may constitute a causal link between CHIP and (PO)AF. It will be interesting to determine the differential roles of the various cardiac macrophage subsets in this process. The present report does not provide information on the resident or resident-like subsets of cardiac macrophages and whether they were altered, quantitatively or qualitatively, in patients with CHIP and POAF. Resident cardiac macrophages play essential homeostatic roles (ie, clearing dysfunctional mitochondria of cardiomyocytes[17] and facilitating electric conduction[18]). They are also suggested to limit fibrosis,[19] potentially through CD74/MIF interactions with cardiac fibroblasts.[20]

FIGURE 1 Potential Mechanisms Linking CHIP to Postoperative Atrial Fibrillation



In the absence of clonal hematopoiesis of indeterminate potential (CHIP), heart injury alters resident cardiac macrophages and promotes the accumulation of monocyte-derived macrophages. The latter eventually die or acquire tissue-resident characteristics, preserving tissue homeostasis. The presence of CHIP promotes increased cardiac monocyte infiltration and impairs the ability of monocyte-derived macrophages to acquire tissue-healing and tissue residency properties, promoting nonresolving inflammation, adverse tissue remodeling, and fibrosis.

It is tempting to speculate that over time, resident cardiac macrophages become progressively outcompeted by infiltrating monocyte-derived macrophages. The latter may acquire tissue-resident characteristics and be able to preserve cardiac homeostasis in the absence of sustained or repetitive injury (Figure 1). CHIP may increase monocyte infiltration into the heart and impair the ability of monocyte-derived macrophages to acquire tissue-healing properties,[21] and more generally, tissue residency characteristics, thereby preventing inflammation resolution and promoting adverse cardiac remodeling and fibrosis (Figure 1).

Ninni et al[15] should be congratulated on an interesting and thought-provoking work. The role of CHIP in driving the pathogenesis of (PO)AF certainly merits further attention.

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