Inflammation plays an important role in the development and progression of a variety of cardiovascular conditions, most notably coronary atherosclerosis and congestive heart failure.\(^1\)\(^2\) A number of inflammatory molecules have been implicated in these processes, including interleukin-1 (IL-1). The IL-1 gene family consists of 3 proteins, IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra). IL-1α and IL-1β exert their similar effects by binding to the IL-1 type I receptor. The IL-1 type II receptor also binds IL-1α and IL-1β but acts as a decoy receptor and is not involved in signal transduction, thereby counterbalancing the inflammatory effects of IL-1α and IL-1β. IL-1ra is an endogenous inhibitor of IL-1α and IL-1β, which competitively binds to the IL-1 type I receptor without activating it.\(^3\)

Both IL-1 and IL-1ra are produced by endothelial cells, smooth muscle cells, and macrophages. IL-1 secretion is induced by microbial products that stimulate toll-like receptors and by certain endogenous triggers, such as uric acid produced during cell death. Both types of agonists stimulate a cytosolic complex of proteins termed the inflammasome, which activates caspase-1 to enable secretion of IL-1β. The potential of this IL-1β pathway for systemic inflammation is demonstrated not only by gout but also by the clinical effects of activating mutations in cryopyrin (also known as NALP3 or CIAS1), one of the inflammasome components, which causes familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.\(^4\)

Cardiac-Related Effects of IL-1 and IL-1ra
Circulating levels of IL-1 are associated with the presence of traditional cardiac risk factors, such as diabetes mellitus, hypertension, smoking, and dyslipidemia. Elevated levels of IL-1 result in secretion of chemokines and other cytokines (eg, IL-6), increased expression of adhesion molecules, activation of endothelial and smooth muscle cell proliferation, macrophage activation, and increased vascular permeability. This cascade promotes atherosclerosis and plaque destabilization. IL-1 and other proinflammatory cytokines have also been implicated in the progression of heart failure, as a result of their negative inotropic effects and deleterious effects on left ventricular remodeling.\(^2\) Another important mechanism by which IL-1 may enhance atherosclerosis and exacerbate left ventricular dysfunction is by contributing to endothelial dysfunction. IL-1 stimulates release of endothelin-1, a potent vasoconstrictor, and IL-1 stimulates inducible nitric oxide synthase, which increases the formation of reactive oxygen species and reactive nitrogen species (eg, nitrotyrosine), which leads to oxidative and so-called nitrosative stress and endothelial dysfunction (Figure).

The important role of IL-1 in the development and progression of atherosclerosis has been highlighted by preclinical studies demonstrating less atherosclerosis in IL-1 knockout or IL-1 type I receptor knockout mice.\(^5\)\(^6\) Moreover, IL-1ra–deficient mice are more prone to neointima development after endothelial injury and more prone to atherogenesis.\(^7\)\(^8\) Administration of IL-1 to porcine coronary arteries leads to neointimal formation, whereas balloon angioplasty results in increased levels of IL-1β at the injured segment of the porcine coronary artery but not at uninvolved sites.\(^9\)\(^10\) Treatment of balloon-injured or stented porcine coronary arteries with IL-1ra reduces neointimal formation.\(^11\)

In clinical studies, IL-β has been found in greater concentration in atherosclerotic human coronary arteries.\(^12\) An association between certain IL-1ra gene polymorphisms and the presence and extent of coronary disease, as well as the occurrence of restenosis after coronary stenting, has also been identified.\(^13\)\(^14\) One of the body’s responses to acute inflammatory processes, such as acute coronary syndromes, is to upregulate IL-1ra. For example, patients with acute coronary syndromes have been shown to have significantly greater concentrations of IL-1ra than those with stable coronary disease or with no coronary disease.\(^15\) Indeed, because of its early release at sites of ruptured plaque, even before myocardial necrosis has occurred, IL-1ra was found to be elevated in patients presenting with ST-segment elevation myocardial infarction earlier than traditional markers of necrosis.\(^16\)

Anakinra
Anakinra is a nonglycosylated, recombinant form of human IL-1ra that, like endogenous IL-1ra, competitively inhibits IL-1 by binding the IL-1 type I receptor. A commercially available form of anakinra (Kinerei) was approved by the US Food and Drug Administration in 2001 for treatment of patients with rheumatoid arthritis on the basis of studies demonstrating its efficacy as monotherapy; a subsequent trial evaluating its role in combination with anti-tumor necrosis...
factor-α therapy did not show additional benefit over anti-
tumor necrosis factor-α alone, which suggests some overlap
in the deleterious inflammatory effects of these 2 cyto-
kines.

Anakinra is administered as a once-daily subcuta-
nous injection; it is rapidly absorbed, with a peak plasma
concentration within hours; and it is cleared by the kidneys. It
is well tolerated, with the primary side effect being injection
site reactions. Serious infections are rare but increased with
anakinra compared with placebo in patients with rheumatoid
arthritis. Given the strong link between IL-1 and coronary
artery disease and the favorable experience with anakinra in
patients with rheumatoid arthritis, interest has grown in
applying anti-IL-1 therapy with anakinra to patients with
vascular disease.

Cardiovascular Effects of Anakinra

In this issue of Circulation, Ikonimidis and colleagues\textsuperscript{21}
evaluate the immediate and short-term effects of anakinra on
coronary flow; left ventricular, aortic, and endothelial func-
tion; and mediators of inflammation. In 23 patients with
rheumatoid arthritis and no known coronary artery disease or
ischemia on stress imaging, the investigators administered a
single dose of anakinra or placebo, in a double-blind fashion,
and at 48 hours gave the other treatment. Three hours after
anakinra, coronary flow reserve and aortic function measured
with transthoracic echocardiography, left ventricular function
assessed with tissue Doppler echocardiography, and endothel-
ial function examined with flow-mediated brachial artery
dilation all improved significantly compared with 3 hours
after placebo. The investigators also found that malondialde-
hyde and nitrotyrosine, markers of oxidative and nitrosative
stress, respectively, decreased significantly after anakinra, as
did the inflammatory marker IL-6 and the vasoconstrictor
endothelin-1.

In a second part of the study, the 23 patients with
rheumatoid arthritis all received daily injections of anakinra
for 30 days. Nineteen separate patients with rheumatoid
arthritis who were matched for age, sex, and disease activity
received prednisolone for 30 days, and 23 age- and sex-
matched patients without rheumatoid arthritis or cardiovas-
cular disease served as normal control subjects. After 30
days, the patients treated with anakinra had significantly
improved coronary flow, left ventricular function, endothelial
function, and markers of inflammation such that they were
similar to the normal control subjects. There was a significant
correlation between changes in the inflammatory biomarkers
and improvement in vascular function and left ventricular
function.

A few limitations of this study should be highlighted. The
investigators included patients with rheumatoid arthritis and
specifically excluded patients with coronary artery disease. It
is not clear that these findings can be extrapolated to those in
whom they would be most relevant, those without rheumatoid
arthritis and with coronary artery disease. In patients with
existing cardiovascular disease, the IL-1–dependent changes in
vascular function and left ventricular function may be
irreversible. Moreover, can the positive findings in this study
be explained in part by the fact that it did include patients
with active rheumatoid arthritis, who had a heightened
inflammatory milieu as evidenced by higher levels of inflam-
matory markers at baseline compared with the control group?
If this is the case, where is the IL-1 coming from? Is it being
produced locally in presumably normal coronary vessels, or
more likely, is it coming from inflamed joints via blood?\textsuperscript{22}

Other limitations include the small sample size and the lack
of randomization of the second part of the study that
evaluated the short-term effects of anakinra. Before the
clinical relevance of these findings can be appreciated fully,
a similar but larger and randomized study will need to be
performed that would include patients without rheumatoid
arthritis and with coronary artery disease.

**Clinical Implications and Future Directions**

Despite the above limitations, the study by Ikonimidis and
colleagues\textsuperscript{21} provides fundamental information regarding the
beneficial effects of anti-IL-1 therapy with anakinra on
vascular and left ventricular function in patients with rheu-
matoid arthritis and without coronary artery disease. It will be
necessary to reproduce these findings in patients with coro-
nary disease and document a reduction or improvement in
clinical end points. Fortunately, more data will be forthcoming
from the MRC-ILA-HEART study, a randomized,
placebo-controlled, multicenter study comparing 14 days of
anakinra therapy to placebo in patients presenting with
non–ST-segment elevation myocardial infarction.\textsuperscript{20} The pri-
mary end point will be the effect of treatment on C-reactive
protein levels, with clinical events as secondary end points.
The rapid antinflammatory effect of anakinra makes it an
attractive intervention for other cardiac conditions, such as
ischemia-reperfusion injury, whereas its antirestenotic prop-
eties suggest the possibility of an anakinra-eluting coronary
stent. Finally, further investigation of this mode of therapy in acute and chronic congestive heart failure is warranted.

**Disclosures**

None.

**References**


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Inflammation and Cardiovascular Disease: Role of the Interleukin-1 Receptor Antagonist
William F. Fearon and Douglas T. Fearon

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