



A Failure of Heart in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic disease we treat with medications that have systemic effects. It is becoming increasingly clear that patients with RA have accelerated atherosclerosis and that RA is an independent risk factor for the development of atherosclerotic coronary artery disease¹. What is less clear is whether the presence of RA and its therapies modulates the course of coronary artery disease and its complications. In this issue of *The Journal* Myasoedova, *et al* use their extensive database from the Mayo Clinic to explore heart failure in patients with RA².

The relationship between heart failure and RA is not clear-cut. Some studies suggest that heart failure may be more frequent in patients with RA³, whereas other studies suggest the opposite⁴. Some of these differences can be explained by the more specific questions that the investigators are asking. Moreover, most studies of this problem are observational and depend on clinical diagnoses made during the course of clinical management, like the one in this issue. Thus, the presence or absence of heart failure is not systematically examined with questionnaires or echocardiograms, for example. This can be problematic in our effort to understand heart failure in RA patients since patients and physicians may ascribe symptoms such as ankle swelling as well as functional limitations to RA that may instead be a consequence of heart failure. Interestingly, studies that systematically used echocardiograms found that compared to other patients, patients with RA more likely had preserved ejection fractions, suggesting greater problems with diastolic rather than systolic function compared to patients without RA⁵. Moreover, while it is tempting to ascribe heart failure to ischemic heart disease, other studies suggest that in RA patients, factors other than ischemic heart disease and its risk factors more likely contribute to heart failure⁶.

The current study and others suggest a prime role for inflammation in the development of heart failure in RA, whether it more directly affects cardiac muscle or through enhanced atherosclerotic coronary artery disease. Indeed, consistent with other studies^{3,7}, Myasoedova, *et al* found the

risk for heart failure increased in patients with positive rheumatoid factors, persistently elevated sedimentation rates, and the presence of severe extraarticular manifestations of RA. Moreover, one of the key findings in this study is that methotrexate reduced the risk for the development of heart failure, presumably through its control of inflammation. These results are supported by other studies as well⁸. In this context, it is also tempting to speculate that the improved hazard ratio for the development of heart failure in the first year compared to subsequent years can be explained by a delay in controlling inflammation with disease-modifying antirheumatic drugs (DMARD). It may further explain why in this study current but not prior use of these agents affected the development of heart failure.

A beneficial effect on heart failure is not consistent with all antiinflammatory therapies, however. In agreement with prior studies⁹, Myasoedova, *et al* found that glucocorticoids increased rather than decreased the risk for heart failure. This most likely suggests that glucocorticoids have additional effects that significantly offset their beneficial antiinflammatory effects, perhaps not surprising since glucocorticoids have a host of serious adverse effects such as hypertension, hyperlipidemia, and diabetes, to name a few. It is instructive to note that while current use of glucocorticoids doubled the baseline risk for developing heart failure, methotrexate reduced the baseline risk by half. This provides yet another reason to favor the use of methotrexate over glucocorticoids in the longterm management of RA. These investigators also found that the beneficial and harmful effects of these medications essentially cancelled each other out: in this study there was no change from the baseline risk for heart failure in patients taking both methotrexate and glucocorticoids. This is certainly a fascinating, but at this point, hypothesis-generating observation. While no effect was found in the current study, other work suggests that at least some nonsteroidal antiinflammatory drugs (NSAID) can be detrimental to heart failure^{8,10}, providing

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an additional rationale to emphasize more aggressive use of DMARD to reduce dependency on these agents as well.

The influence of tumor necrosis factor- α (TNF- α) inhibitors on heart failure in patients with RA is even more complex. There is evidence that use of TNF- α inhibitors can reduce the risk of RA patients developing atherosclerotic coronary artery disease¹¹, thereby also reducing their risk of developing heart failure. The finding of elevated levels of TNF- α in patients with heart failure^{7,12}, coupled with animal studies suggesting that TNF- α inhibitors reduced heart failure¹³, led to studies testing whether TNF- α inhibitors would improve heart failure in patients without RA. While the RENEWAL trial found no benefit¹⁴, patients in the ATTACH study who received TNF- α inhibitors had an increased combined risk for death from any cause or hospitalizations because of worsening heart failure¹⁵. Because TNF- α inhibitors lower the risk for coronary artery disease¹¹, they may nevertheless reduce the risk for developing new-onset heart failure. In observational studies, there is conflicting evidence: one study found that TNF- α inhibitors increased the risk for hospital admissions because of heart failure, even in those without a prior history of heart failure¹⁶, whereas another study found that TNF- α inhibitors reduced the risk for hospitalizations because of heart failure⁸. It is important to interpret these conflicting data in a wider context. In clinical decision-making, rheumatologists and patients also need to consider the potentially marked benefits TNF- α inhibitors can have on reducing joint destruction as well as improving quality of life.

Clearly, we need more research to improve our understanding of the interrelationships between heart failure and both RA and its treatments. But what do we know now that can improve heart health in patients with RA?

1. Control the traditional risk factors for coronary artery disease in patients with RA. Both primary care physicians and rheumatologists need to increase their vigilance to diagnose and effectively treat these problems to reduce the burden of coronary artery disease and heart failure in their patients.
2. Control inflammation by relying less on NSAID and glucocorticoids and more on DMARD. There is ample evidence that methotrexate, for example, is preferable to either of these medications from a heart point of view. TNF- α inhibitors may be detrimental to patients with uncompensated heart failure and should only be used with caution, if at all, in these patients. Overall, however, the benefits of TNF- α inhibitors likely outweigh their risk in most patients, particularly when we consider the patient as a whole.
3. Increase our vigilance to diagnosis of coronary artery disease and heart failure in patients with RA and not misinterpret their symptoms and signs as manifestations of RA. We can expect better outcomes when we treat the appropriate cause.

Such measures should help us prevent a failure of heart in rheumatoid arthritis.

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