High-Density Lipoprotein NO Failure in Heart Failure

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Despite numerous epidemiological studies demonstrating that high-density lipoprotein cholesterol (HDL-C) levels are inversely associated with cardiovascular risk, several lines of evidence now indicate that targeting HDL-C levels to reduce the risk of cardiovascular events is unlikely to be effective. Studies of pharmacological interventions to raise HDL-C, such as niacin and 2 cholesteryl ester transfer protein inhibitors, have shown no benefit in reducing cardiovascular events. In addition, data from a large Mendelian randomization study have shown that some genetic variants associated with HDL-C seem to have little relationship to coronary heart disease. As a result, there is currently skepticism about whether interventions specifically to raise HDL-C levels will decrease the risk of cardiovascular events.

This failure of the so-called HDL cholesterol hypothesis has been accompanied by a shift toward a more rigorous, basic understanding of HDL as a molecule with multiple functions that can be differentiated from simple measures of HDL cholesterol mass. One of the important functions of HDL is its role in promoting cellular cholesterol efflux and reverse cholesterol transport. Our group and others have shown that the capacity of HDL to promote cholesterol efflux from macrophages ex vivo is inversely related to the risk of coronary heart disease even after controlling for HDL-C levels. Furthermore, niacin therapy does not augment cholesterol efflux despite raising HDL levels in statin-treated patients, which could explain the lack of efficacy of niacin despite increased HDL-C levels. Although more studies are certainly warranted, one hypothesis is that therapies that improve cholesterol efflux capacity and reverse cholesterol transport, such as infusion of a reconstructed HDL composed of apolipoprotein A1 and phospholipids, may improve cardiovascular outcomes.

Beyond promoting cholesterol efflux, HDL is known to have anti-inflammatory, antioxidant, and nitric oxide (NO)–promoting functions. HDL particles have been shown to be dysfunctional in various disease states such as diabetes mellitus and psoriasis, with evidence of reduced protective functions of HDL potentially contributing to increased cardiovascular risk. In this issue of Circulation Research, Adams et al show that HDL is dysfunctional in congestive heart failure (CHF) specifically with respect to its ability to promote NO production from endothelial cells. They show that HDL from New York Heart Association Class II and III patients, compared with HDL from healthy subjects, has significantly reduced the ability to activate endothelial NO synthase (eNOS) and generate NO production. They suggest a mechanism linked to significantly reduced paroxonase-1 and increased HDL malondialdehyde, leading to increased stimulation of protein kinase C βII phosphorylation and altered phosphorylation of eNOS. Exercise training in subjects with CHF significantly improved the ability of HDL to promote NO biosynthesis. These studies extend previous work showing that HDL isolated from patients with coronary artery disease and acute coronary syndrome is defective in its ability to promote NO production.

Although these findings are extremely provocative, this is a small, hypothesis-generating study with only 24 heart failure subjects and 16 healthy controls. It is surprising that although >80% of the controls were hypertensive, control subjects did not seem to benefit from exercise training to the same degree as patients with heart failure. Furthermore, although one might predict that patients with ischemic heart disease would be treated with statins compared with healthy controls, the low density lipoprotein (LDL) levels were not significantly lower between the heart failure subjects and controls at the beginning of the study. The authors do not comment on which patients in this study were treated with statins, which have been suggested to attenuate the proinflammatory effects of HDL. Finally, because heart failure often improves with medical therapy alone, the duration of time these patients were stable on optimal medical therapy is an important variable that could explain improvements seen in heart failure, independent of exercise training.

The authors propose that the improvement in endothelial function after exercise training in patients with heart failure may be because of improvements in the quality of their HDL. To support this argument, the authors demonstrate a significant correlation between absolute change in endothelial function and HDL-induced NO production in patients with heart failure. A lack of improvement in endothelial function in the control group, which did not benefit from improved HDL function, would strengthen their argument. It is of course possible that exercise training improved both endothelial function and HDL function and that these 2 effects were independent. Could the improvements in LDL, which are known to negatively affect NO production, be responsible for the changes in endothelial function? Of note, LDL levels did decrease significantly with
exercise training. It is possible that in vivo, increased levels of lipid peroxidases seen by the authors correlate with higher levels of oxidized LDL that disrupt eNOS function. 

Exercise training itself is known to have positive effects on CHF, including reductions in all-cause mortality and heart failure hospitalization. What are the possible mechanisms by which exercise may benefit a patient with CHF? Possibilities include improvements in endothelial function, coronary perfusion, decreased peripheral vascular resistance, skeletal muscle remodeling, or increasing oxygen uptake and resistance to fatigue. In this study, a brief 12-week exercise training program improved peak oxygen consumption, one of the strongest predictors of mortality in CHF. If the benefit of exercise training in heart failure is significantly related to its ability to promote endothelial function, and HDL has the same effects, then improving HDL function in and of itself might be a reasonable target of therapy in heart failure.

To understand whether HDL could be of therapeutic benefit in heart failure, a more detailed understanding of mechanism will be necessary. What are the molecular mechanisms that underlie the effects of exercise training on HDL-stimulated NO production in heart failure? The authors speculate that exercise training reduces overall oxidative load, as assayed by measuring plasma lipid peroxidases, causing a decrease in malondialdehyde binding to HDL. Because there was no effect of exercise training on paraxonase-1 activity or the HDL proteome, the authors eliminate these as possible molecular mechanisms. The authors discuss that HDL binding to scavenger receptor B1 may stimulate eNOS. One possibility is that malondialdehyde-rich HDL is less able to bind to scavenger receptor B1.

Another intriguing, but unexplored, hypothesis is that changes in the HDL lipidome may be responsible for the enhanced NO production that occurs after exercise. The HDL-associated sphingolipid sphingosine 1-phosphate (S1P) binds the S1P3 G-protein–coupled receptor to active phosphoinositide-3 kinase and Akt leading to eNOS activation. Animal models indicate that HDL/S1P may have numerous cardioprotective and vasculoprotective effects. However, in a mouse model of cardiomyopathy, S1P levels are actually increased because of downregulation of the cystic fibrosis transmembrane regulator, the major intracellular important mechanism for S1P. HDL-associated S1P may be decreased in patients with coronary artery disease, but changes in HDL/S1P levels have not been described in CHF or after chronic exercise training in humans. One may speculate that certain lipid-modified HDL, such as malondialdehyde-rich HDL, is not able to properly target S1P to its receptors on endothelial cells, resulting in decreased Akt activation and NO production.

The authors leave unexplored the mechanisms by which dysfunctional HDL may stimulate protein kinase Cβ II, thereby inhibiting NO production. One possibility is that dysfunctional HDL signals through other receptors, such as lectin-like oxidized LDL receptor-1, to stimulate protein kinase Cβ II. Perhaps there are additional modifications of HDL in heart failure, such as increased symmetrical dimethylarginine, which are associated with further endothelial dysfunction via activation of Toll-like receptor-2. We propose a model whereby healthy HDL signals through scavenger receptor B1 and S1PR3 to induce NO production but speculate that dysfunctional HDL may cause decreased NO production via activation of lectin-like oxidized LDL receptor-1 or Toll-like receptor-2 (Figure).

In summary, the findings of Adams et al further highlight that HDL function can be separated from HDL-C mass with regard to association with cardiovascular disease and relevant clinical end points. It remains tempting to speculate that interventions that improve HDL functional properties, such as cholesterol efflux capacity or NO promotion, would reduce...
cardiovascular events. In fact, targeting NO in CHF patients with therapies such as hydralazine and nitrates provides cardiovascular outcome benefit in selected patients. 15 Although it has not been tested in heart failure, reconstituted HDL is known to improve endothelial function in hypercholesterolemic men. 16 In light of this report, it would be of substantial interest to determine whether reconstituted HDL can improve eNOS activity and NO production in patients with CHF. If so, it would then be appropriate to consider whether reconstituted HDL may improve outcomes in patients with CHF.

Disclosures
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References