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Editorial

High-density lipoprotein cholesterol: a new marker in heart failure

HDL: un nuevo biomarcador para la insuficiencia cardiaca

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The function of high-density lipoproteins (HDLs) in cardiology has been the subject of great interest for decades,[1–4] and several new discoveries have been made recently. Initially, HDLs were described as atheroprotective lipoproteins involved in reducing the risk of myocardial infarction, since the concentration of HDL-bound cholesterol (HDL-C) was found to be inversely proportional to the incidence of infarction.[1] In a recent article published in *Revista Española de Cardiología,* Teis et al.[5] take the discussion of the role of HDLs beyond atherogenesis to the field of heart failure (HF).

The atheroprotective effect of HDLs is due to their multiple beneficial effects: in addition accepting the flux of cholesterol from the atheromatous plaque for reverse cholesterol transport, HDLs also have antioxidant, anti-inflammatory, and vasodilator effects.[1–4,6] HDL is synthesized as apolipoprotein A-I in the liver and intestine, collects small quantities of lipids via the ABCA-1 receptor (in the liver, intestine, or macrophages of the atheromatous plaque) and is converted to nascent HDL or small HDL particles (HDL-Ps).[2,3] These small HDL-Ps are protective and highly functional[2,4,6] (with high capacity for accepting cholesterol flux) and are strongly antioxidant and anti-inflammatory. HDL-Ps are loaded with more and more lipids via the SR-BI and ABCG1 receptors, increase in size, and become large HDL-Ps, which are less functional[2,4,6] (less capacity for cholesterol uptake). Therefore, LDL-C concentration does not represent the concentration of the various HDL-P subpopulations, but rather is dominated by the (less functional) large HDL-Ps, meaning that HDL-C is not a good measure of the concentration of the functional, small HDL-Ps.[2–4,6] Therefore, both HDL functionality and small HDL-P concentration are much better predictors of cardiovascular risk than HDL-C levels[2] (the quality/functionality of HDLs is more important than HDL-C quantity).[4,6] This explains the latest findings on HDLs: drugs such as niacin or cholesterol ester transporter protein (CETP) inhibitors do not reduce cardiovascular risk because they increase HDL-C by increasing the total cholesterol load in each HDL particle and large HDL-P levels, but do not increase the concentration of small HDL-Ps (which are the real functional, atheroprotective agents).

Despite almost all HDL research being focused on ischemic heart disease, HDLs are also disrupted in other diseases, such as heart failure. Recent articles have demonstrated that lipoproteins in general and HDLs in particular are deranged in HF. HDL-C is low in patients with both ischemic and nonischemic HF.[7] In addition, low LDL-C levels in patients with HF are one of the most important prognostic factors for predicting mortality and rehospitalization due to HF.[7] This association has been observed in patients both with and without cachexia. However, it has now been determined that HDL-P concentration and HDL functionality are more important than HDL-C concentration.[2,6]

Measurement of HDL-P concentration using nuclear magnetic resonance (MR) spectroscopy has a better capacity for predicting cardiovascular risk than conventional determination of HDL-C or apoA-I.[1–4] Likewise, HDL-P concentration is predictive of risk in HF and not only in ischemic heart disease. A further advantage of this technique is that, given that not all HDL-Ps are equally as protective (small HDL-Ps have stronger beneficial effects than large HDL-Ps[1–4,6]), MR spectroscopy quantifies the concentration and the size of each HDL-P subpopulation (small, medium, or large),[2] not only the total concentration of HDL-Ps, thus providing more sophisticated information. Indeed, Potočnjak et al.[8] demonstrated that total HDL-P and small HDL-P (but not large HDL-P or HDL-C) concentrations were predictive of mortality at 3 months in a registry of patients admitted to hospital with acute HF. Using ultracentrifugation techniques (a more widely-used method in the clinical setting than MR spectroscopy), low values of HDL-3 (higher-density particles, equivalent to small HDL-Ps) are predictive of mortality in acute HF,[9] while HDL-2 levels (equivalent to large HDL-Ps) and HDL-C levels are not, thus confirming the prognostic value of small HDL-Ps. Finally, MR spectroscopy provides mechanistic information as it shows that HDL-Ps are different in HF with reduced ejection fraction (HFrEF) than in HF with preserved ejection fraction (HFpEF).[10] In a registry of 6528 patients, levels of small HDL-Ps and total HDL-Ps were lower in HFrEF than in HFpEF and both were lower in the 2 types of HF than in patients without HF.[10] In parallel, HDL-Ps were larger in HFrEF than in HFpEF, and larger in both types than in patients without HF.[10] Both in HFrEF and in HFpEF, low concentrations of small and total HDL-Ps were predictive of adverse HF prognosis.[10]

We would like to emphasize that HDL functionality is reduced in HF (and not only in atherosclerotic disease). One pioneering article in 2011 demonstrated that patients with HFrEF had a lower antioxidant capacity and lower activity of the antioxidant enzyme paraoxonase-1[11]; indeed, reduced paraoxonase-1 activity was predictive of adverse events in HF. In 2013, a second article

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demonstrated that HDL in patients with HFrEF lost its anti-inflammatory capacity and became proinflammatoty.[12] A third article observed a reduction in the capacity for cholesterol uptake by HDL in patients hospitalized with acute HF[13]; it should be noted that low cholesterol uptake capacity of HDL was superior to HDL anti-inflammatory activity as a predictor of prognosis in HF.[13] Subsequent studies have confirmed the deterioration in antioxidant[14] and anti-inflammatory[15] capacity and cholesterol uptake in patients with HF,[15] and that HDL functionality is predictive of prognosis in HF even after adjusting for brain natriuretic peptide (BNP).[14]

The molecular mechanisms to explain this reduced HDL functionality and HDL-P concentrations have not been studied in depth; only limited evidence is available:

- Inflammation (and HF is a chronic inflammatory state) increases levels of serum amyloid A protein.[12] Serum amyloid A displaces apoA-I[2,3] (the apolipoprotein that brings about the greatest benefit in HDLs) outside of the HDL-Ps and generates both free apoA-I (which is quickly eliminated by the kidneys) and HDL-Ps with a smaller amount of apoA-I (and therefore with less functionality).
- Oxidative stress (and HF is a state of increased oxidative stress) generates malondialdehyde (a product of lipid peroxidation of fatty acids), which is taken up by HDL-Ps.[16] This HDL modified by malondialdehyde loses its vasodilatory ability (it induces a weaker activation of endothelial nitric oxide synthase [eNOS] and lower production of nitric oxide[16]) and antioxidant ability (weaker activation of the antioxidant enzyme paraoxonase-1 and increase in lipid peroxidation[11,12,16]).
- Surfactant protein B (SP-B) is an essential component of lung surfactant in the alveoli. The pulmonary congestion of HF damages type II pneumocytes, which release immature SP-B into the plasma.[17] Therefore, immature SP-B concentration is a marker of alveolocapillary integrity. Immature SP-B is increased in HF,[17,18] correlates with HF severity and the patient's functional capacity (maximal oxygen uptake), and is predictive of prognosis in HF.[17] As immature SP-B is a hydrophobic molecule, it is transported in plasma by the HDL-Ps. A recent article demonstrated that the accumulation of immature SP-B in HDL-Ps reduces the antioxidant capacity and functionality of HDLs.[17]
- Apolipoprotein M (apoM) is a component of HDL-Ps that acts as transporter of sphingosine-1-phosphate (S1P). S1P is a phospholipid with vasodilator (activates eNOS), anti-inflammatory, antioxidant, and antiapoptotic activity.[2,3,19] Patients with HF have lower concentrations of apoM and S1P,[20] which explains the reduced HDL functionality in HF. In fact, apoM values are prognostic in HF, and the therapeutic increase in S1P concentration in HDL-Ps improves HDL functionality.[21]

The article by Teis et al. published in *Revista Española de Cardiología* compares the lipoprotein profile between a group of 429 outpatients with chronic HF and a control group of 428 patients without HF.[5] In this retrospective, observational study, the HF patients were followed up between 2006 and 2014 in a multidisciplinary HF unit at a university hospital in Barcelona. The characteristics of these HF patients were typical of patients seen in a HF clinic: mean age, 67 ± 13 years; 45% had diabetes, 67% had hypertension, mean body mass index was 27.3 ± 4.8; with reduced ejection fraction (35.5% ± 14.4%), and increased NT-proBNP (5393 ± 18 040 ng/L). The control patients were selected from the Di@bet.es study[22] (a population-based, cross-sectional, national study to assess the prevalence of diabetes) if they met the criteria of not having HF and matching the HF cases for age, sex, body mass index, diabetes, and treatment with statins.

The patients with HF had lower plasma concentrations of total cholesterol, HDL-C, and low-density lipoprotein cholesterol (LDL-C) and higher concentrations of very low-density lipoprotein cholesterol, with no differences in triglycerides. The first main result is that HDL-P concentrations were lower in patients with HF (25.7 ± 5.4 vs 27.9 ± 4.8 μmol/L)[5]; specifically, this was due to an 8% reduction in the concentration of small HDL-Ps (< 8 nm; 15.2 ± 4.9 vs 18.6 ± 4.2 μmol/L) despite an increase in medium HDL-Ps (8.2-9 mm) and large HDL-Ps (9-13mm). The concentrations of LDL particles (LDL-Ps) were also lower in patients with HF, due to lower concentrations of the 3 LDL-P subfractions (small, medium, and large). The second main result was that the patients with HF had larger HDL-Ps and LDL-Ps.[5] It is tempting to contemplate that the accumulation of immature SP-B in HDL-Ps[17,18] may be the cause of the larger HDL-Ps. We must point out that the lipoprotein derangement was more pronounced in more severe HF[5]; in fact, patients had lower concentrations and larger HDL-Ps and LDL-Ps as New York Heart Association functional class worsened, with more reduced left ventricular ejection fraction and higher concentrations of NT-proBNP, troponin, and ST2. An interesting corollary is that an analysis of this same population in another recent publication[23] identified larger HDL-P size as a predictor of poor prognosis.

This study[5] has several robust aspects that deserve comment. First, the authors quantified the lipoprotein particles (both concentration and size) using the most precise technique of choice, nuclear MR spectroscopy. Second, although the authors used slightly different spectroscopy techniques to previous articles,[10] this article confirms the reduction in HDL-P concentrations and their prognostic value observed in previous studies.[8–10] Indeed, the authors expand the discussion of lipoprotein derangement in HF to a new population (outpatients with chronic HF), while previous articles were limited to inpatients with acute HF[8,9] or patients with intercurrent HF in the catheterization laboratory.[10] Third, they matched the control group for clinically relevant variables (age, sex, diabetes, statins) including variables intrinsically linked to lipoprotein profile such as diabetes and body mass index.

Despite its knowledge advancement and clinical implications, the article by Teis et al.,[5] like all articles, has certain limitations. First, the retrospective observational design of this study does not allow us to determine a causal relationship between HF and lipoprotein abnormalities, but rather only to generate hypotheses. Nor does it offer mechanistic explanations at a molecular level to explain the causes of lipoprotein derangement. Second, there may have been a selection bias, as it was a single-center study that included only Caucasian patients, which could affect the generalizability of the results. It also included only patients referred to a specific HF clinic with a very close follow-up (at least every 3 months with a nurse and every 6 months with a physician)[23]; this inclusion criterion selected a highly specific patient population, with more advanced HF than the average patient with stable HF. Third, the authors did not measure HDL functionality (cholesterol uptake, antioxidant and anti-inflammatory ability) even though there are standardized techniques to do this.[6] It would have been interesting to study the association between HDL functionality and the concentration of the different HDL-P subpopulations, and to determine which parameter is most relevant in HF (such as whether there is a greater prognostic value from HDL functionality or small HDL-P concentration). Fourth, the samples were taken between 2006 and 2014: the associations between HF and lipoproteins found by the authors could have changed slightly since then due to the recent advances in clinical practice and pharmacological treatment. Fifth, the effect of beneficial drugs for HF on the deep phenotype of lipoproteins was not studied; it is known that sacubitril-valsartan [24] and sodium-glucose cotransporter 2 (SGLT2) inhibitors increase HDL-C and LDL-C in patients

with HF, but it is unknown whether they also improve HDL functionality or HDL-P size or concentration. Last, although the multivariate analysis was adjusted and the patients were matched with controls, unmeasured confounding factors could have had an effect on the results.

Apart from proposing new mechanistic routes between HF and HDL, this study[5] highlights the potential application of HDL-P concentrations (especially small HDL-Ps) as a biomarker for HF severity. The ideal biomarker is one which is accessible, reproducible, and adds clinical value; the lack of hospital access to MR spectroscopy for HDL-P measurement limits the use of these findings as a biomarker, but the creation of external independent companies that perform spectroscopy (such as that used by the authors[5]) represents a possible solution. Also, this study extends to the field of HF (and not only atherosclerosis) the need to develop treatments that improve HDL functionality and small HDL-P concentrations rather than those that simply increase HDL-C concentration.

In conclusion, the study by Teis et al.[5] demonstrates that HF alters patients' lipoprotein profile compared with healthy controls. Outpatients with chronic HF have lower concentrations of HDL-C and small HDL-Ps, as well as larger size and lower concentration of LDL-Ps. Consequently, the authors establish HDL particles as a new biomarker for severity and prognosis in HF.

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CONFLICTS OF INTEREST

None declared.

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