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# Large high-density lipoprotein particle number is independently associated with microvascular function in patients with well-controlled low-density lipoprotein concentration: A vasodilator stress magnetic resonance perfusion study

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**BACKGROUND:** Abnormalities in total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides are associated with microvascular dysfunction. Recent studies suggest that lipid subfractions better predict atherogenic burden than a routine lipid panel. We sought to determine, whether lipid subfractions are more strongly associated with microvascular function and subclinical atherosclerosis, than conventional lipid measurements using vasodilator stress cardiovascular magnetic resonance (CMR).

**METHODS:** Twenty-four adults referred for risk stratification from a lipid clinic with low-density lipoprotein cholesterol (LDL-C) <100 mg/dL underwent vasodilator CMR. Time-intensity curves generated from stress and rest perfusion images were used to determine the area under the curve (AUC) for the mid-ventricular slice myocardium and the left ventricular (LV) cavity. Myocardial perfusion reserve index (MPRi) was defined as stress to rest ratio of mid-ventricular myocardium AUC, normalized to LV cavity AUC. Lipid panels that included subfractions of LDL and high-density lipoprotein (HDL) were measured using nuclear magnetic resonance testing. The association between MPRi and lipid parameters was examined using univariate linear regression; lipid components statistically correlated with MPRi ($P < .05$) were then subjected to multivariate analysis.

**RESULTS:** Univariate regression analysis showed MPRi was associated with HDL-C, triglycerides, large HDL-P, and small LDL-P; no association was found between MPRi and total cholesterol, LDL-C, total LDL-P, or total HDL-P. Using multivariate analysis, large HDL-P was independently associated with MPRi.

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**CONCLUSIONS:** In patients with LDL-C <100 mg/dL, large HDL-P is independently associated with CMR-derived myocardial perfusion reserve, a surrogate for microvascular function and subclinical atherosclerosis. Further studies using lipid subfractions to better understand cardiovascular risks are warranted.


## Introduction

Vasodilator stress cardiovascular magnetic resonance (vsCMR) imaging is increasingly being used for the detection of hemodynamically significant epicardial coronary artery disease. However, because of its ability to assess myocardial perfusion reserve, it can also be used to detect subclinical coronary atherosclerosis and microvascular dysfunction.[1] The presence of microvascular dysfunction is an important predictor of cardiovascular events[2,3] and is associated with coronary atherosclerosis.[4] Several well-described cardiovascular risk factors, such as elevated low-density lipoprotein cholesterol (LDL-C),[5,6] decreased high-density lipoprotein cholesterol (HDL-C),[7] hypertriglyceridemia,[8] tobacco use,[9–11] diabetes mellitus,[12–14] and hypertension[15,16] are implicated in microvascular dysfunction and adverse cardiovascular outcomes. It is also known that treatment of many of these risk factors improves microvascular function.

In addition to lifestyle modifications, smoking cessation, and control of diabetes mellitus and hypertension, lowering LDL-C is the major therapeutic target for the reduction of cardiovascular events. However, the atherogenic burden is not always accurately reflected by measurement of LDL-C due to a large degree of variability in LDL composition with regard to the particle number, size, density, and cholesterol content.[17] One study demonstrated that nearly 50% of the general population exhibits discordance between LDL-C and LDL particle number (LDL-P)[18] and, when discordant, risk follows LDL-P rather than LDL-C.[17–19]

Moreover, data from large population studies, including the Framingham Heart Study, have shown HDL-C is a robust, independent cardiovascular risk factor.[20,21] More recently, in a large post hoc analysis of patients who achieved LDL-C <70 mg/dL with statin therapy, HDL-C levels were inversely correlated with the time to first major cardiovascular event.[7] Despite this, therapies that increase HDL-C have thus far failed to protect from adverse cardiovascular outcomes.[22]

Similar to LDL, HDL is a heterogeneous population of lipoproteins that differ in size, density, and function. Recent evidence suggests subfractions of HDL may be better suited to assess cardiovascular risk.[23] Traditionally, 2 subfractions have been investigated: HDL-2 (large, buoyant) and HDL-3 (small, dense). Cardioprotective properties of HDL have been shown in both HDL-2 and HDL-3 subfractions[24]; however, less is known about how HDL subfractions affect the microcirculation, particular in patients with well-controlled LDL-C. It has been speculated that HDL-C is an inadequate index of HDL function and reverse cholesterol transport. Several studies have suggested the concentration of HDL (HDL-P), measurement of cholesterol efflux capacity, or even the ratio HDL-C/HDL-P more accurately reflects HDL function.[25–27]

We hypothesized that in patients with LDL-C <100 mg/dL, lipid subfractions are more strongly associated with microvascular function and subclinical atherosclerosis than conventional lipid measurements. This study was designed to test this hypothesis using vsCMR-derived myocardial perfusion reserve, which was used as a surrogate for microvascular function.

## Methods

### Study population

Twenty-six patients from the University of Chicago Lipid Clinic were enrolled in the study. A blood sample from each patient was obtained for a nuclear magnetic resonance (NMR) lipid panel (Mayo Clinic; Rochester, MN or LipoScience; Raleigh, NC) that also included conventional lipid parameters. All blood samples were analyzed using the Vantera Clinical Analyzer (LipoScience; Raleigh, NC), an NMR-based platform that detects lipid subfractions. Patients with LDL-C <100 mg/dL were then prospectively recruited to undergo a vasodilator stress CMR study. Patients were excluded if they had an implantable cardioverter-defibrillator, pacemaker or other standard CMR contraindications, claustrophobia, severe reactive airway disease, high-grade AV nodal block, or GFR <30 mL/min/1.73 $m^2$. A 12-lead EKG was performed in all patients before CMR imaging to rule out high-degree AV nodal block. Patients were asked to stop all anti-anginal medications and caffeine-containing products 12 hours before the CMR examination. Each patient underwent a clinical evaluation, in which baseline demographics, current symptoms, past medical history, and exercise capacity were assessed and medications documented. The institutional review board approved the study, and each patient provided informed consent.

### CMR image acquisition protocol

CMR images were acquired using a 1.5-T magnetic resonance imaging scanner (Achieva; Philips, Best, the