JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 14, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.088

# Nonpharmacological Lipoprotein Apheresis Reduces Arterial Inflammation in Familial Hypercholesterolemia

Diederik F. van Wijk, MD,* Barbara Sjouke, MD,* Amparo Figueroa, MD,† Hamed Emami, MD,† Fleur M. van der Valk, MD,* Megan H. MacNabb, BA,† Linda C. Hemphill, MD,† Dominik M. Schulte, MD, PhD,*‡ Marion G. Koopman, MD, PhD,§ Mark E. Lobatto, MD,*‖ Hein J. Verberne, MD, PhD,¶ Zahi A. Fayad, MD, PhD,‖ John J.P. Kastelein, MD, PhD,* Willem J.M. Mulder, PhD,*‖ G. Kees Hovingh, MD, PhD,* Ahmed Tawakol, MD,† Erik S.G. Stroes, MD, PhD*

## ABSTRACT

**BACKGROUND** Patients with familial hypercholesterolemia (FH) are characterized by elevated atherogenic lipoprotein particles, predominantly low-density lipoprotein cholesterol (LDL-C), which is associated with accelerated atherogenesis and increased cardiovascular risk.

**OBJECTIVES** This study used $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) to investigate whether arterial inflammation is higher in patients with FH and, moreover, whether lipoprotein apheresis attenuates arterial wall inflammation in FH patients.

**METHODS** In total, 38 subjects were recruited: 24 FH patients and 14 normolipidemic controls. All subjects underwent FDG-PET imaging at baseline. Twelve FH patients who met the criteria for lipoprotein apheresis underwent apheresis procedures followed by a second FDG-PET imaging 3 days (range 1 to 4 days) after apheresis. Subsequently, the target-to-background ratio (TBR) of FDG uptake within the arterial wall was assessed.

**RESULTS** In FH patients, the mean arterial TBR was higher compared with healthy controls ($2.12 \pm 0.27$ vs. $1.92 \pm 0.19$; $p = 0.03$). A significant correlation was observed between baseline arterial TBR and LDL-C ($R = 0.37$; $p = 0.03$) that remained significant after adjusting for statin use ($\beta = 0.001$; $p = 0.02$) and atherosclerosis risk factors ($\beta = 0.001$; $p = 0.03$). LDL-C levels were significantly reduced after lipoprotein apheresis ($284 \pm 118$ mg/dl vs. $127 \pm 50$ mg/dl; $p < 0.001$). There was a significant reduction of arterial inflammation after lipoprotein apheresis (TBR: $2.05 \pm 0.31$ vs. $1.91 \pm 0.33$; $p < 0.02$).

**CONCLUSIONS** The arterial wall of FH patients is characterized by increased inflammation, which is markedly reduced after lipoprotein apheresis. This lends support to a causal role of apoprotein B-containing lipoproteins in arterial wall inflammation and supports the concept that lipoprotein-lowering therapies may impart anti-inflammatory effects by reducing atherogenic lipoproteins. (J Am Coll Cardiol 2014;64:1418–26) © 2014 by the American College of Cardiology Foundation.

From the *Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; †Cardiac MR PET CT Program and Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; ‡Department of Internal Medicine I, Christian-Albrechts University Kiel, University Hospital Schleswig-Holstein, Kiel, Germany; §Department of Nephrology, Academic Medical Center, Amsterdam, the Netherlands; ‖Translational and Molecular Imaging Institute, Mount Sinai School of Medicine, New York, New York; and the ¶Department of Nuclear Medicine, Academic Medical Center, Amsterdam, the Netherlands. This work was partly supported by a grant from the Dutch Heart Foundation (CVON 2012: Genius, no. 2011B019). Dr. Kastelein is supported by a lifetime achievement award of the Dutch Heart Foundation. Dr. Hovingh received funding from a Veni grant (project number 91612122) from the Netherlands Organisation for Scientific Research (NWO). Dr. Hemphill has received consulting fees from Regeneron. Dr. Kastelein has received consulting and lecturing fees from Novartis, Merck & Co., ISIS, Boehringer Ingelheim, AstraZeneca, Eli Lilly and Company, Amgen, Aegerion, Genzyme, Sanofi-Aventis, Regeneron, Pfizer, and Roche. Dr. Hovingh has received lecture fees from Pfizer, Sanofi-Aventis, Amgen, Roche, and Genzyme. Dr. Tawakol has received consulting fees from BMS, Cerenis, Novartis, and Roche; and has received grants from BMS and Roche. Dr. Stroes has received lecture fees from Amgen, Sanofi-Aventis, Torrent Pharmaceuticals, Roche, Merck & Co., Novartis, ISIS, Boehringer Ingelheim, AstraZeneca, and Genzyme. All other authors have reported that they have no relationships relevant

Atherosclerosis is a chronic, lipid-driven inflammatory disorder of the arterial wall (1). Lipid accumulation in the subintimal compartment ignites a local inflammatory response, perpetuated by oxidized lipoproteins and activated macrophages (2). Findings of prior studies of patients with cardiovascular disease (CVD) exemplify the relevance of this process by demonstrating that both a large lipid-rich necrotic core (3) and increased arterial inflammation (4) strongly predict plaque vulnerability and subsequent rupture. The detrimental interaction between lipids and inflammation is a hallmark in patients suffering from familial hypercholesterolemia (FH). These patients are predominantly characterized by extremely elevated low-density lipoprotein cholesterol (LDL-C) levels, increased levels of inflammatory markers (e.g., C-reactive protein [CRP]), and premature CVD (5,6). Prior studies have demonstrated some beneficial effects of statin therapy in FH patients (7); however, a substantial residual cardiovascular (CV) risk remains (8), possibly as a result of the fact that many FH patients do not reach target LDL-C levels by statins.

SEE PAGE 1427

The direct link between lipid accumulation and induction of local inflammation has been widely demonstrated. Potent lipid-lowering interventions have been shown to attenuate the degree of arterial wall and atherosclerotic plaque inflammation in experimental animal models (9). In humans, high-dose statin therapy has been proven to reduce serum levels of inflammatory biomarkers (5,10) independent of the statin's LDL-lowering effect (11). During the last decade, assessment of the local inflammatory activity of the arterial wall or atherosclerotic plaque has been introduced using novel imaging strategies, including $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) (12). The FDG signal has been shown to correlate with arterial macrophage content (13) and is predictive of subsequent risk of atherothrombotic events (14). Recently, rapid reduction of local arterial wall inflammation via statin therapy intensification was observed using PET imaging and, once again, was independent of lipid profile changes (15). Taking the widely acknowledged pleiotropic effects of statins into account, we therefore cannot dissect whether this statin-induced reduction in arterial wall inflammation is merely LDL-C dependent or due to pleiotropic, anti-inflammatory effects.

In the present study, we assessed whether patients with FH are characterized by increased arterial wall inflammation as determined by $^{18}$FDG-PET/computed tomography (CT) imaging. Subsequently, we explored whether a potent nonpharmacological lipid-lowering strategy can attenuate local arterial wall inflammation.

## METHODS

**STUDY POPULATION.** This pilot study comprised a cross-sectional analysis investigating arterial $^{18}$F-FDG uptake in FH patients versus healthy controls, as well as a prospective interventional analysis examining the effects of lipoprotein apheresis on arterial $^{18}$F-FDG uptake. This study was conducted at 2 centers: the Academic Medical Center, Amsterdam, the Netherlands, and Massachusetts General Hospital, Boston, Massachusetts. For the cross-sectional analysis at the Academic Medical Center, 18 patients with established FH diagnosis were recruited from the outpatient clinic. Healthy and normolipidemic controls without known CVD were recruited via local advertisements. For the prospective analysis, 12 FH patients (6 of whom were also included in the cross-sectional analysis of the study) meeting the eligibility criteria for lipoprotein apheresis according to apheresis guidelines (16) were included (6 from each center). Six FH patients (50%) were apheresis naive, and 6 patients had previously undergone lipoprotein apheresis. Written informed consent was obtained from all participants, and the local institutional review boards approved the protocol.

**$^{18}$F-FDG PET/CT IMAGING.** $^{18}$FDG-PET/CT imaging was performed in all FH patients and healthy controls at baseline. In the apheresis-naive FH patients (n = 6) treated with weekly lipoprotein-apheresis sessions, a second $^{18}$FDG-PET/CT scan was performed after 8 weeks, 3 days after the last apheresis session (median

**ABBREVIATIONS AND ACRONYMS**

**$^{18}$FDG** = $^{18}$F-fluorodeoxyglucose
**BMI** = body mass index
**CRP** = C-reactive protein
**CT** = computed tomography
**CVD** = cardiovascular disease
**FH** = familial hypercholesterolemia
**HDL-C** = high-density lipoprotein cholesterol
**IQR** = interquartile range
**LDL-C** = low-density lipoprotein cholesterol
**Lp(a)** = lipoprotein(a)
**MDS** = most diseased segment
**PET** = positron emission tomography
**SUV** = standardized uptake value
**TBR** = target-to-background ratio
**TG** = triglycerides

to the contents of this paper to disclose. Drs. van Wijk and Sjouke contributed equally to this work. Drs. Tawakol and Stroes are joint senior authors.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.
You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received December 3, 2013; revised manuscript received January 2, 2014, accepted January 20, 2014.