JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 64, NO. 14, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jacc.2014.01.088

Nonpharmacological Lipoprotein Apheresis Reduces Arterial Inflammation in Familial Hypercholesterolemia

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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 ± 0.27 vs. 1.92 ± 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 ± 118 mg/dl vs. 127 ± 50 mg/dl; $p < 0.001$). There was a significant reduction of arterial inflammation after lipoprotein apheresis (TBR: 2.05 ± 0.31 vs. 1.91 ± 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.

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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.

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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.

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

interval: 3 days [interquartile range (IQR): 1 to 4 days]). For FH patients on chronic apheresis therapy (n = 6), a 2-week washout period was introduced, after which the baseline ^{18}FDG-PET/CT scan was performed. The second ^{18}FDG-PET/CT scan in these patients was performed after a single apheresis episode (median interval: 3 days [IQR: 1 to 5 days]). PET/CT imaging of the aorta and carotid arteries was performed using a PET/CT scanner (Philips Gemini, Philips, Best, the Netherlands, or similar). In brief, patients were placed in a supine position for intravenous administration of ^{18}FDG. Approximately 90 min after ^{18}FDG injection (~180 MBq), a PET/CT scan was performed in 2 separate positions. The first position covered the carotid arteries extending inferiorly from the internal auditory meatus (15.5 cm) and acquired in 3-dimensional mode for 15 min. The second position covered the ascending aorta, aortic arch, and upper thoracic part of the descending aorta. Attenuation-corrected PET images were used for analysis.

IMAGE ANALYSIS. All scans were analyzed by 1 investigator (M.H.M.), who was blinded to patient characteristics and the temporal sequence of images. Arterial ^{18}FDG uptake was quantified by drawing a region of interest around each artery on every slice of the coregistered transaxial CT image. Subsequently, the maximal arterial standardized uptake value (SUV_{max}) was recorded as the maximal pixel activity within the region of interest of every vessel slice. The SUV is the decay-corrected tissue concentration of ^{18}FDG in kBq/ml, adjusted for the injected ^{18}FDG dose and patient's body weight. The mean SUV_{max} for each artery was derived as the average of the SUV_{max} of the individual slices of that artery. The mean arterial target-to-background ratio (TBR) was calculated by correcting the mean SUV_{max} for average background blood activity as detailed in prior studies (15,17). Additionally, the artery with the highest FDG uptake (mean TBR) at baseline was identified as the index vessel, as previously described (18). Thereafter, the average of the maximum TBR activity within the most diseased segment (MDS) of the index vessel (MDS TBR) was recorded. The MDS, defined as the 1.5-cm arterial segment that demonstrated the highest FDG uptake at baseline, was calculated as a mean of maximum TBR values derived from 3 contiguous axial segments as detailed in prior studies (15).

LIPOPROTEIN APHERESIS. Twelve FH patients underwent lipoprotein-apheresis procedures performed either with the Direct Adsorption of Lipoprotein (DALI) system (Fresenius Medical Care, Bad Homburg, Germany) or the Liposorber system (Kaneka Corporation, Osaka, Japan). The apheresis procedure-treated time/blood volume was individually calculated according to standard operating procedures. Blood samples were obtained on the day of (n = 10) or within 4 days (n = 2) of PET/CT imaging. Blood was centrifuged for 10 min at 3,000 rotations/min at 20°C. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by a commercially available enzymatic colorimetric assay (Roche, Basel, Switzerland). LDL-C levels were calculated by the Friedewald formula (19). Lipoprotein(a) [Lp(a)] levels were measured by a commercially available immunoturbidometric assay (Abbott Laboratories, Abbott Park, Illinois), as was CRP (assay by Roche, Basel, Switzerland).

STATISTICAL ANALYSIS. Continuous variables were tested for normality of distribution using the Shapiro-Wilk test and are expressed as mean ± SD or median (IQR) for normally and non-normally distributed variables, respectively. Independent samples *t* tests and Mann-Whitney *U* tests were used where appropriate to assess baseline differences between FH patients and healthy controls. Categorical variables are expressed as absolute numbers and percentages throughout this paper, and the chi-square test is employed for between-group analyses. To evaluate the relationship between continuous variables [e.g., LDL-C, Lp(a), and arterial TBR] at baseline, Pearson's correlation coefficient or Spearman's ρ is reported according to the distribution of variables. Furthermore, a linear regression model was fitted when adjustment for potential confounding variables was required, and the unstandardized regression coefficient (β) is reported. For longitudinal analysis in the 12 patients undergoing lipoprotein apheresis, the Wilcoxon signed rank test and paired-samples *t* test were used where appropriate. To assess the relationship between lipoproteins and TBR in these patients, Spearman's ρ was assessed in addition to a linear mixed-model analysis to provide an estimate of fixed effect of different lipoproteins on TBR. In order to limit the confounding effect of different imaging instruments, all between-group comparisons of imaging endpoints (between FH and controls) were confined to subjects imaged on a single PET/CT camera. By contrast, for longitudinal analyses (before and after apheresis of FH patients), where the impact of the imaging instrument is largely controlled for, analysis included subjects from both institutions. A 2-sided p value <0.05 was considered statistically significant. All data were analyzed using IBM SPSS software (version 21, Armonk, New York).

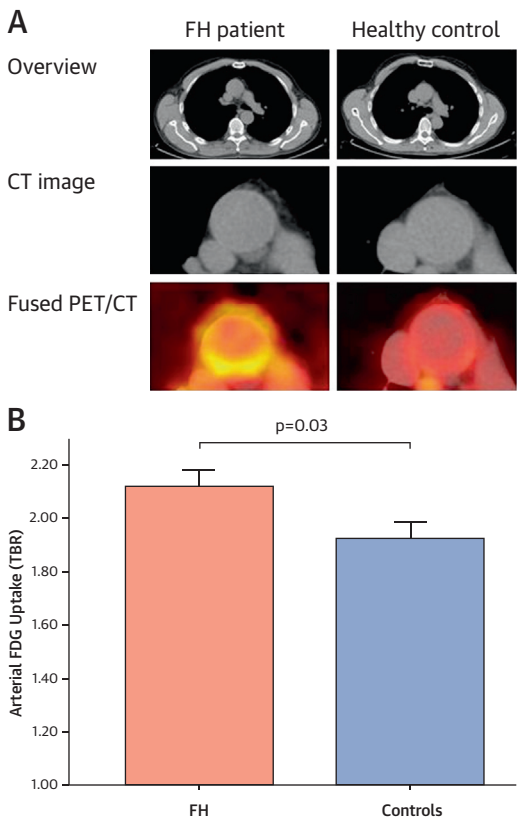


FIGURE 1 Higher Arterial TBR in FH Patients Than Control Subjects

(A) Representative images of CT, PET, and fused PET/CT of the aorta in a patient with FH **(left)** and an age-matched healthy control **(right)**. **(B)** Mean arterial TBR (average TBR of aorta and carotids) is significantly higher in patients with FH compared with healthy controls. This difference remained significant after adjusting for statin use ($\beta = 0.25$; $p = 0.01$) and risk factors of atherosclerosis (age, male, blood pressure, smoking) ($\beta = 0.19$; $p = 0.03$). **Error bars** represent the standard error of the mean. CT = computed tomography; ^{18}FDG = ^{18}F-fluorodeoxyglucose; FH = familial hypercholesterolemia; PET = positron emission tomography; TBR = target-to-background ratio.

TABLE 1 Baseline Demographic and Clinical Characteristics of Subjects

	Familial Hypercholesterolemia (n = 24)	Healthy Controls (n = 14)	p Value
Age, yrs	56.79 ± 5.64	63.21 ± 7.4	0.005
Male	16 (66.7)	11 (78.6)	0.16
BMI, kg/m^2	28.57 ± 4.1	24.35 ± 1.3	0.001
Current smoker	2 (8.3)	2 (14.3)	0.56
CVD	7 (29)	0	0.027
Blood pressure			
Systolic, mm Hg	132.67 ± 9.58	141.21 ± 10.78	0.016
Diastolic, mm Hg	79.21 ± 8.94	83.57 ± 5.64	0.11
Total cholesterol, mg/dl	320.9 ± 112.36	228.7 ± 32.93	0.005
LDL cholesterol, mg/dl	236.4 ± 108.3	147.02 ± 31.14	0.005
HDL cholesterol, mg/dl	54.83 ± 15.11	62.26 ± 11.6	0.12
Triglycerides, mg/dl	140.27 ± 75.5	109.4 ± 79.7	0.24
Lipoprotein(a), nmol/l*	73 [43–401]	197 [40–480]	0.464
CRP, mg/l*	1.1 [0.6–2.0]	0.7 [0.4–1.0]	0.115
Statin use	11 (45.83)	0	N/A
Non-statin lipid-lowering therapy†	11 (45.83)	0	N/A

Values are mean ± SD, n (%) or median [interquartile range (IQR)]. *Data were available for apheresis-naive patients only (n = 6). †Eight subjects were receiving both a statin and a non-statin lipid-lowering agent.

BMI = body mass index; CRP = C-reactive protein; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not applicable.

RESULTS

ARTERIAL WALL INFLAMMATION AND BLOOD BIOMARKERS AT BASELINE. Baseline demographics of 24 FH patients and 14 control subjects are outlined in Table 1. Apart from clear differences in the lipid profile, the control subjects were older and had a lower body mass index (BMI) compared with FH patients. Approximately 46% of FH patients were using statins; most commonly, those who did not were statin intolerant. Although the baseline LDL-C concentration in FH patients was significantly higher compared with the control group, some patients had modestly elevated LDL-C levels. The latter finding might be due to intensive lipid-lowering therapies in these patients. Baseline arterial TBR was significantly higher in FH patients compared with control subjects (2.12 ± 0.27 vs. 1.92 ± 0.19; $p = 0.03$) (Figures 1A and 1B). This difference remained significant after excluding FH patients with prior CVD ($p = 0.04$).

Moreover, arterial TBR remained higher in FH patients after adjusting for statin use ($\beta = 0.25$; $p = 0.01$) and risk factors of atherosclerosis (age, male, blood pressure, and smoking) ($\beta = 0.19$; $p = 0.03$). A significant correlation was observed between baseline arterial TBR and LDL-C ($R = 0.37$; $p = 0.03$) as well as CRP level ($R = 0.48$; $p = 0.006$). The relationship between baseline arterial TBR and LDL-C remained significant after adjustment for statin use ($\beta = 0.001$; $p = 0.02$), and previously stated atherosclerosis risk factors ($\beta = 0.001$; $p = 0.03$). Moreover, the relationship between LDL-C and arterial inflammation remained significant ($\beta = 0.001$; $p = 0.043$) after adjusting for the baseline factors that were significantly different between patient groups (FH diagnosis, age, BMI).

IMPACT OF LIPOPROTEIN APHERESIS ON ARTERIAL INFLAMMATION. The characteristics of the 12 FH patients treated with lipoprotein apheresis are

TABLE 2 Baseline and Post-Apheresis Characteristics of Patients Treated With Lipoprotein Apheresis

	Patients Treated With Lipoprotein Apheresis (n = 12)			
Age, yrs	57 ± 5.8			
Male	7 (58.3)			
BMI, kg/m^2	29.5 ± 2.3			
Current smoker	1 (8.3)			
CVD	7 (58.3)			
Blood pressure				
Systolic, mm Hg	130.3 ± 9.4			
Diastolic, mm Hg	79.1 ± 10.6			
Statin use	3 (25)			
Non-statin lipid-lowering therapy	2 (16.7%)			
	Pre-Apheresis	**Post-Apheresis**	**Change (%)**	**p Value**
Mean arterial TBR	2.05 ± 0.31	1.91 ± 0.33	−6.5	0.02
Index MDS TBR	2.33 ± 0.44	2.03 ± 0.48	−11.8	0.037
Total cholesterol, mg/dl	364.7 ± 117.9	189.2 ± 54.6	−45.1	<0.001
LDL cholesterol, mg/dl	284.3 ± 118.0	127.3 ± 49.8	−51.2	<0.001
HDL cholesterol, mg/dl	52.1 ± 16.8	55.1 ± 20.1	+5.4	0.224
Triglycerides, mg/dl	114.0 [97.5-237.1]	103.1 [75.2-137.5]	−16.6	0.18
Lipoprotein(a), mg/l*	73.0 [43.3-400.5]	29.5 [19.3-174.5]	−56.4	0.043
CRP, mg/l*	1.5 [0.6-5.5]	4.5 [1.1-9.3]	+77.7	0.12

Values are mean ± SD, n (%), or median [IQR]. *Post-apheresis values of lipoprotein(a) and CRP were available from apheresis-naive patients only (n = 6).

MDS = most diseased segment; TBR = target-to-background ratio; other abbreviations as in Table 1.

summarized in Table 2. Of note, 75% of patients undergoing apheresis were intolerant of statins. After lipoprotein apheresis, LDL-C levels were significantly reduced compared with baseline (284 ± 118 mg/dl vs. 127 ± 50 mg/dl; p < 0.001), which corresponded to a mean acute LDL-C reduction of 51 ± 23%. Online Figure 1 displays the LDL-C levels during the apheresis treatment period of the apheresis-naive patients. We observed a significant reduction of arterial wall inflammation (TBR) after LDL apheresis in the mean arterial TBR (aorta and carotids) (2.05 ± 0.31 vs. 1.91 ± 0.33; p = 0.02) (Figure 2A) and in MDS TBR of index vessel (2.31 ± 0.44 vs. 2.03 ± 0.48; p = 0.03) (Figure 2B). Corresponding reductions in mean arterial TBR and index MDS TBR were 6.47 ± 8.08% and 11.8 ± 14.2%, respectively. Notably, in the 6 non-apheresis-naive patients, follow-up PET/CT imaging was performed after a single cycle of lipoprotein apheresis (median interval [IQR]: 3 days [range: 1 to 5 days]). In that subgroup, the index MDS TBR was significantly reduced after a single cycle of apheresis (TBR: 2.05 ± 0.29 vs. 1.73 ± 0.13 pre- vs. post-apheresis, respectively; p = 0.03).

Online Table 1 summarizes TBR values of individual arteries before and after lipoprotein apheresis. Although LDL-C reduction post-apheresis was greater in apheresis-naive subjects (−222 ± 76 mg/dl vs. −91 ± 69 mg/dl; p = 0.01), there was no significant difference in change of arterial TBR between apheresis-naive subjects and patients who previously had undergone lipoprotein apheresis (p = 0.39). Mean arterial TBR and TBR in the MDS of the index vessel strongly correlated with baseline LDL-C (R = 0.71; p = 0.01 and R = 0.59; p = 0.04, respectively) (Figure 3), but not after lipoprotein apheresis (R = 0.42; p = 0.17 and R = 0.44; p = 0.18, respectively). We did not observe a significant change in HDL-C, TG, or CRP after lipoprotein apheresis, whereas we did see reduced Lp(a) levels (Table 2). Additionally, changes in arterial TBR did not correlate with changes in CRP (p = 0.21), TG (p = 0.16), HDL-C (p = 0.20), or Lp(a) (p = 0.78).

DISCUSSION

In the present study, we demonstrate that patients with FH, characterized by severely elevated plasma LDL-C levels, have markedly increased arterial wall inflammation compared with healthy control subjects without a history of CVD or hyperlipidemia as determined by ^{18}FDG-PET/CT scan. The degree of arterial wall inflammation correlated with LDL-C levels after adjusting for statin use and atherosclerotic risk factors. After lipoprotein apheresis in 12 FH patients who met the apheresis-treatment criteria, a significant reduction in arterial wall inflammation was observed.

Previous studies that addressed inflammation in FH patients have consistently reported a systemic, proinflammatory state, usually expressed as increased levels of plasma inflammatory biomarkers such as CRP (20). Children afflicted by FH were characterized by higher levels of CRP compared with healthy control subjects (21,22). Later in life, a low-grade inflammatory state was corroborated in adult FH patients with increased CRP levels as well as other inflammatory markers (23,24). We observed a significant correlation between baseline CRP and arterial FDG uptake in the study subjects. This finding aligns with prior observations concluding that both arterial FDG uptake and CRP are surrogate markers of arterial inflammation. Moreover, arterial TBR was reduced significantly after lipoprotein apheresis. In line with previous studies, we did not find a correlation between change in CRP and arterial TBR (18).

Although numerous studies with B-mode carotid ultrasound and magnetic resonance imaging have confirmed an increased atherosclerotic burden in FH (25), local arterial inflammation and the magnitude of its sensitivity to lipoprotein apheresis remained to

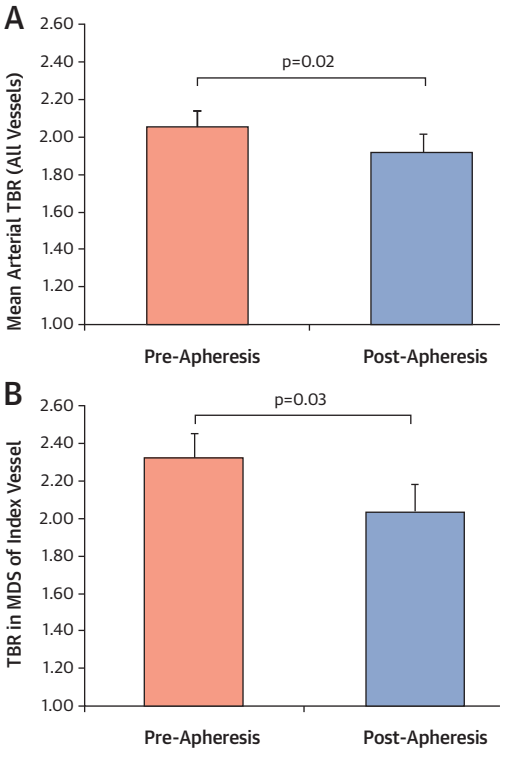


FIGURE 2 Arterial Inflammation Reduction After Lipoprotein Apheresis

Arterial ^{18}FDG uptake is significantly reduced after LDL apheresis of 12 FH patients compared to baseline as assessed by average arterial TBR (aorta and carotids) (2.05 ± 0.31 vs. 1.91 ± 0.33; p = 0.02) **(A)** and index MDS TBR (2.31 ± 0.44 vs. 2.03 ± 0.48; p = 0.037) **(B)**. Corresponding reductions in mean arterial TBR and index MDS TBR were 6.47 ± 8.08% and 11.8 ± 14.2%, respectively. **Error bars** represent standard error of mean. ^{18}FDG = ^{18}F-fluorodeoxyglucose; LDL = low-density lipoprotein; MDS = most diseased segment; other abbreviations as in Figure 1.

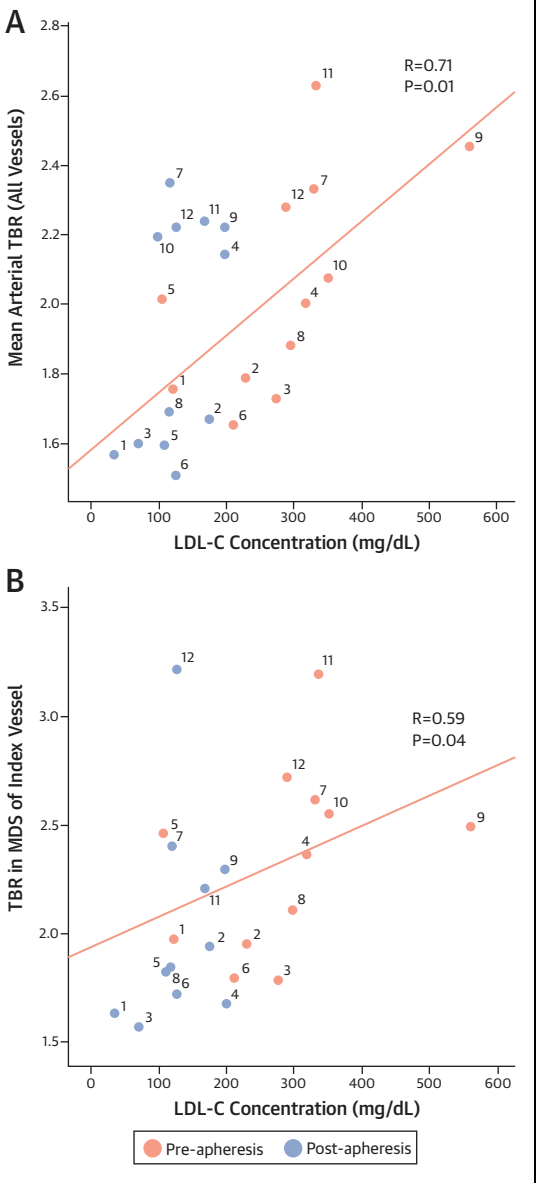


FIGURE 3 Arterial Inflammation Correlates With LDL-C Level in the Course of Lipoprotein Apheresis

Arterial FDG uptake (average TBR of aorta and carotids) **(A)** and TBR in MDS of the index vessel **(B)** significantly correlated with LDL-C levels at baseline before, but not after, lipoprotein apheresis (R = 0.42; p = 0.17 and R = 0.44; p = 0.18, for mean arterial TBR and TBR in MDS, respectively). The regression lines and correlation coefficients represent the baseline data only **(salmon dots)**. Individual subjects are numerically labelled. Abbreviations as in Figures 1 and 2.

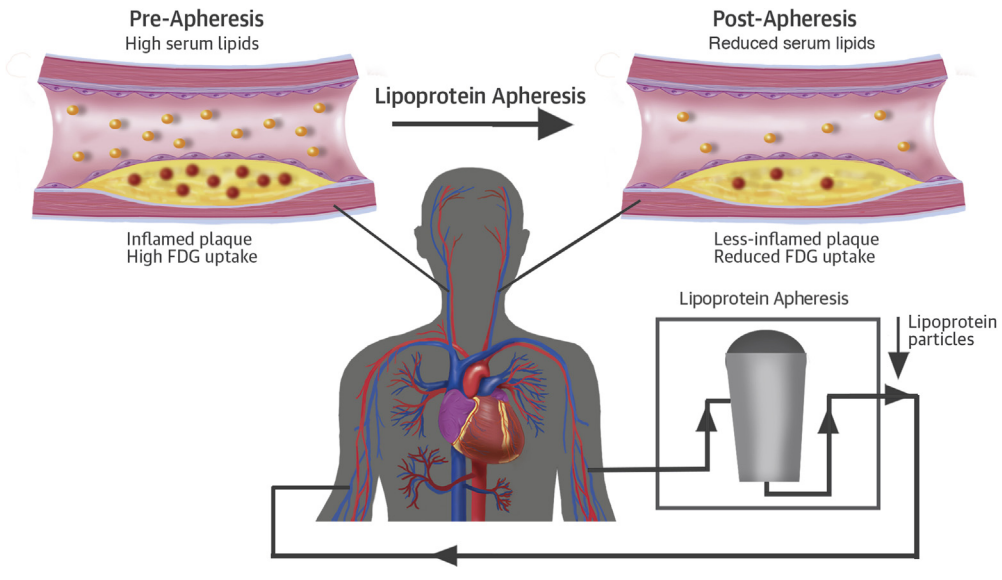
be investigated. The beneficial effect of lipoprotein apheresis at the vascular function level has previously been demonstrated by Igarashi et al. (26), who reported improved endothelial function after lipoprotein apheresis. Recently, PET/CT studies have been introduced as an imaging modality to quantitatively assess inflammation within the vessel wall (27). Subsequent studies showed that an increased TBR correlated with macrophage content (13) as well as with gene expression markers for plaque vulnerability in atherosclerotic lesions (28). Further, increased ^{18}FDG uptake has been associated with the presence of high-risk plaque morphology (29) and with atherosclerosis progression (30). Moreover, the arterial FDG-PET signal is linked to an increased risk of CV events (31,32) and recurrent cerebral infarction (4), and has been shown to be a potent predictor of future CVD after multivariate adjustment (14). Here, we demonstrated that increased local arterial wall

inflammation in patients with FH, irrespective of statin use and other potential confounding factors, was modifiable by lipoprotein-apheresis treatment (**Central Illustration**). This observation underlines the close correlation between elevated lipoprotein levels and inflammatory activation within the arterial wall.

Most studies addressing anti-inflammatory effects of medications in CVD patients have used statins as an LDL-C–lowering agent, because statins exert numerous pleiotropic effects, including anti-inflammatory properties (15,33). To address the impact of atherogenic lipoprotein-lowering therapy independent from pleiotropic effects, we applied lipoprotein apheresis in eligible FH patients. Here, we observed that the magnitude of reduction in arterial TBR seen with apheresis appears to be similar to that seen with high-dose statins (15). However, it also is apparent that statins are associated with a somewhat greater reduction in arterial inflammation per mg/dl reduction in LDL-C. For example, in a prior study evaluating the effects of atorvastatin on arterial inflammation, each 10% reduction in LDL-C was associated with a 2.9% and 3.2% reduction in MDS TBR in the 10-mg and 80-mg atorvastatin groups, respectively (15). With apheresis, the absolute change in arterial TBR was relatively smaller in magnitude compared with changes in LDL-C; each 10% reduction in LDL-C induced a 2.1% reduction in MDS TBR. Thus, on one hand, the significant reduction in arterial PET signal observed after apheresis demonstrates that nonpharmacological LDL-C lowering per se results in reduced atherosclerotic inflammation independently of the pleiotropic effects of pharmacotherapy. On the other hand, the fact that statins are associated with a modestly higher reduction in arterial inflammation per unit reduction in LDL-C supports the concept that a portion—albeit a limited one—of statins' anti-inflammatory actions may also relate to pleiotropic effects.

We also observed a numerically higher reduction in TBR of carotids compared with the aorta by apheresis; a prior study evaluating the effect of high-dose atorvastatin on arterial inflammation made a similar observation (15). The potential superiority of carotids to aorta as an imaging endpoint has been previously suggested (18). Although it is not fully understood why, after lipid lowering, reductions in arterial inflammation (by PET/CT) may be more evident in the carotids over the aorta, which may be potentially due to biological differences in vessel walls or technical issues relating to the PET/CT imaging approach (18).

It is worth noting that reductions in arterial FDG uptake occurred very rapidly in this study. In the subset of non-apheresis-naive subjects who underwent a single session of apheresis, the arterial PET signal was substantially reduced within a median of



CENTRAL ILLUSTRATION Impact of Apheresis on Circulating Lipids and Atherosclerotic Inflammation

Familial hypercholesterolemia (FH) is associated with elevated circulating lipids and increased atherosclerotic inflammation. Lipoprotein apheresis in individuals with FH results in a rapid reduction in circulating lipids as well as in a concordant reduction in atherosclerotic inflammation, measured as a decrease in arterial fluorodeoxyglucose uptake.

3 days after apheresis. Prior studies in humans have noted that lipid lowering with statins produces reductions in arterial FDG uptake within 4 weeks (the earliest time point previously assessed). The current study shows that functional changes in the human artery wall occur even earlier, comparable to that demonstrated in animal studies (34).

Finally, it is notable that the magnitude of reduction in arterial TBR in our study is comparable to the impact potent anti-inflammatory agents, such as anti-tumor necrosis factor (TNF)-α therapy, exert on vessel wall inflammation. Recently, it was reported that after 8 weeks of treatment with a TNF-α antagonist in patients with rheumatoid arthritis, the TBR across the aorta was reduced by 6% (35). Collectively, these data support a direct, strong role of atherogenic lipoprotein particles including LDL-C in driving atherogenic vascular inflammation, which implies that all potent atherogenic lipoprotein-lowering therapies might contain the potential to attenuate vessel wall inflammation in hyperlipidemic, atherosclerotic patients.

STUDY LIMITATIONS. When interpreting the results of this study, several limitations need to be considered. First, matching between FH patients and controls was not optimal. For example, BMI was higher in FH patients compared with controls. Because higher BMI has been associated with increased ^{18}FDG uptake, this may have contributed to the higher signal in FH in our study (36). However, this effect is partly counterbalanced by the more advanced age of controls, which can be expected to result in an increased ^{18}FDG uptake (36). Overall, the matching is unlikely to have been of major influence, because the relation between LDL-C and TBR was retained after adjustment for confounding factors, including both BMI and age.

Second, lipoprotein apheresis affects other plasma factors beyond apoprotein B-containing lipoproteins (37), including inflammatory proteins and oxidized phospholipids (38). Part of these factors are bound to LDL-C and/or Lp(a), making it impossible to separate the impact of pure atherogenic lipoprotein lowering from the impact of lowering of their associated proinflammatory molecules. TBR change was significantly correlated with LDL-C change, whereas no correlation could be demonstrated for Lp(a), suggesting that most of the TBR change appears to be LDL-C driven. However, we cannot exclude the possibility that changes in other plasma factors may have contributed to the TBR decrease.

Additionally, this study had a small sample size, especially in the treatment group, and we did not incorporate a control treatment arm in this study.

CONCLUSIONS

The present data indicate that prolonged and severe elevation of atherogenic apoprotein B-containing lipoproteins comprising LDL-C are important drivers of arterial wall inflammation. The latter remains, however, amenable to improvement as attested by a significant decrease of vessel wall FDG uptake after short-term lipoprotein apheresis. The fact that TBR in FH patients was higher at baseline, independent from statin use, combined with a TBR decrease after lipoprotein apheresis, lends further support to therapeutic efforts aimed at aggressive lowering of atherogenic lipoprotein particles, particularly in patients with severe LDL-C elevations and an increased CVD risk. Our findings emphasize the relevance of incorporating vessel wall inflammation imaging into future studies aimed at lowering atherogenic lipoprotein particles, particularly in high-risk patients with persistent LDL-C elevation. Moreover, the findings support the contention that nonpharmacological lipoprotein removal directly reduces arterial inflammation.

ACKNOWLEDGMENTS The authors wish to thank W.M. de Jong and P.F.C. Groot for their assistance in data acquisition.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The arterial walls of patients with FH are characterized by inflammatory activity, which can be assessed by ^{18}F-fluorodeoxyglucose imaging positron emission tomography, and removal of low-density lipoprotein cholesterol by lipoprotein-apheresis reduces inflammation.

TRANSLATIONAL OUTLOOK: The effect of non-statin lipoprotein-lowering strategies that attenuate vessel wall inflammation on clinical ischemic events in patients with atherosclerosis warrants further investigation.

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KEY WORDS atherosclerosis, PET/CT imaging

APPENDIX For a supplemental figure and table, please see the online version of this article.