The association between saphenous vein endothelial function, systemic inflammation, and statin therapy in patients undergoing coronary artery bypass surgery

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See related editorial on page 277.

Objectives: Endothelial dysfunction and C-reactive protein play a pivotal role in development of atherosclerosis and act as markers for future adverse cardiac events. Statins reduce C-reactive protein levels and improve endothelial function. However, little information is available on endothelial function and its determinants in veins. We investigated the association between saphenous vein endothelial function and C-reactive protein levels in patients treated with statins undergoing coronary artery bypass surgery.

Methods: Seventy-six patients with optimal low-density lipoprotein cholesterol levels ($\leq$1.6 mmol/L) secondary to regular treatment with a minimum of simvastatin 40 mg were recruited. Each subject underwent detailed characterization according to anthropomorphic data, saphenous vein endothelial function (assessed ex vivo by measuring acetylcholine-induced relaxation of venous rings), and markers of systemic inflammation (C-reactive protein and tumor necrosis factor-α).

Results: Despite regular treatment with statins, 26% of patients had C-reactive protein levels in the "high-risk" range (>3.0 mg/L). There was a negative linear correlation between acetylcholine-induced venous relaxation and C-reactive protein ($r = -.30$, $P = .02$) and waist circumference ($r = -0.21$, $P = .03$). In a multivariate regression model, C-reactive protein ($P = .02$) was the only independent predictor of acetylcholine-induced venous relaxation. In turn, correlates of C-reactive protein were assessed. There was a correlation between C-reactive protein and coronary atherosclerotic burden ($r = .46$, $P < .0001$), body mass index ($r = .26$, $P = .03$), fasting glucose levels ($r = .31$, $P = .01$), and waist circumference ($r = .29$, $P = .01$). Using multivariate analysis, coronary atherosclerotic burden ($P < .0001$) was the only independent predictor of C-reactive protein.

Conclusions: In our cohort of patients with coronary artery disease, C-reactive protein level was the only independent predictor of saphenous vein endothelial function. In turn, its levels were independently influenced by the extent of coronary atherosclerotic burden.

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Endothelial dysfunction and systemic inflammation play a pivotal role in the pathophysiology of coronary artery atherosclerosis and acute coronary events.[1,2] Both have also been shown to be accurate predictors of future cardiovascular risk.[1,2] Endothelial dysfunction is thought to be the earliest detect-

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACh = acetylcholine
BMI = body mass index
CABG = coronary artery bypass graft
CAD = coronary artery disease
CRP = C-reactive protein
HDL = high-density lipoprotein
LDL = low-density lipoprotein
L-NMMA = N^G monomethyl-L-arginine
NO = nitric oxide
QCA = quantitative coronary angiography
SNP = sodium nitroprusside
TNFα = tumor necrosis factor-α

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able composite manifestation of a number of vascular pathophysiologic changes leading to the development of atherosclerosis and is often present prior to the development of morphologic/clinical manifestations of atherosclerosis.[1,2] Markers of systemic inflammation such as C-reactive protein (CRP) have also emerged as potential participants in the development of atherosclerosis.[2-4] CRP exerts a direct proinflammatory effect on endothelial cells[3] and may promote the development of clinical complications of atherosclerosis such as arterial thrombosis.[4] Of particular relevance to the present report, in vitro studies have shown that CRP can reduce the production and bioactivity of the potent antiatherosclerotic signaling molecule nitric oxide (NO),[5,6] which is a key step in endothelial dysfunction.

Statins, which lower cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase, are established as standard therapy for patients with coronary artery disease (CAD). Independent of their lipid-lowering effect, statins have also been shown to improve endothelial function in arterial conduits and reduce CRP levels in patients with CAD.[7,8]

Studies investigating the role of endothelial dysfunction in development and clinical manifestations of atherosclerosis and its association with inflammatory markers such as CRP are primarily derived from work on peripheral and coronary arterial conduits. In contrast, there is limited information on the function of the venous endothelium and its determinants. Considering that venous conduits remain an important tool in surgical revascularization of patients with CAD, we examined factors influencing endothelial function in saphenous vein samples of patients undergoing coronary artery bypass graft (CABG) surgery who were treated with statins.

Materials and Methods

Patients

Seventy-six unselected patients referred for elective first-time CABG surgery between January 2003 and June 2004 were recruited to the study. Patients with symptomatic heart failure (New York Heart Association class II–IV), an acute coronary syndrome within the previous 6 months, concurrent infection, or an inflammatory disorder (such as rheumatoid arthritis, which may have led to an elevation in CRP levels) were excluded. One month prior to admission for surgery, each patient was reviewed to establish smoking status (nonsmoker, previous smoker, or current smoker), to undergo detailed anthropomorphic measurements according to published guidelines[9] (weight [kg], height [m], waist and hip circumference [cm], body mass index [BMI, kg/m^2] and waist–to–hip ratio), and to ensure daily medication with a minimum of simvastatin 40 mg.[10] On the morning of surgery, blood was taken for full lipid profile (total cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol), markers of systemic inflammation (high-sensitivity CRP, tumor necrosis factor-α [TNFα]), and serum blood glucose after an overnight fast. During surgery, a sample of saphenous vein was obtained from each patient to assess vasomotor responses as previously reported[11] and outlined below. Vasoactive medication was omitted 24 hours prior to blood sampling and saphenous vein harvest. The extent of coronary atherosclerotic burden was estimated retrospectively from preoperative coronary angiograms.[12] The study protocol and collection of tissue specimens had local research ethics committee approval, and all subjects provided written informed consent prior to recruitment to the study.

Assessment of Saphenous Vein Vasomotor Response

Vasomotor responses to phenylephrine, acetylcholine (ACh), and sodium nitroprusside (SNP) were assessed ex vivo in saphenous vein rings as previously described.[11] A 3-cm length of saphenous vein was harvested at the start of the surgical procedure in each patient. To ensure minimal interference with vascular function, veins were harvested at the start of the surgical procedure using an open technique without distension and with minimal tissue handling prior to administration of heparin and/or antifibrinolytic drugs (for example, aprotonin). The venous rings were transferred immediately to the physiology laboratory in chilled, preoxygenated Kreb's Henseleit buffer without exposure to any medication. None of the venous rings had been exposed to cardiopulmonary bypass prior to and/or during harvesting. All venous rings underwent physiologic examination within hours of harvesting on the same day. Veins were carefully cleared of adherent tissue and sectioned into 6 to 8, 4-mm rings. Rings were suspended between a fixed support and a force transducer in an organ bath containing 10 mL Krebs Henseleit solution at 37°C and bubbled with a mixture of 95% O_2/5% CO_2. All experiments were performed in the presence of indomethacin (10 μmol/L) to inhibit cyclooxygenase.

Forty-five minutes were allowed for equilibration at a resting tension of 3 g (determined from previous work in our laboratory). To check the integrity of the smooth muscle cells in the saphenous vein samples, the maximal contractile response of the vein to KCL (80 mmol/L) was assessed. Venous rings that contracted to <1 g were discarded. The samples were then washed and reequilibrated. A cumulative dose–response curve to phenylephrine ($10^{-9}-10^{-3}$ mol/L) was performed. Samples underwent a second washout. Venous rings were preconstricted to 70% of the maximal phenylephrine-induced tension and relaxation responses to cumulative

doses of ACh ($10^{-9}-10^{-4}$ mol/L) and SNP ($10^{-10}-10^{-4}$ mol/L) measured in separate venous rings. To assess basal NO production, phenylephrine dose response studies ($10^{-9}-10^{-3}$ mol/L) were performed before and after exposure to the nonselective NO synthase inhibitor N^G monomethyl-L-arginine (L-NMMA [10^{-4} mol/L]) in a third venous ring. Vasodilator responses were expressed as a percentage of the preconstricted tension.

Measurement of Atherosclerotic Plaque Burden

Coronary atherosclerotic burden was derived by calculating the coronary atheroma extent score from preoperative angiograms in each patient as described by Sullivan and colleagues.[12] A single experienced angiographer (N.M.), blinded to the patient's vascular function and inflammatory status, reviewed all angiograms. Coronary segments were analyzed in 1 angiographic view. Where possible, angiographic frames were analyzed in end diastole or diastasis and selected to achieve minimal foreshortening and overlap, good visualization of stenoses within the segment, and optimal contrast and image quality. Coronary segments with a diameter of ≤1.5 mm were excluded from analysis. Philips (Eindhoven, The Netherlands) quantitative coronary angiography (QCA) software package was used for analysis. Coronary catheters were used for calibration, assuming the following diameters: 6F = 1.95 mm, 5F = 1.65 mm. Coronary extent score was derived by calculating the proportion of each coronary artery and major side branch involved in angiographically detectable atheroma (identified as any abnormal luminal narrowing or irregularity) and multiplied by a specific factor reflecting the general surface area of that vessel. The overall extent score was derived from the sum of the scores obtained for each vessel to give a maximum total score out of 100. The factors for each coronary artery and its branch were as follows: left main artery, ×5; left anterior descending artery, ×20; major diagonal branch or branches, ×10; first septal perforator, ×5; left circumflex artery, ×20; obtuse marginal artery and its posterolateral branch together, ×10; right coronary artery, ×10; posterior descending artery, ×10. In patients where the major lateral wall branch was an obtuse marginal or intermediate artery, this vessel was given a factor of ×20, and the left circumflex artery, a factor of ×10. Occluded arteries were given the highest extent score calculated in a corresponding artery in the entire study group. Coronary extent scores were calculated for 56 of the 76 patients recruited to the study. Fourteen angiograms were not available for analysis, and 6 angiograms were excluded as QCA was not possible in all coronary territories. To assess reproducibility, extent scores were calculated on 2 different occasions separated by at least 4 weeks in a random group of 15 patients. The reader remained blinded to previous atheroma score obtained, as well as patients' vascular function and inflammatory status. Intraobserver reproducibility was high, with a Pearson correlation coefficient of 0.89 between 2 readings ($P < .01$).

Laboratory Assays

Assays for full lipid profile and glucose were performed in the hospital biochemistry department. Serum samples for CRP and TNFα were stored at −80°C and analyzed at the end of the recruitment period. CRP was measured using a high-sensitivity turbidimetric immunoassay (WAKO Chemicals, Neuss, Germany) on the Cobas Mira Analyser (Roche Diagnostics, Lewes, UK). The lowest detectable CRP concentration was 0.2 mg/L. Within-batch variability was assessed, and a coefficient of variation of 5% at 5.0 mg/L was achieved. TNFα was measured using a commercially available enzyme-linked immunosorbent assay (R&D systems, Abingdon, UK). Between-batch variability was 10% at 13.5 μg/L.

Statistical Analysis

Data analysis was performed with SPSS 12.0 for Windows statistics software. Continuous variables were presented as mean ± SEM. Non-normally distributed data (HDL cholesterol, triglycerides, glucose, TNFα, and CRP) were log transformed for subsequent analysis. Pearson's correlation coefficients were derived to assess the relationship between baseline variables and the vasodilator response to ACh/ACh EC_{50} (concentration of ACh required to produce 50% of the maximum possible response) and circulating CRP levels. A stepwise multiple regression model was produced to identify independent determinants of the vasodilator response to ACh (model 1) and circulating CRP levels (model 2). In Model 1, maximal vasodilator response to ACh was the dependent variable and age, BMI, waist circumference, HDL cholesterol, LDL cholesterol, plasma triglycerides, serum glucose, systolic blood pressure, diastolic blood pressure, TNFα, CRP, and smoking status as covariates. In model 2, circulating CRP level was the dependent variable and age, BMI, waist circumference, HDL cholesterol, LDL cholesterol, plasma triglycerides, serum glucose, systolic blood pressure, diastolic blood pressure, smoking status, and coronary atherosclerotic burden as covariates. Statistical significance was accepted at $P < .05$.

Results

A total of 76 patients were recruited to the study. Table 1 summarizes the baseline clinical characteristics. Seven patients had 2-vessel coronary artery disease and the remainder, 3-vessel disease. All patients had been established on a minimum of simvastatin 40 mg 1 month prior to surgery. In all patients, total cholesterol was ≤3.1 mmol/L (≤120.8 mg/dL), and LDL cholesterol was ≤1.6 mmol/L (≤61.7 mg/dL). Although lipid profile was adequately controlled in all patients, CRP levels remained over 3.0 mg/L in 26% of patients. ACh-induced saphenous vein relaxation varied between −6.5% and 97%, indicating a wide range of venous endothelial function between patients. Venous relaxation to SNP was >80% in all rings, suggesting normal responsiveness of the vascular smooth muscle to exogenous NO.

Factors Influencing Vascular Function in Human Saphenous Vein

The association between baseline characteristics of the 76 patients as outlined above and endothelium-dependent and -independent vasodilatation in saphenous vein samples was investigated. Using univariate analysis, there was a significant negative correlation between ACh-induced venous relaxation and logCRP ($r = -.30$, $P = .02$) and waist circumference ($r = -0.21$, $P = .03$). In a stepwise multivariate regression model, logCRP ($P = .02$) was the only independent predictor of ACh-induced venous relaxation

TABLE 1. Baseline characteristics of patients

Age (y)	66.6 ± 0.9
Male	92%
Anthropomorphic measurements	
Weight (kg)	79.9 ± 1.4
BMI (kg/m^2)	27.1 ± 0.8
Waist (cm)	99.8 ± 1.1
Hip (cm)	98.9 ± 0.7
Waist:hip ratio	1.0 ± 0.01
Full lipid profile	
Total cholesterol (mmol/L)	3.1 ± 0.1
LDL cholesterol (mmol/L)	1.6 ± 0.1
HDL cholesterol (mmol/L)	0.9 ± 0.03
Triglycerides (mmol/L)	1.3 ± 0.1
Fasting glucose (mmol/L)	6.1 ± 0.2
Systolic BP (mm Hg)	138.1 ± 2.5
Diastolic BP (mm Hg)	74.9 ± 1.3
Diabetes	20%
Smoking status	
Current smoker	14%
Previous smoker	51%
Nonsmoker	35%
Number of native coronary arteries with >50% stenosis	
Single vessel	0%
Two vessels	9%
Three vessels	91%
Left ventricular function	
Poor (EF < 30%)	1%
Moderate (EF 30–50%)	19%
Good (EF > 50%)	80%
Markers of systemic inflammation	
CRP (mg/L)	2.4 ± 0.2
<1	30%
1–3	44%
>3	26%
TNFα (μg/L)	3.2 ± 0.32
ACE inhibitors	43%
Antiplatelet agent	100%
Statins	100%

Values presented as mean ± standard error of mean (SEM) or % of total patient population. *ACE,* Angiotensin-converting enzyme; *BMI,* body mass index; *BP,* blood pressure; *CRP,* C-reactive protein; *EF,* ejection fraction; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *TNFα,* tumor necrosis factor-α.

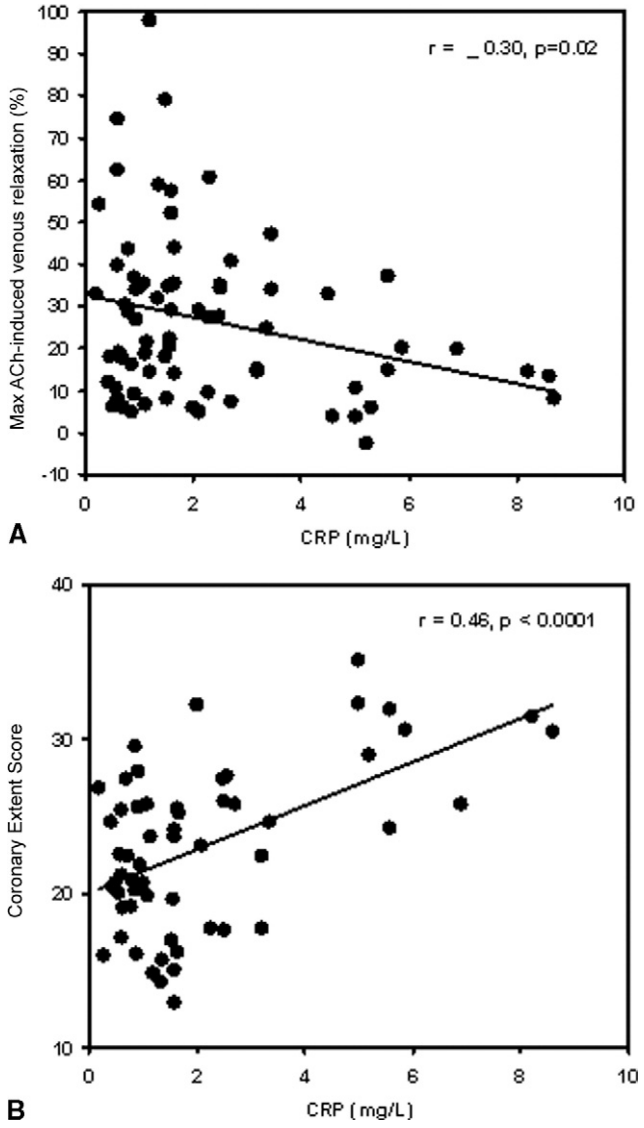

Figure 1. A, Negative correlation between maximal acetylcholine *(ACh)*-induced saphenous vein relaxation and C-reactive protein *(CRP)* levels. B, Positive correlation between coronary atherosclerotic burden (as expressed by the coronary extent score) and CRP levels.

TABLE 2. Stepwise multiple regression analysis to assess independent determinants of acetylcholine saphenous vein relaxation (model 1) and circulating C−reactive protein levels (model 2)

Independent variable	B (±SE)	Beta	t	*P*	95% CI for B
Model 1					
logCRP	−14.10 ± 5.93	− 0.27	−2.38	.02	−25.93–−2.25
Constant	10.57 ± 7.19		1.47	.14	
Model 2					
Atheroma	0.03 ± 0.009	0.46	3.79	<.0001	0.02–0.05
Constant	−0.58 ± 0.20		−2.88	.006	

Model 1: Dependent variable—% peak acetylcholine induced venous relaxation. Model 2: Dependent variable—circulating CRP level. Only variables with a $P \leq .05$ were considered into the final fitted model. *CRP,* C-reactive protein; *atheroma,* coronary atheroma extent score.

(Table 2 and Figure 1). To examine whether the effects of gender influenced venous endothelial function, the multivariate analysis was repeated excluding data from the 6 female patients recruited to the study. LogCRP ($P = .02$) remained the only independent determinant of ACh-induced venous relaxation. We also calculated EC_{50} for ACh-mediated vasorelaxation (mean 340.2 ± 51.2 nmol/L) according to CRP concentrations (<1 mg/L, 1 to 3 mg/L, and >3 mg/L). Using 1-way analysis of variance, there was no association between the 3 groups (F = 2.68, P = NS, data not shown). There was no correlation between contraction of venous rings in response to phenylephrine and CRP concentration ($r = -.07$, P = NS). There was no association between saphenous vein endothelium-independent vasodilatation, as demonstrated by venous relaxation in response to SNP and baseline characteristics of patients.

To examine the influence of CRP on basal NO bioavailability, we performed dose–response curves to phenylephrine before and after exposure to L-NMMA. There was no correlation between logCRP levels and contraction in the presence of L-NMMA ($r = .05$, P = NS).

Determinants of Circulating CRP

We then examined potential factors influencing circulating CRP levels in our cohort of patients with CAD. In univariate analysis there was a correlation between logCRP levels and coronary atherosclerotic burden ($r = .46$, $P < .0001$), BMI ($r = .26$, $P = .03$), log glucose ($r = .31$, $P = .01$), and waist circumference ($r = .29$, $P = .01$). In a stepwise multivariate regression model, coronary atherosclerotic burden ($P < .0001$) was the only independent predictor of plasma CRP levels (Table 2 and Figure 1). Interestingly, there was no correlation between LDL cholesterol and HDL cholesterol and CRP levels.

Discussion

We have demonstrated a number of novel and potentially important findings. Our results indicate that in patients treated with statins, circulating CRP was the only independent predictor of endothelial function in saphenous vein rings ex vivo. In turn, the only independent predictor of circulating CRP level was coronary atherosclerotic burden, with HDL cholesterol, LDL cholesterol, and other conventional risk factors for cardiovascular disease having no independent association with circulating CRP levels. Furthermore, despite regular treatment with statins at doses that significantly reduced LDL cholesterol, a sizeable proportion of patients with CAD undergoing CABG surgery had CRP levels within the "high-risk" range.

Medium- to long-term patency of saphenous vein grafts is a major limitation to the use of venous conduits in patients undergoing CABG surgery.[13] It is estimated that by 5 years around 30% and by 10 years 40% to 60% of saphenous vein conduits occlude.[13] The mechanisms leading to medium- and long-term graft failure remain unclear. Morphologic analysis of venous conduits has shown that atherosclerotic changes can occur as early as 6 months post-CABG surgery, with the incidence of these lesions increasing to 30% 3 years postsurgery.[13] Therefore, examination of the role of factors, such as endothelial dysfunction and systemic inflammation, which are known to be integral to atheroma formation, in the context of venous grafts is important.

Determinants of Saphenous Vein Endothelial Function

Endothelial dysfunction is an early detectable functional change in the development of atherosclerosis in native coronary arteries.[1,2] It has also been shown to be a powerful predictor of future cardiovascular morbidity and mortality in patients with CAD.[1,2] This effect is in part due to loss of NO bioavailability with consequent reduction in endothelial antiatherogenic and antiplatelet effects.[3,4] However, information on endothelial function in venous conduits, such as saphenous vein grafts of patients undergoing CABG surgery, and its clinical implications remain limited. Saphenous vein graft endothelial dysfunction predisposes to the development of neointimal proliferation,[14] a process that can be inhibited by increasing NO bioavailability.[15] Recent studies also support a close correlation between endothelial function in saphenous vein and internal mammary and radial arteries.[16] Therefore, the presence of saphenous vein endothelial dysfunction in patients with CAD undergoing CABG surgery may be relevant to the progression of atherosclerosis and its clinical complications in both venous and arterial conduits post-CABG surgery, as well as native coronary arteries. Previous studies have demonstrated that during surgical vein harvest, there is a risk of significant endothelial denudation.[13] This may introduce important influences of the subendothelial layers on function of the venous graft. For example, the extent of venous graft endothelial disruption is related to the risk of early thrombosis.[17] In the present study, we took great care to avoid endothelial loss, although the extent of endothelial loss was not formally quantified using immunohistochemistry. As discussed, in routine clinical practice, preparation of venous conduits prior to grafting often results in significant endothelial denudation, which may limit the clinical applicability of our results. Nevertheless, in saphenous veins with good endothelial integrity (which one could argue should be a goal during vein harvest), the extent of endothelial dysfunction is potentially important. Preoperative use of statins could address this issue. Furthermore, the effect of local and systemic CRP on endothelial loss warrants attention.

A number of factors are known to influence endothelial function in patients with CAD. Conventional risk factors for CAD (such as smoking, hypertension, abnormal lipid pro-

file, and high glucose levels) lead to endothelial dysfunction,[18] and in contrast, pharmacologic agents, such as angiotensin-converting enzyme (ACE) inhibitors and statins, which are commonly used in patients with CAD, improve endothelial function.[19,20] In our group of patients who had a range of cardiovascular risk factors and were also treated with statins and ACE inhibitors, CRP emerged as the only independent predictor of saphenous vein endothelial dysfunction. This is highly suggestive that CRP directly influences the endothelium. Our study was not designed to examine the mechanisms by which CRP influences endothelial dysfunction. However, a number of in vitro studies indicate that CRP may influence endothelial function by reducing the bioavailability of NO.[5,6] Verma and colleagues[6] have shown that physiologic concentrations of CRP reduce the expression of endothelial nitric oxide synthase in human arterial endothelial cells in culture. Other studies support a role for oxidative stress and CRP-mediated endothelial dysfunction.[21]

Recent studies have shown that patients with acute coronary syndrome who respond to statin therapy by reducing CRP levels have a better clinical outcome than corresponding individuals with higher levels of CRP.[22,23] Similarly, in patients with CAD, the progression of atherosclerosis is significantly blunted in patients achieving lower levels of CRP with statins.[24] Future clinical follow-up data on our cohort of well-characterized patients would be of interest, and further work is required to identify the clinical implications and associations between CRP levels, statin therapy, and endothelial dysfunction on disease progression and patency of saphenous vein conduits in patients undergoing CABG surgery.

CRP Levels and Statin Therapy

CRP levels predict the incidence of future cardiovascular events.[25] In patients with LDL cholesterol of <3.3 mmol/L (<130 mg/dL), CRP levels of <1, 1 to 3, and > 3 mg/L have been shown to correspond to low, medium, and high risk of future cardiovascular events.[26] Treatment with statins reduces CRP levels independent of its effects on lipid reduction.[7,8] This process is thought to account for some of the beneficial effects of statins in patients at risk of cardiovascular events, with the greatest benefit seen in patients with the largest fall in CRP.[22-24] Interestingly, in our group of patients undergoing CABG surgery, despite aggressive reduction in LDL cholesterol in all patients to levels ≤1.6 mmol/L (≤61.7 mg/dL) with regular use of simvastatin preoperatively, CRP levels remained within the higher-risk level at >3 mg/L in over 25% of the patients.

CRP Levels and Coronary Atheroma Burden

Consistent with postmortem studies,[27] in the sample of patients studied, we demonstrated that the extent of coronary atherosclerotic burden was the only independent correlate of circulating CRP levels. In view of our finding that CRP is a potentially important determinant of saphenous vein endothelial function, this may be of clinical relevance. It has recently been demonstrated that saphenous vein grafts express CRP[28] and that CRP can be released from the coronary artery wall.[29] Our data thus raise the intriguing possibility that the actual quantity of atheroma by contributing to local and systemic CRP levels may influence saphenous vein graft dysfunction and possibly graft failure, a finding that warrants future studies.

Conclusions

Our study demonstrated that circulating CRP level was the only independent predictor of endothelial dysfunction in saphenous vein samples of patients with known coronary artery disease who were treated with statins. Furthermore, in our cohort of patients, "optimal" treatment with statins to achieve LDL cholesterol levels of ≤1.6 mmol/L (≤61.7 mg/dL) was insufficient to reduce systemic inflammation (as assessed by CRP) in a substantial proportion of patients. The cross-sectional design of our study precluded investigation of the role of CRP and endothelial dysfunction as markers of subsequent intimal growth in saphenous vein grafts. Future longitudinal studies are required to investigate these changes and their potential clinical implications in patients undergoing CABG surgery. Considering the likely deleterious pathophysiologic role of inflammation in the vessel wall, combined with the relationship between CRP and venous endothelial dysfunction as demonstrated in the current study, as well as CRP >3 mg/L despite optimal statin dosage for lipid control, further approaches to reducing inflammation are warranted. Targeting inflammation and CRP with more aggressive use of statins as used in the PROVE-IT-TIMI 22 study[22,23] or using more novel therapies such as thiazolidinediones, which have significant anti-inflammatory effects,[30] are potentially available options that may improve both the longevity of venous conduits and reduce cardiovascular events in patients with severe CAD already "optimally" treated with statins.

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