Coronary endothelial dysfunction (ED) represents an imbalance between endothelial-dependent vasodilator and vasoconstrictor activity and is linked to an increased risk of adverse cardiovascular events. ED has been proposed to represent an early stage in the development of atherosclerosis. Moreover, ED in early atherosclerotic lesions colocalizes with macrophage-rich necrotic plaques that are vulnerable to rupture and plaque formation. Levels of lipoprotein-associated phospholipase A2, an inflammatory mediator produced by macrophages, are elevated in the blood of ED subjects.

Diagnosis of coronary ED is hampered by the need for invasive testing. Moreover, conventional risk factors for coronary artery disease, such as age, sex, high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDL-C), do not predict patients’ risk of coronary ED. For example, levels of HDL-C are similar in control subjects and subjects with coronary ED and early atherosclerosis. Cholesterol efflux capacity quantified with macrophages in vitro is a much better predictor of prevalent cardiovascular disease (CVD) than is HDL-C. In different cohorts, cholesterol efflux capacity strongly and negatively associated with CVD status. This relationship remained highly significant after correction for HDL-C. HDL-C accounted for only 34% of the variance in efflux capacity, indicating that HDL-C is not a major determinant of cholesterol efflux capacity.

Two recent studies provided strong evidence that impaired cholesterol efflux capacity is also a strong predictor of incident CVD. In the Dallas Heart Study, impaired efflux capacity was the strongest predictor of future CVD events in a large cohort of multiethnic healthy subjects. Similar results were reported....
in the European Prospective Investigation of Cancer (EPIC)-Norfolk study.16 In both studies, impaired cholesterol efflux capacity remained a strong predictor of future events after adjusting for other risk factors, including HDL-C and LDL-C, suggesting that this metric provides clinically valuable information that is independent of traditional lipid risk factors.

Cholesterol efflux capacity is proposed to involve HDL’s ability to protect blood vessels by removing excess cholesterol from macrophages, a process known as reverse cholesterol transport.17–21 Patients with early atherosclerosis and coronary ED have higher cholesterol content in the vascular wall than patients with normal endothelial function,22 raising the possibility that HDL impaired cholesterol efflux capacity is clinically relevant in patients with ED.

HDL levels are generally assessed by its cholesterol content in clinical studies. However, the cholesterol content of different sizes of HDL subspecies, which vary in diameter from 7 to 14 nm, can differ over 4-fold.21 This has led to the proposal that the concentration of HDL or its subspecies might be better metrics of CVD risk than HDL-C.23–26

We recently showed that ion mobility analysis (IMA) can accurately quantify HDL concentration when it is calibrated with protein standards.27 This approach, termed calibrated-IMA, separates nanoparticles by size in the gas phase and reproducibly detects 3 major HDL species: small, medium, and large. The stoichiometry of apoA-I and the sizes and relative abundances of HDL subspecies determined by calibrated-IMA are in excellent agreement with those determined by nondenaturing gradient gel electrophoresis and analytic ultracentrifugation.28,27 Moreover, calibrated-IMA accurately determines the concentration of gold nanoparticles and reconstituted HDL, validating the strength of this approach. We therefore propose a new term, HDL-P_{IMA}, to represent the quantification of the concentration of an HDL species whose size has been determined by calibrated-IMA.

In the current study, we investigated the relationship between cholesterol efflux capacity, HDL-P_{IMA}, and ED in patients with nonobstructive coronary artery disease. Our observations indicate that HDL-P_{IMA} and efflux capacity are distinct from HDL-C—as well as from each other—and may be useful independent metrics for identifying subjects with ED.

Methods

Human Studies

The Institutional Review Boards of the University of Washington, Seattle, and the Mayo Clinic, Rochester, approved all studies. All subjects gave written informed consent. Subjects were prospectively defined as having normal or abnormal endothelial function based on their coronary blood flow (CBF) response to intracoronary infusions of acetylcholine.13,14 Exclusion criteria were >30% diameter stenosis of any coronary artery; ejection fraction <40%; unstable angina, history of angioplasty, myocardial infarction, or cerebrovascular accident within 6 months; previous percutaneous coronary intervention; use of radiographic contrast agents within 12 hours before the study; significant endocrine, hepatic, or renal disorders; local or systemic infectious disease within 4 weeks; inflammatory disease; pregnancy or lactation; use of an investigational agent within 1 month. The control group was selected by propensity score matching to identify subjects with that were similar to ED subjects with respect to the distribution of age, sex, and cardiovascular risk factors.28 Subjects were studied after overnight fasting, and medications that could affect coronary vasoreactivity, such as nitrates and calcium channel blockers, were discontinued >48 hours before the study.

Patients underwent diagnostic coronary angiography using standard clinical protocols. Angiograms were reviewed before the infusion of any pharmacological agents to confirm that subjects with significant coronary artery stenosis (>30%) were excluded from the study. In cases where the severity of stenosis was uncertain, quantitative coronary angiography was used. Endothelial-dependent CBF was then assessed as previously described.29 In brief, after 5000 U of heparin given intravenously, a Doppler guidewire (Flowire, Volcano) was positioned in the midportion of the left anterior descending coronary artery proximal to the lesion to be studied. Acetylcholine (1 μg) was infused at increasing concentrations (10−6, 10−5, and 10−4 M for 3 minutes of each concentration, achieving an estimated coronary circulation time of 10−4, 10−3, and 10−2 M, respectively). Doppler measurements of average peak velocity were performed at baseline and after intraarterial acetylcholine. Hemodynamic data and repeat coronary angiograms were obtained after each infusion. Coronary artery diameter was measured in the segment 5 mm distal to the tip of the Doppler guidewire by an independent investigator blinded to Doppler data, using a computer-based image analysis system.29,31 Endothelial-dependent CBF was then calculated as described29,31: CBF = π(mean peak velocity2)/coronary artery diameter2. The maximal percentage increase in CBF compared with the baseline CBF was then calculated.

Coronary ED was defined as ≤50% change in CBF in response to any dose of acetylcholine.13,14 Previous studies using this criterion have demonstrated a strong association of impaired coronary ED with cardiovascular events.1,29

HDL Isolation

Blood samples were taken from the aorta during cardiac catheterization. EDTA plasma was immediately prepared and frozen at −80°C. HDL (d=1.063–1.21 g/mL) was isolated from EDTA plasma by ultracentrifugation.32

Cholesterol Efflux Capacity

Efflux capacity with isolated HDL and serum HDL was quantified using cAMP-stimulated J774 macrophages (ATCC) as described by Rothblat, Rader and colleagues12,14,32 because this assay has been shown to predict both incident and prevalent CAD status.14,16 Serum was derived from freshly thawed plasma by adding calcium.32 Polyethylene glycol was then used to precipitate lipoproteins containing apolipoprotein (apo) B. After centrifugation, the harvested supernatant was termed serum HDL.32 Cells were washed 2× with PBS, then incubated in Dulbecco’s modified Eagle medium supplemented with 0.1% (wt/vol) fatty acid-free albumin (Dulbecco’s modified Eagle medium-fatty acid-free albumin), [3H]cholesterol (0.5 μCi/mL), and an ACAT inhibitor (34.4 μmol/L; Sandoz) for 24 hours at 37°C in a 5% CO2 atmosphere. After 1 wash with PBS, the cells were incubated in Dulbecco’s modified Eagle medium-fatty acid-free albumin supplemented with Br-CAMP (500 μmol/L; Sandoz) for 24 hours. Cells were washed again with PBS and then incubated with isolated HDL (30 μg protein/mL) or serum HDL (2.8% v/v) for 4 hours. Cholesterol efflux capacity (% total cholesterol) was determined by the ratio of radiolabeled cholesterol in the medium to that of both medium and the cell layer.

Size and Concentration of HDL (HDL-P_{IMA})

HDL-P_{IMA} was quantified by calibrated-IMA, using HDL isolated by ultracentrifugation from EDTA plasma.27 Because electrophoretic...
mobility depends chiefly on size, IMA data are expressed in terms of particle diameter, which corresponds to the calculated diameter of a singly charged, spherical particle with the same electrophoretic mobility. For each spectrum, three HDL subspecies (small, medium, and large) were deconvoluted from the IMA spectra by unsupervised, iterative curve-fitting. HDL peak areas were directly converted to HDL-PIMA, using a calibration curve constructed with a protein standard. For total HDL particle concentration, intra- and interassay coefficients of variation were <10% and <20%, respectively. For the individual subspecies, CVs were <20%.

**Statistical Analysis**
Continuous clinical variables are presented as means and SDs and categorical variables as frequencies and percentages. HDL sizes and particle concentrations are presented as medians and means, respectively. All data were checked for normality. Statistical significance was assessed using Student t test. Correlations were evaluated using the Pearson method. Logistic regression analysis was used to estimate the association between cholesterol efflux capacity, HDL-PIMA, and ED status without and with adjustment for HDL-C levels. Statistical analyses were performed with Prism and R. All P values were 2-tailed. All biochemical and statistical analyses were performed by investigators blinded to subject status.

**Results**
Subjects that met our inclusion criteria were randomly selected from patients with chest pain that were subjected to coronary angiography and assessment of endothelial function to evaluate coronary artery disease at the Mayo Clinic. All 80 subjects were free of obstructive coronary artery disease, defined as >30% stenosis of at least 1 coronary artery at angiography; 47 had ED (change in CBF in response to intracoronary acetylcholine <50% compared with baseline) and 33 had normal endothelial function.

Approximately two thirds of the subjects in our study were women (Table) as previously described. There were no significant differences in demographic factors between the groups (Table). Similar percentages of the 47 ED subjects and 33 control subjects were smokers, had hypertension and diabetes mellitus, and were on statin and aspirin therapy. As previously reported, levels of inflammatory markers (hs-CRP; P=0.95) and traditional lipid CVD risk factors—including HDL-C, LDL-C (P=0.64), triglycerides (P=0.14), and Lp(a) (P=0.62)—did not differ significantly between the control and ED groups.

**ED Subjects Have Impaired Cholesterol Efflux Capacity**
To determine whether HDL might be dysfunctional in ED subjects, we assessed cholesterol efflux capacity of serum HDL (serum depleted of lipoproteins containing apoB) and HDL isolated by centrifugation (Figure 1), using an assay validated by Rader, Rothblat and colleagues. This assay quantifies total cellular cholesterol efflux from J744 macrophages mediated by pathways known to be relevant to macrophages (ABCA1, ABCG1, scavenger receptor B1, and aqueous diffusion). The efflux capacity of serum HDL in the ED subjects was 13% lower than in the control subjects (Figure 1A; P=0.0001), whereas the efflux capacity of isolated HDL was 10% lower (Figure 1B; P=0.0001). The efflux capacity of serum HDL and isolated HDL (Figure 1C) was strongly and positively correlated (r=0.49; P=0.0001). The correlation between the efflux capacity of serum HDL and that of isolated HDL suggests that alterations in HDL itself account for a significant fraction of the impairment cholesterol efflux capacity of serum HDL.

**HDL Particle Concentration (HDL-PIMA) and Size Are Altered in ED Subjects**
We used calibrated-IMA to quantify HDL-PIMA (total HDL particle concentration) and the concentrations of 3 subspecies: small HDL particles (S-HDL-PIMA; diameter, 7.8±0.17 nm [median±SD]), medium HDL particles (M-HDL-PIMA; 8.6±0.16 nm), and large HDL particles (L-HDL-PIMA; 10.3±0.19 nm). Median HDL sizes and total HDL-PIMA were consistent with previously reported values. In the ED subjects, the total concentration of HDL particles (Figure 2A) was 13% lower than in the control subjects (13.7±2.7 versus 15.8±3.4 μmol/L; P=0.005). S-HDL-PIMA levels (Figure 2B) were similar (5.6±2.4 and 5.6±2.1 μmol/L; P=0.90), whereas M-HDL-PIMA levels were 14% lower in the ED subjects (Figure 2C; 6.0±2.2 versus 7.0±1.9 μmol/L; P=0.050). L-HDL-PIMA (Figure 2D) was markedly lower in ED subjects (33%; 2.1±1.5 and 3.2±2.1 μmol/L; P=0.005).

**HDL-PIMA Explains the Variance in Cholesterol Efflux Capacity of Serum HDL More Effectively Than HDL-C**
Using Pearson’s correlation analysis, we next assessed the relationships between serum efflux capacity and HDL-C and

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HDL-C indicates high-density lipoprotein-cholesterol; Hs-CRP, high-sensitive C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.*±, SD.
HDL-PIMA (Figure 3A and 3B). Cholesterol efflux capacity increased with HDL-C ($P=0.0019; r=0.36$), but the correlation was weak, accounting for only $\approx 13\%$ of the variation. HDL-PIMA and the efflux capacity of isolated HDL correlated with serum efflux capacity more strongly than did HDL-C ($P<0.0001, r=0.54$ and $P<0.0001, r=0.49$, respectively). Taken together, these observations suggest that HDL-C and cholesterol efflux capacity are largely independent metrics of HDL. They also indicate that HDL-PIMA explains HDL efflux capacity more effectively than HDL-C in this population of subjects, raising the possibility that particle concentration is one important mediator of HDL’s proposed cardioprotective effects.

Medium and Large HDL Subspecies Correlate Strongly With Cholesterol Efflux Capacity

To assess the cholesterol efflux efficiency of the HDL subspecies, we examined the relationships between the cholesterol efflux capacity of serum HDL and those of S-HDL-PIMA, M-HDL-PIMA, and L-HDL-PIMA in all 80 subjects (Figure 4A–4C). Sterol efflux from the J774 macrophages correlated with the concentrations of both medium and large HDL particles ($r=0.49$ and $r=0.44$, respectively; both $P<0.0001$). In contrast, S-HDL-PIMA did not correlate with cholesterol efflux capacity ($r=-0.096; P=0.42$).

These observations suggest that both M-HDL-PIMA and L-HDL-PIMA contribute significantly to cholesterol efflux capacity as assessed with J774 macrophages.

L-HDL-PIMA, but not S-HDL-PIMA or M-HDL-PIMA, Correlates Strongly With HDL-C

We next determined the relationship between HDL-PIMA and HDL-C in all 80 subjects. HDL-PIMA and HDL-C correlated with each other ($P<0.0001; r=0.54$), but HDL-C only explained $29\%$ of the variance in HDL-PIMA in this population. In contrast, HDL-C explained $59\%$ of the variance in L-HDL-PIMA (Figure 5A; $r=0.77; P<0.0001$). However, HDL-C explained only $30\%$ of the variance in M-HDL-PIMA (Figure 5B; $r=0.55; P=0.0001$). The concentration of S-HDL-PIMA correlated inversely with that of HDL-C (Figure 5C; $r=-0.45; P<0.0001$).
Because levels of HDL-C and triglycerides are inversely related in many different clinical populations and because there was a trend toward lower levels of triglycerides in the ED subjects ($P=0.14$), we also investigated the relationship between triglycerides and HDL-P_{IMA} in 79 of the 80 subjects (Figure 5D–5F), excluding 1 subject with extremely high triglyceride levels (1230 mg/dL, a significant outlier by Grubbs test). There was no correlation between triglyceride levels and HDL-P_{IMA} or M-HDL-P_{IMA}. In contrast, there was a significant positive correlation between triglycerides and S-HDL-P_{IMA} ($r=0.39; P=0.0007$). There was a weaker inverse correlation between triglycerides and L-HDL-P_{IMA} ($r=-0.25; P=0.034$). These observations indicate that triglyceride levels correlate with S-HDL-P_{IMA} but not with total HDL-P_{IMA}.

Other Cardiac Risk Factors Only Weakly Predict HDL Efflux Capacity and HDL-P_{IMA}

We quantified the relationships between traditional cardiovascular risk factors (Table) and cholesterol efflux capacity or HDL-P_{IMA}. These analyses revealed that plasma levels of cholesterol and triglycerides correlated significantly with cholesterol efflux capacity ($P=0.009$ and 0.005, respectively), but the relationships were modest ($r=0.31$ and $r=-0.32$, respectively). High-sensitive C-reactive protein levels also correlated modestly with HDL-PIMA ($P=0.035; r=0.25$). No other lipid or cardiac risk factors correlated significantly with cholesterol efflux capacity or HDL-P_{IMA}.

Impaired Cholesterol Efflux Capacity and HDL-P_{IMA} Associate With ED Independently of HDL-C Levels

The control and ED subjects had similar levels of HDL-C (Table). In contrast, the subjects with ED had significantly lower levels of HDL-P_{IMA} and cholesterol efflux capacity with both serum HDL and isolated HDL than the control subjects (Figures 1 and 2). In a logistic regression model (Figure 6), cholesterol efflux capacity of serum HDL strongly and inversely associated with ED (odds ratio per 1-SD change, 0.34; 95% confidence interval, 0.18–0.57; $P<0.001$). This association remained robust after we added HDL-C as a covariate to the logistic regression model ($P<0.001$). Impaired cholesterol efflux capacity of isolated HDL was even more strongly associated with ED than was the efflux capacity of serum HDL (Figure 6).

Higher concentrations of HDL-P_{IMA} also associated significantly with a decreased odds ratio of ED (odds ratio, 0.45; confidence interval, 0.24–0.78; $P=0.01$). This association remained significant after we added HDL-C as a covariate to the logistic regression model ($P=0.03$). Moreover, L-HDL-P_{IMA} and M-HDL-P_{IMA}, but not S-HDL-P_{IMA}, associated inversely with ED ($P=0.005$, 0.050, and 0.90, respectively). None of the other traditional lipid risk factors, including HDL-C, LDL-C, and triglycerides, was a significant predictor of ED. Collectively, these observations indicate that cholesterol efflux capacity and HDL-P_{IMA} might provide clinical information about ED risk that is independent of traditional lipid risk factors.
Discussion

We found that cholesterol efflux capacity and HDL-PIMA quantified by calibrated-IMA were significantly lower in subjects with coronary ED than in subjects with normal endothelial function. As previously shown, conventional CVD and lipid risk factors did not vary significantly between patients with and without ED. Our observations suggest that impaired HDL function and low particle concentration are makers of ED; they further suggest that abnormalities in these metrics contribute to the pathogenesis of ED and the early stage of coronary atherosclerosis in humans.

Nitric oxide, a potent vasodilator produced by endothelial cells, is thought to be the endothelium-dependent relaxing factor that mediates vascular relaxation in response to acetylcholine in many vascular beds. HDL causes relaxation of aortic vascular rings; vasorelaxation is impaired in mice lacking scavenger receptor B-I, which binds HDL. Moreover, scavenger receptor B-I expression in cultured cells increases nitric oxide production in response to HDL. Many mechanisms have been proposed for regulating endothelial cell nitric oxide production by HDL, including increased expression of endothelial cell nitric oxide synthase, regulation of the lipid environment of caveolae (which contain endothelial cell nitric oxide synthase), and scavenger receptor B-I–dependent activation of kinases linked to endothelial cell nitric oxide synthase activation.

In hypercholesterolemic mice, HDL protects against ED in the artery wall by promoting reverse cholesterol transport by a pathway involving ABCG1, a membrane-associated ATPase that is highly expressed by endothelial cells. Mechanistic studies showed that the promotion of cholesterol efflux by ABCG1 increased the redistribution of cholesterol from caveolae to noncaveolae domains. Based on studies with cultured cells and genetically engineered mice, these investigators proposed that a reduction in caveolae cholesterol regulates endothelial cell nitric oxide production by reversing the inhibitory interaction of Cav-1 with endothelial cell nitric oxide synthase. ABCG1 is thought to contribute >20% of cholesterol efflux in the macrophage model system used in our study. Our demonstration that cholesterol efflux capacity is impaired in ED subjects, even after adjusting for HDL-C, suggests that similar pathways may be important regulators of endothelial function in humans. Moreover, large HDL particles are the most efficient substrates for promoting cholesterol efflux from cells by the ABCG1 pathway, and large HDL particles were markedly reduced in ED subjects in our study. Patients with early atherosclerosis and ED have higher lipid content in the vascular wall than patients with normal endothelial function. Taken together, these observations raise the possibility that a selective decrease in large HDL particles contribute to impaired cholesterol efflux capacity in subjects with ED. Other processes may also be involved in regulating endothelial function, such as the ability of HDL to regulate cellular proliferation.

We also found a strong and inverse association between HDL-PIMA and ED that persisted after adjustment for HDL-C levels. Moreover, total HDL-PIMA explained 29% of the variation in cholesterol efflux capacity, whereas HDL-C explained only 13% of the variation. Similar results have been previously reported for the weak correlation of HDL-C with cholesterol efflux capacity, both in model systems and in subjects with CVD. HDL is a collection of heterogeneous particles that vary widely in sterol content, size, and protein cargo. Variation in large and medium HDL particles—both of which were less numerous in ED subjects than control subjects—each accounted for >25% of the variation in cholesterol efflux capacity of serum HDL.

For our efflux studies, we used both isolated HDL and serum HDL (serum depleted of LDL, intermediate-density lipoprotein, and very low-density lipoprotein), which avoids subjecting HDL to ultracentrifugation and also mimics a more physiological milieu. Importantly, the cholesterol efflux capacity of serum HDL and isolated HDL correlated strongly (r=0.49), in marked contrast to the correlation of HDL-C with the efflux capacity of serum HDL (r=0.36). These observations indicate that alterations in HDL itself also likely account for a significant fraction of the variation in cholesterol efflux capacity. It further suggests that ultracentrifugation does not markedly affect this functional property of HDL.

In future studies, it will be important to determine whether certain subspecies of HDL promote cholesterol efflux by specific cholesterol transport pathways in endothelial cells and macrophages. It will also be necessary to determine how therapies targeted to HDL affect HDL-PIMA, cholesterol efflux capacity, and other potential cardioprotective properties of HDL, particularly statins, which have been shown to improve endothelial function beyond their effects on lipid profile.
cholesterol efflux capacity and HDL concentration and size. Potential limitations include the lack of data on apoA-I levels, another widely used HDL metric, in our study subjects. However, the correlation of apoA-I with cholesterol efflux capacity is weaker than that of HDL-C, and we have previously shown that apoA-I levels also correlate less well with HDL-PMA than does HDL-C. This is not surprising because the number of apoA-I molecules per HDL particle ranges from 2 to 6. Another limitation of our study was the relatively small number of subjects, which reflects the need for invasive testing to accurately diagnose ED and the unique population we studied.

In summary, we showed that cholesterol efflux capacity, a proposed cardioprotective function of HDL, and HDL-PMA are abnormal in subjects with ED and that they predict ED independently of HDL-C. Our observations raise the possibility that reduced HDL function and particle concentration contributes to the pathogenesis of ED and that the two metrics may be used to predict the risk of ED. Importantly, ED is an early manifestation of atherosclerotic vascular disease and is associated with plaque progression and adverse cardiovascular events. Our findings suggest that quantifying cholesterol efflux capacity and HDL-PMA might prove useful for identifying subjects with ED and for developing new therapeutic targets for CVD.

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Disclosures
J.W. Heinecke is named as a co-inventor on patents from the US Patent Office on the use of high-density lipoprotein metrics to predict the risk of cardiovascular disease. He has served as a consultant to GlaxoSmithKline, Merck, Amgen, and Kowa and is the recipient of research support from GlaxoSmithKline, Bristol Meyer Squibb, and Kowa. A. Lerman has served as a consultant to Itamar Medical and GlaxoSmithKline and is a recipient of research support from GlaxoSmithKline. The other authors report no conflicts.

References
CEC is proposed to involve HDL’s ability to protect blood vessels by reverse cholesterol transport. Both HDL metrics remained strong predictors of endothelial dysfunction after adjustment for HDL-C levels.

The concentration of a specific subpopulation of HDL particles—large HDL—was even lower in subjects with coronary endothelial dysfunction. Our observations strongly support the proposal that CEC, a measure of HDL function, is a better predictor of coronary endothelial dysfunction than HDL-C. This suggests that the beneficial effects of HDL on endothelial dysfunction are mediated through cholesterol efflux pathways.
Patients With Coronary Endothelial Dysfunction Have Impaired Cholesterol Efflux Capacity and Reduced HDL Particle Concentration

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