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Relationship Between Atheroma Regression and Change in Lumen Size After Infusion of Apolipoprotein A-I Milano

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OBJECTIVES The aim of this study was to determine the relationship between atheroma regression and arterial wall remodeling.

BACKGROUND Infusion of reconstituted high-density lipoprotein (rHDL) containing recombinant apolipoprotein A-I Milano (AIM) has been reported to promote rapid regression of coronary atherosclerosis. The current study analyzed intravascular ultrasound (IVUS) to define the changes that take place in the arterial wall that accompanied atheroma regression in this study.

METHODS Forty-seven patients, ages 30 to 75 years, after an acute coronary syndrome were randomized to receive five weekly infusions of placebo or rHDL containing either low- or high-dose AIM. External elastic membrane (EEM) and lumen volumes were compared between coronary IVUS studies at baseline and follow-up.

RESULTS In comparison with baseline, infusion of rHDL was associated with a 4.6% reduction in EEM volume. Lumen volume did not change. In 10-mm arterial subsegments with the greatest plaque burden at baseline, atheroma volume regressed by 10.9% with a similar reduction in EEM volume but with no change in lumen size. In contrast, EEM and atheroma volume did not change in the 10-mm segments containing the least plaque burden. The reduction in EEM in the most diseased segments was only apparent in subjects who underwent plaque regression. Reduction in EEM volume correlated with the decreased atheroma volume ($r = 0.62$), but there was no correlation between change in lumen size and change in plaque volume.

CONCLUSIONS Remodeling of the arterial wall is a focal and heterogeneous process. After infusion of rHDL containing AIM, regression of coronary atherosclerosis is accompanied by reverse remodeling of the EEM, resulting in no change in luminal dimensions. (J Am Coll Cardiol 2006;47: 992–7) © 2006 by the American College of Cardiology Foundation

Accumulating evidence supports the concept that enhancing the circulating levels or biologic activity of high-density lipoprotein cholesterol (HDL-C) might produce important clinical benefits. Recently, a pilot study using intravascular ultrasound (IVUS) reported that five weekly infusions of a synthetic nascent HDL-like particle resulted in regression of coronary atherosclerosis (1). This therapy (ETC-216) comprised complexes of phospholipid combined with recombinant human apolipoprotein A-I Milano (AIM). Two IVUS examinations were compared, the first obtained within two weeks after an acute coronary syndrome and the second six weeks later. A surprisingly large extent of atheroma regression (4.2%) was observed after this short-term therapy.

Little is known, however, about the mechanisms underlying regression of atherosclerosis after HDL-enhancing therapies. Because of the ability of IVUS to visualize the entire thickness of the vessel wall, this imaging modality enables assessment of serial changes in the arterial wall structure in vivo. Considerable evidence supports the concept that the vessel wall actively responds to atheroma accumulation by undergoing alterations in size and structure. This dynamic process, termed arterial remodeling, seems to be bidirectional (2). The early stages of atherogenesis are typically accompanied by outward expansion of the external elastic membrane (EEM), referred to as expansive remodeling. Expansion of the EEM has been described as an adaptive mechanism that maintains lumen size, thereby compensating for accumulating atheroma (3). Expansive remodeling is thought to predominate in early disease development but might be followed at a later stage by a gradual shrinkage of the EEM, referred to as constrictive remodeling, resulting in luminal narrowing.

No data exist, however, regarding the extent and direction of remodeling during regression of atherosclerosis when studied systematically throughout an artery. The aim of the current study was to characterize the remodeling response of the arterial wall during regression produced by infusion of ETC-216.

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Abbreviations and Acronyms

AIM = apolipoprotein A-I Milano
EEM = external elastic membrane
ETC-216 = phospholipid:apolipoprotein A-I Milano complexes
HDL-C = high-density lipoprotein cholesterol
IVUS = intravascular ultrasound

METHODS

Experimental protocol. The study protocol of this trial has been previously reported in detail (1). Briefly, patients aged 30 to 75 years who required coronary angiography for clinical indications within 14 days after an acute coronary syndrome were considered eligible to participate in the study. Patients were required to have an obstructive lesion in a major epicardial vessel with at least a 20% luminal diameter stenosis by visual inspection of the angiogram. Furthermore, a target vessel was required to have no more than a 50% luminal stenosis throughout a segment with a minimum length of 30 mm, defined as the target segment. The target vessel must not have undergone percutaneous intervention in the past or at the time of the baseline study. Patients were randomized to receive treatment with either placebo (0.9% normal saline) or a low dose (15 mg/kg) or a high dose (45 mg/kg) of ETC-216, a complex of recombinant human AIM/1-palmitoyl-2-oloeyl-sn-glycero-3-phosphocholine. Treatments were administered as an intravenous infusion at weekly intervals for five doses. Within two weeks of receiving the final dose, patients underwent repeat IVUS imaging of the target vessel to allow for comparison of paired examinations at the two time points.

Analysis of IVUS images. All pullbacks were analyzed in the core laboratory by a single operator, blinded to patient characteristics. After digitization of the videotape, the origin of the most distal side-branch was selected as the beginning point for analysis. Every 30th image, spaced 0.5 mm apart, was subsequently analyzed. The final image analyzed was the most proximal in the sequence before the appearance of the left main coronary artery or right coronary ostium, defined as the proximal fiduciary site. As a result, a series of slices over a pullback of 30 mm to 80 mm in length was assessed. Analysis was performed for both baseline and follow-up studies with identical landmarks to ensure that the same segment was compared at the two time points.

Intravascular ultrasound measurements were performed in accordance with the standards of the American College of Cardiology and European Society of Cardiology (4). For each cross-sectional image, the leading edges of the lumen and EEM borders were traced by manual planimetry. Atheroma area was calculated as EEM area minus luminal area. The total atheroma volume was calculated with the Simpson rule as mean atheroma area multiplied by the length of pullback in millimeters. Similarly, the total volumes occupied by the EEM and lumen respectively were calculated using their summated areas. Plaque volumes contained within consecutive 10-mm segments of images were calculated by summation of the areas of those images to determine which subsegments contained the most and least atheroma burden in each pullback at baseline. Segments spaced 0.5 mm apart were analyzed. Therefore, a 10-mm segment was defined by 21 consecutive measured segments.

Statistical analysis. All analyses were performed with SPPS 11 for Mac OS X (SPSS Inc., Chicago, Illinois). Variables are reported as mean values ± SD as well as median and interquartile ranges. The difference in atheroma, EEM, and lumen volumes between baseline and follow-up were compared by Wilcoxon signed rank tests. Spearman correlations were employed to determine the relationships between changes in plaque volume and changes in EEM and lumen volumes. A two-sided p value <0.05 was considered to meet statistical significance.

RESULTS

Patient characteristics. The baseline characteristics of patients have been previously presented in detail (1). Of 57 patients who were randomly assigned therapy (placebo n = 12, 15 mg/kg AIM n = 23, and 45 mg/kg AIM n = 22), 47 completed the study (2 withdrew with an adverse event, 3 withdrew consent, and 5 had baseline IVUS studies that were unsuitable for analysis). There were no significant differences in baseline characteristics between the treatment groups. For the entire cohort, mean age was 55 ± 9 years and weight 87 ± 14 kg; 61% of patients were male and 97% were white; 60% of patients were current smokers; 72% had concomitant hypertension and 14% were diabetic; and 44% had received statin therapy before enrolment. The preceding clinical episode was classified as unstable angina pectoris (72%) in the majority, whereas fewer patients had a recent episode of non–ST-segment elevation myocardial infarction (19%) or ST-segment elevation myocardial infarction (9%). The plasma lipid profile at baseline included total cholesterol (179 ± 41 mg/dl), low-density lipoprotein cholesterol (117 ± 38 mg/dl), HDL-C (42 ± 8 mg/dl), and triglycerides (160 ± 95 mg/dl).

Effect of AIM on arterial volumes. The effect of ETC-216 infusions on coronary atheroma has been previously reported (1). The effect of treatment on both total EEM and lumen volumes has not been previously reported and are summarized in Table 1. Infusion of ETC-216 had no effect on the total lumen volume (375 ± 204 mm^3 at baseline and 366 ± 194 mm^3 at follow-up). In contrast, pooled results for the low-dose and high-dose ETC-216 groups (the prespecified analysis) was associated with a 4.8% reduction in the total EEM volume at follow-up (629 ± 355 mm^3 at baseline and 599 ± 320 mm^3 at follow-up, p = 0.03).

Variable response of EEM to infusion. To determine whether the remodeling response to infusion of ETC-216 was uniform or variable throughout the length of the arterial

Table 1. Effect of Infusing Placebo, Combined rHDL, or rHDL Containing Either Low-Dose or High-Dose AIM on the EEM and Lumen Volumes Measured on Matched Coronary Intravascular Ultrasound Examinations Performed at Baseline and After Treatment

	Placebo (n = 11)		Combined rHDL (n = 36)	
	Baseline	Follow-Up	Baseline	Follow-Up
EEM volume (mm^3)	429 ± 257	424 ± 254	629 ± 355	599 ± 320*
	(357) 186–694	(356) 218–542	(578) 328–872	(562) 354–794
Lumen volume (mm^3)	273 ± 144	265 ± 145	375 ± 204	366 ± 194
	(280) 134–382	(238) 146–408	(340) 227–508	(348) 244–487

Results expressed as mean values ± SD and (median) interquartile ranges. *p = 0.03 for comparison between baseline and follow-up studies.

AIM = apolipoprotein A-I Milano; EEM = external elastic membrane; rHDL = reconstituted high-density lipoprotein cholesterol.

pullback, serial changes in arterial dimensions were assessed in the 10-mm segments that contained the greatest and least plaque burden at baseline. Segments containing the greatest amount of atheroma at baseline were characterized by a reduction in plaque volume of 17.8 mm^3 (10.9%), from 163.4 ± 54.3 mm^3 at baseline to 145.6 ± 46.9 mm^3 at follow-up ($p < 0.0001$). The EEM volume was reduced by 19.3 mm^3 (5.6%), from 343.8 ± 92.5 mm^3 at baseline to 324.5 ± 97.3 mm^3 at follow-up ($p = 0.006$). There was no change, however, in lumen volume (from 180.1 ± 68.3 mm^3 at baseline to 178.9 ± 76.6 mm^3 at follow-up) (Table 2). Within these most diseased segments, the change in plaque volume correlated with the change in EEM volume ($r = 0.62$, $p < 0.0001$) but not the change in lumen volume ($r = 0.13$, $p = 0.45$) (Fig. 1).

In contrast, in the 10-mm segments containing the least plaque burden at baseline, there was no significant change in plaque volume (69.6 ± 39.4 mm^3 and 71.2 ± 45.2 mm^3 at baseline and follow-up, respectively), EEM volume (221.2 ± 99.9 mm^3 and 222.2 ± 105.4 mm^3 at baseline and follow-up, respectively), or lumen volume (151.5 ± 68.7 mm^3 and 151.0 ± 66.6 mm^3 at baseline and follow-up, respectively) (Table 2). This phenomenon is depicted in Figure 2, which demonstrates that sites that undergo plaque regression and shrinkage of the EEM with preservation of luminal dimensions; however, at sites where there is no change in plaque area at serial follow-up, there is no change in either the dimensions of the lumen or EEM.

Table 2. Effect of Infusing ETC-216 (n = 36) on the Plaque, EEM, and Lumen Volumes in the 10-mm Segments That Contained the Greatest and Least Plaque Burden at Baseline

Volume (mm^3)	Baseline	Follow-Up	p Value
Greatest diseased segment			
Plaque	163.4 ± 54.3	145.6 ± 46.9	<0.0001
	(164.9) 132–210	(149.7) 120–182	
EEM	343.8 ± 92.5	324.5 ± 97.3	0.006
	(349.4) 306–397	(315.4) 273–383	
Lumen	180.1 ± 68.3	178.9 ± 76.6	0.59
	(181.9) 128–216	(162.8) 125–212	
Least diseased segment			
Plaque	69.6 ± 39.4	71.2 ± 45.2	0.86
	(63.9) 37–103	(65.7) 31–112	
EEM	221.2 ± 99.9	222.2 ± 105.4	0.94
	(219.3) 135–276	(210.4) 128–295	
Lumen	151.5 ± 68.7	151.0 ± 66.6	0.99
	(127.9) 102–189	(134.4) 97–214	

Results expressed as mean values ± SD and (median) interquartile ranges.

EEM = external elastic membrane; ETC-216 = phospholipid:apolipoprotein A-I Milano complexes.

DISCUSSION

The findings of this study demonstrate that, for the first time, regression of atherosclerotic plaque after infusion of a synthetic HDL is characterized by a concomitant shrinkage of the EEM. This results in a lumen size that is virtually unchanged (Fig. 2). These observations suggest an exquis-

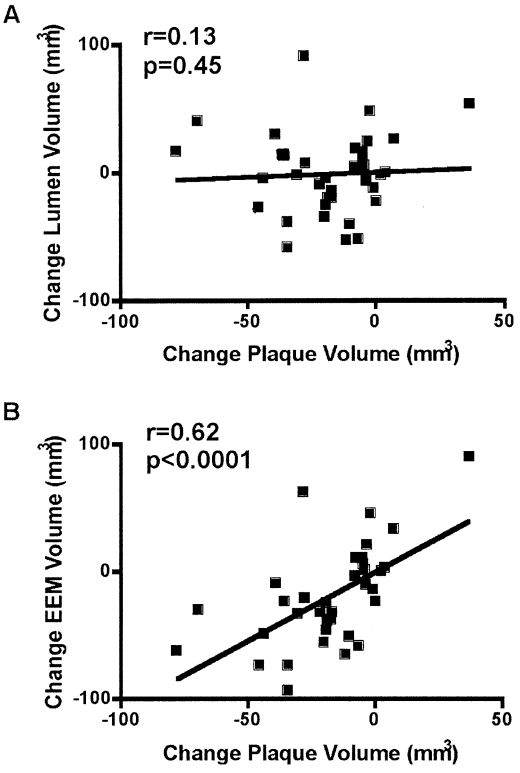

Figure 1. Correlation between the change in plaque volume and the change in lumen volume **(A)** and external elastic membrane (EEM) volume **(B)** in the 10-mm segments harboring the greatest plaque burden at baseline after infusion of phospholipid:apolipoprotein A-I Milano complexes (ETC-216).

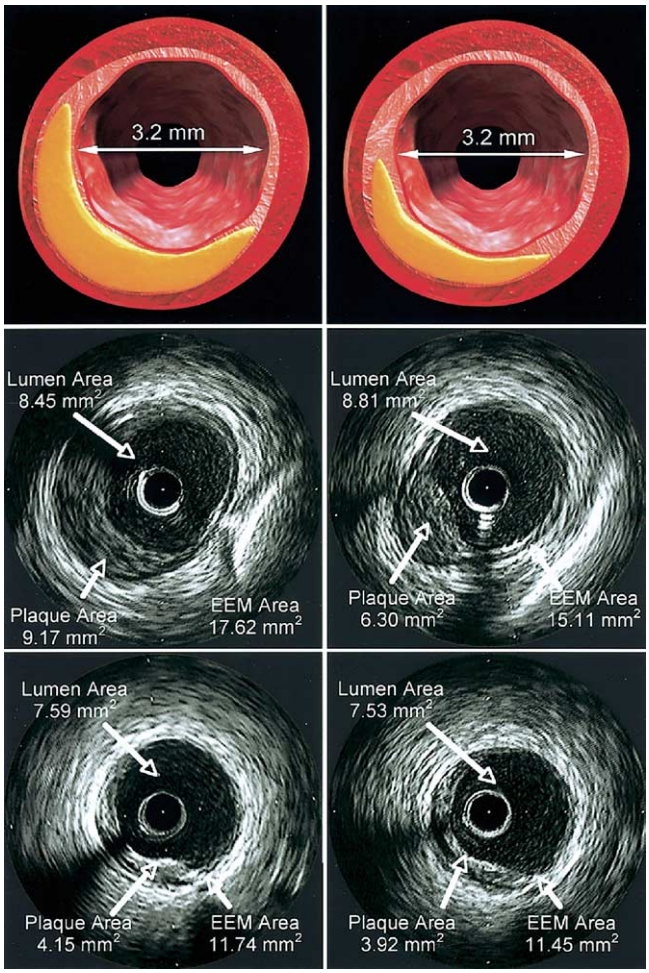

Figure 2. Representative cross-sectional intravascular ultrasound images of matched arterial segments at baseline **(left)** and follow-up **(right)**. At sites that underwent atheroma regression in response to infusions of reconstituted high-density lipoprotein cholesterol containing recombinant human apolipoprotein A-I Milano **(top and middle panels)**, there was concomitant reduction in external elastic membrane (EEM) area with no change in the lumen size. At sites where there was no change in plaque area **(bottom panels)**, there was no change in either the EEM or lumen.

itely sensitive regulatory mechanism that allows maintenance of a constant lumen size during atherosclerosis regression by a precisely compensatory reduction in EEM dimensions. This phenomenon is the exact inverse of the remodeling process originally described by Glagov et al. (3), who proposed that, during the initial stages of atheroma formation, expansion of the EEM compensated for plaque accumulation, thereby preventing compromise of the lumen.

These observations provide a potential explanation for an important clinical conundrum. In angiographic studies of anti-atherosclerotic agents, changes in luminal dimensions have been extremely small, typically representing a change in stenosis severity of only a few percentage points (5–7). These same studies, however, demonstrate a much larger reduction in clinical events after administration of treatments that effectively slowed or reversed atherosclerosis. Some authorities have attributed the differences in magnitude of angiographic and clinical benefit to unknown mechanisms, such as changes in atheroma morphology (plaque stabilization). The current study suggests a radically different possibility. Because reverse remodeling preserves lumen size during regression, large changes in atheroma volume might appear as only small changes in luminal dimensions. Accordingly, a substantial reduction in atheroma burden might occur despite minimal changes in lumen size.

This is further illustrated by subsegmental analyses in the current study. Analysis of the 10-mm arterial segment with the greatest atheroma burden demonstrated major regression of disease after administration of an HDL mimetic. Strikingly, in the most diseased subsegment, HDL therapy removed nearly 11% of atheroma volume within six weeks with virtually no change in luminal dimensions. This effect is substantially greater than the extent of regression observed using the same analytical methods after administration of 80 mg of atorvastatin for 18 months (8). Similarly, the effect is six-fold larger than that observed after 18 months of moderate lipid lowering with 40 mg of pravastatin in the same study. The magnitude of these changes in the most diseased segments suggests a high potential for HDL modulating therapies to benefit patients with coronary disease.

The absence of any meaningful change in luminal dimensions during regression of atherosclerosis also has important implications for design of studies of HDL-modulating therapies. Most previous studies of atherosclerosis progression have used quantitative coronary angiography to assess disease burden. Angiographic studies assess disease progression by measuring a projected silhouette of the vessel lumen. Such methods have proven useful in describing the effects of low-density lipoprotein cholesterol-lowering therapies on coronary atherosclerosis (6,7,9–13); however, the current study suggests that imaging techniques that measure luminal dimension might provide unreliable results if used to evaluate therapies designed to enhance reverse cholesterol transport (14). During administration of HDL-enhancing agents, rapid reverse remodeling might completely compensate for plaque regression, resulting in no change in lumen size. It has also been reported that regression of aortic atheroma after chronic statin therapy is similarly accompanied by no change in luminal dimensions when assessed by magnetic resonance imaging of the arterial wall (15).

Several studies have shown a strong relationship between the progression of atherosclerosis and clinical outcome (16,17). The current study suggests several potential mechanisms underlying the effects of therapies that promote disease regression on cardiovascular morbidity and mortality. The majority of acute ischemic events occur in the setting of a culprit lesion that represent only a mild to moderate stenosis by angiography (18–20); however, because of EEM expansion (positive remodeling), the arterial wall can harbor substantial amounts of plaque before the development of luminal narrowing detectable by angiography (21–23). Several studies have demonstrated a strong association between the extent of positive remodeling (in-

creased EEM area) and an unstable clinical presentation (24–26). Conversely, constrictive remodeling (decrease in EEM area) has been associated with stable angina. The current study suggests an intriguing hypothesis—that regression of atherosclerosis reduces expansive remodeling, thereby conferring mechanical plaque stability.

In the current study, the conclusion that there is a close linkage between regression and reverse remodeling is supported by several observations. Analysis of different subsegments within the arterial pullback permitted examination of the regional relationships between EEM shrinkage and plaque regression. In segments not undergoing regression, there was no reverse remodeling, whereas in segments with reduction in atheroma volume, there was a compensatory reduction in EEM volume. In minimally diseased segments, regression did not occur and there was virtually no change in atheroma volume, lumen volume, and EEM volume. These finding emphasize that the compensatory changes associated with plaque regression represent a focal phenomenon, not a generalized response to the therapy or a patient-specific response. The exact signaling mechanism by which reverse remodeling is initiated remain undefined, but some studies suggest that coronary shear stress might represent an important factor (27,28).

Previously, remodeling of the vessel wall has been considered a gradual adaptive process that occurred during many years of atherosclerosis development (3). The current study demonstrates that changes in EEM area in response to regression can occur in only a few weeks. These findings also suggest that remodeling is a heterogeneous process throughout the course of an artery. The demonstration that serial arterial remodeling is not homogeneous highlights the advantage of performing volumetric analysis of the entire artery. This approach provides a more accurate reflection of dynamic changes in the arterial wall than assessment of individual cross-sectional images.

The study has several important limitations, including the small sample size in the active treatment group and few placebo-treated patients. Intravascular ultrasound is limited in its ability to characterize plaque composition, and therefore it remains to be determined whether infusing synthetic HDL containing AIM in humans has beneficial effects on plaque in addition to promoting regression. Although it is theoretically possible that the results were influenced by regression to the mean, the absence of corresponding changes in segments containing the least amount of atherosclerotic plaque makes this possibility remote. Nonetheless, the study provides strong evidence that significant regression of atherosclerosis can occur without any change in lumen size after administration of a synthetic HDL-mimetic based on AIM to patients after an acute coronary syndrome. Evaluation of new therapies that promote reverse cholesterol transport might require application of methods that image the vessel wall, such as IVUS, carotid ultrasound, or magnetic resonance imaging, rather than methods that depict the vessel lumen such as quantitative coronary angiography. These findings further highlight the dynamic role that the arterial wall plays in the progression and regression of atherosclerotic plaque. Changes in EEM area can occur in only a few weeks when a particularly active therapy is administered. Arterial remodeling is clearly a focal phenomenon, not a generalized response to the systemic factors associated with atherosclerosis progression or regression.

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