Atherosclerotic Plaque Evolution in the Descending Thoracic Aorta in Familial Hypercholesterolemic Patients

A Transesophageal Echo Study

Cesar J. Herrera, Lee J. Frazin, Peter C. Dau, Paul DeFrino, Neil J. Stone, David J. Mehlman, Michael J. Vonesh, James V. Talano, David D. McPherson

Abstract

We explored the concept that transesophageal echocardiography can be used as a tool to detect, characterize, and study plaque morphology in the descending thoracic aorta. The pattern of atherosclerotic plaques in the descending thoracic aorta in familial hypercholesterolemic (FH) patients was evaluated. Additionally, evolution of plaque characteristics as a result of therapy was analyzed. In a randomized prospective protocol, eight FH patients (five men and three women, aged 23 to 65 years [mean±SD, 42±14 years]) receiving standard therapy (n=3; baseline low-density lipoprotein [LDL] cholesterol, 222±71 mg/dL, mean±SD) or LDL apheresis (n=5; baseline LDL cholesterol, 262±51 mg/dL) were studied. Baseline and follow-up (mean, 12 months) transesophageal echocardiographic studies were performed. Measurements obtained were atherosclerotic plaque area (PA), aortic wall area (WA), total arterial area (TAA), and plaque-to-wall area ratio (PWR). LDL cholesterol decreased in both groups. The greatest severity of plaque was detected at 30 to 35 cm from the incisors (approximately 15 to 20 cm from the aortic arch). The smallest plaques were present at the arch and more distal descending aorta. In the control group, TAA, PA, and PWR did not change significantly (P=NS versus baseline). In the LDL-apheresis group, TAA increased (P<.05 versus baseline), PA decreased in three of five patients (P=NS versus baseline), and PWR fell (P<.05 versus baseline). When represented in absolute percentages, the changes between baseline and follow-up among the control group were TAA +4%, PA +32%, and PWR -24%; among the LDL-apheresis-treated group, they were TAA +38%, PA -24%, and PWR -46%. These preliminary data suggest that transesophageal echocardiography is a useful tool to study atherosclerosis evolution in the descending thoracic aorta. In this preliminary study, LDL apheresis was associated with greater plaque regression than standard therapy. (Arterioscler Thromb. 1994;14:1723-1729.)

Key Words

- transesophageal echocardiography
- atherosclerosis
- plaque regression
- hyperlipidemia

Atherosclerosis remains a major cause of morbidity and mortality in the western world. Despite major improvements in therapeutic modalities, methods to evaluate their impact on vascular disease remain limited. Traditionally, atherosclerotic involvement of different vascular beds is studied with angiography. We and others have shown the potential limitations of this technique, particularly in the study of the coronary circulation. Unlike angiography, ultrasound permits detailed analysis of wall substructure and plaque, making this technique potentially useful to follow atherosclerotic plaques in different vascular beds.

With the development of transesophageal echocardiography (TEE), areas of the cardiovascular system previously not studied are now readily accessible. As the esophagus is in close proximity to the thoracic portion of the descending aorta, we and others have studied types and degrees of aortic abnormalities.

Familial hypercholesterolemia is associated with early atherosclerotic plaque development and subsequent ischemic sequelae. Standard medical therapy of this inherited form of hyperlipidemia frequently fails to achieve adequate results despite triple drug therapy. This has prompted the use of more aggressive, less conventional therapeutic interventions such as low-density lipoprotein (LDL) apheresis. Reports now available demonstrate improvement of coronary atherosclerosis, decreased frequency of anginal attacks, and regression of xanthomas.

Because of the latent nature of atherosclerosis, it is important to detect and assess atheroma progression in the presymptomatic phase by measuring rates of growth or change of plaques in various body locations. TEE of the descending aorta may be an excellent technique by which to assess and monitor plaque progression.

The objective of this study was to explore the concept of TEE as a tool to detect, characterize, and study plaque morphology in the descending thoracic aorta of familial hypercholesterolemic patients. In addition, evolution of plaque characteristics as a result of therapy was analyzed.

Methods

Patient Population

The individuals involved in this study were part of a separate multicenter trial comparing the true effect of LDL apheresis...
on lipid levels, among other end points. Seven heterozygous subjects and one homozygous subject with familial hypercholesterolemia were studied. Five constituted the LDL apheresis–treated group, and three were control subjects. The diagnosis of familial hypercholesterolemia was made from the clinical course, family history, and serum lipid profile. Patients accepted for LDL apheresis had a total serum cholesterol level >240 mg/dL despite appropriate diet and maximum tolerated drug therapy. Control patients had a similarly high cholesterol level and received at least one drug. All subjects had to be either on the American Heart Association step 1 diet or a more restrictive diet initiated by the patient’s personal physician. Hypolipidemic medication included a minimum of lovastatin in a dosage of up to 80 mg daily as tolerated and one other drug with a different mechanism of action, such as a bile acid sequestrant or niacin. Before entry, patients were stabilized on drug and diet therapy, and these treatments were not changed during the period of study unless clinically indicated.

**LDL Apheresis**

LDL apheresis was carried out as part of a multicenter controlled trial using the Kaneka LA-15 system (Kaneka America Corporation), which generates plasma with a hollow-fiber separator and selectively absorbs LDL and very-low-density lipoprotein by perfusion over two dextran sulfate cellulose columns that are alternately charged and desorbed. The amount of plasma to be processed by each LDL apheresis was targeted at up to 1.5 plasma volumes as tolerated. Subject plasma volumes were calculated from standard height, weight, and hematocrit tables. During the study phase, LDL apheresis was carried out every 1 to 2 weeks. During the maintenance phase, LDL apheresis was carried out every 2 to 3 weeks. Time-averaged cholesterol values were calculated for the study and maintenance phases. Time-averaged LDL cholesterol was calculated for the apheresis group from the rebound curves using the point-to-point method as reported by Gordon et al. LDL cholesterol value was calculated as the baseline, follow-up, and mean for the control group.

**Echocardiography and Image Analysis**

All patients underwent routine baseline and follow-up TEE with attention to the proximal and descending thoracic aorta. Two-dimensional echocardiographic images were obtained with one of two phased-array echocardiographic systems (Acuson 128, Acuson, Inc; HP SONOS 500, Hewlett Packard, Inc) using 5.0-MHz variable-focus, esophageal echo probes. Follow-up studies were taken on the same imaging unit as originally used. For the purpose of this study, plaques were defined as protrusions of the aortic wall into the lumen that were separate and distinct from the bright specular reflectors of the aortic wall. These plaques were traced being careful not to include wall (media and adventitia). Lumen areas (LA) were manually traced along the central interface between the lumen and intimal plaque wall. Total arterial area (TAA) including lumen, intima, plaque, media, and dense adventitia was traced along the bright outer reflector at the dense adventitial interface with care taken to avoid artifacts. Areas were independently calibrated for each image using 1-cm markings displayed in the two-dimensional images. Areas were integrated by the Freeland Medical System and recorded. Wall area was determined as the difference between LA and TAA. Plaque-to-wall area ratio (PWR) was defined as the quotient of plaque area (PA) over wall area. A mean of 10 different frames representing the same area of plaque involving a particular aortic segment was traced. We chose to represent plaque density alterations through the entire descending thoracic aorta. Specifically for each patient, measurements throughout the entire descending thoracic aorta were summed, and a mean value was determined for the total number of measurements. Each value is the mean of PA, TAA, and PWR for that individual.

Tracing variability was defined as the percentage of difference obtained (for every parameter measured) in each area of interest after it was traced twice consecutively.

Identification variability of similar regions of the descending thoracic aorta over time was defined as the percentage of difference obtained (for every parameter measured) in each area of interest after it was reimaged and retraced before withdrawal of the probe in each patient.

Interobserver variability was defined as the percentage of difference obtained (for every parameter measured) in each area of interest by two different observers (C.J.H. and P. DeFrino).

**Statistical Analysis**

For each parameter, mean measurements were compared between baseline and follow-up studies. A value of $P < .05$ was considered significant. Values of $P > .05$, if indicating trends, are listed. Values are expressed as mean±SD.
plaque progression associated with LDL apheresis was less than that seen in the control group (PWR of control versus LDL apheresis; P=.02).

When plaque density (PWR) of all segments was analyzed individually and depicted as absolute percentage, in the control group two patients had progression (54% and 20%, respectively), and a third did not change. In the LDL-apheresis group, three patients had regression at all segments (64%, 55%, and 47%), and two others did not change. When expressed in absolute percentages, the changes between baseline and follow-up for the control group were +4% for TAA, +32% for PA, and +24% for PWR. Among the LDL-apheresis patients, TAA, PA, and PWR changed by +38%, −24%, and −46%, respectively (Table 3).

Discussion

The major findings of our study are that (1) TEE is a useful technique for the detection of atherosclerotic plaques in the descending thoracic aorta of familial hypercholesterolemia patients; (2) plaque progression/regression in response to therapy can be followed with this technique; and (3) standard therapy was associated with less regression than LDL apheresis in this select group of severely hypercholesterolemic patients.

Atherosclerotic Plaques in the Descending Thoracic Aorta

Pathologically, the incidence of plaque formation in the general population is greatest around the ostia of major arteries of the abdominal aorta and somewhat lower in the descending thoracic aorta.19 Hammer et al19 reported localized atherosclerotic plaques in 41 of 84 patients studied after myocardial infarction with TEE. Plaque severity was greatest at 35 cm from the incisors and lowest at 25 and 45 cm from the incisors (15, 5, and 25 cm from the arch, respectively). There is a relation between plaques in the aorta and lipid levels, increased

**Table 1. LDL Cholesterol Values**

<table>
<thead>
<tr>
<th>Control, mg/dL (n=3)</th>
<th>LDL Apheresis, mg/dL (n=5)</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>222±71</td>
</tr>
<tr>
<td>Follow-up</td>
<td>221±41</td>
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<tr>
<td>Maintenance</td>
<td>138±16*</td>
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</tbody>
</table>

+P<.05 vs baseline; tP<.05 vs treatment; tP<.05 vs control follow-up.

**Results**

Clinical Characteristics

Eight patients (five men, three women; aged 23 to 65 years [mean, 42±14 years]) with familial hypercholesterolemia were studied. Baseline and follow-up TEE were performed in three patients in the control group (7±2.1; range, 5 to 9 months; mean±SD) and in five in the LDL apheresis–treated group (20±5.3; range, 11 to 24 months) (P<.05 versus control). Table 1 presents LDL cholesterol values for the subgroups. Baseline LDL cholesterol for the control group was 222±71 mg/dL, and for the LDL-apheresis group it was 262±51 mg/dL (P=NS versus control). In the LDL-apheresis group, during treatment, time-averaged LDL cholesterol fell to 138±16 mg/dL and was 183±40 mg/dL in the maintenance phase (P<.05 for treatment versus baseline, maintenance versus baseline, and treatment versus baseline). In the control group, follow-up LDL cholesterol level was 221±41 mg/dL (P=NS for follow-up versus baseline and baseline LDL apheresis versus baseline control; P<.05 for treatment LDL apheresis versus control follow-up).

Descending Thoracic Aorta Structural Characteristics

Fig 2 illustrates the baseline plaque distribution by segments of descending thoracic aorta studied in the entire population. The greatest density of plaque was detected at 35 to 45 cm from the incisors (approximately 15 to 20 cm from the aortic arch). Areas with the lowest frequency of protruding plaques corresponded to the arch and the more distal descending aorta. Plaque evolution patterns are illustrated in Fig 3 for a control patient and a treated patient. Note that even when large plaques were present the lumen remained large with no obstruction to flow.

The combined variability for tracing and identifying similar regions of interest of the descending thoracic aorta was 9%, 13%, and 5%, respectively, for TAA, LA, and PA (Table 2). Overall variability was acceptably low for all parameters. Interobserver variability was 7%, 10%, and 8% for TAA, LA, and PA, respectively.

The baseline and follow-up measurements separated for control and LDL apheresis–treated patients are shown in Table 3 and Fig 4. Among control patients, PA, TAA, and PWR increased, although not significantly (PA, 0.4±0.21 versus 0.6±0.36 cm²; PWR, 0.09±0.05 versus 0.12±0.08; and TAA, 5.3±1.40 versus 5.5±0.90 cm²) (P=NS versus baseline for all). Among LDL apheresis–treated patients, PA decreased in 3 of 5 patients (P=NS versus baseline), PWR decreased, and TAA increased (PA, 0.6±0.11 versus 0.5±0.32 cm² [P=NS versus baseline]; PWR, 0.15±0.04 versus 0.08±0.05 [P<.05 versus baseline]; and TAA, 4.0±0.94 versus 5.4±0.97 cm² [P<.05 versus baseline]). Individual data points are presented in Fig 4. Specific mean PA in control patients ranged from 0.12 to 0.90 cm² during baseline studies; at follow-up, it ranged from 0.15 to 1.10 cm². For the LDL-apheresis group, during baseline studies PA ranged from 0.40 to 1.00 cm² and from 0.10 to 1.09 cm² during follow-up. Note that even though plaque severity was similar in both groups at baseline, the level of plaque progression associated with LDL apheresis was less than that seen in the control group (PWR of control versus LDL apheresis; P=.02).

When plaque density (PWR) of all segments was analyzed individually and depicted as absolute percentage, in the control group two patients had progression (54% and 20%, respectively), and a third did not change. In the LDL-apheresis group, three patients had regression at all segments (64%, 55%, and 47%), and two others did not change. When expressed in absolute percentages, the changes between baseline and follow-up for the control group were +4% for TAA, +32% for PA, and +24% for PWR. Among the LDL-apheresis patients, TAA, PA, and PWR changed by +38%, −24%, and −46%, respectively (Table 3).
Age, hypertension, coronary artery disease, and embolic potential.\textsuperscript{20-24} Our experience studying a general population of patients referred for routine TEE revealed that roughly 26\% of patients (mean age, 62 years) had atherosclerotic plaques at various levels of the descending thoracic aorta.\textsuperscript{22} Others have recognized the embolic potential of some of these plaques.\textsuperscript{22-23}

We have demonstrated a high prevalence of plaques in a select group of severely hyperlipidemic patients. The distribution was generally diffuse through the entire descending thoracic aorta but primarily occurred at 30 to 35 cm from the incisors (15 to 20 cm from the arch). This pattern of plaque distribution may be due to flow-related phenomena, such as intercostal arterial branching and other hydraulic, neural, or humoral factors. However, it was not the purpose of this study to investigate this finding.

Most plaques protrude into the lumen of the thoracic aorta without creating major interference with flow. It is unknown whether arterial remodeling that occurs in other arterial beds occurs in the descending thoracic aorta as a result of plaque growth.\textsuperscript{2,3,25,26} Whether greater degrees of plaque deposition and varying degrees of elasticity in the aorta may cause variable remodeling in response to expanding atherosclerosis remains to be determined. Plaque distribution in the abdominal aorta cannot be readily documented because of lack of apposition of this portion of the aorta to the esophagus.

Techniques to Evaluate Plaque Regression: LDL Apheresis to Control Progression

Data are now available demonstrating plaque growth retardation or reversal as a result of various therapeutic

<table>
<thead>
<tr>
<th>TABLE 2. Tracing and Identification Variability</th>
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<tr>
<td>Variability, %</td>
</tr>
<tr>
<td>Tracing</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>PA</td>
</tr>
<tr>
<td>TAA</td>
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<tr>
<td>LA</td>
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</table>

PA indicates plaque area; TAA, total arterial area; LA, lumen area; and n, number of frames traced.
Quantitative coronary angiography has been the traditional method used to study coronary arterial plaque growth density. Although it may demonstrate residual luminary changes, it cannot demonstrate changes in plaque deposition and, because of remodeling, may be unable to identify ongoing plaque enlargement. The carotid circulation is easily accessible and could be an additional vascular bed to study; however, it requires highly standardized expertise.16,18,27,33 Our data suggest that alterations in plaque characteristics could be accurately demonstrated by TEE and that such alterations respond to specific forms of therapy. This is a preliminary study in the exploration of the potential ability of TEE and its methodological problems in assessing plaque characteristics in the arch of the descending thoracic aorta. The group of patients treated with LDL apheresis demonstrated improvement in plaque severity when compared with the control group despite having a relatively (although not statistically significant) higher LDL level. Of the five patients in the LDL-apheresis group, two had no change in plaque. One was an older individual in whom long-standing diffuse atherosclerosis may have explained the lack of regression. The other was a heavy smoker who continued to smoke throughout the period of study. Changes in our data should not be attributed to tracing or identification variability as both were shown to be within 5% to 8%. Among the control group, plaque did not change during follow-up in one case and increased in two others. Despite the different levels of skill in image analysis of the two tracers (C.J.H. and P. De-Frino), the interobserver variability was quite low. This suggests that this methodology is reproducible despite its relative sophistication.

**Mechanisms of Plaque Regression**

The extraction of LDL particles from the serum of patients with severe familial hypercholesterolemia has been shown to influence different end points: lipid levels, progression of coronary atherosclerosis, and xanthoma growth. This study shows progression of atheroma in the aortic arch of the descending aorta in the control group treated with standard medical therapy, but it shows regression in the experimental group whose LDL levels were aggressively lowered with LDL apheresis. The changes in lipid levels induced by LDL apheresis, though short-lived, seem nonetheless to be important in altering the characteristics of newly formed lipid-rich plaques.

It should be emphasized that plaque density alterations were represented through the entire descending thoracic aorta. When specific segments were compared, the alterations still occurred but in a less reproducible and predictable fashion; specific plaques may remain unchanged, progress, or regress. Given the diffuse nature of atherosclerosis, plaque evolution may be more appropriately studied as a sum of lesions rather than individual data points, as we have done.

### TABLE 3. Baseline and Follow-up Changes: Control Versus LDL-Apheresis Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Control Baseline</th>
<th>Control Follow-up</th>
<th>% Change</th>
<th>LDL Apheresis Baseline</th>
<th>LDL Apheresis Follow-up</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>0.4±0.21</td>
<td>0.6±0.36</td>
<td>+32</td>
<td>0.6±0.11</td>
<td>0.5±0.32</td>
<td>-24</td>
</tr>
<tr>
<td>TAA</td>
<td>5.3±1.40</td>
<td>5.5±0.90</td>
<td>+4</td>
<td>4.0±0.94</td>
<td>5.4±0.97*</td>
<td>+38</td>
</tr>
<tr>
<td>PWR</td>
<td>0.09±0.05</td>
<td>0.12±0.08</td>
<td>+24</td>
<td>0.15±0.04</td>
<td>0.08±0.05*</td>
<td>-46t</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; PA, plaque area; TAA, total arterial area; and PWR, plaque to wall ratio. *P<.05 vs baseline; tP<.05 LDL apheresis vs control (mean follow-up: control, 7 months; LDL apheresis, 19 months; P<.05 vs control).

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**PLAQUE AREA**

**TOTAL ARTERIAL AREA**

**PLAQUE/WALL RATIO**

**FIG 4.** Graphs show individual data points for control (C) and LDL apheresis–treated patients (L) at baseline T\(_1\) and at follow-up T\(_2\). *P<.05 vs baseline.
Factors Influencing Results

Study of a larger number of patients will be needed to confirm our findings and to extrapolate the use of this technique to follow medical or interventional techniques in patients with less aggressive and more chronic atherosclerosis.

Despite a shorter follow-up period among the control than the experimental patients, plaque progression was still evident in the control patients. It is conceivable that more pronounced degrees of progression or regression could have occurred had either group been studied longer.

Reports by Small et al36 and others have described a phenomenon in which small plaque thickening during early follow-up may evolve into regression at a later date. This phenomenon may have been illustrated in our control population and requires further study.

Other potential factors that could have influenced our results include variances in the ability to trace and identify similar areas of interest in the aorta and technical limitations. Our results fall out of the range of our demonstrated technique variability. The additional use of multiplane TEE, due to its ability to depict perpendicular views of the aorta, could allow better delineation of additional plaques, particularly those located in the anterior portion of the descending thoracic aorta and the arch. However, monoplane TEE allows multiple side-by-side cross-sectional views of the descending thoracic aorta. With proper angulation and by studying the entire descending thoracic aorta, variations should occur randomly across patients. Errors in gain setting as well as equipment variability, although potentially significant, should also occur randomly. Three-dimensional imaging of ultrasonic images would allow reconstruction of entire vascular segments and provide further insights into more detailed substructure analysis of these complex atherosclerotic plaques.33

Clinical Implications

TEE may allow evaluation of plaque progression in response to medical and interventional therapies. This modality would be a useful adjunct to other techniques such as intravascular ultrasound for coronary and peripheral arteries, transcutaneous ultrasound for carotid vessels, and angiography for luminal evaluation as well as identification of high-risk individuals.34

Conclusions

Among patients with familial hypercholesterolemia, atherosclerotic plaques are common and diffusely distributed throughout the descending thoracic aorta. TEE easily and accurately detects plaques and changes after interventions. In this study, LDL apheresis therapy delayed plaque progression in the descending thoracic aorta.

Acknowledgments

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