An Update on the Pathogenesis of the Acute Coronary Syndromes

Peter Libby
Brigham & Women's Hospital
Harvard Medical School

ADVANCES IN HEART DISEASE
University of California San Francisco
December 29, 2015

Characteristics of Atherosclerotic Plaques Associated with Various Presentations of Coronary Artery Disease

We tend to face today’s battle prepared to fight the last war
 ♥ Is the “vulnerable plaque” a valid concept in 2015?

Challenges to the “vulnerable plaque” concept
♥ Few thin-capped plaques actually rupture!
Only 5% of thin-cap fibroatheromas cause events at a median follow-up of 3.4 Years (PROSPECT)

Challenges to the “vulnerable plaque” concept

Thin capped, lipid-rich atheromata most often persist for years without causing a clinical event

Thin capped, lipid-rich atheromata are not solitary, rather often multiple and affect several arterial beds in the same individual

The risk profile and demographics of ACS patients is shifting worldwide (global burden, younger patients, more women, more insulin resistance/diabetes, more hypertriglyceridemia, less LDL excess)

Statin treatment and other preventive measures have begun to modify atherosclerotic disease

The character of human plaques is changing- Why?

Statin use is on the rise

ACS Treatments Changing with Time
Previous Use of Medication on an Outpatient Basis

Yeh RW et al.

Favorable Effects of Lipid Lowering in Experimentally Produced Atherosclerotic Plaques

Table 2. Favorable Effects of Lipid Lowering in Experimentally Produced Atherosclerotic Plaques:

- Reduces inflammation (lowered levels of macrophages, cytokines, and chemokines and expression of interleukin-6)
- Reduces expression of interstitial collagenase (MMP-1)
- Increases levels of interstitial collagen
- Lowers levels of oxidized low-density lipoprotein
- Reduces production of reactive oxygen species
- Increases expression of endothelial nitric oxide synthase
- Reduces thrombotic potential (reduced tissue factor content and activity)
- Increases fibrinolytic potential (reduced level of plasminogen activator inhibitor-1)


Challenges to the “vulnerable plaque” concept

The character of human plaques is changing in the statin era

Time-Dependent Changes in Atherosclerotic Plaque Composition in Patients Undergoing Carotid Surgery

Gaur W, van Laarhoven, MD, PhD; Heister M, den Boer, PhD; Joyce EJ, Vrijvehoud, MD; Yasser W, van der Lee, MSC; Evelyn Selim, MSC; Jean Paul FM, de Vries, MD, PhD;
Dominique P, van der Kogel, PhD; Ayyar Vithal, MD, PhD; Gerrit A de Borst, MD, PhD;
Franz L, Med, MD, PhD; Michel L, Bars, MD, PhD; Gerard Penterkamp, MB, PhD

Background—Time-dependent trends in the incidence of cardiovascular disease have been reported in high-income countries. Because atherosclerosis underlies the majority of cardiovascular diseases, we investigated temporal trends in the composition of atherosclerotic plaques in patients undergoing carotid endarterectomy in the presence of ultrasound from 1987 to 2011. Biopsies of lesions of plaques of 185 patients were analyzed in intervals of 7 years. The analysis included quantification of collagen, cholesterol, lipoproteins, foam cells, macrophages, smooth muscle cells, and necrobiotic.

Methods and Results—The Actra-Express study is an ongoing, longitudinal, vascular health study that includes the collection of atherosclerotic plaques of patients undergoing procedures in the presence of ultrasound from 1987 to 2011. Biopsies of lesions of plaques of 185 patients were analyzed in intervals of 7 years. The analysis included quantification of collagen, cholesterol, lipoproteins, foam cells, macrophages, smooth muscle cells, and necrobiotic.

Large atherosclerotic plaques, macrophages, and collagen were less frequently observed over time, with adjusted odds ratios of 0.48 (95% confidence interval 0.32-0.75) and 0.30 (95% confidence interval 0.19-0.50). There were also significant increases in the concentration of lipids and cholesterol over time, with adjusted odds ratios of 1.48 (95% confidence interval 1.06-2.07) and 1.30 (95% confidence interval 1.04-1.63), respectively. These changes in plaque characteristics were consistently observed in patient subgroups presenting with acute ischemic stroke, angina, and asymptomatic patients. Consistently, risk factor management and secondary prevention strategies among those patients who had hospitalization significantly improved over the past decade.

Conclusions—In conclusion, over the past decade, atherosclerotic plaques in carotid endarterectomy show a time-dependent change in plaque composition characterized by a decrease in foam cells, macrophages, and necrobiotic and an increase in lipid concentration, cholesterol, and collagen. These changes in plaque composition may be related to risk factor management and secondary prevention strategies implemented over the past decade.


Human plaques are getting less fatty in the statin era

Human plaques are getting less "inflamed" in the statin era

Figure 1. Sensitive multiparametric plaque imaging on intravascular ultrasound: (A) IVUS, (B) macrophages (CD68+), and (C) necrobiotic (CD68+ with positive staining) (violet). Lammeren et al. Circulation. 2014;130:2039-2049.
Meanwhile, the profile of ACS patients and presentations is changing

♥ STEMI is decreasing as NSTEMI rises as a proportion of ACS
We tend to face battle prepared to fight the last war

♥ Our current therapies likely contribute to the decline in STEMI by “stabilizing” so-called “vulnerable plaques.”

We tend to face battle prepared to fight the last war

♥ Yet, despite statins, the residual burden of cardiovascular events even with contemporary preventive measures remains unacceptably high

The Forgotten Majority: Residual Burden of Events in the Statin “Megatrials”


We tend to face battle prepared to fight the last war

♥ We understand the pathophysiology of plaque rupture

♥ We understand how lipid lowering limits plaque rupture

♥ Let’s now address residual risk in statin-treated patients with the current risk factor profile
The Changing Face of the Acute Coronary Syndromes

What mechanisms beyond plaque rupture may contribute to the residual burden of events in the current era?

Superficial erosion of an atheroma causing thrombosis

Farb...Virmani Circulation 93:1354 (1996)
Incidence of Plaque Rupture, OCT-Erosion, and OCT-CN in Patients With ACS. Among the 126 culprit lesions, 55 (44%) lesions were classified as plaque rupture, 39 (31%) lesions were classified as optical coherence tomography (OCT)-erosion, 10 (8%) lesions were classified as OCT-calcified nodule (CN), and 22 (17%) lesions were classified as others. ACS = acute coronary syndrome.

STEMI
Rupture
Erosion
N=39
N=16
N=15
N=24

In Vivo Diagnosis of Plaque Erosion and Calcified Nodule in Patients With Acute Coronary Syndrome by Intravascular Optical Coherence Tomography

Hypotheses re Mechanisms of Superficial Erosion - 2000

Endothelial cell desquamation due to lysis of the extracellular matrix
Endothelial cell death (including apoptosis)

Basement membrane (type IV collagen rich)
MMP-2


Activated ECs can induce NETs and become susceptible to NETosis-mediated cell death

Neutrophil extracellular traps (NETs)

TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion

Thibault Quillard1,2, Hervé Alves Araújo1, Gregory Francck1, Eugenia Shvarts1, Galina Sokolova1, and Peter Libby2

1Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, USA and 2HUMVR, Laval University, Quebec City, Quebec, Canada

European Heart Journal Advance Access published March 8, 2016

FASTTRACK BASIC SCIENCE

European Heart Journal
Advance Access published March 8, 2016

TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion

Thibault Quillard1,2, Hervé Alves Araújo1, Gregory Francck1, Eugenia Shvarts1, Galina Sokolova1, and Peter Libby2

1Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, USA and 2HUMVR, Laval University, Quebec City, Quebec, Canada

Activated ECs can induce NETs and become susceptible to NETosis-mediated cell death

Neutrophil extracellular traps (NETs)
Human plaques with erosion characteristics associate with NETS

- Stable
- Erosion-prone
- Rupture-prone

**Neutrophil Extracellular Traps (NETs) in Human Atherosclerotic Plaques**

EC apoptosis associates with luminal PMNs and TLR2 expression only in SMC-rich lesions

The innate immune receptor TLR2 promotes endothelial functions related to superficial erosion.

- Promotes endothelial (EC) death
- Promotes EC desquamation
- Impairs EC monolayer healing
- Sets the stage for formation of neutrophil extracellular traps
The Changing Face of the Acute Coronary Syndromes

Superficial erosion appears on the rise in the statin era and may account for some of the residual burden of risk.

Table 1

<table>
<thead>
<tr>
<th>Determinant</th>
<th>NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Requiem for the ‘vulnerable plaque’

Peter Libby* and Gerard Pasterkamp

European Heart Journal doi:10.1093/eurheartj/ehv349

Contrasts between superficial erosion and fibrous cap rupture as causes of arterial thrombosis

Plaque erosion
- Lipid-poor
- Proteoglycan and glycosaminoglycan rich
- Non-fibrous collagen breakdown
- Few inflammatory cells
- Endothelial cell apoptosis
- Secondary neutrophil infiltration
- Female predominance
- High triglycerides

Plaque rupture
- Lipid-rich
- Collagen poor, thin-fibrous cap
- Intact fibrous collagen breakdown
- Abundant inflammation
- Smooth muscle cell apoptosis
- Macrophage predominance
- Male predominance
- High LDL

Requiem for the ‘vulnerable plaque’

Peter Libby and Gerard Pasterkamp

European Heart Journal doi:10.1093/eurheartj/ehv349

Thanks!

Thibaut Quillard
Haniel Araújo
Grégory Franck
Eugenia Schvarz
Galina Sukhova
Eduardo Folco

D.W. Reynolds Foundation
National Heart, Lung, and Blood Institute
American Heart Association

Thanks to the people who do the work

Center for Excellence in Vascular Biology 2015