CHAPTER (2)
THE VULNERABLE PLAQUE
UNSTABLE OR HIGH RISK ATHEROSCLEROTIC PLAQUE

- Definition and Composition
- Plaque Destabilization and Disruption
- Fate of Disrupted Plaque
- Clinical Presentation
- Diagnosis
  - Serum Markers
  - Imaging
  - Thermography
• Vulnerable or unstable plaque is an atherosclerotic plaque which is liable to complications and is thrombus prone.
• Atherosclerotic plaques vary in their composition, size of lipid core, thickness of fibrous caps, number of inflammatory and smooth muscle cells, state of endothelial function and degree of calcification. Also, they vary in their location in vessel wall, extent of encroachment on coronary lumen or bulge externally outside the arterial wall (positive remodeling).
• Plaque disruption and superimposed thrombus formation are the leading causes of acute coronary syndromes (ACS) and cardiovascular death.
• Plaque composition, rather than luminal stenosis, is the major determinant of outcome in patients with ASO plaque.

CASCADE OF EVENTS LEADING TO PLAQUE RUPTURE

ENDOTHELIAL INJURY

ENDOTHELIAL DYSFUNCTION

ATHEROSCLEROTIC PLAQUE

PLAQUE VULNERABILITY

PLAQUE RUPTURE

DEFINITION AND COMPOSITION OF THE VULNERABLE PLAQUE

THE VULNERABLE PLAQUE
PLAQUES PRONE TO RUPTURE

• Fibrous Cap Thickness < 65 um
• Macrophages > 25 cells per 0.3 mm diameter field
• Lipid Core > 40 % of plaque area
• High vulnerability Index : ratio of plaque area occupied by lipid components (macrophages + extracellular lipids) to the area occupied by fibromuscular components (SMC + collagen)
- Depending upon their composition, plaques can be classified into two types (Fig 15):
  1. Stable and low risk plaques, which are relatively benign and less prone to thrombotic complications. This type has usually a benign coarse. It produces clinical symptoms when it is large enough to compromise coronary artery lumen and produce myocardial ischemia.
  2. Vulnerable, unstable or high risk plaque. This is the dangerous type of ASO plaque which is liable to complications, namely rupture, tear, erosion and production of coronary thrombosis.

**Figure (15):**
- Upper panel shows the structure of unstable or vulnerable plaque. The fibrous cap is thin contains few VSMCs and collagen fibers. There are a large number of macrophages particularly at the shoulder region where the cap meets the healthy endothelium. There is a large lipid core.
- Lower panel shows a stable plaque with a thick fibrous cap and a small lipid core. There as many VSMCs and collagen fibers.


**Characteristics of Vulnerable Plaque**

The majority (60-80%) of these vulnerable plaques have the following characteristics:

1. Thin fibrous cap with little collagen fibers. The cap thickness is less than 65 microns.
2. Large lipid core more than 40% of the plaque volume.
3. Lipid content of the lipid core has a large amount of cholesterol esters and is soft. These soft plaques are less stable and have a higher propensity to rupture than the fibrotic plaques.
4. Large number of inflammatory cells, macrophages, foam cells and T-lymphocytes. Macrophages are more than 25 cells per 0.3 mm diameter field.

5. Small number of VSMCs.


7. Endothelial dysfunction.

8. Outward (positive) remodeling.

**Plaque Erosions**

- A minority of plaques (20-30%) responsible for the production of ACS lack the above features, and are characterized by a small lipid core and a thick fibrous cap rich in VSMCs and proteoglycans but without inflammatory cell infiltrates. The underlying mechanism of coronary thrombosis in this type is plaque erosion, where endothelium is absent at site of erosion. The type is more common in women and young men.

**Table: Definitions**

| Culprit lesion | A lesion in a coronary artery considered, on the basis of angiographic, autopsy or other findings, to be responsible for the clinical event. In unstable angina, myocardial infarction and sudden coronary death, the culprit lesion is often a plaque complicated by thrombosis extending into the lumen. |
| Eroded plaque | A plaque with loss and/or dysfunction of the luminal endothelial cells leading to thrombosis. There is usually no additional defect or gap in the plaque, which is often rich in smooth muscle cells and proteoglycans. |
| High-risk, vulnerable and thrombosis prone plaque | These terms can be used as synonyms to describe a plaque that is at increased risk of thrombosis (or rethrombosis) and rapid stenosis progression. |
| Inflamed thin-cap fibroatheroma (TCFA) | An inflamed plaque with a thin cap covering a lipid-rich, necrotic core. An inflamed TCFA is suspected to be a high-risk/vulnerable plaque. |
| Plaque with a calcified nodule | A heavily calcified plaque with the loss and/or dysfunction of endothelial cells over a calcified nodule, resulting in loss of fibrous cap, that makes the plaque at high-risk/vulnerable. This is the least common of the three types of suspected high-risk/vulnerable plaques. |
| Ruptured plaque | A plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque. This is the most common cause of thrombosis. |
| Thrombosed plaque | A plaque with an overlying thrombus extending into the lumen of the vessel. The thrombus may be occlusive or non-occlusive. |
| Vulnerable patient | A patient at high-risk (vulnerable, prone) to experience a cardiovascular ischemic event due to a high atherosclerotic burden, high-risk/vulnerable plaques, and/or thrombogenic blood. |

Role of Fibrous Cap
The fibrous cap is a dynamic structure (Fig 5), its thickness and collagen content depends upon the balance of:

- Collagen synthesis by VSMCs driven by cytokines (TGF-B).
- Collagen degradation by matrix metalloproteinases produced by macrophages, driven by cytokines (TNF-α and IL-1).

INF-γ and TNF-α produced by T-lymphocytes decrease the function and induce apoptosis of VSMCs.

- Thin fibrous cap is the result of increased collagen degradation and decreased collagen formation.
- Unstable plaques most commonly rupture at thin areas of their cap at plaque shoulder, where T-lymphocytes and macrophages predominate and SMCs are less common. The shoulder region is the junction of the fibrous cap with adjacent, more normal intima.

PLAQUE DESTABILIZATION AND DISRUPTION

- Majority of ACS are secondary to rupture, fissuring or erosion of an atherosclerotic plaque.
- By exposing the strongly thrombogenic lipid core of plaque to the blood elements, platelet and fibrin thrombi are formed (Fig 16), these partially or totally occlude the coronary artery lumen.
- Development of coronary spasm secondary to platelet activation and release of serotonin contributes to the occlusion of the coronary artery.
- Serious complications secondary to interruption of coronary flow, may result particularly in absence of good collateral flow.
Figure (16): Fissuring, tear or rupture of the vulnerable plaque exposing the lipid core to the blood. Release of tissue factor from activated macrophages will initiate blood coagulation through combination with coagulation factor VII/VIIa activating the coagulation cascade leading to thrombin generation and fibrin formation. Blood platelets adhesion to exposed subendothelial matrix adhesion proteins (collagen, von Willebrand factor) results in platelet activation.

Plaque rupture is complicated by thrombus formation and coronary artery occlusion. Partial occlusion by a platelet rich thrombus gives rise to unstable angina. Total occlusion by a fibrin rich thrombus results in MI.


**Factors contributing to plaque instability and rupture**

1. **Plaque inflammation**: local and systemic inflammatory states.
2. **Endothelial dysfunction** secondary to cardiovascular risk factors: hypertension, diabetes, dyslipidemia and cigarette smoking, acting through increased oxidative stress produce endothelial dysfunction.
3. Increased **plaque thrombogenicity**: in ACS there are evidence of increased PAI-1, plasma fibrinogen, tissue factor, platelet activation and aggregation. These factors contribute to development, growth and persistence of coronary thrombi.
4. Increased **wall stress**:
   - Excessive pressure on the thin fibrous cap which separates the plaque lipid core from the vessel lumen can lead to cap tear or rupture.
   - Excessive sympathetic stimulation during severe emotions or physical exercise can sharply increase wall stress.
Sequelae of Disruption of the Vulnerable Plaque

- The subendothelial extracellular matrix and the lipid core are exposed to the blood stream whether disruption is due to a plaque erosion or due to rupture or tear of the fibrous cap (Fig 16).
- Both the subendothelial matrix and the lipid core are very rich in procoagulant factors particularly tissue factor (TF) (Figs 11, 17).
- TF exposed to the blood will bind with plasma coagulation factors VII/VIIa initiating the extrinsic pathway of blood coagulation by activating coagulation factor IX and X resulting in thrombin generation and fibrin formation.
- Circulating platelets are recruited at site of intimal tear and are attracted to adhesion proteins (collagen, von Willebrand factor) exposed in the subendothelial space. Platelet adhesion is followed by activation and platelet aggregation (Figs 11, 17).
- Thrombi formed at site of plaque erosion or rupture can either:
  1. Dissolve spontaneously through the natural body fibrinolytic defenses.
  2. Fragment and embolize distally to small coronary arterioles.
  3. Persist and grow.
  4. Become incorporated in the vessel wall.
  5. Protrude in the lumen, invaded by fibroblasts, change to fibrous tissue and covered by endothelium (healing) (Fig 18).
- Majority of vulnerable plaques are asymptomatic and the majority of plaque ruptures and erosions are silent.
- Repeated plaque rupture, thrombosis and healing will result in growth of the plaque (Fig 18) and encroachment on coronary lumen.
Figure (17): Plaque fissuring or rupture will expose the strongly thrombogenic lipid core and the extracellular matrix to the blood. Platelet and fibrin thrombi are formed at site of fissuring. Partial or intermittent occlusion of the coronary artery by thrombi will result in unstable angina while complete and persistent occlusion results in myocardial infarction.

Tissue factor (TF) released from activated macrophages into blood will initiate blood coagulation though combination with factor VIIa and activation of the coagulation factors IX and X leading to thrombin and fibrin formation.

Triggers of Plaque Disruption

- Majority of vulnerable plaques rupture spontaneously as a result of fibrous cap fatigue from the continuous exposure to the daily wall stresses and progressive wear and tear.

- Increase in sympathetic nervous activity can trigger plaque disruption through:
  1. Sudden increase in arterial pressure triggers plaque rupture through an increase in circumferential wall stress* that exceeds the tensile strength of the cap.
  2. Increase vascular tone at the site of the plaque. Inappropriate vasoconstriction could exert direct and shear stresses* on the top of the plaque, precipitating disruption.

- Conditions associated with increased sympathetic activity and can trigger plaque disruption:
  - Sudden, unexpected, severe physical exercise specially in untrained individual.
  - Sexual activity.
  - Severe emotions, anger.

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* Stress is the applied force normalized over an area and is divided into normal and shear stress.
  - Normal stress: stress applied in a direction perpendicular to the surface. It can be compressive (squeeze the material) or tensile (pull the material apart).
  - Shear stress: stress applied tangentially to a surface.

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**Figure (18):** Rupture of the ASO plaque and thrombus formation is a recurrent and silent process in the majority of cases and is followed by healing of the ruptured plaque. Rupture of vasavasorum in the lipid core produce a hematoma in vessel wall. Collagen formed by activated VSMCs generates a thick fibrous cap. ASO plaque can be the site of repeated and multiple ruptures and healing. (1) collagen overlying first healed rupture. (2) second necrotic core.

Source: Burke et al. Circulation 2001
- Drugs: cocaine, amphetamine.
- Circadian variations: highest incidence of acute coronary events in the morning hours following awakening.

- Local plaque factors
  - Cellular and biochemical processes within the plaque- accumulation of inflammatory cells and increased activity of proteolytic enzymes accelerates destruction of the cap.
  - Chlamydia infection
  - Severe endothelial injury.

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**THE VULNERABLE PLAQUE**

Triggers of Rupture

- Circadian: time of the day
- Sympathetic Activity:
  - Heavy exercise
  - Anger
- Endothelial Injury:
  - Infection
  - Toxins: tobacco, cocaine

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**RAS Activation in ACS**

- ACE activity is markedly increased in coronary arteries of patients with ACS.
- There are evidences of systemic RAS activation in patients with ACS.
- Degree of RAS activation is related to the clinical condition.
- When MI is complicated by CHF, cardiogenic shock or arrhythmias there is an early and excessive RAS activation.
- Extensive MI is associated with high levels of renin and AII.
- RAS activation is an important compensatory reaction in patients with cardiogenic shock. However, it has detrimental effects on cardiovascular function during the acute and convalescent phases of MI.
- There is an association between RAS activation and increased risk of MI.
- Following AMI there are increased levels of plasma inflammatory (MCP-1) and coagulation (tissue factor) markers. Enalapril, an ACE-I reduced the levels of plasma MCP-1 and tissue factor in these patients. ACE-I therapy therefore reduces the increased procoagulant and proinflammatory activity in patients with ACS.

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**Inflammation** plays a central role in atherosclerotic plaque formation, progression, instability and finally plaque rupture. There is close association between inflammation and thrombosis.
Whether disruption of the vulnerable plaque remains silent, leads to plaque growth, or result in the production of a large coronary thrombus which partially or totally occlude the coronary artery resulting in ACS or cardiovascular death will depend upon both local factors at the site of the disrupted plaque and systemic factors related to the body’s internal milieu.

**FATE OF THE DISRUPTED PLAQUE**

1. **Thrombus formation**
   - Exposure of collagen and athermanous core contents to coronary blood.

2. **Plaque healing** - Sealing of the intimal tear (Fig 21).
   - Organization and fibrosis of the thrombus (invasion by fibroblasts and fibrous tissue).
   - Incorporation in vessel wall. Endothelial coverage.

3. **Plaque growth**
   - Following repeated disruption, thrombosis and healing a multilayered thrombus is formed (Fig 18).

4. **Coronary vasoconstriction**
   - Release of vasoconstriction substances (serotonin, TXA₂, thrombin) from the thrombus, activated platelets and injured endothelium.
Acute Coronary Syndromes

Figure (20): The fate of coronary thrombus following plaque rupture will determine the clinical outcome. Majority of coronary thrombi undergo spontaneous lysis and disappear.

Figure (21): Structure of recurrent and healed plaque ruptures. New plaques form on top of old ones resulting in formation of multilayered plaque. A: areas of intimal lipid-rich core. B: higher magnification of SMCs proliferation within neointimal showing clear demarcation with more fibrous region of old plaque. C: dark collagen surrounding lipid hemorrhagic cores.

Source: Burke et al. 2001.
Factors Favoring Thrombus Growth and Progression

- **Local factors:**
  1. Plaque composition:
     - Large lipid core, heavy inflammatory cell infiltration, increased TF expression and severe local inflammatory activity.
     - In patients with severe unstable angina, a transient acute wide spread coronary endothelial inflammatory process is present.
  2. Extent of rupture
     - Large deep tears.
  3. Endothelial dysfunction
     - Impaired production of natural anticoagulants (thrombomodulin, AT III) and fibrinolytic (t-PA) defenses.
     - Excessive generation of procoagulant and anti fibrinolytic molecules such as TF, PAI, All, TXA$_2$, thrombin.
     - Impaired NO and PGI production will favour platelet aggregation and vasoconstriction.
     - Endothelial dysfunction is secondary to both local inflammatory reaction and to systemic injury due to cardiovascular risk factors.
  4. Slow coronary flow secondary to:
     - Severe coronary stenosis.
     - Increase blood viscosity.
     - Coronary vasospasm.

- **Systemic Factors**
  1. Systemic Inflammatory State:
     - Inflammation promotes thrombosis and vice versa.
     - Prolonged increase in the levels of fibrinogen and CRP.
     - Systemic inflammation augments local inflammation.
  2. Systemic Procoagulant State:
     - Extensive atherosclerosis is associated with increased blood thrombogenicity.
     - Conditions leading to hypercoagulable state are diabetes mellitus, hypercholesterolemia and cigarette smoking due to high levels of circulating TF.
     - An active fibrinolytic system may be able to prevent luminal thrombosis in severe cases of plaque disruption. Low fibrinolytic activity will favor growth and persistence of the thrombi.
     - A transient shift in the coagulation and anticoagulation balance may result in acute event.
     - Metabolic factors, such as postprandial metabolic changes, are associated with increased blood coagulability.
- ACS can sometime follow a heavy fatty meal, postprandial hyperlipidemia can lead to both vascular endothelial injury and increased blood coagulability.

**CLINICAL PRESENTATION OF CORONARY ASO PLAQUE** (Fig 19)

- Majority of ASO plaques are clinically silent and are asymptomatic. Their first mode of presentation may be sudden death or AMI.
- Stable (inactive) plaques when encroach on coronary lumen produce myocardial ischemia and stable angina pectoris.
- Plaque growth, thrombosis and coronary vasospasm will limit the coronary flow and induce anginal symptoms.
- Unstable (vulnerable or active) plaques may remain silent (asymptomatic) or rupture with coronary thrombosis.
- Plaque rupture and thrombosis are frequently silent, it appears to be a frequent event that only occasionally leads to luminal obstruction.
- A number of factors determine the clinical manifestations of plaque disruption and coronary thrombosis:

![Diagram of Coronary Thrombosis]

**Coronary Thrombosis**

**Factors Determining Outcome**

- **Obstruction**
  - Acuteness Degree
  - Duration

- **Collaterals**
  - Available
  - Recruitment

- **Myocardial Demands**
  - HR
  - Inotropy
  - Loading
Factors Determining the Clinical Outcome Following Coronary Thrombosis

1. Coronary occlusion
   - Acuteness (sudden, gradual).
   - Extent (total, partial).
   - Duration/ Persistence (seconds, hours).
   - Site (proximal, distal).

2. Coronary collaterals
   - Established.
   - Recruited.

3. Myocardial oxygen requirements at time of occlusion
   - Blood pressure.
   - Heat rate.
   - Inotropic state (contractility).

- The size, extent, site and persistence of the coronary thrombus will determine the outcome which will vary from no symptoms to ACS to cardiac death.
- There is unpredictability of patient outcomes due in part to fluctuation of risk factors and triggers, e.g. day to day changes in diet, activity, stress, cold weather, smoking, infection, blood pressure.
- It is not clear why some plaques lead to clinical manifestations, whereas many others remain asymptomatic and heal with subsequent fibrosis, frequently associated with luminal narrowing.

DIAGNOSIS OF THE VULNERABLE PLAQUE

- The aim of vulnerable plaque detection is to identify patients at high risk for acute coronary events. However, it is impossible to predict:
  - When vulnerable plaques will rupture after their detection.
  - Whether rupture will lead to acute coronary event.
  - Whether they rupture as a result of mechanical stress, spasm, acute inflammatory endothelial activation, or the chronic inflammatory component of atherosclerosis.
- Most myocardial infarctions (MIs) result from the rupture of mild to moderately sized cholesterol-laden plaques in coronary arts followed by thrombosis and vessel occlusion.
- In general, these lesions can not be characterized by currently available imaging techniques prior to rupture.
Biochemical Methods - Serum Markers:

- Vulnerable unstable ASO plaques are generally associated with local vascular and systemic inflammatory reactions.

- Elevated serum markers of inflammation may give a clue to the presence of vulnerable plaques.
  1. hs-CRP:
     - Levels significantly higher in patients who are at risk of developing AMI and ischemic stroke (See also page 24 for more information about hs CRP).
     - Elevations have been associated with thin cap ASP plaque.
  2. IL-6: an independent marker of increased mortality in unstable CAD.
  3. Soluble adhesion molecules: ICAM-1, VCAM-1, selectins, CD-40 ligand*.
  5. Markers of immune activation: - Anti-LDL antibody, and Anti-HSP (heat shock protein) antibody.

* Co-40 ligand:
  - Present in membrane-bound and soluble forms (s CD40L).
  - Interact with CD 40 receptor, expressed on B-lymphocytes, macrophages, endothelial cells, VSMCs and activated platelets.
  - Stimulation of endothelial cells by CD40L causes increased expression of adhesion molecules and cytokines.
  - sCD40L promote MMP expression in VSMCs and macrophages.
  - It serves as a link between platelets and leukocytes.
  - Elevation of sCD40L is detectable in serum of patients with ACS and serves as a prognostic marker.
Coronary Imaging

Intravascular Ultrasound: IVUS

- Provides two dimensional cross-sectional tomographic views.
- It can identify plaque constituents such as calcification, fibrous tissue, thrombus, plaque tears, fractures or dissection (Figs 22, 23, 24).
- It has limited resolution (>100 micron), there is the confounding influences of surrounding tissue, calcification masks the underlying structures (Fig 23).
- Echolucent lesions have higher lipid content and are more frequently observed in patients with unstable angina.
- It can help define the degree and the direction of arterial remodeling in the plaque.
- It is of little use in determining the instability of the plaque and its subendothelial components.
- Arterial calcifications can be present in stable plaque.

Figure (22): Intravascular ultrasound (IVUS) of a coronary artery with ruptured vulnerable plaque showing the site of rupture. Fibrous tissue appears white and echo dense while lipid pool appears echo lucent grey block. Blood appears black.
**Figure (23):** IVUS showing a ruptured plaque with area of calcification. Calcification produce a dark shadow that masks the underlying tissue.

**Optical Coherence Tomography: OCT**

- OCT is analogous to ultrasound, measuring the intensity of backreflected infrared light rather than acoustic waves.

- A beam of coherent infrared laser light is directed and reflected within the tissues to create an image with higher resolution (2-30 microns).

- It precisely quantifies fibrous cap thickness, differentiates intima and lipid pool, define fissuring of plaque, generate high contrast between lipid and non lipid tissue.

- Limitations include: - low penetration depth.
  - requires coronary catheterization and that blood in the artery be washed away, since blood absorbs light signal.
IVUS can help identify plaque morphology and structure. Stable plaques have thick fibrous cap which appears as dense white strongly echogenic structure (left image). Image on the right shows a thin cap and large lipid core consistent with a vulnerable plaque.

**Angioscopy**
- Optic fibers are used to observe the intracoronary lumen directly.
- It can discriminate between a stable plaque which appears white and unstable one which appears red or yellow.
- It can detect intracoronary thrombi.
- Limitations: - blood should be washed from the coronary artery and vessel wall before an image can be obtained by saline irrigation after blocking blood flow.

**Near-Infrared (NIR) Spectroscopy - Experimental**
- NIR spectroscopy is based on absorbance of light by organic molecules.
- Reflectance spectra from wave length between 400 and 2400 nm allow detailed analysis of chemical composition: cholesterol, HDL, LDL, metallo proteins, fibrous cap, lipids, thrombus, ulceration and necrosis.
- Can identify histological features of vulnerability in aortic plaques at autopsy.
- NIR light can be delivered to human coronary arts by a fibro optic catheter.

**Magnetic Resonance Imaging (MRI)**
- The most promising method for noninvasive imaging of vulnerable plaques.
- MRI allows the discrimination of lipid core, fibrosis, calcification and thrombus deposits (Fig 25).
- It provides imaging without ionizing radiation that can be repeated.
- During the examination, the patient is subjected to strong local magnetic field that aligns the protons in the body. These protons or spins are excited by a radiofrequency pulse and subsequently detected with receiver coils.
- Atherosclerotic plaque characterization by MR is based on the signal intensities and morphological appearance of the plaque.
- At present, the sensitivity and specificity are not of sufficiently high quality for reliable clinical application.
- The new technique of intravascular MRI allow high-resolution image (78 micron) with no significant motion artifacts.

**Figure (25):** In vivo magnetic resonance (MR) image of a plaque (arrow) in the left anterior descending artery (LAD). The inset represents a magnified view of a large eccentric LAD plaque.

**Source:** Fayad et al. Circulation 2000.

**Thermography**
- Intracoronary thermistor devices to measure the temperature of the plaques (Fig 26).
- Plaques that are hot or have thermal heterogeneity are associated with inflammation and are at high risk for rupture.
- There is temperature rise of up to 2.2 °C in macrophage rich areas.
- Most atherosclerotic plaques showed higher temperature compared with the healthy vessel wall (Fig 27).
A 3F thermography catheter demonstrated thermal heterogeneity with a special resolution of 0.5 mm in the coronary arts of 20% of patients with stable angina, 40% of those with unstable angina and 67% of those with AMI. No thermal heterogeneity is seen in arterial specimens from control subjects.

Increased local temperature in human coronary ASO plaques was identified as an independent predictor of clinical outcomes in patients undergoing PCI and associated with increased risk of adverse events.

**Figure (26):** Thermography catheter. The engaged distal end of the catheter, with the four thermisters widely expanded

**Source:** Verheye et al. Circulation 2002
Figure (27): Recording of temperature through thermography catheter in rabbit passed from aortic arch to abdominal aorta. Arrow points to atherosclerotic plaques. Unstable atherosclerotic plaque shows higher temperature compared with the healthy vessel wall and stable plaques (arrow head) following 3 months of dietary cholesterol lowering.