Metabolic Imaging of Atherosclerotic plaque

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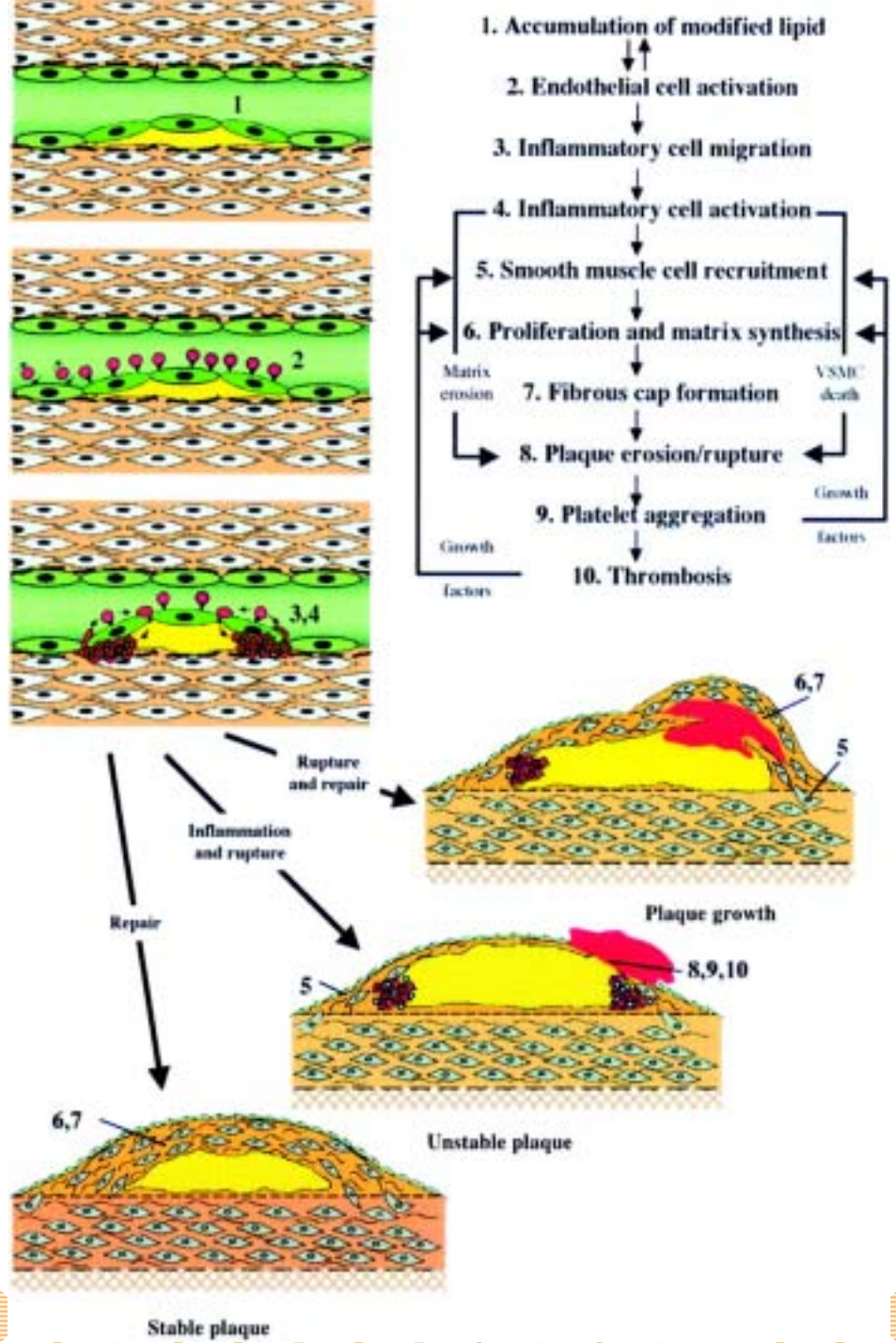
Atherosclerotic plaque

- Central lipid core bounded on its lumen side by an endothelialized fibrous cap
- Positive remodeling; vessel expand as plaque grow.
- Eventually plaque encroach into the lumen,causing obstruction.


1. Accumulation of modified lipid
2. Endothelial cell activation
3. Inflammatory cell migration
4. Inflammatory cell activation
5. Smooth muscle cell recruitment
6. Proliferation and matrix synthesis
Matrix erosion
7. Fibrous cap formation
VSMC death
8. Plaque erosion/rupture
9. Platelet aggregation
Growth factors
Growth factors
10. Thrombosis
1
2
3,4
Rupture and repair
Inflammation and rupture
Repair
6,7
5
Plaque growth
5
8,9,10
Unstable plaque
6,7
Stable plaque

Why Plaque imaging?

- Predict the risk of future plaque rupture.
- Monitor the effectiveness of systemic atheroma-modifying treatment.

Macrophage vs. VSMCs

macrophage:

- Metalloproteinase: break down the matrix protein.
- Inflammatory cytokines:
- Direct cell to cell contact lead to VSMCs death.

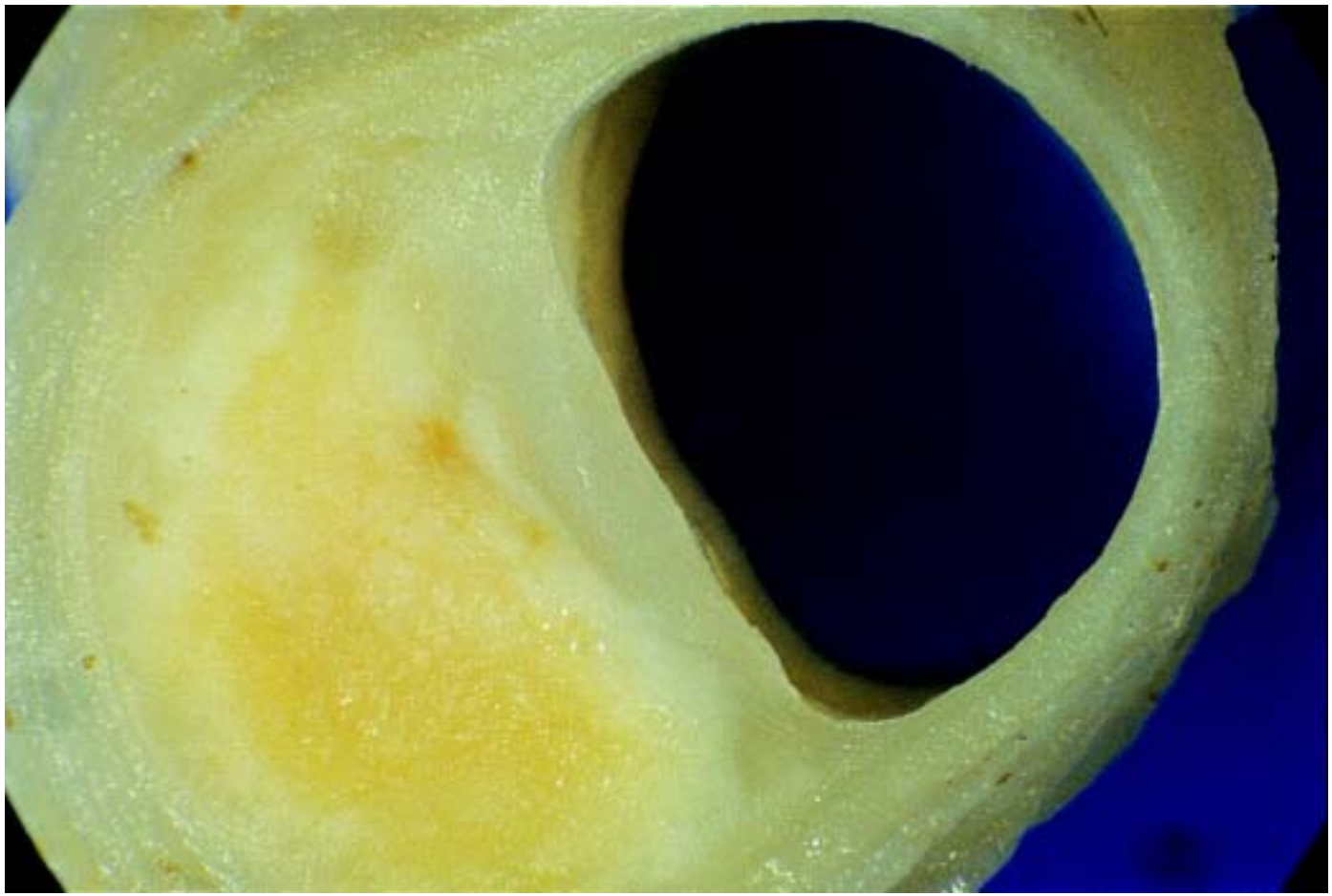
VSMCs:

- reduced proliferative capacity and propensity to apoptosis.

Highest risk of plaque rupture

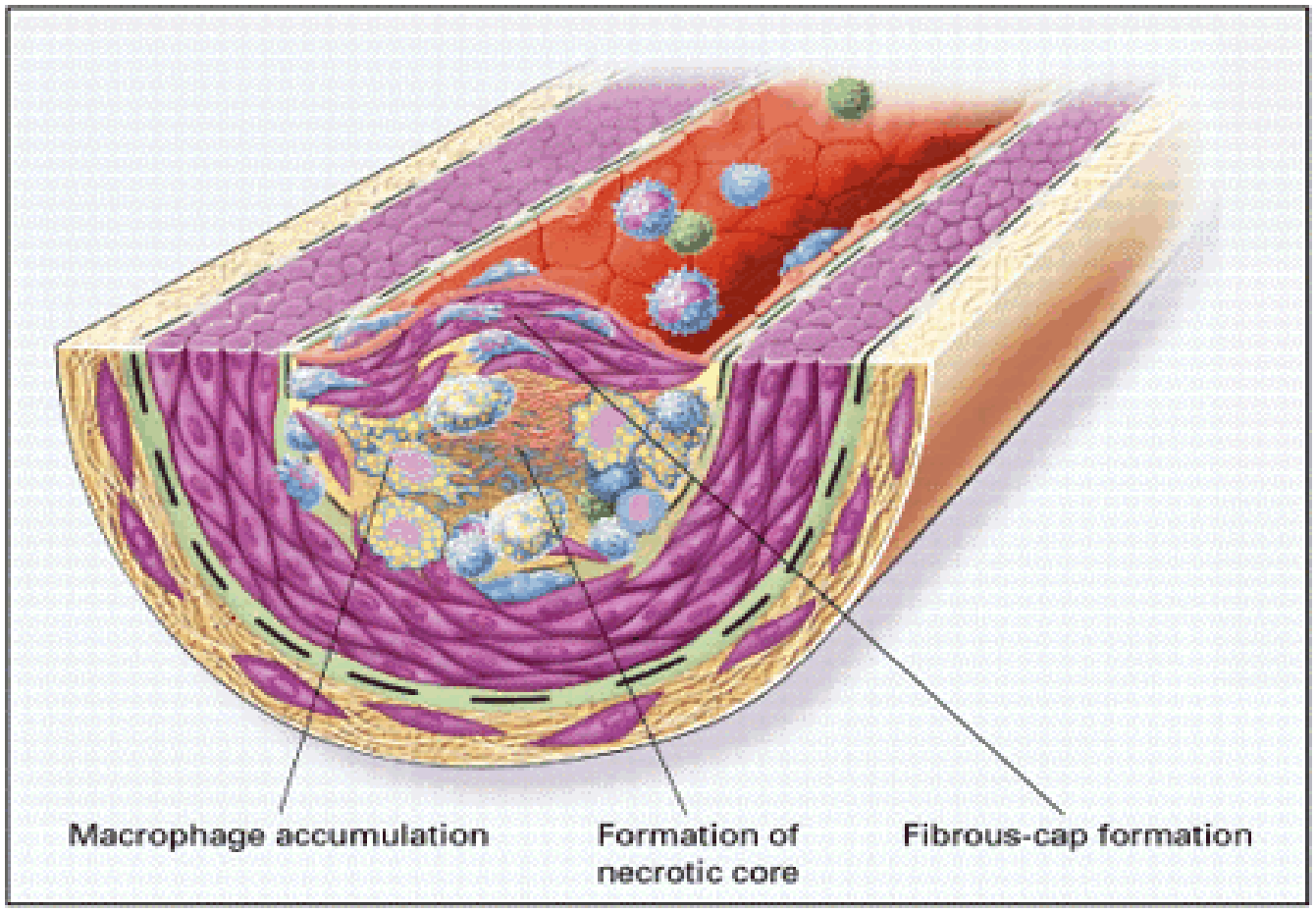
- Large lipid core.
- Thin fibrous cap.
- Preponderance of inflammatory cells.
- Paucity of vascular smooth muscle cells.

Human coronary atherosclerotic plaque with a yellow core of lipid separated from the lumen by a fibrous cap

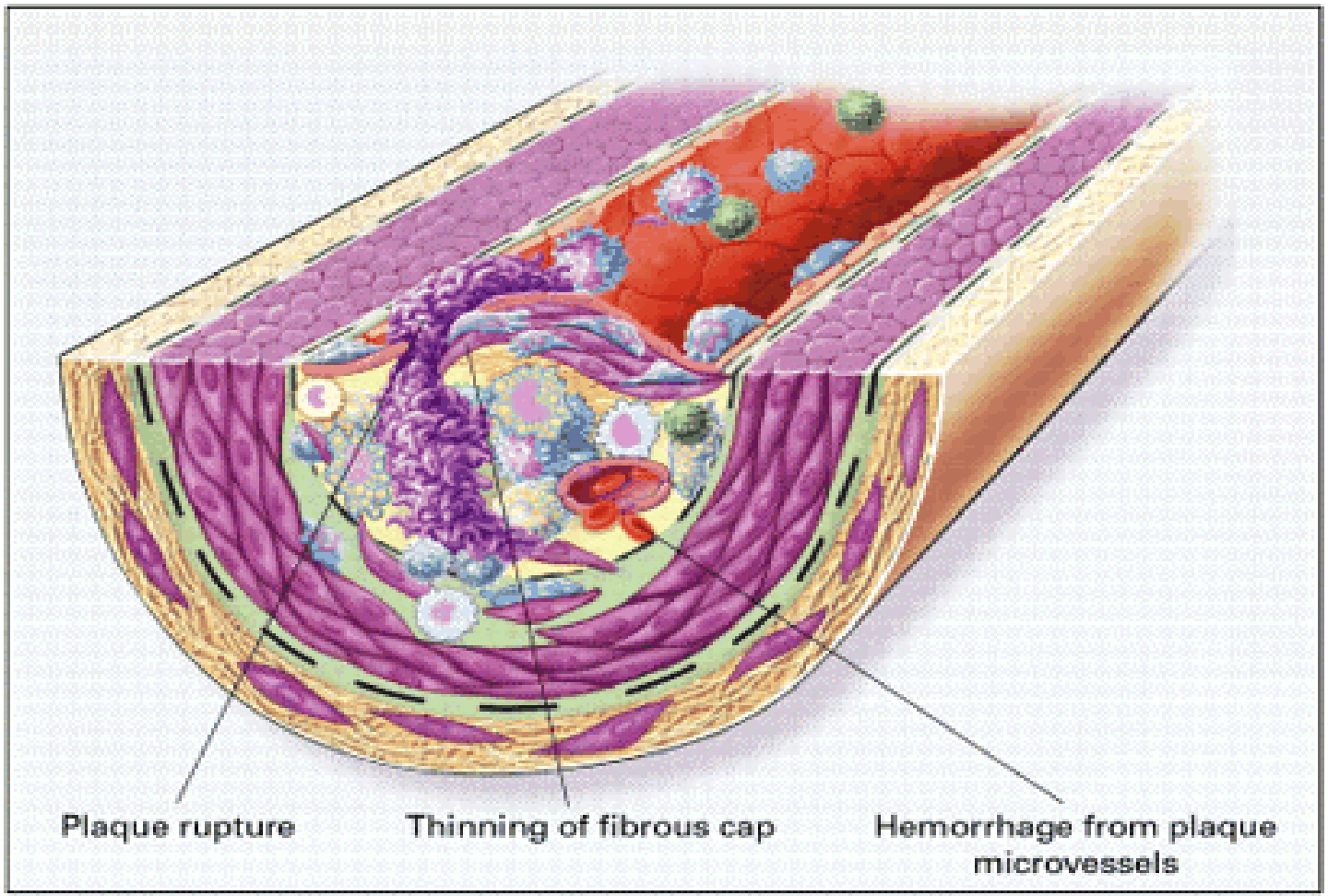


Davies, M. J. Circulation 1996;94:2013-2020

Formation of an advanced complicated lesion of atherosclerosis



Unstable fibrous plaques in atherosclerosis

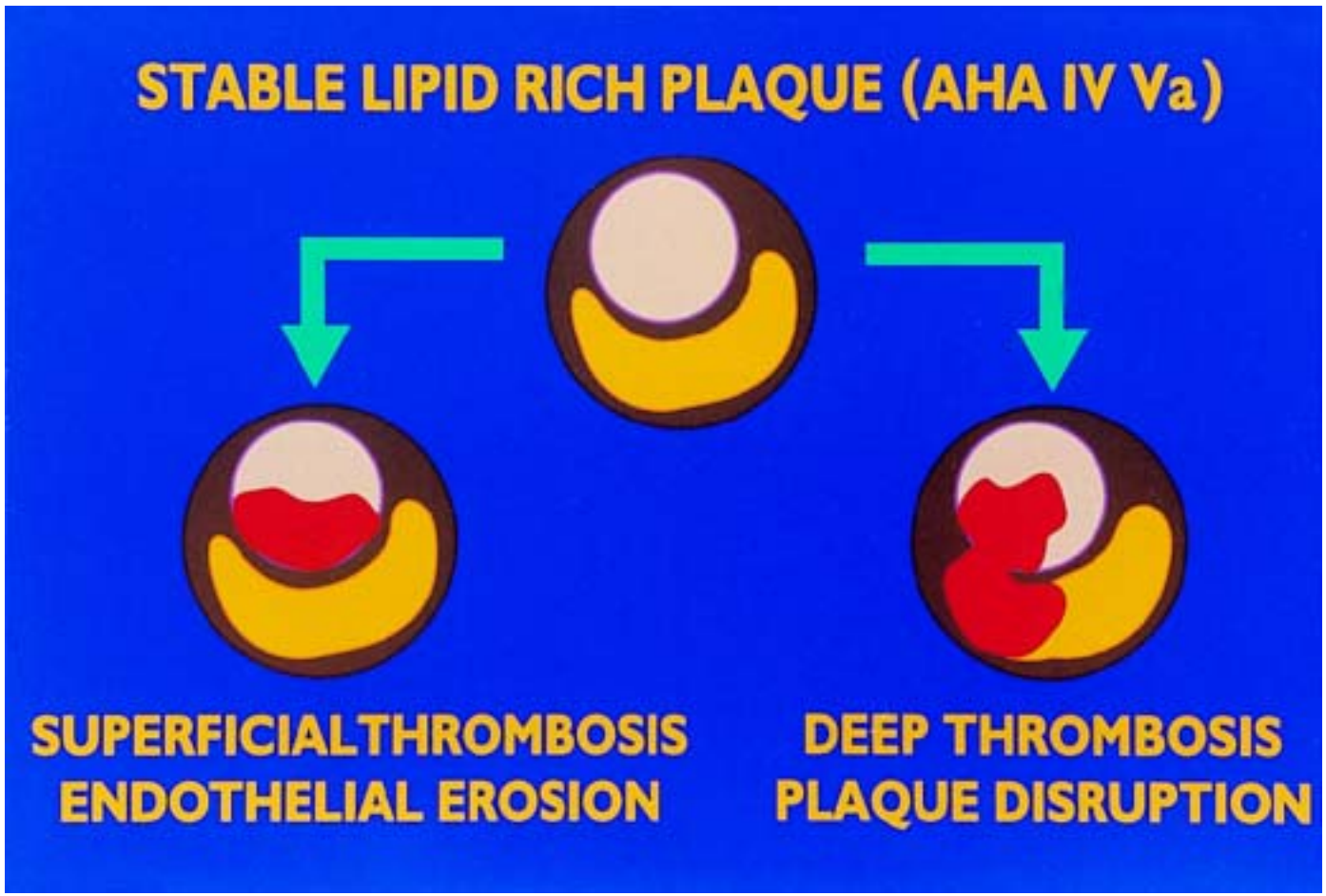


Thrombus(fibrin+platelet)

- Platelet: glycoprotein IIb/IIIa.
  platelet aggregation.

- Clotting factors: VII and XI
  thrombin, fibrinogen, fibrin.

Diagram of the two forms of thrombosis that can complicate stable lipid-rich plaques



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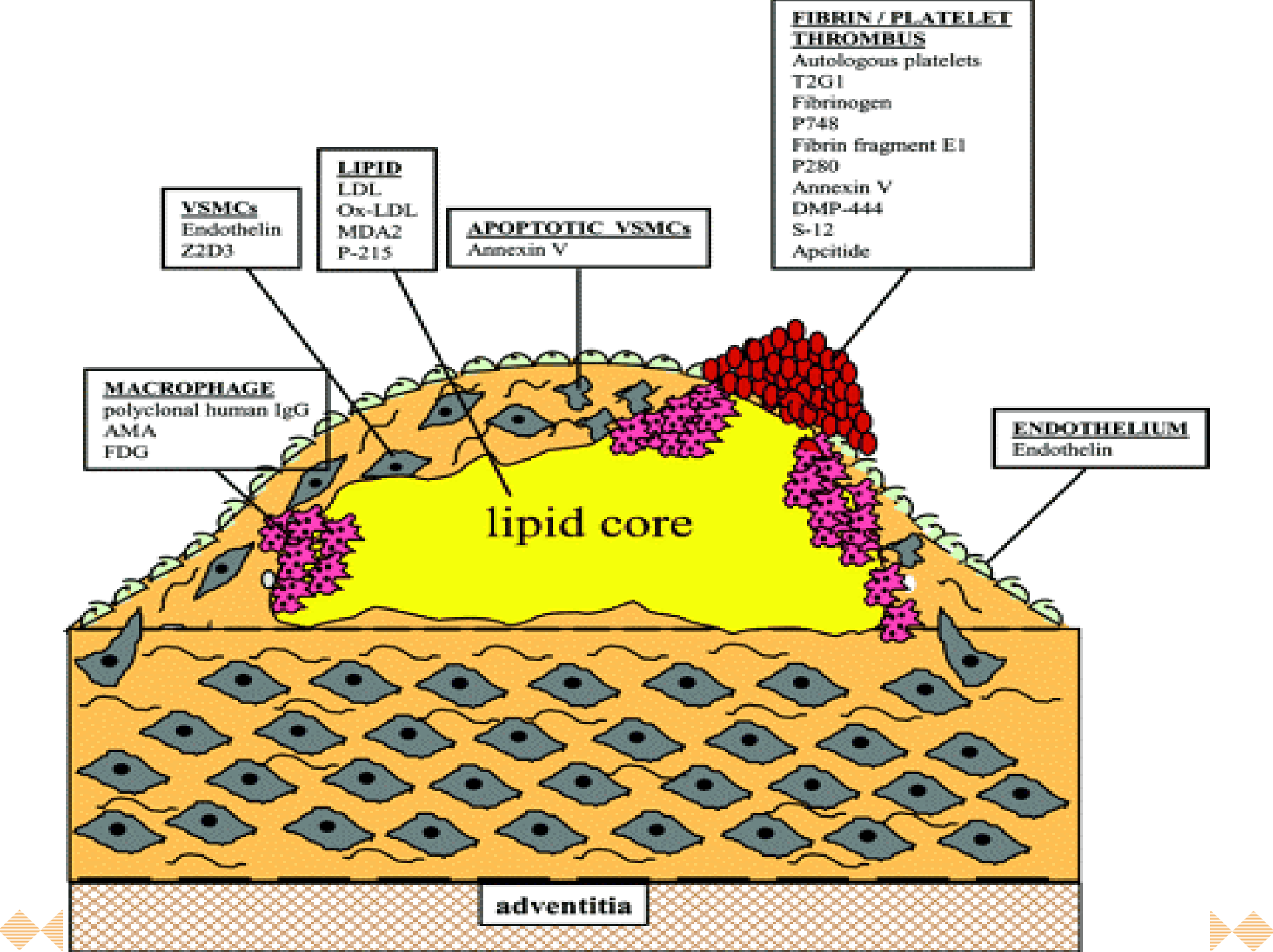
Functional Imaging of atherosclerosis

- To get information on cell biologic events that determine risk of plaque rupture.

- Radiolabeled tracer imaging:
  bind or taken up by constituents of
  1) plaque.
  2) thrombus.
  3) macrophage(FDG-PET).


FIBRIN / PLATELET THROMBUS
Autologous platelets
T2G1
Fibrinogen
P748
Fibrin fragment E1
P280
Annexin V
DMP-444
S-12
Apcitide
LIPID
LDL
Ox-LDL
MDA2
P-215
VSMCs
Endothelin
Z2D3
APOPTOTIC VSMCs
Annexin V
MACROPHAGE
polyclonal human IgG
AMA
FDG
ENDOTHELIUM
Endothelin
lipid core
adventitia

Radiotracers for plaque

- **Lipoprotein:**

1) Low density lipoprotein(LDL)
2) Oxidized LDL.
3) Antibody to LDL(MDA2)

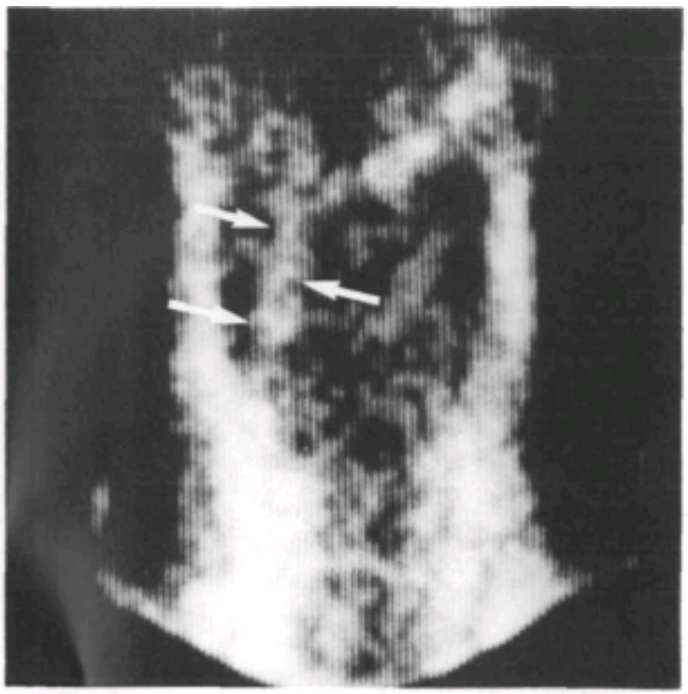
- **Peptide:**

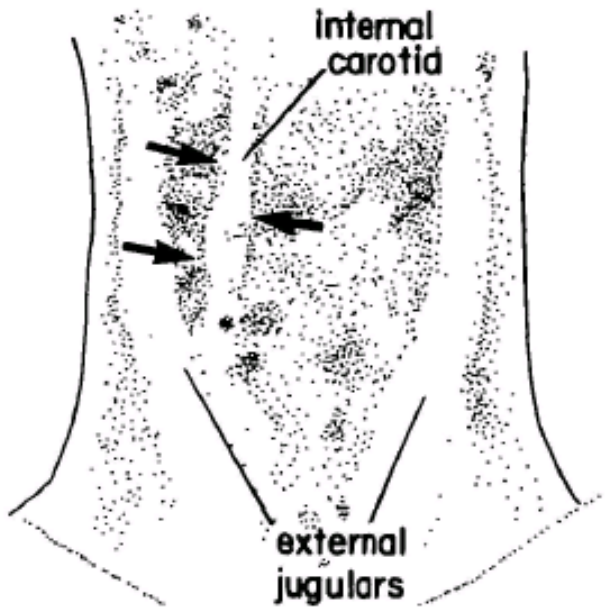
1) apo-B portion of LDL. (SP-4)
2) endothelin peptide

- **Antibody:**

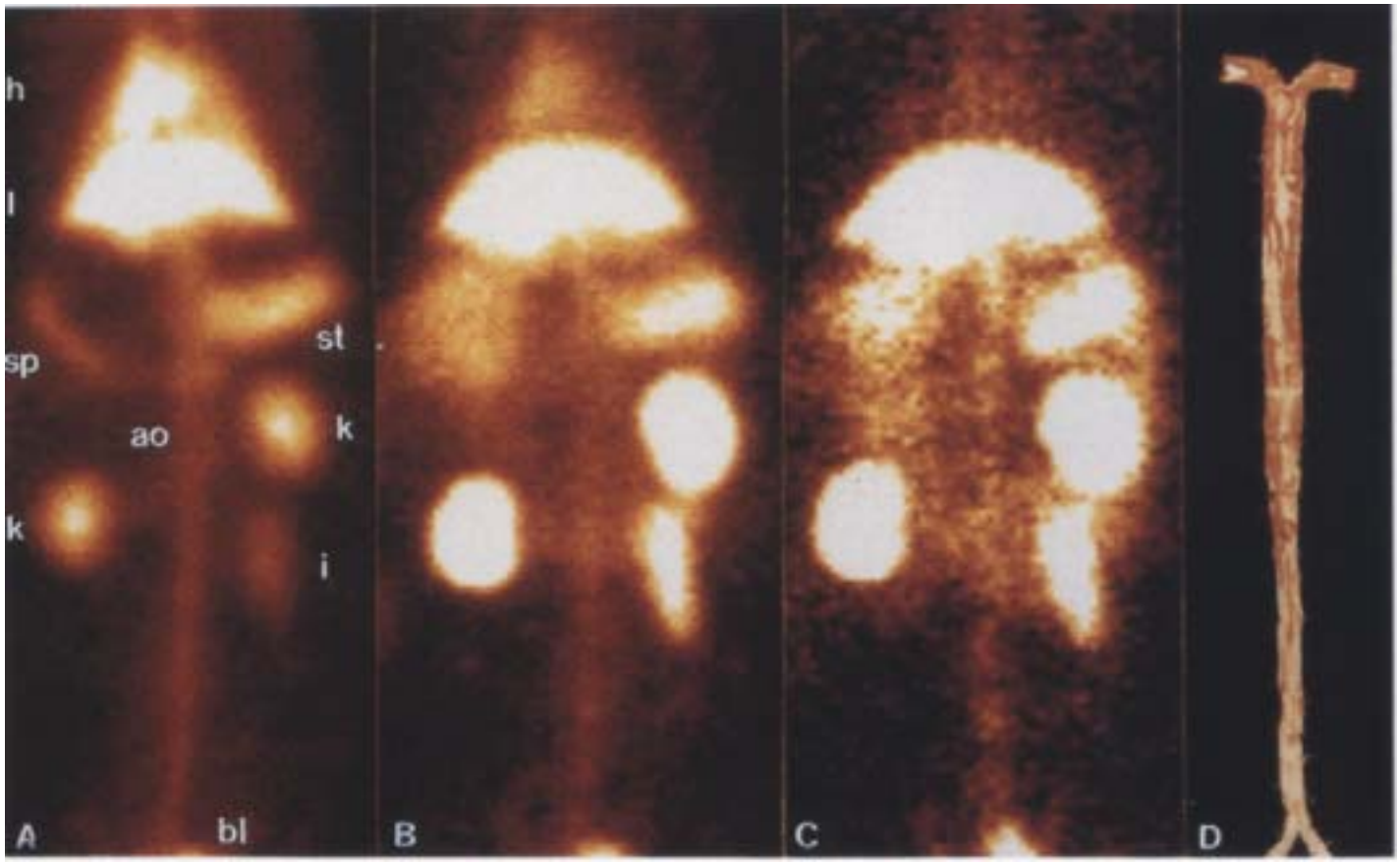
1) Polyclonal human IgG
2) Ab to aminomaloic acid(AMA).

Tc-99m LDL





Tc-99m MDA2



10 minutes Images

12 hours Images

14 hours Images

Sudan IV Stained Images

Peptide

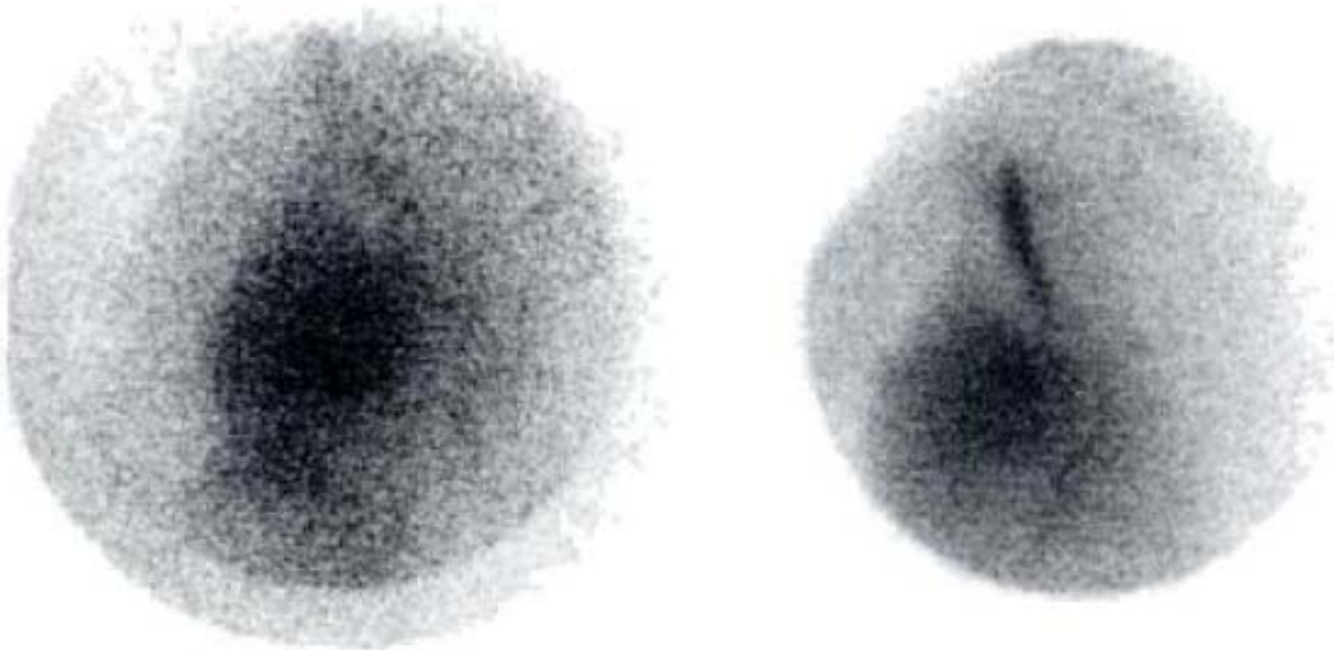
Clear from circulation quickly and theoretically could improve the target to background activity.

Apo-B portion analogue(SP-4):

small enough to be rapidly cleared from plasma.

Endothelin peptide:smooth muscle cell&endothelial cells.

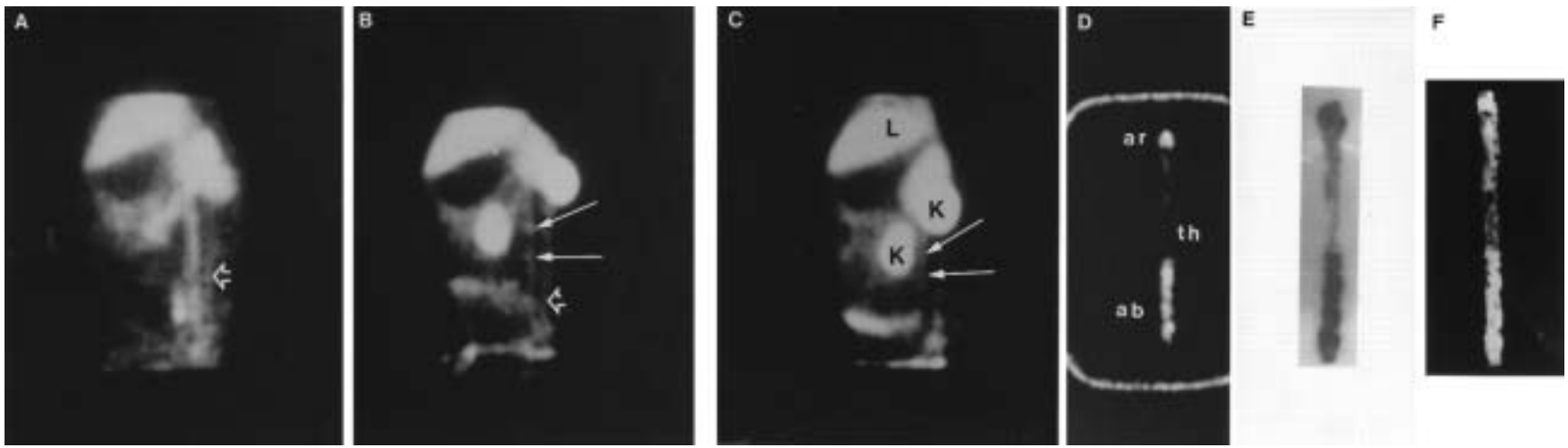
I-123-SP-4



Antibody

- Polyclonal human IgG:
- Antibody against amino malonic acids (AMA)
- Antibody against vascular smooth muscle cells(VSMCs)

In-111 nonspecific human IgG1 F(ab')2



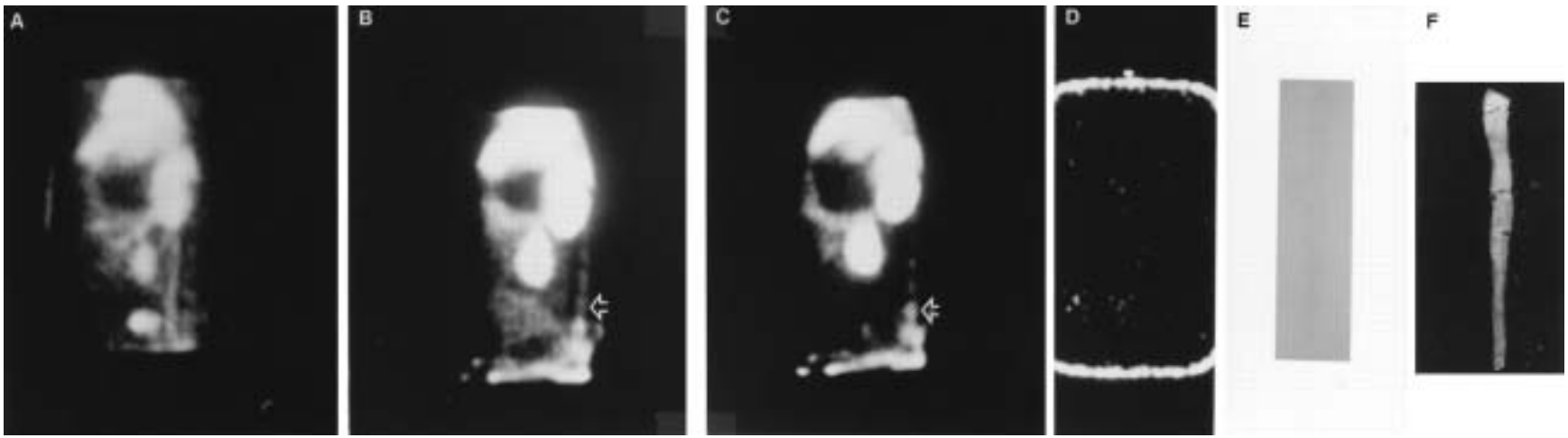
Immediately Images

24 hours Images

48 hours Images

Autoradiograph

In-111 chimeric Z2D3-73.30 F(ab')2

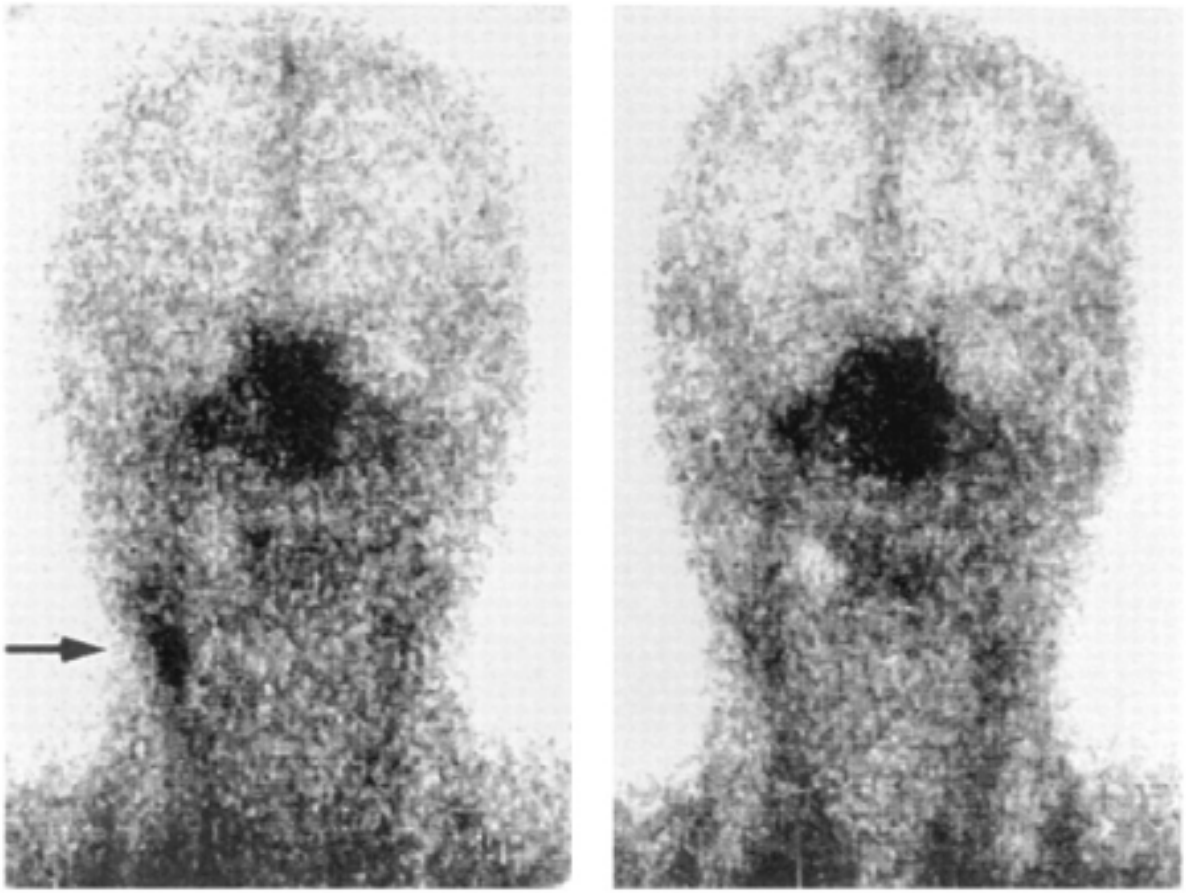


Radiotracers for Thrombus

- Thrombus in plaque means vulnerable.

- Targets:
  - platelet,
  - fibrinogen,
  - fibrinolytic molecules.

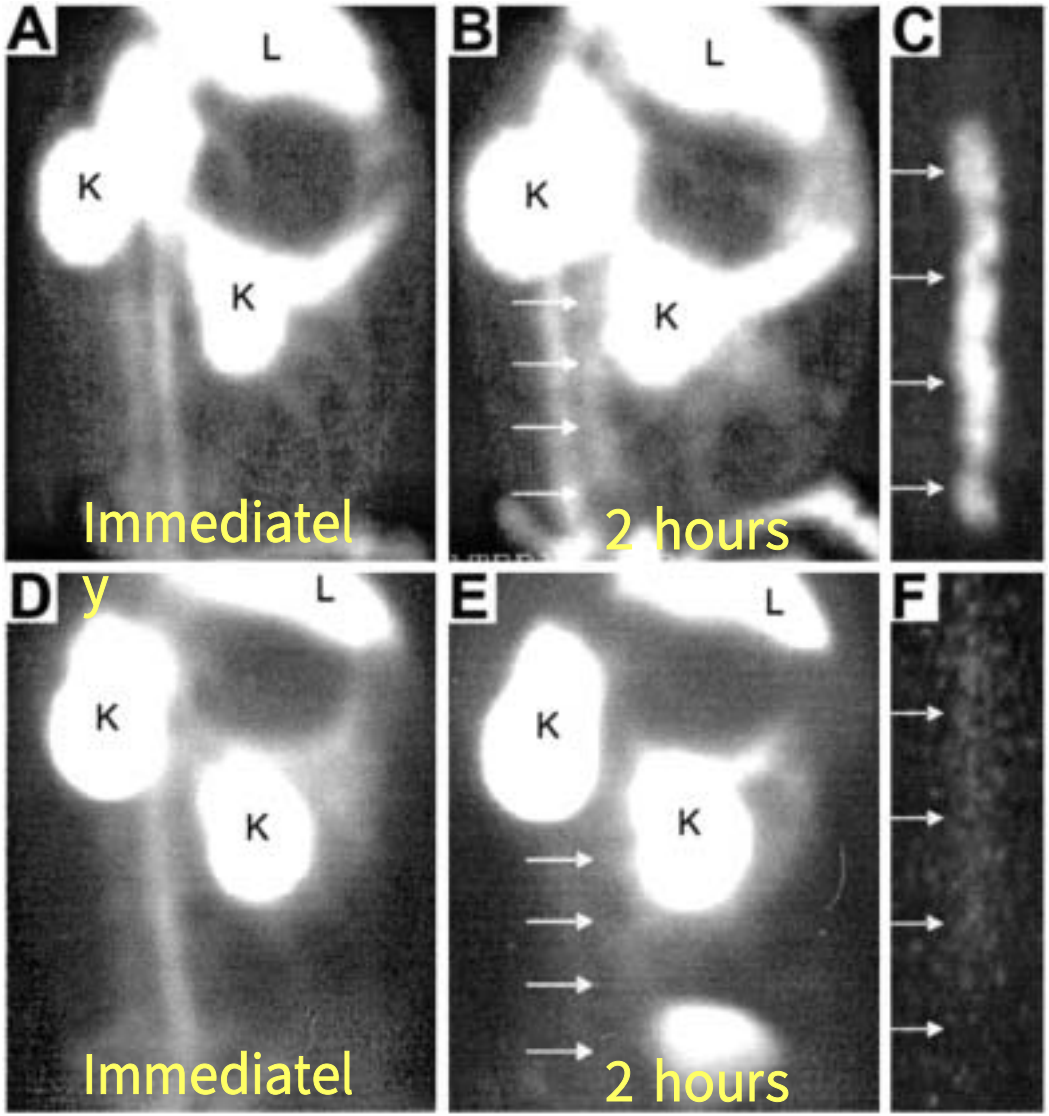
In-111 Platelet vs. Tc-99m HSA



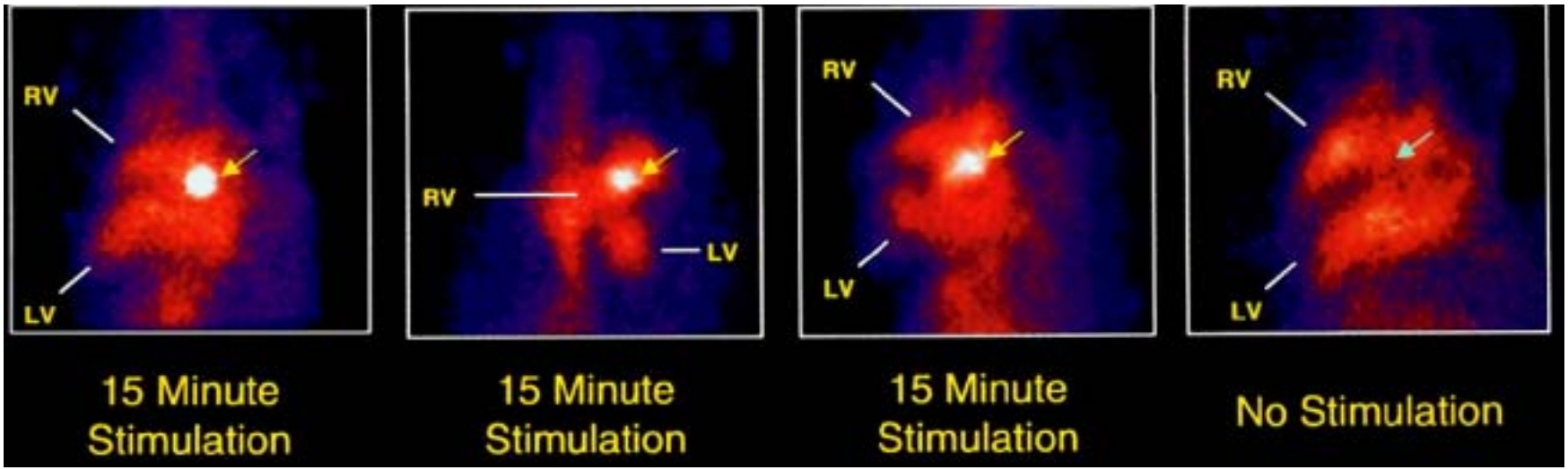
Radioiodinated fibrinogen

Slow fibrinogen accumulation with low fibrin content in arterial thrombus than venous thrombus.

99mTc-annexin V



Tc-99m DMP-444

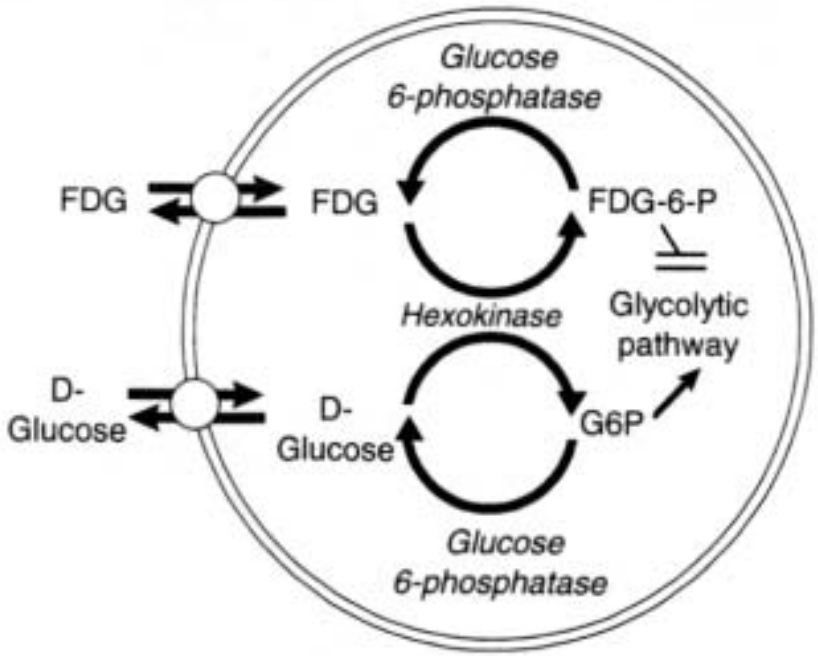


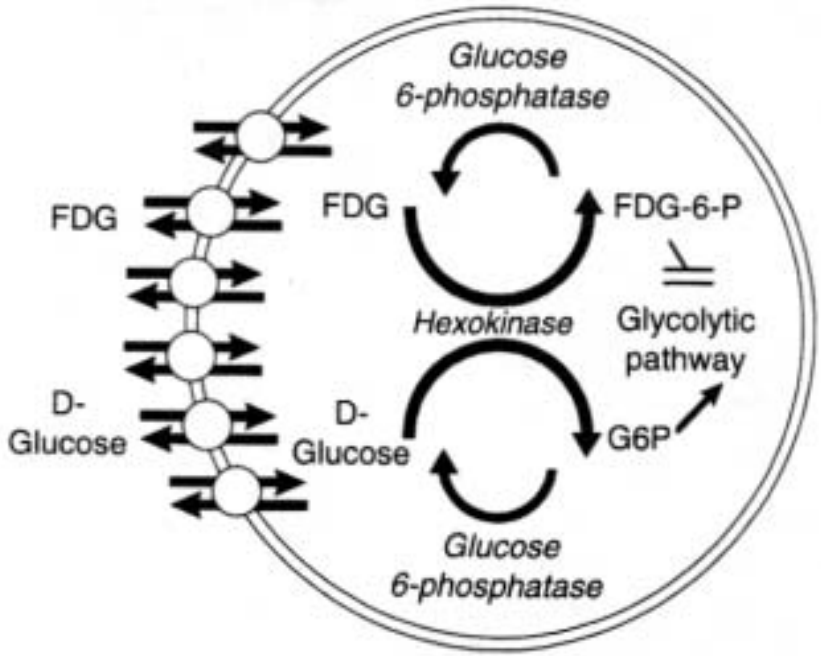
FDG-PET

- FDG accumulates in cancer cells due to their increased glucose metabolism.
- However, inflammatory cells such as activated lymphocytes, neutrophils and macrophages have increased glucose utilization.

NORMAL

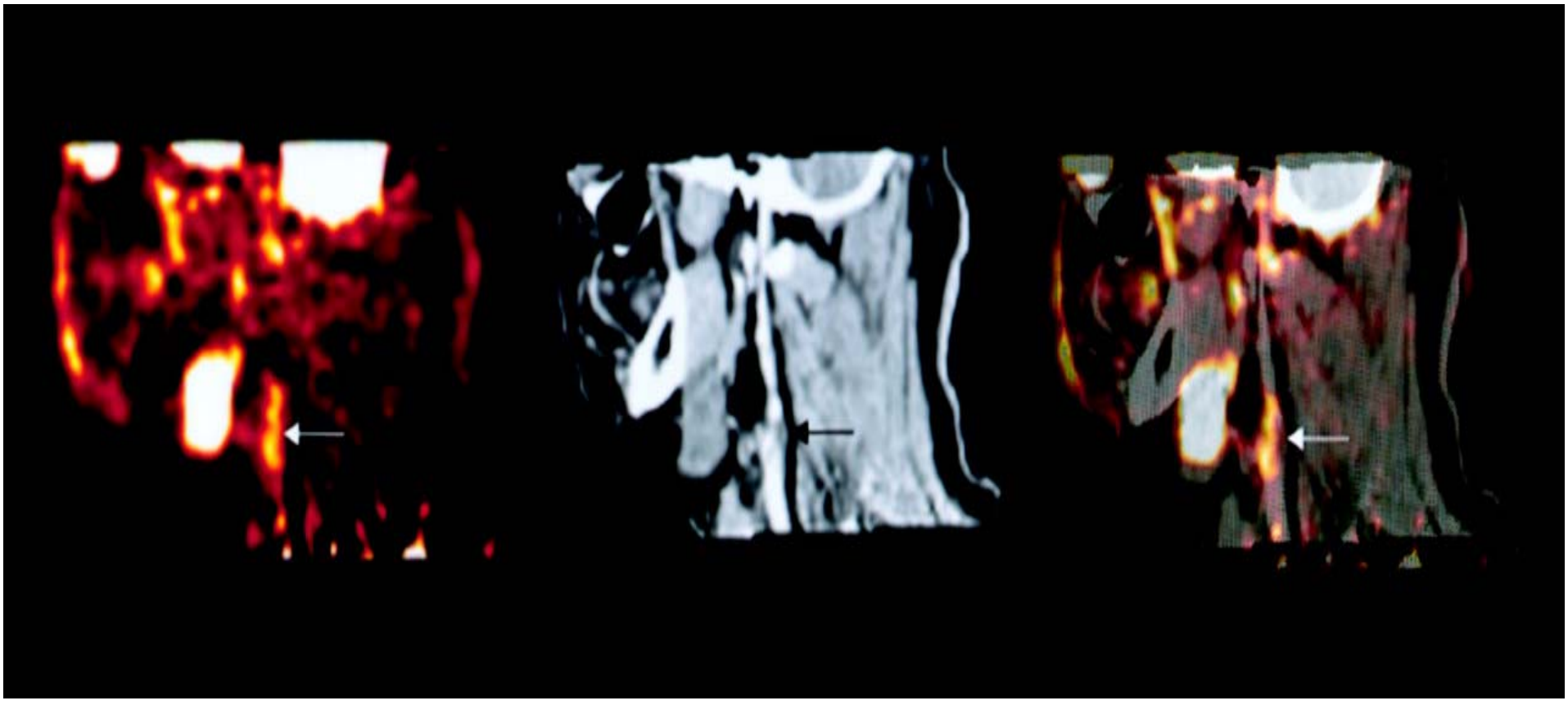
TUMOR

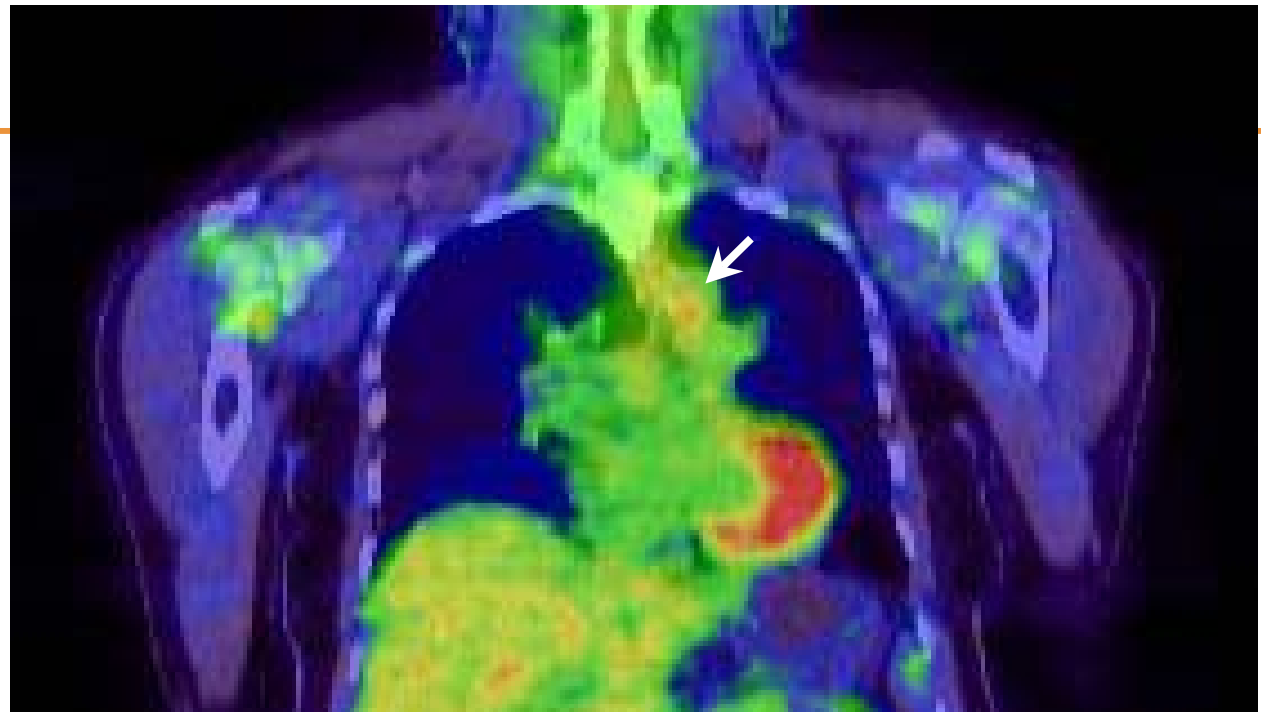


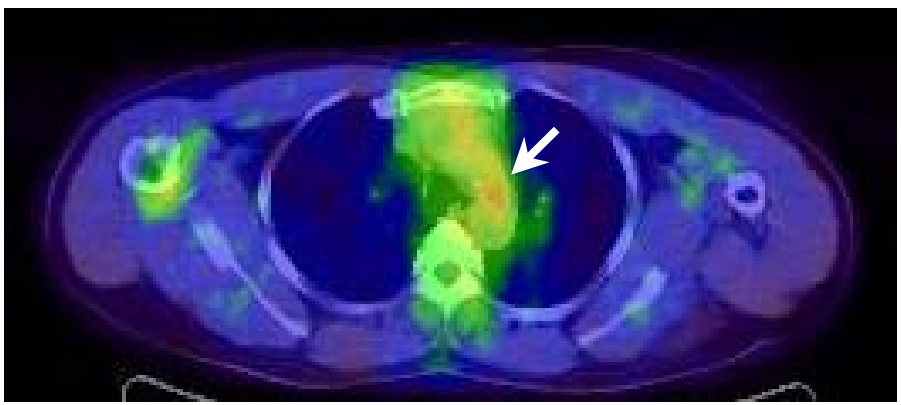


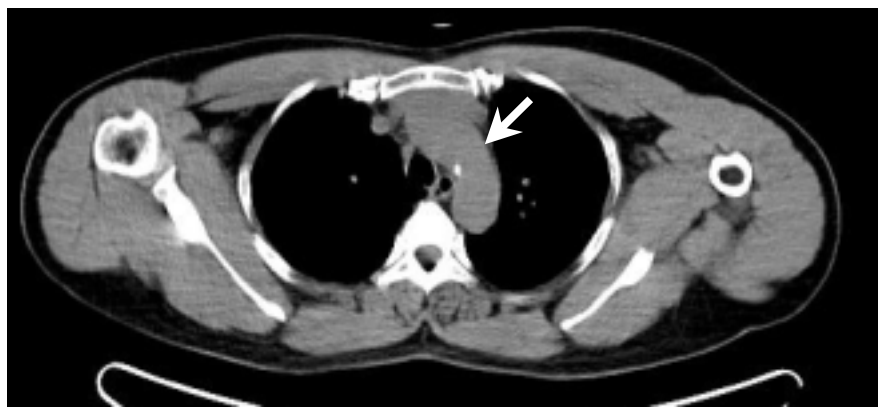
- Overexpression of Glucose transporters
- Higher levels of Hexokinase
- Down-regulation of Glucose-6-phosphatase
- Anaerobic glycolysis, less ATP per glucose molecule, more glucose molecules needed for ATP production
- General increase in metabolism from high growth rates

FDG-18 PET/CT









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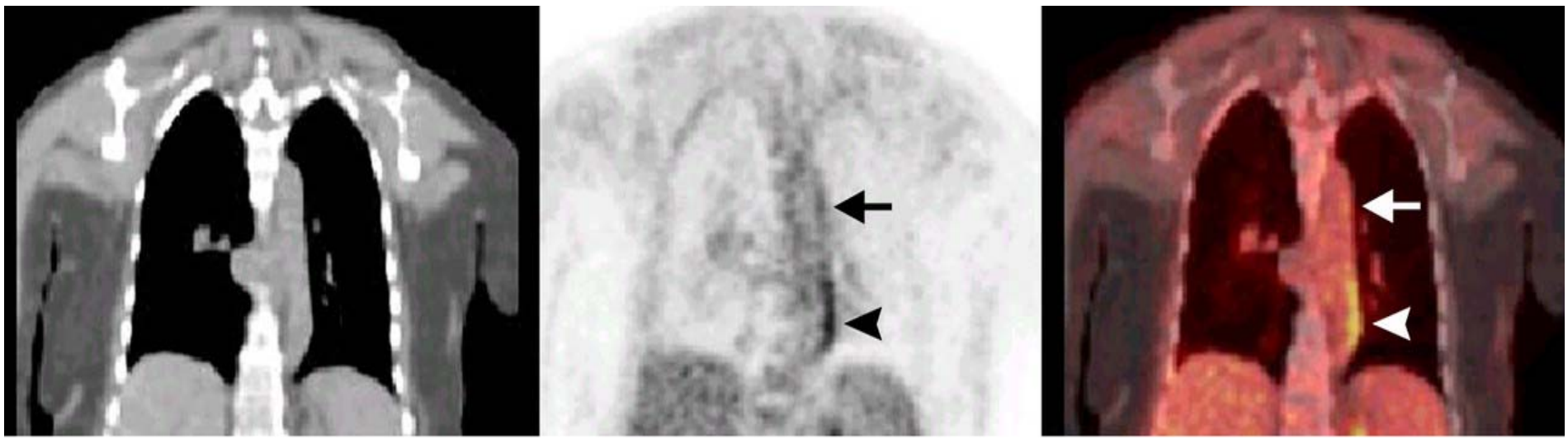

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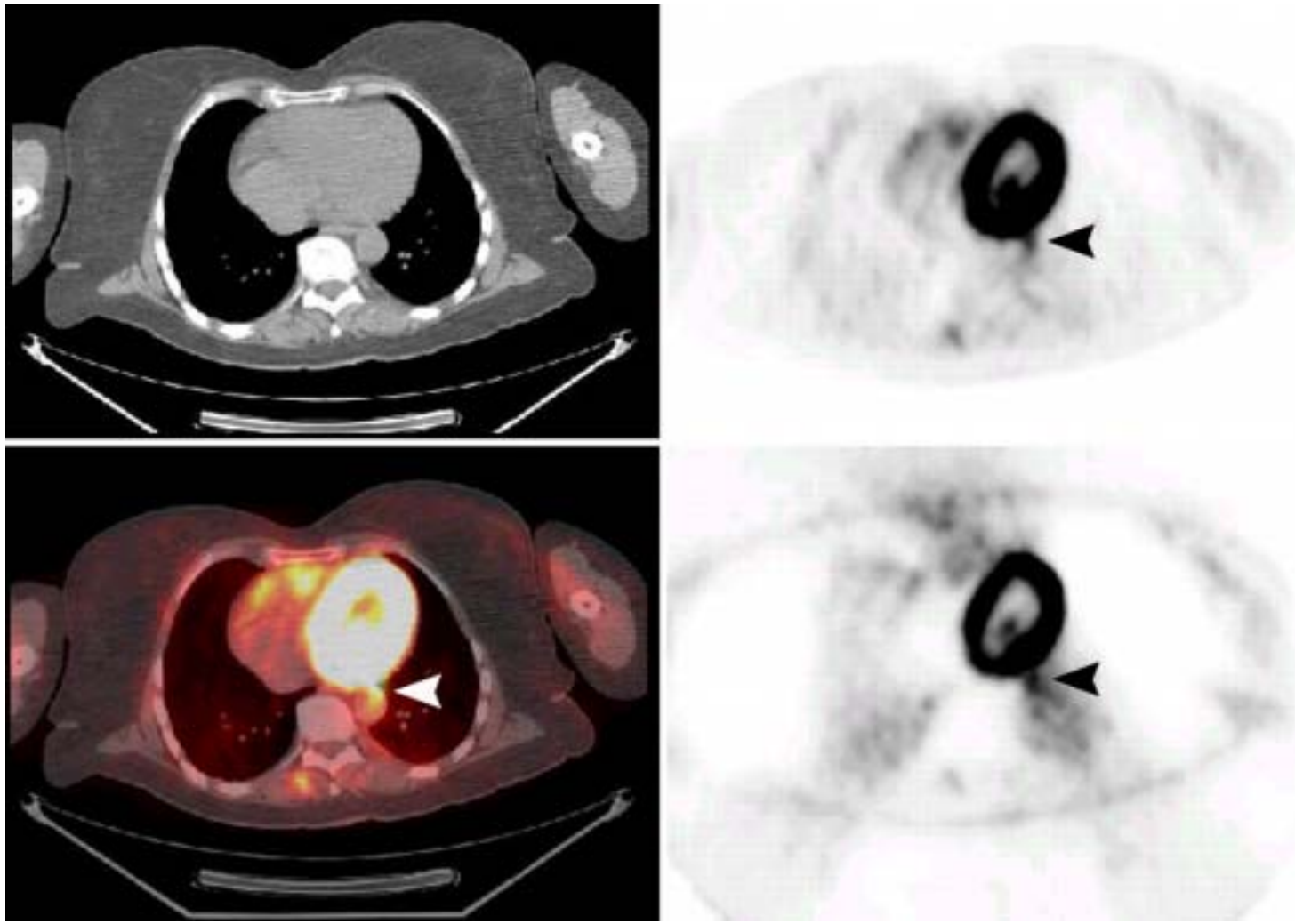

PK 11195

- Macrophage specific ligand for PET.
- Bind to benzodiazepine receptors in mitochondrial membranes in macrophage.
- Can be used to detect coronary atheroma.

Conclusion

- IVUS and MRI can provide evaluate the plaque composition but not the inflammatory cell activity.
- Nuclear imaging can provide the information on the cellular,metabolic and molecular composition of the plaque.
- However, nuclear scanning technology and radiotracer should be further improve to get clear image.