Why does medial artery calcification lead to SAD? A numerical model based analysis of endothelial shear stress could explain
Disclosure
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No conflict of interest with this presentation
In the past, MAC was considered an innocent bystander. However, studies now demonstrate that MAC can be considered the **silent killer** of the cardiovascular system because MAC is a strong marker of future cardiovascular events and death.


MAC and elevated ABI are associated with foot ulcer, occlusive PAD and lower limb amputations.
Risk factors for CLTI
Odds Ratio (95% CI)

SAD is strongly and independently associated with CLTI and must be considered the main actor in CLTI.

The power of PAD in leading to CLTI is stronger in small vessels.
SAD & MAC are the same disease! From now on I will talk about SAD-MAC
A relevant decrease in the thickness of the media occurs; this apparent reduction is due to the fact that the calcification takes place on degenerated muscle fibers that are no longer contractible and slack.

In the highest degrees of MAC, the artery is transformed into a rigid tube..., on such vessels there is usually a diffuse intimal overgrowth.

I am unable to prove whether the secondary intimal growth in pure MAC can lead to obliteration of the vessel; but some of my cases make it likely.
The most common findings were calcification of the media (72% of arteries) and intimal thickening without lipid (68% of arteries), with the presence of atheromas in only 23% of arteries. Intimal calcification occurred in 43% and was generally much less extensive than medial calcification. Nonatheromatous intimal thickening was frequently severe, resulting in complete occlusion in some vessels.

The majority of arteries in patients with PAD have a vascular lesion that is distinct from atherosclerosis, suggesting a different pathogenesis. The bulk of vascular calcification in the lower extremities is medial rather than intimal.
Anatomo-pathological study on amputated limbs (20) due to CLTI – preliminary results
Atherosclerosis disappears in BTK while MAC is homogeneously diffuse.
MAC is significantly associated with IT

P < .02
IT (Intimal thickening)

Obstructive IT
(≥ 50% lumen)

IT is non-obstructive in SFA-POP, highly obstructive in BTK & FOOT
MAC → IT → SAD?

Is it possible to explain this association with pure hemodynamic forces?

1. Does endothelial shear stress (SS) play a key role?

2. Are arterial fractures important?
Preliminary results of a computational model-based analysis of endothelial SS of the lower limb arterial tree

3 cm element

\[
C \frac{dV}{dt} = I_1 - I_2
\]

\[
V_1 - V_2 = L \frac{dI}{dt} + R \cdot I
\]
Shear Stress (SS) set point

Endothelium constantly senses SS magnitude, pulsatility, and directional characteristics and compare it with a pre-existing value, the SS set point; any deviation from this value activates remodeling mechanisms to alter vessel diameter, maintain proper perfusion of tissue and return SS to the steady-state level.

1. Normal SS

Under physiologic conditions (laminar flow), the mean SS is remarkably constant, 10–15 dynes/cm$^2$, whatever the part of the arterial network considered.

2. High SS

High SS (>15 dynes/cm$^2$), as found in faster laminar flow, promotes outward remodeling (dilatation and expansion of the luminal radius $\rightarrow$ returning SS to a lower level)

3. Low SS

Low SS (<4 dynes/cm$^2$) or changing shear stress direction as found in turbulent flow leads to inward remodeling and IT with reduction of the inner radius and returning SS to a higher level. It has a strong pro-atherosclerotic effect.
Normal arterial tree

MAC development
Progressive loss of elasticity, increase of vessel stiffness

Failure of the cushion function of the elastic arterial system

Standard transmission of blood flow from heart to peripheral tissues: the cushion effect of elastic arteries permits a slow pulsatile laminar peripheral flow

The pulse wave becomes:
- Shorter + higher + faster
- Pulsatility is transmitted more distal: smaller vessels are pulsating

“Hummer pulse effect” in small arteries changes shear stress
The higher the stiffness, the higher the SS in small vessels.

SS % changes according to different vessel stiffness

-50% 0% 50% 100% 150% 200%

**SFA-POP**

**BTK**

**FOOT**

- Stiffness x 2.5
- Stiffness x 5
1. Does endothelial shear stress (SS) play a key role?

   The high SS could induce vessel growth which constricts within the MAC shell $\rightarrow$ IT could be the result.

2. Are arterial fractures important?
When an artery suffers advanced calcification acute flexion may fracture some of the calcareous rings, particularly when the tortuous course of the vessel does not permit it to move readily nor to adapt a more easy curve in the surrounding tissues. These processes of repair are not uncommonly accompanied by the formation of bone at the ends of the broken calcareous rings.
1. Does endothelial shear stress (SS) play a key role? The high SS could induce vessel growth which constricts within the MAC shell → IT could be the result

2. Are arterial fractures important? Arterial stiffness could be associated with arterial fractures leading to IT, stenosis, turbulence & thrombosis