Media artery calcification (MAC) and its relevance for wound healing and limb salvage

Vincenzo Foppa, 1462
“The miracle of the salvaged foot”
Cappella Portinari, S. Eustorgio Church
Milan, Italy
Disclosure

Roberto Ferraresi, MD

In the last 2 years I have the following potential conflicts of interest to report:

**Consultant:** Medtronic, Abbott, Boston Scientific, Contract Medical International, Cook, Asahi, Ivascular, Biotronik, Limflow, Spectranetics, Shire, Kardia, Astra Zeneca, Orbus, Bard, Philips, Volcano, Novena, Angiodroid, M&L Healthcare, VOTIS

**Virtual shareholder:** Limflow
<table>
<thead>
<tr>
<th>Aggregated segments</th>
<th>Risk factors for CLTI</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG</td>
<td></td>
<td>0.53 (0.26 - 1.1)</td>
</tr>
<tr>
<td>SFA</td>
<td></td>
<td>0.51 (0.29 - 0.89)</td>
</tr>
<tr>
<td>P-TPT</td>
<td></td>
<td>1.17 (0.68 – 2.01)</td>
</tr>
<tr>
<td>Prox BTK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 artery ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 artery</td>
<td>1.7 (0.76 - 3.83)</td>
<td></td>
</tr>
<tr>
<td>2 arteries</td>
<td>1.86 (0.72 - 4.83)</td>
<td></td>
</tr>
<tr>
<td>3 arteries</td>
<td><strong>4.84 (1.12 - 20.88)</strong></td>
<td></td>
</tr>
<tr>
<td>Dist BTK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 artery ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 artery</td>
<td>1.69 (0.74 - 3.87)</td>
<td></td>
</tr>
<tr>
<td>2 arteries</td>
<td><strong>5.81 (1.91 - 17.62)</strong></td>
<td></td>
</tr>
<tr>
<td>3 arteries</td>
<td><strong>5.71 (1.03 - 31.78)</strong></td>
<td></td>
</tr>
<tr>
<td>BTA vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of BTA and Arch</td>
<td></td>
<td><strong>13.25 (1.69 - 104.16)</strong></td>
</tr>
</tbody>
</table>

SAD is strongly and independently associated with CLTI, diabetes and dialysis and must be considered as a leading actor in CLTI.
BAD → transmission failure

SAD → distribution failure
SAD-score

No SAD
Absence of disease or mild disease with a well-represented network of forefoot and calcaneal arteries

Moderate SAD
Diffuse disease with narrowing and poverty of arch, metatarsal, digital and calcaneal arteries

Severe SAD
Occlusion or severe disease with extreme poverty of arch, metatarsal, digital and calcaneal arteries
SAD-score is difficult to obtain!

- Contrast dye/multiple injections
- Movement artifacts
- Spasm/slow flow

- Is it really a desert foot or an angiographic technical failure?

- We can get a realistic SAD-score only in a minority of pts

- The operators’ evaluation is subjective

We need something easier, reproducible, and feasible in every pt!
What is MAC?

MAC, also known as Mönckeberg's medial sclerosis, occurs independently of atherosclerosis and is strongly associated with aging, DM and CKD. MAC tends to affect the artery diffusely, appearing as a linear contiguous rail-track pattern of calcification on plain radiography.

MAC is a strong marker of future cardiovascular events and death


MAC & PAD are strongly associated

MAC and elevated ABI are associated with foot ulcer, occlusive PAD and amputation


N. Narula et al., “Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia,” J. Am. Coll. Cardiol., vol. 72, no. 18, pp. 2152–2163, 30 2018


Abstract
Medial arterial calcification (MAC) is a known risk factor for cardiovascular morbidity. The association between vascular calcifications and poor outcome in several vascular districts suggest that infrapopliteal MAC could be a risk factor for lower-limb amputation (LLA). This study’s objective is to review the available literature focusing on the association between infrapopliteal MAC and LLA in high-risk patients. The PubMed and Embase databases were systematically searched. We selected original studies reporting the association between infrapopliteal MAC and LLAs in patients with diabetes and/or peripheral artery disease (PAD). Estimates were pooled using either a fixed-effects or a random-effects model meta-analysis. Heterogeneity was evaluated using the Q and I² statistics. Publication bias was investigated with a funnel plot and Egger test. The trim-and-fill method was designed to estimate the possibly missing studies. Influence analysis was conducted to search studies influencing the final result. Test of moderators was used to compare estimates in good versus non-good-quality studies. Fifteen articles satisfied the selection criteria (n = 6489; median follow-up: 36 months). MAC was significantly associated with LLAs (pooled adjusted risk ratio (RR): 2.27; 95% CI: 1.89–2.74; I² = 25.3%, Q-test: p = 0.17). This association was kept in the subgroup of patients with diabetes (RR: 2.37; 95% CI: 1.76–3.20) and patients with PAD (RR: 2.48; 95% CI: 1.72–3.58). The association was maintained if considering as outcome only major amputations (RR: 2.11; 95% CI: 1.46–3.06). Our results show that infrapopliteal MAC is associated with LLAs, thus suggesting MAC as a possible new marker of the at-risk limb.
The wrong concept:
MAC as a non-obstructive disease

Despite this strong association between MAC and PAD, the interaction in determining the clinical manifestations of the disease is still unknown, essentially because MAC is considered by most authors a “non-obstructive” disease.

However, in our daily practice in treating CLTI pts, we very often observe the coexistence of SAD & MAC.
In our daily practice we observe a strong association between SAD & MAC
A Novel Scoring System for Small Artery Disease and Medial Arterial Calcification Is Strongly Associated With Major Adverse Limb Events in Patients With Chronic Limb-Threatening Ischemia

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLTI pts</strong></td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>74 yy</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>76%</td>
</tr>
<tr>
<td>DM</td>
<td>191</td>
<td>86%</td>
</tr>
<tr>
<td>ESRD-HD</td>
<td>53</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Limbs</strong></td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>Wifl-WOUND 1</td>
<td>37</td>
<td>14%</td>
</tr>
<tr>
<td>Wifl-WOUND 2</td>
<td>198</td>
<td>77%</td>
</tr>
<tr>
<td>Wifl-WOUND 3</td>
<td>24</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Mean FU</strong></td>
<td>19 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3-59)</td>
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</tbody>
</table>
MAC-score

- 5-steps MAC-score
- Simple foot X-ray: latero-lateral and antero-posterior
- Look for “rail-tracking” calcification length
Sum all points up

1. 2 cm?  yes = 1 or no = 0
2. yes = 1 or no = 0
3. yes = 1 or no = 0
4. ≥ 1 cm? yes = 1 or no = 0
5. yes = 1 or no = 0

0-1 = no MAC
2-3 = moderate MAC
4-5 = severe MAC

Ferraresi et al, JEVT 2020
Distribution in 259 CLTI-limbs

MAC-score

- Severe MAC: 44%
- Moderate MAC: 35%
- No MAC: 21%

SAD-score

- Severe SAD: 45%
- Moderate SAD: 29%
- No-SAD: 26%
MAC-score versus SAD-score

<table>
<thead>
<tr>
<th>MAC-score</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 no-MAC</td>
<td>100 %</td>
<td>98.1 %</td>
</tr>
<tr>
<td>2-3 moderate MAC</td>
<td>99.1 %</td>
<td>92.7 %</td>
</tr>
<tr>
<td>4-5 severe MAC</td>
<td>100 %</td>
<td>98.1 %</td>
</tr>
</tbody>
</table>

Ferraresi et al, JEVT 2020
MAC-score versus SAD-score

SAD & MAC are the same disease!
From now on I will talk about SAD-MAC

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Healing rate

By MAC score groups

![Graph showing healing rate by MAC score groups.]

Group 0 vs 1 P < 0.023
Group 0 vs 2 P < 0.001
Group 1 vs 2 P < 0.007

By SAD score groups

![Graph showing healing rate by SAD score groups.]

Group 0 vs 1 P > 0.366
Group 0 vs 2 P < 0.001
Group 1 vs 2 P < 0.014

Groups (24 months)
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing rate (%)</td>
<td>79.9</td>
<td>59.4</td>
<td>33.2</td>
</tr>
<tr>
<td>N. at risk</td>
<td>5</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>St. error (%)</td>
<td>6.8</td>
<td>6.1</td>
<td>5.0</td>
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Groups (24 months)
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing rate (%)</td>
<td>65.6</td>
<td>57.2</td>
<td>41.8</td>
</tr>
<tr>
<td>N. at risk</td>
<td>12</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>St. error (%)</td>
<td>6.7</td>
<td>6.4</td>
<td>5.7</td>
</tr>
</tbody>
</table>

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Limb salvage

By MAC score groups

By SAD score groups

Ferraresi et al, JEVT 2020
Survival

By MAC score groups

By SAD score groups

Ferraresi et al, JEVT 2020
FF unscheduled podiatric surgical reintervention

By MAC score groups

By SAD score groups

The “salami” effect!

Ferraresi et al, JEV 2020
FF redo-revascularization

By MAC score groups

By SAD score groups

The “DRG factory”

Ferraresi et al, JEVt 2020
FF MALEs

By MAC score groups

Group 0 vs 1 P .007
Group 0 vs 2 P .001
Group 1 vs 2 P .065

By SAD score groups

Group 0 vs 1 P .027
Group 0 vs 2 P .001
Group 1 vs 2 P .06

Groups (24 months) 0 1 2
Freedom from MALEs (%) 53.6 31.4 22.1
N. at risk 11 9 7
St. error (%) 8 6 4.5

Groups (24 months) 0 1 2
Freedom from MALEs (%) 48.7 28.4 21.9
N. at risk 12 5 10
St. error (%) 7.3 6.3 4.4

Ferraresi et al, JEVT 2020
## Cox regression multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Complete healing</th>
<th>Redo foot surgical reintervention</th>
<th>Redo revascularization</th>
<th>Major amputation</th>
<th>Survival</th>
<th>MALEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
<td><strong>OR / IC95% / P value</strong></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1.05 / 0.64–1.72 / 0.84</td>
<td>0.58 / 0.29-1.16 / 0.12</td>
<td>1.43 / 0.83-2.47 / 0.19</td>
<td>0.89 / 0.34-2.32 / 0.82</td>
<td>1.85 / 0.95-3.58 / 0.06</td>
<td>0.74 / 0.44-1.23 / 0.24</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td>1.34 / 0.87–2.05 / 0.17</td>
<td>1.42 / 0.9-2.23 / 0.12</td>
<td>1.48 / 0.91-2.41 / 0.11</td>
<td><strong>2.56 / 1.23-5.34 / 0.012</strong></td>
<td>1.68 / 0.89-3.17 / 0.1</td>
<td><strong>1.65 / 1.11-2.45 / 0.013</strong></td>
</tr>
<tr>
<td><strong>WIFI-Wound 2</strong></td>
<td>0.98 / 0.58–1.65 / 0.94</td>
<td>1.09 / 0.62-1.93 / 0.7</td>
<td>0.6 / 0.36–1.01 / 0.051</td>
<td>1.77 / 0.53-5.84 / 0.34</td>
<td>1.23 / 0.53-2.82 / 0.62</td>
<td>0.93 / 0.59-1.44 / 0.73</td>
</tr>
<tr>
<td><strong>WIFI-Wound 3</strong></td>
<td>1.72 / 0.84-3.53 / 0.14</td>
<td><strong>2.26 / 1.01-5.04 / 0.04</strong></td>
<td>0.66 / 0.29-1.54 / 0.34</td>
<td>1.75 / 0.34-8.97 / 0.5</td>
<td>2.3 / 0.78-6.8 / 0.13</td>
<td>1.26 / 0.64-2.49 / 0.5</td>
</tr>
<tr>
<td><strong>MAC score 1</strong></td>
<td>1.36 / 0.75-2.45 / 0.3</td>
<td>1.82 / 0.93-3.53 / 0.07</td>
<td><strong>2.78 / 1.47-5.25 / 0.002</strong></td>
<td>3.02 / 0.86-10.63 / 0.08</td>
<td>0.94 / 0.4-2.22 / 0.89</td>
<td><strong>1.87 / 1.14-3.09 / 0.014</strong></td>
</tr>
<tr>
<td><strong>MAC score 2</strong></td>
<td>1.64 / 0.9-3.0 / 0.1</td>
<td><strong>2.96 / 1.53-5.73 / 0.001</strong></td>
<td><strong>2.57 / 1.32-4.97 / 0.005</strong></td>
<td>2.68 / 0.74-9.65 / 0.13</td>
<td>1.73 / 0.77-3.88 / 0.18</td>
<td><strong>2.24 / 1.33-3.75 / 0.002</strong></td>
</tr>
</tbody>
</table>

Ferraresi et al, JEVT 2020
SAD-MAC is a single non-atherosclerotic disease and must be considered the leading actor in CLTI. CLTI-pts with high SAD-MAC scores present at 2yy:
- only 30% healing rate
- double risk of major amputation and death
- higher rate of foot and vascular reinterventions

These no-option CLTI pts should be considered for alternative therapies such as:
- primary major amputation
- palliative care
- foot vein arterialization

In the last 50 yy our attention was focalized on pure atherosclerotic BAD-PAD, for which we developed wonderful weapons: bypass, PTA, drugs. Now we are facing a worldwide epidemic of old/DM/CKD CLTI pts that are not pure-BAD-PAD.