The Clinical Utility Of Flow-Mediated Dilation In Systemic Sclerosis

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Evidence-Based Medicine


Background

1. Raynaud's phenomenon is a nearly universal feature in systemic sclerosis (SSc, scleroderma).
2. SSc vasculopathy can result in critical ischemia and digital ulcer (DU).
3. Non-invasive vascular measurements for monitoring vascular progression and response to vasodilators in SSc are needed.

Flow-Mediated Dilation (FMD) Approach

1. In human subjects there are two ways to assess endothelial function:
   - Placement of an arterial catheter and infusion of endothelial agonists.
   - Another simpler, non-invasive, method uses a mechanical stimulus to evoke an endothelial dependent dilation, which is FMD.
2. FMD Approach:
   - Inflating a cuff on a limb to a supra-systolic external pressure for temporary ischemia.
   - After rapid deflation of the cuff, measurement of the dilation in a segment of an artery proximal to the occlusion.
   - The ischemia-evoked dilation of resistance vessels distal to the occlusion:
     - Produces hyperemia in the proximal conduit arteries that can be properly quantified.
     - Peripheral conduit arteries dilate in response to the physiological stimulus of intravascular shear stress.
   - FMD has been used in SSc:
     - Do not adhere to current practice guidelines for established researchers in the area.

Objective:

The objective of this current study was to use guideline compliant FMD in the clinical setting:

1) To examine SSc and healthy control differences.
2) To evaluate the correlation of clinical features in SSc to FMD parameters.
3) Inform its use for monitoring therapeutic response.

Disclosures

1. I have no conflicts of interests.
FMD Procedure:

SSc Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SSc (n=43)</th>
<th>HC (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean)</td>
<td>55.7±14.1</td>
<td>27.9±5.4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>14 (33)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (11)</td>
<td>4 (8)</td>
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<tr>
<td>Other</td>
<td>24 (56)</td>
<td>30 (59)</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>25.3±5.3</td>
<td>20.9±3.0</td>
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<tr>
<td>Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (14)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>No</td>
<td>37 (86)</td>
<td>48 (94)</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>25.3±5.3</td>
<td>20.9±3.0</td>
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<tr>
<td>Scleroderma Subtype</td>
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<td></td>
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<tr>
<td>Early</td>
<td>6 (14)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Limited</td>
<td>5 (12)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>5 (12)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>mRSS (mean)</td>
<td>33 (10)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>ANA</td>
<td>1 (2)</td>
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</tr>
<tr>
<td>DU</td>
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<tr>
<td>SRC</td>
<td>26 (59)</td>
<td>31 (61)</td>
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<tr>
<td>PAH</td>
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<td>0 (0)</td>
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<tr>
<td>mRSS</td>
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<td>0.5±0.5</td>
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<tr>
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<td>21 (41)</td>
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<tr>
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<td>30 (59)</td>
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<tr>
<td>Enopausal status matched</td>
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<td>19 (37)</td>
</tr>
<tr>
<td>Leaner (p=0.01)</td>
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</table>

Baseline differences

- SSc patients had increased forearm flow and significantly decreased brachial artery diameter at baseline
  - 39 SSc on calcium channel blockers
  - 5 SSc on phosphodiesterase inhibitors
  - 3 SSc on endothelin receptor antagonists
  - 2 SSc on prostacyclin analogs

Statistical Analysis

- Differences between SSc and healthy control (HC):
  - Student’s t-test for continuous variables
  - Chi-squared analysis for categorical variables

- Differences between SSc with and without digital ulcer (DU):
  - Determined by one-way ANOVA

- For repeated FMD in SSc
  - Paired t-test

- Pearson correlation analysis was used to assess bivariate relations between the change in %FMD and the change in variables that could influence FMD.

- All FMD measurements were adjusted for differences in age and BMI between SSc and HC.

- Significance was set at P<0.05

Cuff deflation measurements:

Vascular Function by DU:
Clinical Utility for DU Follow-up:
6 patients at 4 months

SSc Patient (red):
• Low baseline flow, peak hyperemia, and FMD
• Developed an DU on follow measurement at 4 months

Limitations

- We did not stop vasodilator therapy in SSc patients.
- We did not minimize menstrual effect by only performing measurements on specific days during the menstrual cycle.
- We did not have comprehensive antibody testing on all subjects.

Conclusions

- FMD is a noninvasive, objectively measured parameter of SSc-vasculopathy.
- Our study demonstrates that selected measures determined in FMD testing are significantly abnormal in SSc patients.
- FMD parameters may predict those SSc patients at risk for DU.
- FMD warrants further study and validation in SSc:
  - Studies of end-stage vasculopathy.
  - Pharmacologic response to SSc therapeutics.

Acknowledgements

SSc patients
  - SSc Clinical Care Team
    - Anthony Donato Lab
      - Ashley Walker
      - Zachary Barrett-Okeefe
  - Funding:
    - CCTS KL2: Grant RULTR000105 (formerly UL1RR025764).

Questions?

PAH

- SSc patients with and without PAH had significant differences:
  - FMD maximum diameter (p=0.02)
  - Hyperemia AUC (p=0.04)
- Suggesting patients with PAH not only had smaller brachial arteries, but also perhaps less of an ability to dilate those small arteries.
- Peripheral reactive hyperemia and FMD measurements were not affected by use of PDE5-I, ERA, and/or PCA.
Previous FMD and SSc studies


