The Role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Diagnosis of Left-sided Endocarditis: Native vs Prosthetic Valves

De Camargo, et al

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Recommendations Guidelines ESC 2015:

(Prosthetic valve): ‘possible’ / ‘rejected’ but high level of clinical suspicion:
Repeat echocardiography + blood culture + other imaging techniques,
either for diagnosis of cardiac involvement (cardiac CT, \( ^{18} \text{F-FDG PET/CT} \)
or radiolabelled leucocyte SPECT/CT) or for imaging embolic events
(cerebral MRI, whole-body CT and/or PET/CT). Integration of results in
the ESC 2015 modified diagnostic criteria.

1. (...)

2. Prosthetic valve: abnormal activity around the site of implantation
by \( ^{18} \text{F-FDG PET/CT} \) (only if the prosthesis was implanted for >3
months) or radiolabelled leucocyte SPECT/CT: major criterion.

3. Recent embolic events or infectious aneurysms by imaging only (silent
events): minor criterion.
Study design / Methods

Retrospective cohort study in Brazil, 2014 - 2017

• Heart Institute (InCor), University of São Paulo Medical School (500 beds)
• Determination of 18F-FDG-PET/CT accuracy in cases of left-sided suspected endocarditis
• Histopathological Patterns of PET-positive and PET-negative (cohort) **AND pattern of PVE vs NVE** (145 patients: 32 cohort + 113 from the service database)
Patients: >14 years, suspected left-side IE

1. **Risk factor** (Valve disease, PV, previous IE, cyanotic congenital heart disease) + 1 of the following
   - “Inflammatory syndrome” (Fever >37.8°C or CRP >20mg/l or Leuk >12 000 mm3
   - New embolic event
   - Acute heart failure (due to valve regurgitation)

2. **FUO + new heart murmur or embolic event**
Diagnostic work up

- EKG, 3 blood cultures, TTE/TEE, culture of explanted valve tissue and 18F-FDG-PET/CT
- Definition of final diagnosis at discharge by multidisciplinary endocarditis team using mDC (excl. PET)
- 18F-FDG-PET/CT Analysis: Interpretation by 2 nuclear medicine physicians (blind to clinical data and diagnoses)
  - **Focal pattern**: positive for IE
  - **Diffuse pattern**: negative for IE
- Histopathological Analysis: Compared with PET-CT-results

**Probleme / Unklarheiten:**
1. Behandelnde Ärzte wahrscheinlich nicht verblindet hinsichtlich Ergebnisse PET
Diffuse
Focal
Results

Patients with suspected left-sided IE (n = 372)

Excluded (n = 54)
- Early death (<5 days, n = 6)
- Urgent surgery (<5 days, n = 21)
- Haemodynamic instability/respiratory distress (n = 27)

PET/CT performed (n = 318)

Excluded (n = 15)
- Increased physiologic uptake of $^{18}$F-FDG in the myocardium

Analyzed (n = 303)
Results

Analyzed (n = 303)

Cardiac Status

Prosthetic valve/ascending aortic tube (n = 188)
  ➢ Prosthetic valve only (n = 151)
  ➢ Ascending aortic tube (n = 14)
  ➢ Bentall de Bono graft (n = 23)

Native valve (n = 115)

Final Modified Duke Criteria Multidisciplinary Endocarditis Team

➢ Definite (n = 60)
➢ Possible (n = 28)
➢ Rejected (n = 100)

➢ Definite (n = 36)
➢ Possible (n = 10)
➢ Rejected (n = 69)
<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Prosthetic Valves/Ascending Aortic Prosthesis (n = 188)</th>
<th>Native Valves (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspected endocarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>58 ± 18 (14–87)</td>
<td>57 ± 17 (17–95)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>61% (114/188)</td>
<td>53% (61/115)</td>
</tr>
<tr>
<td>Prosthetic valves only</td>
<td>80% (151/188)</td>
<td>NA</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>75% (141/188)</td>
<td>NA</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>5% (10/188)</td>
<td>NA</td>
</tr>
<tr>
<td>Ascending aortic prosthesis</td>
<td>20% (37/188)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Echocardiography at admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transoesophageal</td>
<td>90% (170/188)</td>
<td>84% (97/115)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>60 ± 12 (18–79)</td>
<td>60 ± 12 (20–82)</td>
</tr>
<tr>
<td>Abscess/fistula/valve perforation</td>
<td>10% (18/188)</td>
<td>3% (4/115)</td>
</tr>
<tr>
<td>New periprosthetic valve leak</td>
<td>14% (21/151\textsuperscript{a})</td>
<td>NA</td>
</tr>
<tr>
<td>Vegetation on echocardiogram</td>
<td>24% (46/188)</td>
<td>31% (36/115)</td>
</tr>
<tr>
<td>Vegetation ≥10 mm</td>
<td>6% (12/188)</td>
<td>16% (18/115)</td>
</tr>
<tr>
<td></td>
<td>Prosthetic Valves/Ascending Aortic Prosthesis (n = 188)</td>
<td>Native Valves (n = 115)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Infective endocarditis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Modified Duke criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>47% (88/188)</td>
<td>40% (46/115)</td>
</tr>
<tr>
<td>Final definite</td>
<td>68% (60/88)</td>
<td>78% (36/46)</td>
</tr>
<tr>
<td>Final possible</td>
<td>32% (28/88)</td>
<td>22% (10/46)</td>
</tr>
<tr>
<td>Histologically proven endocarditis</td>
<td>36% (32/88)</td>
<td>41% (19/46)</td>
</tr>
<tr>
<td><strong>Causative pathogen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture positive for infective endocarditis</td>
<td>70% (62/88)</td>
<td>74% (34/46)</td>
</tr>
<tr>
<td>Coagulase negative <em>Staphylococcus</em></td>
<td>16% (10/62)</td>
<td>6% (2/34)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>11% (7/62)</td>
<td>24% (8/34)</td>
</tr>
<tr>
<td><em>Streptococcus spp.</em></td>
<td>44% (27/62)</td>
<td>47% (16/34)</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>8% (5/62)</td>
<td>15% (5/34)</td>
</tr>
<tr>
<td><em>Fungi</em></td>
<td>5% (3/62)</td>
<td>3% (1/34)</td>
</tr>
<tr>
<td><em>Haemophilus species, Aggregatibacter s hominis, Eikenella corrodens, and Kin.</em></td>
<td>8% (5/62)</td>
<td>3% (1/34)</td>
</tr>
<tr>
<td>Others</td>
<td>10% (6/62)</td>
<td>9% (3/34)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve surgery</td>
<td>45% (40/88)</td>
<td>43% (20/46)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>23% (20/88)</td>
<td>5% (10/46)</td>
</tr>
<tr>
<td></td>
<td>SE % (95% CI)</td>
<td>SP % (95% CI)</td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Prosthetic valves only (N = 151)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission echocardiography</td>
<td>60 (48-71)</td>
<td>95 (91-100)</td>
</tr>
<tr>
<td>PET/CT cardiovascular focal uptake</td>
<td>91 (84-98)</td>
<td>94 (89-99)</td>
</tr>
<tr>
<td>Admission DC*</td>
<td>42 (30-54)</td>
<td>88 (81-95)</td>
</tr>
<tr>
<td>Admission DC* + PET/CT major criteria</td>
<td>91 (84-98)</td>
<td>88 (81-95)</td>
</tr>
<tr>
<td><strong>Prosthetic valves / ascending aortic prosthesis (N = 188)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission echocardiography</td>
<td>59 (49-69)</td>
<td>96 (92-100)</td>
</tr>
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<td>PET/CT cardiovascular focal uptake</td>
<td>93 (88-98)</td>
<td>90 (84-96)</td>
</tr>
<tr>
<td>Admission DC*</td>
<td>41 (31-51)</td>
<td>90 (84-96)</td>
</tr>
<tr>
<td>Admission DC* + PET/CT major criteria</td>
<td>93 (88-98)</td>
<td>90 (83-95)</td>
</tr>
<tr>
<td><strong>Ascending aortic prosthesis only (N = 37)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Admission echocardiography</td>
<td></td>
<td></td>
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<tr>
<td>PET/CT cardiovascular focal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission DC*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission DC* + PET/CT major criteria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Echo results negative in 36/88 with PVE/AAPI vs. PET 2/88

**Probleme / Unklarheiten:**

1. «admission echo» → TTE oder TEE?
2. Vergleich DC bei admission mit finaler Diagnose (BK ausstehend? Kein TEE?)
3. Sens./Spez. des PET abh. der postulierten Endokarditis (Possible + definite).
   - Follow up der «rejected»-Fälle?
   → Besser: Analyse nur mit «definite» + klar definiertes follow up um verpasste Diagnosen zu erfassen
<table>
<thead>
<tr>
<th>N</th>
<th>SE % (95% CI)</th>
<th>SP % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native valves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission echocardiography</td>
<td>115</td>
<td>70 (56-83)</td>
<td>93 (87-99)</td>
<td>86 (75-98)</td>
<td>82 (74-91) 83.5%</td>
</tr>
<tr>
<td>PET/CT cardiovascular focal uptake</td>
<td>115</td>
<td>22 (10-34)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>66 (57-75) 68.7%</td>
</tr>
<tr>
<td>Admission DC*</td>
<td>115</td>
<td>54 (40-69)</td>
<td>91 (85-98)</td>
<td>81 (67-95)</td>
<td>75 (66-84) 76.5%</td>
</tr>
<tr>
<td>Admission DC* + PET/CT major criteria</td>
<td>115</td>
<td>65 (51-79)</td>
<td>91 (85-98)</td>
<td>83 (71-96)</td>
<td>80 (71-89) 80.9%</td>
</tr>
<tr>
<td>Admission DC* + PET/CT major criteria + emboli**</td>
<td>115</td>
<td>78 (66-90)</td>
<td>91 (85-98)</td>
<td>86 (75-96)</td>
<td>86 (78-94) 86%</td>
</tr>
</tbody>
</table>
Histopathological results – 45 patients with suspected infectious endocarditis

Probleme / Unklarheiten:
1. Absolute Zahlen?
2. Mischbilder/Überschneidungen?
Histopathological results – 145 (32 study + 113 database) patients with histological proven infectious endocarditis

Probleme / Unklarheiten:
1. Absolute Zahlen?
2. Mischbilder/Überschneidungen?
Diskussion / Zusammenfassung

- «high accuracy for the diagnosis of IE in cases of PVE»

- «Low sensitivity in NVE»
  - «potential pathophysiologica](https://www.annualreviews.org/doi/10.1146/annurev-ecology-081319-093748)l explanation: PVE had a predominance of PMNC, while more extensive fibrotic tissues were noted in NVE ».

- «No effect on (false neg./pos.) results across different time intervals between valve implantation and PET-exam (small sample size)»
Diskussion / Limitationen

(Weitere) Limitationen:
• Keine klar definierten Kriterien des Aufnahmemusters von $^{18}$F-FDG-PET Sensitivität/Spezifität auf «possible + definite» bezogen (Anteil falsch positiver bei «possible»?)
• Keine Angaben zum Follow-up (Spezifität korrekt?)
• Angaben hinsichtlich Rekategorisierung «possible» auf «definite» oder «rejected»: Auf «admission» bezogen, nicht bei Entlassung
• Keine Angaben bez. Therapie (Therapeutische Konsequenz?); Teils keine absoluten Zahlen
• Bias bei wahrscheinlich fehlender Verblindung der behandelnden Ärzte hinsichtlich Ergebnisse PET-CT
• ESC: «Radiolabeled WBC SPECT/CT is more specific for the detection of IE and infectious foci than $^{18}$F-FDG PET/CT and should be preferred in all situations that require enhanced specificity»
Vielen Dank für die Aufmerksamkeit!
<table>
<thead>
<tr>
<th>Interval after prosthetic implant and PET/CT</th>
<th>N</th>
<th>SE % (95% CI)</th>
<th>SP % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>AC</th>
<th>LKR + (95% CI)</th>
<th>LKR - % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valves only</td>
<td>151</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 3 months</td>
<td>22</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 3 months and 12 months</td>
<td>25</td>
<td>100 (100)</td>
<td>90 (71-100)</td>
<td>94 (82-100)</td>
<td>100 (100)</td>
<td>96%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>104</td>
<td>88 (78-97)</td>
<td>93 (86-100)</td>
<td>91 (83-99)</td>
<td>90 (82-97)</td>
<td>90%</td>
<td>12.3 (4.7-31.7)</td>
<td>0.1 (0.06-0.3)</td>
</tr>
<tr>
<td>Prosthetic valves / ascending aortic prosthesis</td>
<td>188</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 3 months</td>
<td>32</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 3 months and 12 months</td>
<td>29</td>
<td>100 (100)</td>
<td>85 (65-100)</td>
<td>89 (74-100)</td>
<td>100 (100)</td>
<td>93%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>127</td>
<td>90 (83-98)</td>
<td>88 (79-96)</td>
<td>90 (83-98)</td>
<td>100 (100)</td>
<td>89%</td>
<td>7.3 (3.8-14.1)</td>
<td>0.1 (0.05-0.2)</td>
</tr>
</tbody>
</table>

**Antimicrobial treatment time before PET/CT**

| Prosthetic valves only                     | 151|                |               |               |               |         |                |                 |
| 0 to 3 months                              | 84 | 94 (87-100)    | 92 (84-99)    | 89 (80-99)    | 96 (90-100)   | 93%     | 11.3 (4.4-29.1)| 0.06 (0.02-0.2) |
| ≥ 7 e < 14 days                            | 46 | 84 (70-98)     | 96 (88-100)   | 95 (87-100)   | 86 (73-99)    | 89%     | 21.0 (3.1-144.4)| 0.17 (0.07-0.4) |
| ≥ 14 days                                  | 21 | 100 (100)      | 100 (100)     | 100 (100)     | 100 (100)     | 100%    | -              | -               |

| Prosthetic valves / ascending aortic prosthesis | 188|                |               |               |               |         |                |                 |
| 0 to 3 months                              | 105| 96 (90-100)    | 88 (80-96)    | 87 (77-96)    | 96 (91-100)   | 91%     | 7.9 (4.0-15.9) | 0.05 (0.01-0.19) |
| ≥ 7 e < 14 days                            | 56 | 85 (72-99)     | 93 (84-100)   | 92 (81-100)   | 87 (75-99)    | 89%     | 12.4 (3.2-47.5)| 0.16 (0.06-0.4) |
| ≥ 14 days                                  | 27 | 100 (100)      | 92 (78-100)   | 93 (81-100)   | 100 (100)     | 96%     | -              | -               |

| Native valves                             | 115|                |               |               |               |         |                |                 |
| 0 to 3 months                              | 58 | 50 (31-69)     | 100 (100)     | 100 (100)     | 71 (58-84)    | 67%     | -              | -               |
| ≥ 7 e < 14 days                            | 42 | 50 (19-81)     | 97 (91-100)   | 83 (54-100)   | 86 (75-97)    | 81%     | 16.0 (2.1-121.4)| 0.5 (0.3-1.0)   |
| ≥ 14 days                                  | 15 | 60 (30-90)     | 100 (100)     | 100 (100)     | 56 (23-88)    | 40%     | -              | -               |