Chronic thromboembolic pulmonary hypertension and totally implantable central venous access systems

To the Editor:

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by obstruction of the pulmonary arteries by unresolved, organised thrombi, with a concurrent microvasculopathy [1–3]. Several medical conditions are associated with the development of CTEPH, including lupus anticoagulant/antiphospholipid antibodies, splenectomy, chronic inflammatory disorders, cancer, ventriculoatrial shunts and infected cardiac pacemakers [3–5]. Patients with a clinical history of totally implantable central venous access systems (TICVAS) and CTEPH have been reported in expert CTEPH centres, but published data on this association are lacking. TICVAS are used for chronic intravenous treatment and for patients who require long-term intermittent vascular access. The main complications related to TICVAS are infection, thrombosis, catheter obstruction and migration [6]. Port-associated bloodstream infections are the most common complications, occurring in 5.6–8% of cases, with the primary microbiological pathogens isolated being *Staphylococcus epidermidis* and *Staphylococcus aureus* [6, 7].

In the present research letter, we report a large retrospective series of CTEPH patients with TICVAS who were diagnosed, treated and followed up in the French reference centre for pulmonary hypertension (PH) between January 2006 and January 2017. The diagnosis of CTEPH was established according to guidelines that were current during the observational period [1]. When a history of cancer was present, a remission time of more than 2 years was required for inclusion in the analysis. The assessment of operability and decisions regarding other treatment strategies were decided based on a consensus among a multidisciplinary team of experts including experienced thoracic surgeons, chest physicians and radiologists.

A case-control method (1:4 case:control ratio) was used to compare the prevalence of TICVAS in CTEPH patients with that of patients with idiopathic pulmonary arterial hypertension (IPAH) matched for age, sex and diagnosis period (±6 months). The prevalence of TICVAS was calculated for both groups and the 95% confidence intervals were determined. Baseline clinical and haemodynamic characteristics, management and peri-operative outcomes of CTEPH patients with TICVAS were then compared with those of CTEPH patients without TICVAS diagnosed during the same period. All data were collected from the French PH registry. This registry was established in accordance with French bioethics laws (Commission Nationale de l’Informatique et des Libertés), and all patients provided informed consent. Data are presented as mean±SD for continuous variables and number of subjects and percentage for categorical variables. Comparisons between groups were performed using the independent t-test. Categorical variables were compared using the Chi-square test for independence. The Kaplan–Meier method was used to estimate overall survival in patients with TICVAS. A p-value of <0.05 was considered to indicate statistical significance.

During the study period, 735 CTEPH patients were referred to our centre. Among them, 39 (5.3%; 95% CI 3.7–6.9%) had TICVAS at CTEPH diagnosis (51% female, mean age 56±12 years), as compared to a single case among 156 IPAH patients (0.6%; 95% CI 0–1.9%) matched for age, sex and diagnosis period (odds ratio 8.69; 95% CI 1.18–63.7; p=0.03). The mean interval between TICVAS placement and CTEPH diagnosis was 5.3±3.4 years. TICVAS were used to administer chemotherapy for cancer in 35 patients (89.7%), parenteral nutrition in two patients (5.1%), immunosuppressive treatment in one patient (2.6%)
and blood transfusions in one patient (2.6%). A history of pulmonary embolism was identified in six (15%) out of 39 patients. All TICVAS were removed at the time of CTEPH diagnosis and a microbiological examination was performed in 18 patients (46.1%). Port-related bloodstream infection was diagnosed in 10 out of 18 patients. Bacteriologically, the causative agents were \textit{S. epidermidis} (n=6), \textit{S. aureus} (n=3) and \textit{Micrococcus luteus} (n=1). In three patients, a diagnosis of catheter-related thrombosis was also made.

Baseline characteristics of CTEPH patients with and without TICVAS are summarised in table 1. CTEPH patients with TICVAS had significantly worse baseline haemodynamics and a higher proportion were in New York Heart Association (NYHA) functional class III and IV.

After multidisciplinary CTEPH team assessment, 15 (38%) out of 39 patients with TICVAS and 400 (56%) out of 696 patients without TICVAS were considered suitable candidates for pulmonary endarterectomy (PEA) \((p=0.02)\). Among the 15 operable patients with TICVAS, one died before surgery and 14 underwent PEA. Of the 14 operated patients, three died during the perioperative period resulting in a 21.4% mortality, as compared with 4\% in CTEPH patients without TICVAS \((p<0.01)\). At 6-months post-PEA, a significant improvement in NYHA functional class was observed in eight out of the 14 operated patients and there was also a significant decrease in pulmonary vascular resistance (PVR) \((\text{from 10.4±3.9 to 4.6±2 Wood units; } p=0.002)\).

24 (62\%) patients with TICVAS were deemed inoperable. Among them, 23 (96\%) were treated with pulmonary arterial hypertension (PAH) drugs (mostly with single (25\%) or dual (54\%) oral therapy). Three patients underwent balloon pulmonary angioplasty (BPA) in combination with PAH-targeted therapy and one patient was treated by BPA alone. At 6 months, there was a significant improvement in NYHA functional class in 19 out of the 24 treated patients and a significant reduction in PVR \((\text{from 12.3±3.9 to 7.4±2.5 Wood units; } p=0.001)\) was also noted. The estimated survival rate of CTEPH patients with TICVAS was 82\% and 78\% at 1 and 3 years, respectively.

The present study shows a significantly higher prevalence of TICVAS in CTEPH patients (5.3\%; 95\% CI 3.7–6.9\%) than in IPAH patients (0.6\%; 95\% CI 0–1.9\%), and therefore suggests an association between TICVAS and CTEPH. There is insufficient evidence to firmly consider TICVAS as a risk factor for developing CTEPH due to an unidentifiable number of device insertions in France and the lack of rigorous prospective studies. However, it seems plausible that long-term TICVAS may result in higher risk of catheter-related thrombosis, infection and inflammation, which may promote CTEPH. Indeed, bacterial cultures were positive for a \textit{Staphylococcal} pathogen in a significant proportion of studied cases. Moreover, some studies have shown that \textit{Staphylococcus} infection may be associated with septic emboli and may also be involved in thrombus non-resolution and fibrosis, thereby triggering the transition from fresh thromboembolic material to fibrotic tissue \([6, 8]\). There is also a growing body of evidence in support of inflammatory mediators in the pathogenesis of CTEPH, which have been found to be upregulated in

### TABLE 1 Baseline characteristics of chronic thromboembolic pulmonary hypertension (CTEPH) patients with or without totally implantable central venous access systems (TICVAS) diagnosed during the same period

<table>
<thead>
<tr>
<th>Baseline parameters</th>
<th>CTEPH with TICVAS</th>
<th>CTEPH without TICVAS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>39</td>
<td>696</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>4 (11)</td>
<td>278 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>27 (69)</td>
<td>369 (53)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8 (20)</td>
<td>49 (7)</td>
<td></td>
</tr>
<tr>
<td>6MWD m</td>
<td>307±134 (n=32)</td>
<td>333±144 (n=653)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean RAP mmHg</td>
<td>10±7</td>
<td>8±5</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean PAP mmHg</td>
<td>47±11</td>
<td>45±11</td>
<td>0.31</td>
</tr>
<tr>
<td>PAWP mmHg</td>
<td>7±3</td>
<td>9±4</td>
<td>0.05</td>
</tr>
<tr>
<td>Cardiac output L·min(^{-1})</td>
<td>3.8±1.3</td>
<td>4.5±1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiac index L·min(^{-1}·m(^{-2})</td>
<td>2.2±0.8</td>
<td>2.5±0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>PVR Wood unit</td>
<td>11±4</td>
<td>9±4</td>
<td>0.001</td>
</tr>
<tr>
<td>(SvO_2) %</td>
<td>55±10 (n=30)</td>
<td>61±9</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd, unless otherwise stated. NYHA: New York Heart Association; 6MWD: 6-min walking distance; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; \(SvO_2\): mixed venous oxygen saturation.
CTEPH patients, such as C-reactive protein, tumour necrosis factor-α, interleukin-6, interferon-γ-induced protein-10, macrophage inflammatory protein-1α, matrix metalloproteinase-9 and monocyte chemotactic protein-1 [9–13].

Our study also suggests that CTEPH patients with TICVAS have a more severe and a less frequently operable disease, compared with CTEPH patients without TICVAS. In addition, patients with TICVAS who underwent PEA have a substantially higher perioperative mortality than those without TICVAS. Similar observations have been previously reported in patients with other associated medical conditions such as ventriculoatrial shunt, infected pacemaker, splenectomy, inflammatory bowel disease and osteomyelitis [14].

The main limitation of the present study is its retrospective nature. In addition, the high prevalence of cancer may confound the association between TICVAS and CTEPH. However, all studied patients were in complete remission from their cancer for at least 2 years and no relapses were observed during follow-up.

In conclusion, long-term TICVAS implantation may contribute to the development of CTEPH and have a negative impact on perioperative survival after PEA. Clinicians should be aware of this potential late complication of TICVAS and early removal of TICVAS should be offered to patients with cancer in complete remission.

Mitja Jevnikar1,2,3, David Montani4,5, Laurent Savale1,2,3, Andrei Seferian1,2,3, Etienne-Marie Jutant1,2,3, Athénaïs Bouchy1,2,3, Mariana Preda1,2,3, Jason Weatherald4,5, Sophie Bulifon1,2,3, Florence Parent1,2,3, Philippe Brenot1,2,6, Elie Fadel1,2,7, Olivier Sibiton8,9, Gérald Simonneau1,2,3, Marc Humbert1,2,3,8 and Xavier Jais4,5,6,8

1Université Paris-Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France. 2INSERM UMR_S 999, “Pulmonary Hypertension: Pathophysiology and Novel Therapies”, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. 3Assistance Publique - Hôpitaux de Paris (AP-HP), Dept of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. 4Dept of Medicine, Division of Respiratory, University of Calgary, Calgary, AB, Canada. 5Lbin Cardiovascular Institute, Calgary, AB, Canada. 6Dept of Radiology, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. Dept of Thoracic and Vascular Surgery and Heart-Lung Transplantation, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. 8These authors contributed equally.

Correspondence: Xavier Jais, Service de pneumologie, Le Kremlin-Bicêtre, France, 78 rue du général Leclerc, 94270 Le Kremlin Bicêtre, France. E-mail: xavier.jais@gmail.com

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References


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