Pulmonary Embolism and Fever
When Should Right-Sided Infective Endocarditis Be Considered?
Gaetano Nucifora, MD; Luigi Badano, MD; Fjoralba Hysko, MD; Giuseppe Allocca, MD; Pasquale Gianfagna, MD; Paolo Fioretti, MD

Case presentation: A 39-year-old woman with chronic alcoholism became febrile (38.8°C) and markedly dyspneic on the fourth postoperative day of gastric surgery. Laboratory evaluation revealed anemia (hemoglobin 8.5 g/dL), thrombocytopenia (platelet count 30 000/mm³), and elevation of inflammatory markers (white blood cell count 18 000/mm³, C-reactive protein 187 mg/dL, and erythrocyte sedimentation rate 50 mm/s). Limb venous ultrasonography was negative for deep vein thrombosis, but pulmonary embolism (PE) was diagnosed on the basis of contrast-enhanced multidetector-row spiral computed tomography (MSCT; Figure 1A). Anticoagulation therapy was considered to be contraindicated because of recent surgery and thrombocytopenia, and a retrievable inferior vena cava filter was placed. With persistent high-grade fever and dyspnea and with the finding of *Streptococcus agalactiae* bacteremia, the patient underwent a transthoracic echocardiography examination on the sixth postoperative day that showed a large, mobile vegetation attached to the pulmonary valve (Figure 1B). A diagnosis of infective endocarditis (IE) of the pulmonary valve complicated by septic PE was then made, and the patient was referred for vena cava filter removal and pulmonary valve replacement. During vena cava filter removal, an acute thromboembolic stroke occurred, and transesophageal echocardiography documented a patent foramen ovale with right-to-left shunt. Ten days later, the patient underwent successful pulmonary valve replacement and surgical closure of the patent foramen ovale.

Clinical Significance of Fever During PE
Fever has long been recognized as commonly accompanying PE. Stein et al.¹ reported a temperature >37.5°C in 50% of patients with acute PE, but whether the fever was caused by the PE or an associated disease was not clarified. Murray et al.² encountered fever >38°C attributed solely to acute PE in 57.1% of patients, whereas fever without any other definite or possible explanatory cause was observed in 14% of 311 patients in the PIOPED (Prospective Investigation Of Pulmonary Embolism Diagnosis) study.³ PE-related fever is usually low-grade, rarely exceeding 38.3°C, and short-lived, reaching its peak the same day on which the PE occurs and gradually disappearing within 1 week.²–⁴

The pathogenesis of PE-related fever has not yet been fully clarified. It has been suggested that 1 or a combination of a variety of potential pyrogenic mechanisms occurs: infarction and tissue necrosis, hemorrhage, local vascular irritation or inflammation, atelectasis, or self-limited occult superinfections.²⁻⁵ The presence of a slight inflammatory response is indirectly confirmed by the concomitant increase of serum markers of inflammation.⁴⁻⁶ The presence of a modest leucocytosis (rarely exceeding 20 000/mm³) during the first hospital week is not uncommon, being described in up to 20% of patients with PE who have no other possible or defined cause of leucocytosis.²⁻⁷ The differential white blood cell count usually remains normal, only rarely showing a slight neutrophilia.⁷ Similarly, a slight increase in erythrocyte sedimentation rate and in C-reactive protein can also be observed.⁴⁻⁸

True PE-related fever is not associated with the extension of vascular obstruction and does not have any prognostic role⁵⁻⁶; its presence should not dissuade the clinician from diagnosing

From the Departments of Cardiopulmonary Science (G.N., L.B., G.A., P.G., P.F.) and Radiological Science (F.H.), Azienda Ospedaliero-Universitaria di Udine, Udine, Italy.
Reprint requests to Gaetano Nucifora, MD, Cardiopulmonary Science Department, Azienda Ospedaliero-Universitaria di Udine, P. le S. Maria della Misericordia 15, 33100 Udine, Italy. E-mail gnucifora@cardionet.it

(Circulation. 2007;115:e173–e176.)
© 2007 American Heart Association, Inc.

*Circulation* is available at [http://www.circulationaha.org](http://www.circulationaha.org) DOI: 10.1161/CIRCULATIONAHA.106.674358

---

**CLINICIAN UPDATE**

---

**doi:** 10.1161/CIRCULATIONAHA.106.674358
PE and initiating appropriate therapy. Furthermore, PE-related fever usually subsides after anticoagulant treatment, whereas the addition of antibiotics does not provide any additional benefit.4,9 The features of PE-related fever are similar to postoperative fever. Most early postoperative fevers (within the first 48 hours after surgery) have no clearly defined infectious cause and resolve without therapy. Therefore, among patients with onset of PE in the early postoperative period, fever could be also ascribed to the surgical procedure.10 Conversely, high-grade fever, especially if long-lasting or remittent and associated with a marked increase of serum markers of inflammation, could indicate advanced malignancy or pneumonia or other infections, or it could be the expression of septic embolic phenomena; it should prompt an exhaustive search for its cause, because management could be strongly affected (Figure 2; Table 1).2–4,6,11

**Figure 1.** A, MSCT shows a large filling defect in the main pulmonary artery, above the pulmonary valve (black arrow), and a filling defect in the terminal part of the right pulmonary artery (white arrow). B, 2D transthoracic echocardiography performed a few days later shows a large vegetation attached to the arterial surface of the medial cusp of the pulmonary valve. Ao indicates ascending aorta; LA, left atrium; PA, pulmonary artery; and Veg, vegetation.

**Figure 2.** PE and fever: a clinical diagnostic algorithm. TEE indicates transesophageal echocardiography; TTE, transthoracic echocardiography; PM, pacemaker; and post-op, postoperative.

**Diagnostic Role of Computed Tomography and Echocardiography**

The introduction of MSCT has greatly improved the visualization of peripheral pulmonary arteries and detection of small emboli compared with spiral computed tomography (CT) angiography.12,13 Because of its better spatial resolution, MSCT is becoming the new standard of reference for imaging nonmassive PE, and it is frequently used as the first-line imaging modality, alone or in combination with lung scintigraphy and inferior limb venous ultrasonography.12,13 MSCT allows diagnosis of PE by disclosing vascular abnormalities (intravascular filling defects, total cutoff of vascular enhancement, or enlargement of an occluded vessel) and ancillary findings (pleura-based, wedge-shaped areas of increased attenuation with no contrast enhancement, linear atelectasis; Figure 3).12 CT can also evaluate the presence of deep venous thrombosis in the abdomen, pelvis, thighs, and calves without additional intravenous injection of contrast mate-
rial by scanning the lower limbs 3 to 4 minutes after scanning of the pulmonary vessels.12 However, among persistently high-grade febrile patients, the presence of signs of PE should not deter one from searching for other potential causes of fever. The same CT examination can provide alternative explanations of fever (ie, thoracic or abdominal cancer, pneumonia or other infections) and is a valuable tool to identify septic PE phenomena.11,12 Characteristic CT findings in septic PE consist of discrete nodules with varying degrees of cavitation and subpleural, wedge-shaped heterogeneous areas of increased attenuation with rimlike peripheral enhancement. The nodules tend to be most numerous in the lower lobes. In many cases, a vessel can be seen leading directly to the nodules (“feeding vessel sign”).11,12 Unfortunately, these hallmark CT signs of septic PE are not always present (especially in case of fresh or large embolization), nor is the cause of PE always identifiable by CT (Table 2).14 Right-sided IE, a common cause of septic PE, is particularly difficulty to diagnose by CT because of the low temporal resolution of the technique, its inability to evaluate motion, and the presence of motion artifacts.15 Occasionally, some features, such as a filling defect inside the main pulmonary artery close to the pulmonary valve rather than the classic saddle embolus at the level of the bifurcation of pulmonary trunk, could suggest pulmonary IE (Figure 1). It is therefore crucial to maintain a high clinical suspicion of right-sided IE among patients with fever that is not justified by PE alone and without CT findings that potentially explain fever or septic PE phenomena, especially if the patient has risk factors for right-sided IE (ie, intravenous drug use, congenital heart defects, pacemaker leads, central venous lines, chronic alcoholism, dermal infections, malignancies, or immunologic deficiency).16,17 In this clinical scenario, transthoracic and transesophageal echocardiography should be performed without delay, even if not recommended by current guidelines on PE.18–20 Echocardiography has a strong diagnostic and prognostic role, with crucial therapeutic implications. Transthoracic echocardiography is generally adequate to correctly diagnose tricuspid vegetations.21 Transesophageal echocardiography should also be performed, because it is more sensitive in the diagnosis of pulmonary valve IE and pacemaker lead infections.22,23 Transesophageal echocardiography is also more valuable in recognizing prosthetic valve endocarditis and unusual locations of right-sided endocarditis (ie, the Eustachian valve) and in detecting IE complications (right-sided valvular insufficiency or dehis-

**TABLE 1. Other Possible Causes of Fever Among Patients With PE**

<table>
<thead>
<tr>
<th>Cause</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced malignancy</td>
<td>33</td>
</tr>
<tr>
<td>Other infection with or without septic embolic phenomena</td>
<td>22</td>
</tr>
<tr>
<td>Recent operation</td>
<td>13</td>
</tr>
<tr>
<td>Trauma or multiple fractures</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
</tr>
<tr>
<td>Intracerebral bleed or acute stroke</td>
<td>4</td>
</tr>
<tr>
<td>Endotracheal tube</td>
<td>2</td>
</tr>
<tr>
<td>Delirium tremens</td>
<td>2</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>2</td>
</tr>
<tr>
<td>Intraperitoneal catheter</td>
<td>2</td>
</tr>
</tbody>
</table>

Data derived from Stein et al.3

**TABLE 2. Possible Causes of Septic PE**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemierre syndrome (septic thrombophlebitis of the internal jugular vein secondary to acute oropharyngeal infection)</td>
</tr>
<tr>
<td>Right-sided IE</td>
</tr>
<tr>
<td>Infected central venous catheter</td>
</tr>
<tr>
<td>Dental abscess</td>
</tr>
<tr>
<td>Perinephric abscess</td>
</tr>
<tr>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Soft tissue infections</td>
</tr>
</tbody>
</table>

Figure 3. A, MSCT shows filling defects at the bifurcation of the left and right pulmonary arteries (white arrow) and multifocal filling defects in the segmental level of the left pulmonary artery (white arrowhead). B, MSCT (lung window) of the same patient shows focal peripheral confluent opacities in the anterior segment of the left upper lobe (white arrow), which suggests pulmonary infarction.
currence, congestive heart failure, and para-
valvular abscesses).15,24,25

In this group of patients, early imple-
mentation of echocardiography in the
diagnostic algorithm alerts the clinician
to appropriate antimicrobial therapy,
which is usually sufficient to achieve
remission of the infective disease with-
out complications.11 Persistent fever de-
espite antimicrobial therapy, vegetations
larger than 1 cm, multivalvular involve-
ment, and right-sided heart failure iden-
tify patients at higher risk who may
benefit from surgical treatment.16,26 Con-
trol of fever, early implementation of echocar-
diography, and right-sided heart failure iden-
tify patients at higher risk who may
benefit from surgical treatment.16,26 Con-
trol of fever, early implementation of echocar-
diography, and right-sided heart failure iden-
tify patients at higher risk who may
benefit from surgical treatment.16,26 Conversely,
not performing echocardiogra-
phy or performing it too late in these
patients could expose them to potential
complications that sometimes lead to
death or significant morbidity, related
not only to the progression of infection
but also to an incorrect or even harmful
treatment.

Conclusions

MSCT is frequently the first-line imaging
modality in patients with suspected
massive PE. The use of echocardiogra-
phy is limited to patients who are
hemodynamically unstable and those
with suspected massive PE; echocardi-
ography may also be used to identify
patients who could benefit from
thrombolytic therapy.18,19 In the clinical
scenario of documented nonmassive PE
associated with unexplained persistent
fever, early implementation of echocar-
diography could be of stronger diagnos-
tic value, because right-sided IE could be
the cause of septic PE. Its correct diag-
nosis can avoid potential complications
related to inappropriate or even harmful
treatment and to progression of infec-
tion, and it can address the appropriate
antimicrobial (and eventually, surgical)
therapy.

Disclosures

None.

References

1. Stein PD, Willis PW III, DeMets DL. History and physical examination in acute pulmonary embolism in patients without pre-
endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. J Am Coll Cardiol. 2005;
45:1467–1471.
6. Calvo-Romero JM, Lima-Rodriguez EM, Perez-Miranda M, Bureu-Dacal P. Low-grade and high-grade fever at presenta-
8. Soderberg M, Hedstrom U, Sjunnesson M, Larfars G, Jorup-Ronstrom C. Initial symptoms in pulmonary embolism differ from those in
endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. J Am Coll Cardiol. 2005;
45:1467–1471.
12. Herrera CJ, Mehlman DJ, Hartz RS, Talano JV, McPherson DD. Comparison of trans-
estophageal echocardiography in right-sided endocarditis. J Am Coll Cardiol. 1993;21:
1226–1230.
13. Vilacosta I, Sarria C, Sanchez-Harguindeguy L. Trans-
estophageal echocardiography in right-sided endocarditis. J Am Coll Cardiol. 1993;21:
1226–1230.
17. Laguno M, Miro O, Font C, de la SA. Pacemaker-related endocarditis: report of 7 cases and review of the literature. Car-
18. Task Force on Pulmonary Embolism, European Society of Cardiology. Guidelines on diagnosis and management of acute pul-
20. American College of Emergency Physicians Clinical Policies Committee; Clinical Policies Committee Subcommittee on Suspected Pul-
monary Embolism. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected pulmo-
22. Cook RJ, Ashton RW, Aughenbaugh GL, Ryu JH. Septic pulmonary embolism: present-
25. Sawhney N, Palakodeti V, Raisinghani A, Rickman LS, DeMaria AN, Blanchard DG. Usefulness of transesoph-
26. Bach DS. Transesophageal echocardiograph-
27. Sawhney N, Palakodeti V, Raisinghani A, Rickman LS, DeMaria AN, Blanchard DG. Eustachian valve endocarditis: a case series
and analysis of the literature. J Am Soc Echocardio-
g. 2001;14:1139–1142.
Pulmonary Embolism and Fever: When Should Right-Sided Infective Endocarditis Be Considered?
Gaetano Nucifora, Luigi Badano, Fjoralba Hysko, Giuseppe Allocca, Pasquale Gianfagna and Paolo Fioretti

_Circulation_. 2007;115:e173-e176
doi: 10.1161/CIRCULATIONAHA.106.674358
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/6/e173