Title
The incidence of pulmonary embolism and associated FDG-PET findings in IV contrast-enhanced PET/CT.

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Acute pulmonary embolism (PE) represents a potential life-threatening complication of venous thrombosis and is notoriously variable in presentation. Oncology patients have a higher risk of PE (1,2) and often present without the typical clinical manifestations (3). These so-called asymptomatic PEs are clinically significant in oncology patients. They serve as a marker for future symptomatic venous thromboembolism (VTE), a term that encompasses both deep venous thrombosis (DVT) and PE (4), and are associated with decreased survival (5). The current consensus is for therapeutic intervention in these patients despite the absence of symptoms (1).

Several previous studies have investigated the rates of incidental PE (IPE) on contrast-enhanced computed tomography (CT) studies in the oncologic population, with reported rates ranging from 0.58% to 4.0% (2,4,6–13). Since its approval by the Food and Drug Administration in 2000, fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography fused with concurrent computed tomography (PET/CT) has rapidly evolved into a cornerstone imaging modality in oncology. At our institution, approximately 95% of PET/CT studies are performed in patients with known or suspected malignancy, and the routine imaging protocol includes intravenous (IV) contrast. In general, most centers perform low-dose, noncontrast-enhanced CT as part of their routine FDG-PET/CT protocol. At our institution, there is a consensus between referring clinicians and the radiology department that patients undergoing PET/CT have a contrast-enhanced diagnostic quality CT unless there is a
contraindication such as renal failure or contrast allergy. One previous study found IPE in 13 of 2216 patients (0.59%) who had a contrast-enhanced PET/CT (13). The aim of our study was to evaluate the incidence of IPE in patients referred for FDG-PET/CT studies in a much larger cohort. An additional goal was to identify and characterize associated PET findings and their relative frequency.

**MATERIALS AND METHODS**

**Patient Selection**

This is a retrospective study based on the analysis of all FDG-PET/CT studies performed at our institution from January 1, 2005 to October 31, 2012. We searched our database of all PET/CT performed at our institution for the presence of any one of the terms “embolus,” “emboli,” “embolism,” “PE,” or “thromboembolism.” Only FDG-PET/CT studies performed at our institution were included in this study. Thus, outside studies submitted for internal review were excluded from further analysis. This was because of the potential for in-homogeneity in preparation and imaging acquisition protocols. The study was approved by our institutional review board.

**Scan Technique**

FDG-PET/CT examinations were performed on either a Biograph 16 (Hi-Rez) PET/CT scanner (Siemens AG, Erlangen, Germany) with an integrated PET and 16-MDCT scanner or a Discovery VCT PET/CT scanner (GE Medical Systems, Milwaukee, WI) with an integrated PET and 64-MDCT scanner. All patients fasted with hydration for at least 6 hours. Patients had blood glucose levels <200 mg/dL. Fluorine-18 FDG (0.45 ± 0.09 GBq) was injected intravenously followed by a 10-mL normal saline flush. Patients rested for 60 ± 15 minutes and voided before being positioned supine on the scanner table.

CT examinations were performed in neutral breath hold after the injection of 150 mL of iohexol (Omnipaque 350; GE Healthcare) at 3 mL/second. Acquisition was performed at kilovoltage peak of 120 with auto–milliampere second. Images were reconstructed as contiguous 5-mm slices. Additional lung reformats were generated with contiguous 2-mm slices. PET was performed immediately after CT, without patient repositioning. PET images were obtained in a three-dimensional mode at 7–10 bed positions per patient, with an acquisition time of 3–4 minutes per station, from the skull vertex through the mid thigh, except for patients with clinical indication to scan to the toes such as melanoma and myeloma. The CT, PET, and fused PET/CT images were displayed in orthogonal planes on an Advantage Workstation (GE Healthcare). Maximum standardized uptake value (SUVmax) was based on a total body weight and determined on the Advantage Workstation. All scans were initially interpreted and reported by members of both the nuclear medicine section and the thoracic, abdominal, or neuroradiology sections.

**Imaging and Chart Review**

The medical charts of patients included in the study were reviewed for demographic data, initial diagnosis, metastatic disease, and the presence and location of PE.

All cases were reviewed independently for the presence of PE by three radiologists (R.F., a radiology resident with 2 years of experience; S.B., attending radiologist with fellowship training in body CT and nuclear medicine; and D.N., attending radiologist with fellowship training in chest CT and nuclear medicine). The presence of PE was determined using commonly accepted methodology (14). Only cases in which all three radiologists independently agreed with the diagnosis of PE were included. The largest affected vessel (main, lobar, segmental, or subsegmental) was noted. The presence or absence of PE on previous chest CT was reviewed. The PET scan associated with each CT was reviewed for cardiac or pulmonary uptake, which was not attributable to metastatic disease. The electronic medical record was reviewed for the presence of symptoms attributable to PE or DVT. The medical record was also reviewed to see if patients were treated with anticoagulation or inferior vena cava (IVC) filter placement.

To estimate the total number of IV contrast-enhanced FDG-PET/CT studies performed over the relevant time frame, we used the search engine to identify all studies done in the month of August for each year from 2005 through 2012. All studies were independently reviewed to determine whether IV contrast was injected. The number of IV contrast-enhanced and noncontrast-enhanced FDG-PET/CT performed in the month of August from a given year was used to determine an estimated number of total for that year in its entirety. Numbers were adjusted from 2008 (leap year) to 2012 (leap year and only days up through October) to reflect the difference in total number of days included in the period of our search. A search of all reports for the year 2011, using the search term “Omnipaque” (the type of IV contrast used at our institution), demonstrated that the rate of IV contrast-enhanced FDG-PET/CT including this term in the report was consistent throughout the year at approximately 8.02 scans per day with a standard deviation of 0.88. Although this term was not included in all reports, it suggests a rate of FDG-PET/CT studies that did not vary significantly over months, which validated our approach. A similar approach was used to determine the total number of PET/CT studies done in breast cancer and melanoma patients.

**RESULTS**

**Total Number of Cases Reviewed**

Because of the very large number of PET/CT examinations performed it was not possible to individually review all reports for the administration of contrast. Using the method outlined previously, we estimate a total of 18,272 IV contrast-enhanced PET/CT scans performed during the study period (Supplemental Fig. 1A). Our data show that there has been
a steady increase in the number of FDG-PET/CT studies performed at our hospital from 2005 to 2011, and the percentage of FDG-PET/CT studies performed with IV contrast enhancement has steadily declined at a rate of about 1.25% per year (Supplemental Fig. 1B). This likely reflects a variety of factors, including advanced age of the patients being referred for imaging leading to an increased prevalence of renal failure, and perhaps trends in patient refusal of IV contrast administration.

**Incidence of PE**

Between January 2005 and October 2012, 72 FDG-PET/CT studies were identified which reported a PE. On review, seven studies were excluded because of insufficient findings for the diagnosis of PE by any of the three readers. An additional six cases had been seen on previous contrast-enhanced CT, with the amount of time from initial detection to the PET/CT ranging from 17 to 1702 days. None of the studies were done as a result of clinical concern for a PE. In total, 59 FDG-PET/CT studies containing a finding of an IPE were included in our cohort. This represents an estimated 0.32% incidence of IPE on FDG-PET/CT imaging at our institution (Table 1).

The demographics of patients with IPE are included as Table 2. The mean age was 55.8 years old. There were nearly equal numbers of males (n = 29) and females (n = 30). The vast majority (n = 57; 96.6%) had a primary diagnosis of malignancy, reflecting the prevalence of cancer in the population of patients who undergo PET/CT scanning. Of those patients diagnosed with a solid tumor, 34 of 51 (66.7%) had metastatic disease. Information about treatment was available in 47 of 59 patients with IPE. Of those 47 patients, 30 were undergoing chemotherapy (63.8%), 13 had prior surgical resection of their neoplasm (27.6%), 7 had undergone radiation (14.9%), and 19 had not yet received treatment.

The primary diagnosis of all cases in our cohort was determined by chart review. Two patients did not have diagnosis of cancer, although all were imaged because of concern for possible malignant disease. In all, 57 of 59 cases (96.6%) had a primary malignant disease at the time of IPE. This result is not surprising, because of the prevalence of malignancy in the patient population undergoing PET/CT. The most prevalent diagnoses are summarized in Table 3. This distribution is different from previously reported cohorts of IPE (4,10), likely reflecting institution-specific referral patterns in addition to the proven utility of PET/CT in these cancers.

Previous studies have shown that there is large variability in the incidence of VTE according to the type of primary malignancy, with lower rates in breast cancer compared to other primary sites like pancreatic cancer, lung cancer, and tumors of gastrointestinal origin (4,10,12,15,16). Given that the largest number of IPE cases in our cohort were found in breast cancer and melanoma patients, we next determined the rate of IPE detection per tumor type to delineate if our incidence reflected a higher number of these patients at our institution, or a true deviation from previously reported IPE patterns. Our data show that within our cohort of patients the overall incidence of IPE on IV contrast-enhanced FDG-PET/CT studies is 0.51% in breast cancer patients and
0.35% in melanoma patients (Table 3), which is consistent with a previous report (15).

**Pulmonary Emboli Characteristics**

In nearly half of the 59 cases (n = 27; 45.8%) a segmental branch of the pulmonary artery was the largest vessel involved, whereas in 24 of 59 cases (40.7%) either a lobar or main branch of the pulmonary artery was involved (Table 1). This distribution is similar to a previous retrospective study in a cohort of cancer patients, where 58.8% of IPE were segmental and 21.6% were in major vessels, namely main or lobar branches (4). Sample images from several cases of variable severity are included as Figures 1–5 and Supplemental Figures 2–4.

**Clinical Symptoms and Treatment with Anticoagulation**

Of the 59 patients with IPE, 23 did not have sufficient information in the electronic medical record to determine if they were treated with anticoagulation or if they had any clinical symptoms. Of the 36 remaining patients, 2 (6%) were not treated. One patient was not treated because of the presence of hemorrhagic brain metastasis and very poor prognosis excluding IVC filter placement. A second patient was not treated because of the presence of only isolated subsegmental PE, brain metastases, and a negative lower extremity ultrasound study for DVT. Of the remaining patients, 31 (86%) were treated with therapeutic anticoagulation, and 3 (8%) had an IVC filter placed. All the patients were treated based on the PET/CT findings, without confirmatory CT angiogram. In the 36 patients where sufficient clinical information was available, 30 patients were asymptomatic, even in retrospect (83%), whereas two had lower extremity swelling, suggesting DVT (6%), one had fever (3%), and three had dyspnea (8%).

**Review of Associated FDG-PET Findings**

We reviewed the PET images associated with all the studies that were positive for PE for additional findings. These results are summarized in Table 4. We found a qualitatively discernable focal increase in FDG uptake within the pulmonary artery at or adjacent to the PE, in comparison to other pulmonary arteries in the same patient, in 9 of 59 cases of IPE. A sample case is demonstrated in Figure 1 and Supplemental Figure 2. The mean SUV\textsubscript{max} of these lesions was 2.2 ± 0.7 (SD). A single case of documented chronic PE in the right main pulmonary artery, which had been seen on multiple CT scans over a period of 1702 days, demonstrated an associated hypometabolic filling defect (Fig. 2 and Supplemental Fig. 3).

We also reviewed all cases for the associated finding of a pulmonary infarction. We used commonly accepted criteria for pulmonary infarction as a peripheral, triangular consolidation with central lucency, located in the expected vascular distribution of the associated embolism (17). We found pulmonary infarction in only three cases of PE (Figs. 3 and 4 and Supplemental Fig. 4). All these cases demonstrated hypermetabolism. One case demonstrated a complete rim of FDG avidity (Fig. 3), whereas the other two did not (Fig. 4 and Supplemental Fig. 4).

Given the potential for right heart strain as a result of increased vascular resistance in the setting of PE, we also reviewed all cases for the presence of an abnormal pattern of cardiac uptake. One case demonstrated markedly increased uptake in the right ventricular wall (Fig. 5). This case was associated with saddle PE and bowing of the interventricular septum seen on CT.

**DISCUSSION**

Cancer patients are known to be prone to the development of VTE because of an underlying hypercoaguable state (18,19). Thromboembolism is the second leading cause of death among cancer patients undergoing chemotherapy (20). In fact, 15% of patients with malignant disease develop a clinically significant VTE at some point during the course of their disease (19), a number that does not include asymptomatic PE.

We estimate that between January 2005 and October 2012 there were 20,815 FDG-PET/CT scan done at our institution, 18,272 (87.8%) of which were done with IV contrast (Supplemental Fig. 1). From the cohort of IV contrast-enhanced images, we identified 59 cases of IPE, representing an estimated 0.32% of studies. The rate of IPE in cancer patients, when reported on a per CT study basis has varied significantly across previous studies, ranging from 0.58% to 4.0% (7–9,15). Our rate of 0.33% is lower than these reported values, likely because of multiple factors that have previously been reported to affect the rate of IPE (21). Firstly, our study includes only outpatients, as the PET/CT scanners at our institution are located at separate facility from inpatients. One meta-analysis found an overall rate of 1.2% of IPE in outpatients, similar but still greater than the rate determined in our study (21). Secondly, our study was a retrospective review from reports, so the reported incidence is likely less than the true incidence because of search error.

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**TABLE 4. PET Findings Associated with IPE**

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SUV in right ventricle</td>
<td>1/59</td>
<td>2%</td>
</tr>
<tr>
<td>Hypermetabolic pulmonary infarction</td>
<td>3/59</td>
<td>5%</td>
</tr>
<tr>
<td>Hypermetabolic pulmonary artery</td>
<td>9/59</td>
<td>15%</td>
</tr>
<tr>
<td>Mean SUV</td>
<td>2.2 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Max SUV</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
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<tr>
<td>Segmental PA</td>
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<td></td>
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<tr>
<td>Subsegmental PA</td>
<td>2/9</td>
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</tbody>
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IPE, incidental pulmonary embolism; PA, pulmonary artery; SUV, standardized uptake value.
Figure 1. Example of pulmonary artery hypermetabolism. A 75-year-old woman with history of melanoma. (a) Incidental right lower lobe segmental pulmonary embolism seen on computed tomography. (b) The associated PET demonstrates mild focal pulmonary arterial hypermetabolism, with an SUV$_{\text{max}}$ of 2.0. PET, positron emission tomography; SUV, standardized uptake value.

Figure 2. Example showing hypometabolism in chronic pulmonary embolism. A 66-year-old man with history of non-Hodgkin’s lymphoma. (a) Contrast-enhanced CT demonstrates a calcified, eccentrically located filling defect in the right main pulmonary artery. This defect had been present on previous CTs and is consistent with a chronic pulmonary embolism. (b) The associated PET demonstrates a hypometabolic pulmonary arterial filling defect. CT, computed tomography; PET, positron emission tomography.

Figure 3. Example of peripheral pulmonary infarction with associated complete rim of FDG avidity. A 66-year-old woman with a history of gastric cancer. Contrast-enhanced computed tomography demonstrates a pulmonary embolism involving the interlobar pulmonary artery (a) and a right lower lobe pulmonary infarction (b). The associated PET demonstrates a rim of FDG avidity at the borders of the infarction (c). FDG, fluorodeoxyglucose; PET, positron emission tomography.

Figure 4. Example of peripheral pulmonary infarction with associated FDG avidity. A 61-year-old woman with history of breast cancer. Contrast-enhanced computed tomography demonstrates a segmental left lower lobe pulmonary embolism (a) and a small left lower lobe pulmonary infarction (b). The associated PET demonstrates an incomplete rim of FDG avidity surrounding the area of the infarction (c). FDG, fluorodeoxyglucose; PET, positron emission tomography.
and prospectively underdetecting IPE. Thirdly, the contrast bolus timing in our contrast-enhanced studies is optimized for tissue enhancement rather than for detection of PE. It is likely that a substantially greater fraction of examinations would demonstrate PE in these patients if they had undergone an appropriate protocol and interpreted CT angiogram. Finally, it is likely that the referral base for PET/CT represents a different patient cohort than those receiving standard chest CT. For example, our cohort includes a large number of patients with breast cancer and melanoma, but relatively few patients with gastrointestinal malignancies. Accordingly, when comparing disease-specific incidence of IPE in breast cancer and melanoma, we found rates of 0.51% and 0.35%, respectively, similar in comparison to a previous report (15). One previous study reviewed a smaller cohort of cancer patients undergoing contrast-enhanced PET/CT and found the rate of PE to be 0.59% (13). These results are similar to our own, likely because of similar patient cohort as in our study. Taken together, these factors of CT protocol, interpretation, and patient selection explain the relatively low rate of IPE in our study.

In the 36 cases of IPE where sufficient clinical information was available, most cases (34, 94%) were treated either with therapeutic anticoagulation or an IVC filter. These data are similar to previously published series and congruent with the clinical consensus that incidental pulmonary embolus be treated with anticoagulation (1,4,6,12,15). Most patients (30/36, 83%) were asymptomatic, even in retrospect. Two patients had retrospectively identified symptoms of DVT (6%), and four (11%) had either fever or pulmonary symptoms.

Multiple PET findings have been described in association with pulmonary emboli, including pulmonary artery hypermetabolism (13,22–24), four-chamber cardiac uptake (25), and the presence of a rim of hypermetabolism surrounding a pulmonary infarction (26,27). However, the relative frequency of these findings has not been previously described. One additional novel sign of PE identified in this study was the presence of a hypometabolic filling defect in the pulmonary artery tree. This finding was associated with a single case of a large chronic right main pulmonary artery embolism (Fig. 2 and Supplemental Fig. 3). This finding was only identified in one of six cases of previously identified PE and is therefore unlikely to be present in most cases of chronic PE. However, as no mimics of this sign have been previously reported, we propose that the finding of a hypometabolic pulmonary arterial filling defect should prompt search for underlying embolism.

We found qualitatively increased focal or curvilinear FDG uptake in the pulmonary arterial in 9 of 59 cases of IPE, with a mean SUVmax of 2.2 (Fig. 1, Supplemental Fig. 2, and Table 4). This value is similar to previously published reports of 1.65 (13), 2.3 (23), and 1.7 (24). We found that focal pulmonary arterial hypermetabolism could only be qualitatively detected in 15.2% of cases, indicating that this is an insensitive secondary sign of PE. The differential diagnosis for the finding of pulmonary arterial hypermetabolism includes pulmonary artery sarcoma, pulmonary artery metastasis, and FDG microembolism secondary to paravenous injection (23,24,28). These should be readily distinguishable because of the much higher SUV reported for pulmonary artery malignancies, and because of the presence of extravasation of FDG at the injection site in the case of microembolism.

The physiology underlying the variability in pulmonary artery uptake associated with PE is unclear. The resolution of PET/CT is insufficient to determine if the uptake is associated with the thrombus itself, or with the wall of the vessel. It is possible that the hypermetabolism may reflect vessel wall inflammation, as previously suggested (13). Pathologic analysis of pulmonary thrombectomy specimens commonly demonstrates mild inflammation, but may demonstrate moderate or severe inflammation in a minority of cases (13.4% and 1.3% of cases, respectively) (29). The fact that we observed increased pulmonary artery hypermetabolism in 15.2% of cases is similar to the incidence of inflammation in previous pathologic series, suggesting that these findings may be correlated. However, this remains a possibility for further study.

We found pulmonary infarction in only 3 of 59 cases of PE (Figs. 3 and 4 and Supplemental Fig. 4). All these cases demonstrated some focal hypermetabolism associated with the infarction, as has been previously described (13,30). One demonstrated a complete rim of FDG avidity (Fig. 3), the previously described “rim sign” (27). Although only seen in a single case in our series, the rim sign may represent a relatively specific secondary sign of PE. A more homogeneous pattern of uptake, such as seen in other cases of pulmonary infarction (Fig. 4 and Supplemental Fig. 4), is not specific and could be seen in pneumonia or atelectasis.

![Figure 5. Example showing increased right ventricular uptake. A 29-year-old woman with metastatic melanoma. (a) Saddle pulmonary embolus was seen on contrast-enhanced CT. (b) CT demonstrating bowing of the interventricular septum. (c) PET demonstrating near-circumferential increased FDG uptake in the right ventricular wall. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.](image-url)
Finally, we assessed for an abnormal pattern of cardiac uptake. We did not identify any cases of four-chamber increase in cardiac uptake, as has been previously described (25). We identified a single case that demonstrated markedly increased right ventricular myocardial uptake in a patient with a saddle PE (Fig. 5). CT also demonstrated marked dilation of the right ventricle in proportion to the left ventricle and bowing of the interventricular septum, a known secondary sign of elevated right heart pressure (31). An increase in right ventricular myocardial FDG uptake has been described in association with pulmonary arterial hypertension (32–34). Therefore, the finding of increased right ventricular wall uptake in this patient likely reflects acutely increased pulmonary arterial and right heart pressure because of the massive PE. The finding of markedly increased right ventricular myocardial uptake is unlikely to represent a specific sign for PE, as there are numerous causes of pulmonary arterial hypertension.

Our study has several limitations. As a single institution study, our patient population undergoing FDG-PET/CT may not be the same as other institutions. Patient populations at other institutions will reflect the referral pattern unique to that institution. The patient population undergoing PET/CT imaging at our institution may have a different prevalence of metastatic disease, undergo chemotherapy at a different rate, and have a different proportion of outpatients than those being imaged at other facilities. As a tertiary care hospital with a large associated cancer center, we are probably witnessing the evolving role of FDG-PET/CT from a predominantly first line imaging modality for staging to the modality of choice for the assessment of response to therapy. Finally, because of the very large number of studies analyzed, it was not possible to estimate the rate of PE on a per-patient basis, limiting direct comparison against some previous studies.

CONCLUSIONS

Our findings indicate that IPE are found in 0.32% of IV contrast-enhanced FDG-PET/CT scans, and that a large percentage of these lesions are found in the lobar or main branches of the pulmonary artery. We found focal pulmonary artery hypermetabolism in 15.2% of the cases of IPE and focal pulmonary artery hypometabolism in a single case of chronic PE. Furthermore, we found three cases of hypermetabolic pulmonary infarction (5.1% of cases) and one case of pulmonary infarction with a complete rim of FDG avidity. A single case (1.7%) demonstrated isolated increased right ventricular uptake, associated with a saddle pulmonary embolus and CT evidence of elevated right heart pressure. Although these secondary signs are present in a minority of cases, we propose that the findings of focal pulmonary artery hypermetabolism or hypometabolism, and hypermetabolic pulmonary infarction with rim sign are likely to represent specific secondary signs for PE. Therefore, the presence of these findings on noncontrast PET/CT should alert the radiologist to the possibility for underlying PE.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.acra.2014.02.013.

REFERENCES