



# Methods of Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III)

Paul D. Stein, MD,\* Alexander Gottschalk, MD,<sup>†</sup> H. Dirk Sostman, MD,<sup>‡</sup> Thomas L. Chenevert, PhD,<sup>§</sup> Sarah E. Fowler, PhD,<sup>||</sup> Lawrence R. Goodman, MD,<sup>||</sup> Charles A. Hales, MD,<sup>\*\*</sup> Russell D. Hull, MBBS, MSc,<sup>††</sup> Emanuel Kanal, MD,<sup>‡‡</sup> Kenneth V. Leeper, Jr, MD,<sup>§§</sup> David P. Nadich, MD,<sup>¶¶</sup> Daniel J. Sak, DO,<sup>|||</sup> Victor F. Tapson, MD,<sup>\*\*\*</sup> Thomas W. Wakefield, MD,<sup>†††</sup> John G. Weg, MD,<sup>‡‡‡</sup> and Pamela K. Woodard, MD<sup>§§§</sup>

In this work, the methods of the Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III) are described in detail. PIOPED III is a multicenter collaborative investigation sponsored by the National Heart, Lung and Blood Institute. The purpose is to determine the accuracy of gadolinium-enhanced magnetic resonance angiography in combination with venous phase magnetic resonance venography for the diagnosis of acute pulmonary embolism (PE). A composite reference standard based on usual diagnostic methods for PE is used. All images will be read by 2 blinded and study-certified central readers. Patients with no PE according to the composite reference test will be randomized to undergo gadolinium-enhanced magnetic resonance angiography in combination with venous phase magnetic resonance venography. This procedure will reduce the proportion of patients with negative tests at no loss in evaluation of sensitivity and specificity. *Semin Nucl Med* 38:462-470 © 2008 Elsevier Inc. All rights reserved.

The purpose of the Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III) study is to estimate the diagnostic accuracy of gadolinium-enhanced magnetic resonance pulmonary angiography (Gd-MRA)

and venous phase venography (Gd-MRV) for the diagnosis of acute pulmonary embolism (PE). If shown to be a valid test, it may eliminate the need for iodinated contrast material in patients with a relative contraindication, and it would eliminate the exposure of patients to ionizing radiation. The performance and evaluation of MRA is technically demanding, and it may be more prone to artifacts than computed tomography angiography (CTA). The Evidence Report/Technology Assessment of the Agency for Health care Research and Quality has identified a need to study the feasibility of Gd-MRA in PE patients with tachypnea and tachycardia.<sup>1</sup>

The diagnostic accuracy of Gd-MRA alone or the combination of Gd-MRA/MRV will be expressed as the sensitivity, specificity, likelihood ratio for a positive test, and likelihood ratio for a negative test. The sensitivity and specificity of Gd-MRA/MRV also will be evaluated in combination with previous clinical assessment by the Wells criteria.<sup>2</sup> Previous investigations of Gd-MRA showed a sensitivity that ranged from 77% to 100% in studies of 8 to 35 patients with PE and specificity ranged from 95% to 98% among 22 to 83 patients in whom PE was excluded (Table 1).<sup>3-5</sup> More recently, one study reported sensitivities that differed considerably between readings by teams of experienced radiologists.<sup>6</sup> Among 63 patients with PE, sensitivities were 31% with readings by outside radiologists and 71% with readings by local radiologists. Speci-

\*Department of Research, St. Joseph Mercy Oakland Hospital, Pontiac, MI, and Department of Medicine, Wayne State University, Detroit, MI.

<sup>†</sup>Department of Radiology, Michigan State University, East Lansing, MI.

<sup>‡</sup>Office of the Dean, Weill Cornell Medical College and Methodist Hospital, Houston, TX.

<sup>§</sup>Department of Radiology, University of Michigan, Ann Arbor, MI.

<sup>||</sup>The Biostatistics Center, Department of Epidemiology and Biostatistics, George Washington University, Rockville, MD.

<sup>|||</sup>Department of Radiology, Medical College of Wisconsin, Milwaukee, WI.

<sup>\*\*</sup>Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

<sup>††</sup>Department of Medicine, University of Calgary, Calgary, Alberta, Canada.

<sup>‡‡</sup>Department of Radiology, University of Pittsburgh, Pittsburgh, PA.

<sup>§§</sup>Department of Medicine, Emory University, Atlanta, GA.

<sup>¶¶</sup>Department of Radiology, New York University Medical Center, New York, NY.

<sup>|||</sup>Department of Medicine, St. Joseph Mercy Oakland Hospital, Pontiac, MI.

<sup>\*\*\*</sup>Department of Medicine, Duke University, Durham, NC.

<sup>†††</sup>Department of Surgery, University of Michigan, Ann Arbor, MI.

<sup>‡‡‡</sup>Department of Medicine, University of Michigan, Ann Arbor, MI.

<sup>§§§</sup>Department of Radiology, Washington University, St. Louis, MO.

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Address reprint requests to Paul D. Stein, MD, St. Joseph Mercy Oakland, 44405 Woodward Ave, Pontiac, MI 48341-5023. E-mail: [steinp@trinity-health.org](mailto:steinp@trinity-health.org)

**Table 1 Sensitivity and Specificity of Gd-MRA for PE**

Sensitivity n/N (%)	Specificity n/N (%)	Reference
8/8 (100)	21/22 (95)	Meaney et al <sup>3</sup>
27/35 (77)	81/83 (98)	Oudkerk et al <sup>4</sup>
11/13 (85)	22/23 (96)	Gupta et al <sup>5</sup>

ficiencies among 26 patients who did not have PE were 85% and 92%, respectively.<sup>6</sup>

## Research Plan

PIOPED III is a multicenter prospective study of consecutive patients incorporating standardized inclusion/exclusion criteria, ascertainment of patient characteristics and outcomes, uniform diagnostic criteria, and unbiased central interpretation of imaging studies. The study will include a broad spectrum of patients with and without PE and a variety of patients with comorbid conditions that are commonly associated with PE. All patients will undergo a reference test and a pretest objective clinical assessment based on the Wells criteria.<sup>7</sup> All patients with PE and a random sample of patients without PE will undergo Gd-MRA/MRV. Expert readers will interpret the results of Gd-MRA/MRV and the results of the reference tests independently without knowledge of the results of clinical or ancillary tests.

## Included Patients

Patients will be 18 years of age or older in whom acute PE is of diagnostic concern. An attempt will be made to recruit all patients with suspected PE. Patients with suspected acute PE will be identified and recruited in the emergency department, outpatient clinic, consultation service, hospital beds, or radiology department. As soon as an eligible patient with suspected PE is identified, the patient will be recruited, and written informed consent will be obtained (Fig. 1). The patient will undergo any diagnostic tests for PE that are required according to the judgment of the attending physician.

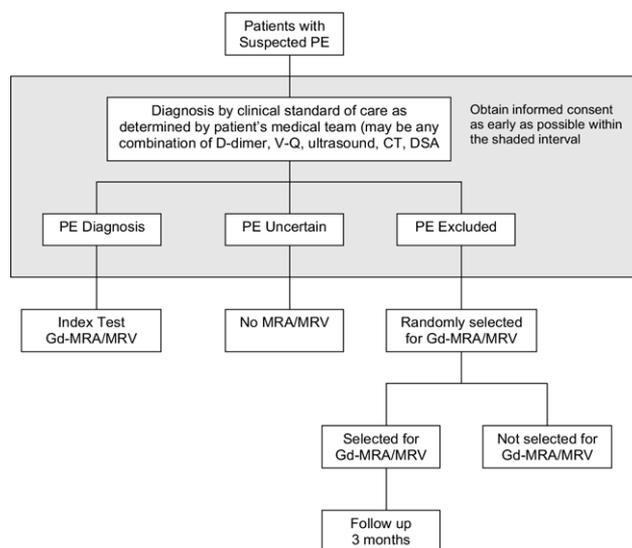
## Excluded Patients

Contraindications for Gd-MRA/MRV include any implanted ferromagnetic foreign body.<sup>8</sup> Contraindications also include dependency on a continuous connection to an external electrical device or pump. Additional contraindications include severe claustrophobia, severe shaking, an inability to lie still for 30 minutes, and a body size too large for scanner. Pregnant women and nursing mothers will be excluded because it is not known whether there may be adverse effects of gadolinium-based contrast material on the fetus or to what extent such contrast material is excreted in human milk (gadopentetate dimeglumine package insert). Additional exclusion criteria are shown in Table 2.

Concern exists regarding nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD), which occurs rarely in patients with poor renal function who receive gadolinium-containing contrast material.<sup>9,10</sup> Recommended

exclusions, based on levels of serum creatinine or estimated glomerular filtration rate (GFR), underwent several iterations following the US Food and Drug Administration (FDA) alert in June 2006, which indicated that NSF/NFD may occur after exposure to a gadolinium-containing contrast agent.<sup>9</sup> As more information about the risks of NSF/NFD was obtained, the protocol of PIOPED III was modified accordingly. The June 2006 FDA alert reported 25 cases of NSF/NFD in patients who received gadodiamide (Omniscan; Amersham Health, Oslo, Norway) for MRA.<sup>9</sup> All had advanced renal failure requiring dialysis or with a glomerular filtration rate  $\leq 15$  mL/min/1.73 m<sup>2</sup>.<sup>9</sup> On December 22, 2006, the FDA issued a Public Health Advisory indicating that they received reports of 90 patients with NSF/NFD.<sup>11</sup> According to the International Center for Nephrogenic Fibrosing Dermopathy Research Registry, “over 215 cases have been identified in the Registry so far.”<sup>10</sup> In December 2006, the FDA indicated that NSF/NFD has occurred in patients with moderate renal disease (GFR 30-59 mL/min/1.73 m<sup>2</sup>) as well as severe (GFR 15-29 mL/min/1.73 m<sup>2</sup>) and end-stage renal disease after exposure to Gd-containing contrast agents.<sup>12</sup> Two patients, in addition, had a “mild” decrease in renal function (GFR  $>30$  mL/min/1.73 m<sup>2</sup>), but both also had acute renal failure.<sup>13</sup> The literature described 1 or 2 cases in other patients with a GFR  $>60$  mL/min/1.73 m<sup>2</sup>, but these cases have been refuted because of the improper calculation of the GFR in patients experiencing acute kidney injury (S. Cowper, International Center for Nephrogenic Fibrosing Dermopathy Research [ICNFDR], personal communication, April 23, 2007).

Since Gd-containing contrast agents were introduced in the 1980s, 200 million patients have received it.<sup>14</sup> Among 100 cases reviewed in detail, 95% received a gadolinium chelate within 2 to 3 months of exposure.<sup>15</sup> Gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ), gadodiamide (Omniscan), and gadoversetamide (OptiMARK; Mallinckrodt Inc, St. Louis, MO) had been used in some of these patients.<sup>16</sup> There is a potential for NSF/NFD to occur



**Figure 1** Diagram of study protocol.

**Table 2** Exclusion Criteria

- Critically ill
- Currently suffer from shock or hypotension (systolic pressure <80 mm Hg) or hemodynamically unstable
- On ventilatory support
- Documented episodes of ventricular fibrillation or sustained ventricular tachycardia within the past 24 hours
- Myocardial infarction within the past month
- Sickle cell disease, other hemoglobinopathies, and other hemolytic anemias
- Estimated creatinine clearance <60 mL/min/1.73 m<sup>2</sup>
- Acute renal insufficiency or likely causes or findings with acute renal insufficiency
- Severely dehydrated
- Severe hemorrhage
- Oliguria
- Anuria
- Severe trauma, within 7 days
- Renal transplant, ever
- Liver transplant, ever
- Rhabdomyolysis
- End-stage malignancy
- Third-degree burns within 7 days
- Poisoned (methanol, ethylene glycol) within 7 days
- Increase in creatinine of >1.5 times initial level during hospitalization or in past 2 weeks
- On renal dialysis
- Gd-enhanced MRA within the previous 3 months
- Gd-enhanced MRA is planned or likely within the next 3 months
- History of allergy to gadolinium-containing contrast agents or to iodinated contrast media (because patients allergic to iodinated contrast material are sometimes allergic to gadolinium containing contrast media)
- Currently symptomatic asthma
- Pregnant
- Nursing mother
- Previously enrolled in PIOPED III
- Institutionalized or mentally handicapped
- Prisoners
- Unable to personally give informed consent

with any of the 5 approved Gd-containing contrast agents,<sup>11</sup> especially at high doses.<sup>17,18</sup> Differences in the structure of gadolinium complexes may affect their propensity to trigger NSF/NFD.<sup>16</sup> No cases have been reported with gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ) alone (E. Kanal, personal communication, April 16, 2007). One case was reported in a patient who received Omniscan a few days before MultiHance (E. Kanal, personal communication, April 16, 2007).

Before May 2006, PIOPED III excluded patients with serum creatinine levels >2.5 mg/dL. On May 23, 2006, the protocol was revised to exclude patients with an abnormal serum creatinine (>1.5 mg/dL for men and >1.4 mg/dL for women). In July, 2006, the protocol was revised again to exclude patients on renal dialysis or with an estimated GFR <95 mL/min for men or <75 mL/min for women based on

the Cockcroft-Gault equations modified for lean body weight<sup>19</sup> as follows:

Males: GFR (mL/min)

$$= \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72}$$

Females: GFR (mL/min)

$$= \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \times 0.85$$

Lean body weight:

Male: 50 kg + [(2.3 kg) × (each inch of height >5 ft)]

Female: 45.5 kg + [(2.3 kg) × (each inch of height >5 ft)]

On September 29, 2006, the protocol was changed to exclude patients with an abnormal serum creatinine based on local institutional values. On January 25, 2007, based on new information, exclusions were based on an abnormal estimated GFR ( $\leq 90$  mL/min/1.73 m<sup>2</sup>) as measured by the Modification of Diet in Renal Disease.<sup>20</sup> Finally, on May 1, 2007, the protocol was modified to require a GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> based on this equation. MultiHance became the only contrast agent allowed. The recommended dose, 0.1 mmol/kg, could not be exceeded. Patients who received a previous administration of a Gd-contrast agent within 3 months or in whom a repeat MRA was expected in the next 3 months were excluded. The estimated GFR will be calculated no more than 24 hours before the MRA. All patients who undergo MRA will receive a follow-up call at 3 months. Those with an estimated GFR <90 mL/min/1.73 m<sup>2</sup> will be contacted at least twice at 3-month intervals after enrollment.

The Modification of Diet in Renal Disease equation<sup>20</sup> is calculated as follows:

Estimated GFR (mL/min/1.73 m<sup>2</sup>)

$$= 175 \times \text{Cr}^{-1.154} \times \text{age}^{-0.203}$$

$$\times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

Until the end of March 2007, the MDRD.com website used 175 as the factor in the equation to calculate estimated GFR. The appropriate equation for computing estimated GFR depends on the creatinine method. On approximately March 27, 2007, the protocol required that the user identify the creatinine method used in the local laboratory. Using a method that is isotope dilution mass spectrometry traceable (the gold standard) the factor is 175.<sup>21</sup> For the method that is not isotope dilution mass spectrometry traceable (the standard method), the factor in the Modification of Diet in Renal Disease Equation is 186.<sup>21</sup>

## Diagnostic Reference Standard for PE

The diagnosis of PE will be based on any one of the following:

1. Positive contrast enhanced spiral CT angiogram showing PE in a main or lobar pulmonary artery irrespective of clinical assessment.
2. Positive contrast-enhanced spiral CT angiogram or ve-

nous phase imaging of the lower extremities (CT venogram) in a patient with a high or intermediate clinical probability by the Wells criteria. If the CT venogram is positive, it will be a surrogate for the diagnosis of PE.

3. High probability ventilation-perfusion (V/Q) lung scan in a patient with no previous PE and high or intermediate probability clinical assessment by the Wells criteria.
4. Positive venous ultrasound in a patient with no previous deep venous thrombosis (DVT) at the same site in a patient with a nondiagnostic V/Q scan and high or intermediate clinical probability by Wells criteria. This is a surrogate for the diagnosis of PE.
5. Positive conventional digital subtraction pulmonary angiogram (DSA).

The diagnosis of PE will be excluded on the basis of on any one of the following:

1. Normal D-dimer by quantitative rapid enzyme-linked immunosorbent assay (ELISA) (D-dimer <500 ng/mL), in a patient with a low or intermediate probability objective clinical assessment based on the Wells criteria. If whole blood or latex D-dimer is used, clinical assessment must be low probability.
2. Negative contrast-enhanced spiral CTA in a patient with a low probability clinical assessment by the Wells criteria.
3. Negative CTA and negative venous phase CT venogram in a patient with a low or intermediate clinical probability by the Wells criteria.

After February 20, 2008, the protocol was revised to permit a negative ultrasound of the legs if CT venography is not obtained.

4. Normal V/Q lung scan.
5. Low probability V/Q lung scan, low clinical probability by Wells criteria, and negative venous ultrasound. Some of these patients had a very low probability V/Q scan interpretation.<sup>22,23</sup>
6. Negative conventional DSA.

The study excludes patients from further investigation if a definitive diagnosis or exclusion of PE cannot be achieved. All patients undergoing CTA will also undergo venous phase CT venography in combination. During the course of PIOPED III, data analyzed from PIOPED II showed that venous phase CT venography and venous ultrasound were diagnostically equivalent.<sup>24</sup> Therefore, after nearly 2 years of recruitment, some centers substituted venous ultrasound for CT venography. Untreated patients in whom PE was excluded by the composite reference test will be followed 3 months. Deaths, new studies for PE, and new studies for DVT will be reviewed by an Outcome Committee. A positive clinical outcome may reverse a negative reference test. The composite criteria for the diagnosis or exclusion of PE eliminates the ethical problem of asking patients to volunteer for a conven-

tional DSA, which carries some risk, although the risk is small.<sup>25</sup>

## Random Sampling to Reduce Number of Negative Tests

A random sample of patients in whom PE is excluded by the composite reference test will undergo Gd-MRA/MRV. Random sampling of PE negative patients for Gd-MRA/MRV is a design feature that makes the investigation feasible and ethical and provides valid, informative and relevant answers with optimal precision and optimal use of resources. If all patients with PE excluded by the composite reference test were required to undergo Gd-MRA/MRV, many more patients without PE than with PE would be evaluated, because the prevalence of PE in the previous PIOPED studies was 23% and 28%.<sup>26,27</sup> This would give an unnecessarily narrow confidence interval for specificity at great financial cost, diminished feasibility, and burden on a large number of patients. It would cause overloading of heavily scheduled magnetic resonance imaging systems and perhaps raise a question on the ethics of investigating so many normal subjects.

The Data and Coordinating Center will manage the computer-based random sampling system to achieve approximately equal numbers of patients positive and negative by the reference standard. Characteristics of PE-negative patients by the composite reference test who were selected by random sampling for Gd-MRA/MRV will be compared with PE-negative patients who were not elected for Gd-MRA/MRV. The proportion of patients randomized for Gd-MRA/MRV may change during the period of recruitment, depending on the prevalence of PE at each clinical center. The goal is to achieve an approximately equal number of subjects with and without PE.

## Time of Recruitment

Informed consent may be obtained any time after the patient with suspected PE is identified and before Gd-MRA is obtained, or before randomization for Gd-MRA if PE is excluded by the reference test.

## Central Readings of Imaging Studies

Investigators from each clinical center may serve as central readers of images from other centers. For each patient undergoing Gd-MRA/MRV, 2 study-certified central readers will interpret the V/Q scan, CTA/CT venogram, and DSA used for the definitive reference test. Central readers also will interpret Gd-MRA/MRVs and assess quality. Central readers will not reinterpret venous compression ultrasounds. Central readers will not have clinical information, nor will they have the results of other imaging studies except chest roentgenograms for V/Q readers. All reference tests will be obtained before Gd-MRA/MRV. The reference tests of PE-negative patients not randomized for Gd-MRA/MRV will not be read

**Table 3** MRI Equipment and Characteristics

Site	MRI	Field Strength (T)	Max Gradient Field Strength (mT/m)	Slew Rate mT/ms
Calgary	Siemens Sonata	1.5	30	200
Emory	GE Signa Horizon LX High Speed	1.5	40	150
MGH	Siemens Sonata	1.5	30	200
Michigan	GE Signa Horizon LX Echo Speed	1.5	30	150
	Philips Achieva	3.0	40	200
NYU	Siemens Sonata	1.5	30	200
St. Joseph	Toshiba XGV Vantage, GE EXCITE HD TwinSpeed	1.5	30	130
Washington	Siemens Sonata	1.5	30	200

centrally because such patients will be excluded from analysis of the data.

Contrast-enhanced CTAs, pulmonary DSA, and Gd-MRA will require adjudication if there is disagreement on which lobes contain acute PE. Both CT venograms and MRVs will require adjudication if there is disagreement on which vein shows acute DVT. Adjudication for V/Q scans will be required if there is disagreement on the diagnostic probability (high probability, intermediate probability, low probability, or normal). Adjudicated readings will be performed blindly by a third reader who does not possess knowledge of the other 2 readings.

### Central Reader Training, Certification, and Variability

Each central reader will be certified as having participated in training before reading any images for the study. Reader variability will be compared in central readers on the basis of detailed per-vessel readings. Differences between central and local readers on whether PE is present or absent also will be determined.

### Differences Between Local and Central Readers

Potential differences between local and central interpretations of diagnostic images will not result in many lost cases. If the local reading is positive and the central reading is negative, the patient would receive a Gd-MRA/MRV and all necessary data would be obtained. Final interpretation would be based on the central reading (except venous ultrasound). If the local reading is negative and the central reading is positive and if the patient is randomized for a Gd-MRA, all of the necessary data would be obtained. Only if the patient is randomized for no Gd-MRA/MRV, would the case be lost. Loss of a case would, therefore, require the combination of a misread local reading as negative plus randomization to no Gd-MRA/MRV.

### Standard for Reporting Diagnostic Accuracy

The design of PLOPED III conforms to the design requirement of studies of diagnostic accuracy,<sup>28-30</sup> and to the Standards for Reporting of Diagnostic Accuracy statements.<sup>28,29</sup>

An important design requirement for a study of diagnostic accuracy is that the study should include a wide spectrum of patients having the condition to be diagnosed.<sup>28,29</sup>

### Time Intervals for Imaging

Gadolinium enhanced Gd-MRA will be obtained within 72 hours of the definitive imaging study.

## Gadolinium-Enhanced MRA/MRV

### Gd-MRA for PE: Methods

Gadolinium-enhanced MRA/MRV will be performed on commercially available 1.5-T systems with fast gradient-echo capability (30-40 mT/m max gradient field strength) and slew rate 130 to 200 mT/ms (Table 3). At one center (University of Michigan), a 3.0-T unit (max gradient strength of 40 mT/m and 200 mT/ms slew rate) will be used in some patients. The protocol is otherwise analogous to that designed for the 1.5-T scanner. At all centers, parallel imaging will be used. Thus, a specialized multichannel (6-12 channel) phased array coil will be used for reception of the pulmonary MRA data. The body coil will be used for signal transmission.

### MR Imaging Protocol

All scout imaging of both the chest and thighs will be obtained at the beginning of the examination with the table prescribed to move to the thigh station automatically. A torso multichannel phased array coil will be used for the pulmonary Gd-MRA. MRV of the thigh will be performed with the body coil. A single bolus of gadolinium-containing contrast material timed to the main pulmonary artery will be used for all imaging, with multiple measures (data acquisitions) obtained immediately and consecutively in the thighs to avoid missing the maximal venous opacification.

### Patient Preparation

A 20-gauge catheter will be placed in an antecubital vein and connected to a power injector by an intravenous tubing extension. The patient will be positioned supine within the bore of the magnet. A torso/body multichannel phased array coil will be placed around the chest as well as a respiratory bellow

sensor, if the MR system requires it. The patient will receive 2 L/min of oxygen through a nasal cannula throughout the study.

### Scout Imaging

Sagittal and transverse locators will be performed at the thorax, centered at the midline in the left-to-right direction and at the nipple line in the superior-to-inferior direction. A second coronal locator will be acquired mid thighs for graphical thigh MRV prescription.

## Gd-MRA of Pulmonary Arteries

### Scan Parameters

Pulmonary Gd-MRA imaging will be performed using a 3D gradient recalled echo sequence in the coronal plane using the following parameters: "MinTR" (TR  $\leq$  6.6 ms), and "MinTE" ( $\leq$  2.3 ms), flip angle = 20-35°, T1-weighting approximately 384 by 288 matrix, 40-cm field of view, bandwidth 380 to 1500 Hz/pixel, single acquisition/number of excitations, 3-mm slice thickness (interpolated to 1.5), and at least 44 (88 interpolated) slices or sufficient to cover the anatomy. In large or obese patients, phase wrap artifact can be a significant problem with parallel imaging. For studies in which phase wrap is likely to occur, parallel imaging will not be used. With obese patients the breath-hold length (no more than 22 s) and field of view will be kept constant (40 cm) and the matrix will be reduced, thus decreasing the in-plane resolution in the phase-encoding direction.

### Scan Location

The coronal volume will be prescribed from the midline sagittal or transverse locator slice. The posterior aspect of the imaging volume will be placed in the thorax at or near the posterior border of the vertebral body at the level of the heart. The position of the imaging volume will be set to ensure that the descending pulmonary arteries, segmental and proximal subsegmental branches are included in the imaging region.

### Scan Timing

Imaging time (breath hold) will be approximately 14 to 22 seconds. The MR technologists will record breath hold duration relative to the scan duration (breath-hold duration 0-25% to 100% of scan). The scan delay will be determined using 1 to 2 mL of contrast agent as a test bolus during a gradient recalled echo sequence performed at 1 image/second of one slice positioned sagittally through the main pulmonary artery. The scan delay will be calculated to place the peak of the infusion enhancement at the center of "k-space" of the pulmonary MRA since the reconstructed image contrast depicts the imaged object contrast at the time the center of k-space was acquired.

### Contrast Injection

Immediately before the administration of gadolinium-containing contrast material, the patient will hyperventilate for 30 seconds and then suspend breathing in full inspiration during the pulmonary Gd-MRA scan ( $<$ 22 seconds). Before recognition of the dangers of NSF/NFD, pulmonary Gd-MRA was performed during an intravenous infusion of 0.2

mmol/kg (approximately 40 mL) of conventional gadolinium-based MR contrast agent (gadodiamide or gadopentetate dimeglumine). In response to the increased awareness of the risk of NSF/NFD, the protocol was changed to require MultiHance, and the maximum dose was 0.1 mmol/kg body weight (approximately 20 mL). The contrast agent is injected by a commercially available magnetic resonance-compatible power injector at an infusion rate of 2 mL/s followed by an injection of 15 mL of normal saline.

## Gd-MRA: Diagnostic Criteria for PE

The diagnostic criteria for acute PE are as follows:

1. A partially occlusive intraluminal filling. This may be shown as "railway tracking," ie, a small amount of contrast material between the central filling defect and the arterial wall or, in cross sectional images, as a filling defect surrounded by contrast material.
2. Complete arterial occlusion with termination of the column of contrast material in a meniscus that outlines the trailing edge of the embolus.<sup>31</sup>

## Examination Time

Total examination time for Gd-MRA of the pulmonary arteries will be 20 minutes. This includes scout scanning for position of the images and the test bolus.

## State-of-the-Art Technology

With newer 1.5-T scanners that allow whole-body multichannel potential (eg, the Siemens Avanto, Siemens Medical Systems, Darmstadt, Germany), the same sequences planned can be used, with the added advantage that whole body, multichannel, phased array imaging is present. This permits an improved signal-to-noise ratio in the legs.

## MR Perfusion Imaging

Some have used Gd-MRA to show pulmonary perfusion based on filling of small vessels.<sup>32</sup> This is analogous to the perfusion phase of a pulmonary angiogram, which has been shown to be useful, but nonspecific.<sup>33</sup> It is also analogous to a perfusion lung scan. Most perfusion studies have been physiological investigations.<sup>34-36</sup> Those that have focused on detection of perfusion defects from PE have been preliminary and showed inconclusive results.<sup>32,37,38</sup> Newer time-resolved 3-dimensional contrast-enhanced MRA sequences, such as time-resolved imaging of contrast kinetics, that can provide both pulmonary angiography and perfusion in a single breath-hold sequence, have been developed.<sup>39,40</sup> Although these methods are now commercially available on most systems, they were not widely available at the start of PIOPED III. In addition, they typically provide lower spatial resolution MRA images in comparison to nontime resolved methods. These methods, therefore, will not be used in PIOPED III and perfusion will not be evaluated.

## Delayed-Enhanced MRV of the Veins of the Thighs

On completion of the pulmonary MRA, MRV of the thighs will be performed with the table prescribed to immediately move to the region of scout of the thighs performed at the beginning of the examination. The same imaging sequence performed for pulmonary Gd-MR angiography will be performed in the thighs with minor modifications of the parameters.

### Scan Parameters

Delayed MRV will be performed using a transmit-and-receive body coil and 3D gradient-recalled echo sequence. Dynamic thigh Gd-MRV imaging will be performed in the coronal plane using "MinTR" (TR  $\leq$  6.6 ms), and "MinTE" ( $\leq$  2.3 ms), flip angle = 20-35°, 384 by 288 matrix, 40 cm field of view, bandwidth 380 to 1500 Hz/pixel, 3- to 4-mm slice thickness (interpolated to 1.5–2.0 mm) and 44 slices (88 interpolated slices). Parallel imaging will not be used, because breath holding is not an issue. Six measurements will be performed in rapid succession before image construction to ensure that the bolus is not missed. Each measurement will take approximately 30 seconds.

### Scan Location

Imaging will be prescribed in the coronal plane to cover the thighs from the acetabulum to the tibial plateaus. The posterior aspect of the imaging volume will be set at the sacrum and the anterior aspect set anterior to the pubic symphysis to encompass femoral to popliteal veins. Veins of the calf will not be studied.

### Scan Timing

Scanning will begin immediately on completion of the pulmonary MRA station. Six measurements over the course of approximately 3 minutes will be performed to ensure that the bolus will not be missed.

### Contrast Injection

No additional gadolinium-based contrast material is necessary for the Gd-MRV after MRA. The protocol does not acquire baseline (ie, precontrast) images for subsequent subtraction from Gd-MRA/MRV images. Coronal source images of the pulmonary Gd-MRA will be submitted for interpretation. Transverse images of the thigh MRV data set obtained at greatest venous opacification will be constructed at 5 mm intervals contiguously and submitted for interpretation. A single projection image created by subtracting the first (arterial phase) of thigh imaging from the most opacified venous phase images will also be created to be used at the discretion of the central MR reader.

## Gd-MRV: Diagnostic Criteria for Acute DVT

The diagnostic criteria for acute DVT on Gd-MRV are as follows:

- Occlusive = complete filling defect, ie, failure to opacify the entire lumen due to a central filling defect (the vessel may enlarge compared with the opposite vein); and
- Nonocclusive = partial filling defect surrounded by opacification.

## Comprehensive Examination

The use of MRV of the veins of the lower extremities in combination with Gd-MRA of the pulmonary arteries creates a comprehensive study for thromboembolism comparable to the combination of contrast enhanced pulmonary spiral CT of the pulmonary arteries in combination with venous phase CT of the veins of the lower extremities.<sup>26,41,42</sup> The pelvic veins will not be investigated to decrease the duration of the examination. In PIOPED II, it was shown that most patients with pelvic vein DVT also had DVT of the veins of the thighs.<sup>26</sup>

## MRI Workstations

Workstations with a minimum resolution of 1 k pixel  $\times$  1 k pixel will be used for readings of all Gd-MRA and Gd-MRV images. All source images will be reviewed systematically using dynamic paging at appropriate gray-scale windows, followed by review of thin slab reformations at least in the coronal and sagittal planes for the pulmonary arteries and coronal and transverse planes for the veins of the lower extremities. Source images will be loaded into 3D reformat software routines for interactive display of full volume maximum intensity projection and limited volume maximum intensity views. Reformations, including maximum intensity projection images, will be made at the discretion of the reader. Principal central reader interpretation will be made from the original, unsubtracted source images. Multiple window/level settings, including "custom" settings, will be used.<sup>43</sup> In selected cases, the readers may reformat images parallel or perpendicular to the long axis of the vessel, using sliding thin slab reformations. Because most of the pulmonary arteries have an oblique course (particularly the middle lobe and lingular arteries), this can help eliminate the possibility of volume averaging.<sup>44</sup> Although the range of tissue signal intensity that must be accommodated in Gd-MRV data sets is less, and the anatomy is more conducive to straightforward cross-sectional image review than the pulmonary Gd-MRA, dynamic visualization of the veins of the thighs is still advantageous.

Incomplete visualization of the popliteal veins may result in patients taller than 6 feet because the plan is to avoid moving the patient and move only the table. The distal thighs in tall patients, therefore, may be outside of the field of view. A correction filter will be used to insure homogeneous linearity at the periphery of the image.

## Quality Control for MRI Equipment

System performance tests will be performed with the American College of Radiology MRI phantom. The relevant phantom components for this study include uniform signal and background noise regions, geometric accuracy, and a high-contrast resolution insert. Tests will be performed on a semiannual basis. All images will be submitted on compact disc to the University of Michigan for analysis. The standard American College of Radiology MRI head coil test protocol is performed to assess overall system status. In addition, the high-contrast resolution performance of each site will be measured using a protocol close to the local pulmonary MRA settings to scan the high-contrast resolu-

tion insert of the MRI phantom reoriented for a coronal acquisition. Comparable performance of all scanners will be confirmed and monitored for signal-to-noise ratio. The value of the signal-to-noise ratio will also reflect system performance for the thigh MRV scan that utilizes the body coil.

### Clinical Assessment: Methods

The Wells scoring system for a pretest clinical probability of PE will be used.<sup>2</sup> It was described previously.<sup>26</sup>

## D-Dimer

### D-Dimer: Methods

D-dimer, measured by the quantitative rapid enzyme-linked immunosorbent assay, will be considered normal if <500 ng/mL.<sup>45</sup>

## Venous Compression Ultrasound

### Compression Ultrasound: Methods

Bilateral venous duplex imaging of the lower extremities will use B-mode real-time venous compression in combination with color Doppler. Ideally, the patient will be supine, with the hip externally rotated and the knee slightly flexed. Knee flexion is used for popliteal evaluation. B-mode real time venous compression will be performed in the transverse orientation. The common femoral, femoral, popliteal, and proximal greater saphenous veins will be evaluated with sequential compression throughout with identification of flow characteristics. The calf veins will not be evaluated. Acute DVT will be diagnosed if there is noncompressibility of the vein in combination with: (a) vein enlarged in size, (b) hypoechoic vein lumen, and (c) lack of significant collaterals.

## Chest Radiograph

An upright 6-foot posterior-anterior and lateral chest radiograph will be obtained within 2 hours of the V/Q lung scan if possible and within 12 hours in all cases. If the patient is unable to sit or stand, an anterior-posterior supine chest radiograph will be obtained.

## Ventilation Lung Scan and Perfusion Lung Scan Methods

Ventilation lung scan and perfusion lung scan methods and criteria for interpretation were described in detail in the methods of PIOPED II.<sup>46</sup> The criteria for interpretation of V/Q scans are based on the revised PIOPED criteria.<sup>47</sup>

## Contrast-Enhanced Spiral CT

All clinical centers are encouraged to use scanners with 16 or more detectors. Newer scanners installed during PIOPED III will be used. In general, the techniques described for PIOPED II will be used,<sup>26,46</sup> but local centers may modify the techniques. For scanners with 16 or more detectors, the scan may start at the

diaphragm or start at the top of the apex of lung and proceed to 2 cm below the lowest hemidiaphragm. The diagnostic criteria for acute PE are as described in PIOPED II.<sup>26,46</sup>

## Venous Phase Spiral CT of the Veins of the Lower Extremities

Venous phase contrast enhanced spiral will be performed and interpreted as in PIOPED II,<sup>46</sup> except scans will commence at the acetabulum rather than the iliac crest.

## Pulmonary DSA

Pulmonary DSAs typically will require the use of 1024 × 1024 pixels when possible to allow 6 frames/s. Maximum magnification, which allows visualization of the entire lung on both views, will be used. Pulmonary DSAs will be obtained during the intrapulmonary artery injection of 25 to 50 mL of a low or iso-osmolar nonionic contrast agent injected at 20 to 25 mL/s by power injector through a 5- to 8-French side hole catheter. The criteria for interpretation will be as in PIOPED II.<sup>46</sup>

## Design Similarities and Differences Compared With PIOPED II

The methods of PIOPED III will parallel the methods of PIOPED II<sup>46</sup> to the extent that a composite reference standard will be used for the diagnosis and exclusion of PE and all images will be read by 2 blinded and study-certified readers at centers other than where the images were obtained.<sup>26</sup> An important difference is that patients with no PE according to the composite reference test will be randomized to undergo Gd-MRA/MRV. This will reduce the proportion of patients with negative tests at no loss in evaluation of sensitivity and specificity, and reduce the cost of the trial.

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