Contrast Peripheral Phlebography and Pulmonary Angiography for Diagnosis of Thromboembolism

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Abstract—At one time, direct intravascular contrast angiography was the standard method for confirmatory diagnosis of venous or pulmonary arterial thromboembolism. Although sensitive and specific, conventional catheter-based contrast imaging is invasive and associated with a risk of phlebitis and thrombosis. These procedures require specialized training and experience in catheter manipulation, as well as specialized vascular imaging equipment. In current practice, less invasive techniques have largely superseded conventional angiography because they can be performed by technologists using widely available, multifunctional apparatus under physician supervision. When results using these newer approaches are inconclusive or impractical, however, catheter-based techniques are still relied on for definitive diagnosis. The purpose of this article is to review the indications, techniques, and interpretations of contrast angiography as applied to venous thromboembolic disease. (Circulation. 2004;109[suppl I]:I-22-I-27.)

Key Words: thrombosis ■ imaging ■ angiography ■ catheterization

Radiographic Contrast Agents
Discussion of catheter-based angiography properly begins with a review of intravascular contrast agents and the potential adverse effects associated with their clinical use. The chemistry of iodine and the physics of its interaction with X-rays make it a valuable material for radiographic vascular imaging, but currently available formulations share nephrotoxic and allergenic side effects. Such events may be reduced with the use of newer agents, which are nonionic and have reduced osmolality, but they have not yet been completely eliminated. Although the pathophysiology of these effects has not been clearly delineated, several clinical features appear to increase the risk of adverse reactions and management strategies have been developed to reduce the associated risk.

Contrast-Induced Nephropathy
Baseline elevation of serum creatinine concentration is associated with worsening renal function after contrast exposure, and iodinated contrast should be administered very cautiously in patients with azotemia. Nonionic, low-osmolality agents should be employed in such cases. Additional caution is warranted in patients with diabetic nephropathy who are using metformin, the active ingredient in certain oral antihyperglycemic medications. Among these individuals, contrast exposure has been associated with severe lactic acidosis and further compromise of renal function. Medications containing metformin should be withheld for at least 48 hours after contrast exposure, and their use reinitiated only after postangiographic verification of a stable serum creatinine level. Current literature suggests a role for prophylactic medical therapy in patients at risk for renal injury.1–3 Nephrotoxicity can be minimized by hydration before and after angiography; a recent study found that contrast removal by continuous arteriovenous hemofiltration may also be protective.4

Prophylactic medical therapy with fenoldopam mesylate or N-acetylcysteine may provide renal protection when baseline function is compromised. Fenoldopam, a dopamine-1 agonist, preferentially dilates the renal vasculature and increases renal blood flow without decreasing systemic blood pressure. When used as a renal protective agent, fenoldopam is administered by intravenous infusion in a dose of 0.1 μg/kg/min for 2 hours before contrast administration followed by 0.5 μg/kg/min during and for 4 hours after angiography. However, the clinical utility of this agent was questioned in a recent prospective study, which reported no significant difference between fenoldopam and placebo in protecting renal function among 315 patients undergoing cardiac catheterization.5 N-acetylcysteine also protects against contrast-induced nephropathy. Although the method by which it does so is unclear, as a free-radical scavenger it has been shown to prevent oxidative injury when administered orally in a dosage of 600 mg twice a day for 4 doses beginning 1 day before contrast examination. Neither fenoldopam nor N-acetylcysteine has been approved by the US Food and Drug Administration for this indication. The choice of agent varies by institution and by physician, but the lower cost and relative ease of administration of N-acetylcysteine make it the more attractive option for many practitioners.

Other intravascular contrast agents with less potential for nephrotoxicity are under development, and materials currently available for other applications have been used with some success.6 Chief among these is gadolinium, a ferrous
contrast agent approved for MRI. Gadolinium has no known nephrotoxicity in humans and is relatively opaque to ionizing radiation. When injected directly into a target vessel, gadolinium has sufficient radiodensity for use as an imaging agent. It is rapidly diluted to radiographic invisibility, however, and is of little use for imaging large vascular territories. Although larger volumes of gadolinium may overcome this limitation, the safety of this approach has not been established. Carbon dioxide gas can also be effective in vascular imaging after bolus injection into the target vessel, displacing blood and demonstrating the vascular lumen as an area of decreased (rather than increased) density. The carbon dioxide bubbles dissolve rapidly in the blood and rarely cause symptomatic toxicity, but this technique should not be used in patients with right-to-left shunts. It has been used for aortography, peripheral venous scanning, and imaging of the vena cava. As with gadolinium, carbon dioxide gas performs poorly for imaging large vascular territories. Its use in pulmonary arteriography has not been described.

Allergic Reactions
Although allergic reactions to iodinated contrast agents can be severe, it is important to differentiate between true contrast allergy and transient contrast-induced nausea, which frequently occurs after intravenous administration. Mild allergic reactions can be treated with oral antihistamines, whereas more severe reactions may require subcutaneous or intravenous epinephrine. Although prevention strategies vary among institutions, a typical regimen for patients with a history of severe contrast allergy (including anaphylaxis) is to orally administer 50-mg prednisone 12, 6, and 1 hour before the procedure, and to accompany the last dose with 25-mg oral or intravenous diphenhydramine. Nonionic, low-osmolality agents—which may be less allergenic—should be employed.

Peripheral Venography
Although duplex ultrasound imaging has become the diagnostic modality of choice for extremity thrombosis, contrast venography is still used for patients in whom ultrasound imaging is compromised by recent surgery or injury involving the affected limb, confusing anatomy or poor visualization, and those with known lesions that require further delineation before treatment. Indications for venography include the delineation of deep vein thrombosis (DVT) as a prelude to catheter-directed intervention such as thrombolysis or thrombectomy, the presence of a nondiagnostic or technically poor ultrasound, and a need to obtain superior imaging of calf veins.

Technique
Catheter-based contrast venography can be performed using ascending or descending techniques. The former, used most often, involves injection of contrast into a peripheral vein followed by imaging in a proximal direction to identify DVT or occlusion. With the latter, contrast is injected centrally to evaluate reflux flow in a retrograde direction.

Ascending venography begins with placement of a catheter in a peripheral vein. The access device most often used is the familiar short intravenous catheter inserted into a superficial vein on the dorsum of the hand or foot. Fifty to 100 mL of contrast material is injected and the bolus followed by radiographic imaging as the material flows to the central veins. Upper extremity studies can be performed with the patient recumbent, whereas lower extremity studies are usually performed on a tilting fluoroscopic table with the patient initially in a standing position and then tilted to recumbency as the bolus is tracked. This approach enhances visualization of the large-capacity lower extremity venous anatomy as gravity delays the outflow of contrast.

Descending venography always requires direct catheter access into the deep veins. In most cases, the access site is the common femoral vein contralateral to the side of interest. The catheter is advanced to the vena cava and then along the iliac vein to the common femoral vein of the symptomatic lower limb. A transjugular approach may be employed to direct the retrograde catheter into both lower extremities from a single access site. With the catheter tip in the common femoral vein and the table tilted to position the patient upright, contrast is injected and tracked by fluoroscopy as it flows caudally through incompetent venous valves.

Special Considerations
When edema associated with venous occlusion makes identification and percutaneous catheterization of peripheral veins difficult, ultrasound may be necessary to guide vascular access. The saphenous veins are large superficial pathways. It is critical that access for ascending venography not be established via the saphenous vein adjacent to the medial malleolus at the ankle, which may be large and tempting, as contrast injected in this location may preferentially fill the superficial system without demonstrating the deep venous system. The likelihood that this will occur can be reduced by compressing the superficial veins with tourniquets at the ankle and knee, which drives contrast into the deep venous channels. These tourniquets should be released just before image acquisition to relieve extrinsic compression and avoid pinching both the deep and superficial veins.

Even with appropriate venous access and the use of tourniquets, opacification of the deep veins during ascending venography of the lower extremities may be difficult. Nonvisualization of the deep veins can be caused by contrast dilution in the large volume of venous blood, preferential deep-to-superficial flow that allows contrast to escape from the deep veins, or venous occlusion. Differentiating these etiologies may be impossible without direct catheterization of the deep veins. In such cases, the popliteal vein is entered under ultrasound guidance, with subsequent introduction of a 4 to 5 French angiographic catheter. Direct contrast injection into the popliteal or femoral vein should fully opacify the deep venous system of the thigh and pelvis.

Interpretation
The classical phlebographic sign of venous thrombosis is a luminal filling defect with a surrounding rim of contrast (Figure 1). The resulting appearance of parallel lines of contrast around the thrombus is referred to as the ‘tram-track’ sign. An intravascular contrast column that terminates abruptly is another good indicator of thromboembolism made more reliable when the transition forms a meniscus. Without such abrupt transition,
however, failure to visualize an expected vein is not a reliable sign of occlusion. In such cases, contrast may simply circumvent the vein through parallel superficial or deep channels. In some cases, as described above, tourniquets or direct puncture may be required to resolve this issue.

**Vena Cavography**

**Indications**
Thrombosis of the superior or inferior vena cava is suggested when symptoms of extremity venous obstruction are present bilaterally, especially when no extremity thrombus is identi-
Catheter-based imaging of the vena cava is indicated when other studies are inconclusive or equivocal, as they often are in obese patients or when bowel gas obscures the ultrasound picture. It is also used in conjunction with insertion of a vena cava filter to determine caval diameter (which influences filter selection) and to identify anatomic variants such as accessory renal veins and duplication of the infrarenal vena cava (which influence filter positioning).

Caval venography involves contrast injection rates of 15 to 20 mL/sec over 1 to 2 seconds, with filming at a rate of 2 to 4 frames per second. The image should be centered over the abdomen, encompassing the confluence of the iliac veins and the diaphragm. Lateral views are sometimes helpful when images in the frontal projection suggest a filling defect en face.

**Special Considerations**

Partial or complete duplication of the infrarenal vena cava is an uncommon anomaly, and may easily be missed on catheter imaging. Catheter-based imaging of the vena cava is indicated when other studies are inconclusive or equivocal, as they often are in obese patients or when bowel gas obscures the ultrasound picture. It is also used in conjunction with insertion of a vena cava filter to determine caval diameter (which influences filter selection) and to identify anatomic variants such as accessory renal veins and duplication of the infrarenal vena cava (which influence filter positioning).

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**Figure 3.** Artifact caused by nonopacified inflow from the renal veins simulating mural thrombus in the vena cava (arrows). Note the symmetrical appearance of this finding and the loss of distinction superiorly.

**Figure 4.** Pulmonary angiograms showing acute thromboembolism. A, A solitary embolus in the lower lobe artery of the left lung (arrow). B, Extensive involvement of the right lung of another patient with a ‘saddle’ embolus at the upper lobe artery (arrow), multiple peripheral emboli (asterisks), and poor opacification of peripheral arteries. This patient was in extremis, with a systemic arterial oxygen saturation of 72% and a pulmonary arterial pressure of 48/28 mm Hg. Right ventricular end-diastolic pressure was 18 mm Hg.
venography performed through the right femoral approach. Some have therefore advocated performing all catheter-based imaging of the vena cava from the left femoral vein, with the catheter positioned at the level of the common iliac vein for contrast administration. When the anatomy of the vena cava is unclear, it may be useful to inject contrast into both common iliac veins simultaneously at rates of 8 to 10 mL/sec.

Interpretation
As with lower extremity venography, the most reliable sign of thrombus in the vena cava is a luminal filling defect with a surrounding rim of contrast (Figure 2). Nonopacified inflow from renal and hepatic veins can be erroneously interpreted as mural-based thrombi, as it presents smoothly-marginated defects along the lateral aspect of the otherwise well-opacified vena cava (Figure 3). Correct interpretation of these normal findings is based on recognizing the typical location for renal or hepatic vein confluences, the presence of bilaterally symmetrical defects, and their loss of distinction in the more cephalad aspect of the cava, where mixing of enhanced and unenhanced blood occurs.

Pulmonary Arteriography
Indications
In many centers, catheter-based pulmonary arteriography has become an adjunct to the evaluation of patients in whom CT (computed tomography) or MR (magnetic resonance) angiography has yielded inconclusive or otherwise nondiagnostic results, or when negative studies conflict with a strong clinical suspicion for pulmonary embolism. Traditional pulmonary angiography is superior to CT or MR angiography for identification of small or subtle abnormalities such as peripheral or chronic emboli, and for detection of emboli in vessels oriented along the axial plane (which may be missed by CT angiography). In addition, a pulmonary arterial catheter provides direct measurement of pulmonary arterial pressure.

Technique
Selective pulmonary arteriography is performed using a 5 to 8 French (2 to 3 mm diameter) pigtail catheter introduced via a femoral or jugular approach and advanced through the right atrium and ventricle. This catheterization can be difficult, as indicated by the wide array of guide wires, catheters, and techniques that have been developed specifically for this purpose.

Once the target artery has been selectively catheterized, baseline pulmonary arterial pressure measurements are obtained. Although injection into the main pulmonary artery is feasible, it is safer to examine the left and right pulmonary arterial trunks separately. Contrast is injected at rates of 15 to 25 mL/sec in total volumes of 30 to 50 cc per injection. Filming is performed at high frame rates (4 to 15 frames per second), and some operators utilize cineangiography. If possible, the patient’s respirations should be suspended during image acquisition to reduce motion artifact. Digital subtraction enhancement can be extremely helpful in image evaluation. Some operators routinely perform frontal and oblique views of each pulmonary artery, resulting in contrast loads of 200 mL or more for the examination.

Special Considerations
The introduction of a catheter through the right ventricle can produce transient right bundle-branch block. Although this is of little concern in most cases, patients with left bundle-branch block (LBBB) may develop complete heart block when conduction block affects the right-sided Purkinje fibers. For this reason, LBBB represents a relative contraindication to catheter-based pulmonary arteriography unless a temporary pacemaker apparatus is immediately available; some advocate prophylactic pacemaker electrode placement in this situation.

In patients with pulmonary hypertension, rapid delivery of large volumes of fluid into the pulmonary arteries can cause fatal acute right heart failure. Most patients with chronic, compensated pulmonary hypertension, however—even those with pulmonary artery systolic pressure >60 mm Hg—tolerate pulmonary angiography without difficulty. It has been suggested that the best prognostic indicator of a successful outcome is a right ventricular end-diastolic pressure (RVEDP) <20 mm Hg. An RVEDP >20 mm Hg should be viewed as a relative contraindication to high-volume contrast injection, and contrast should be injected only in small volumes by hand in such cases.

Interpretation
The classical angiographic sign of acute pulmonary embolism is one or more intraluminal filling defects with diminished distal contrast enhancement (Figure 4). These defects can be large (as in cases of central ‘saddle’ emboli) or quite subtle. In questionable cases, additional image acquisition at varying obliquities or super-selective catheterization may help verify the presence or absence of thrombus (Figure 5).

Chronic pulmonary emboli are more difficult to identify than acute occlusions and are typically identified as stenoses, webs, or mural thickening representing organized thrombus (Figure 6). Fat emboli are generally not angiographically demonstrable.
Catheter-based angiography remains a valuable tool in the diagnosis of peripheral venous and pulmonary arterial thromboembolism. Employed when less invasive imaging modalities are impractical or have failed to provide definitive information, catheter angiography remains the gold standard. Catheter techniques require certain additional considerations, but these examinations can be safely performed by appropriately trained physicians.

References

Figure 6. Angiographic demonstration of chronic pulmonary emboli. A, A large peripheral perfusion defect in the right lung without luminal filling defects suggests long-standing arterial occlusion. B, Magnification of the upper lobe branches demonstrates multiple branch stenoses (arrows). C, Mural thickening in the hilum of the left lung is demonstrated as a wide gap between the arterial wall (black arrows) and the contrast-enhanced lumen (white arrows). This patient was dyspneic with systemic arterial oxygen saturation 82%, pulmonary arterial pressure 99/33 mm Hg, and right ventricular end-diastolic pressure 12 mm Hg.
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