The Simon nitinol filter for percutaneous interruption of the vena cava to prevent pulmonary embolism is currently undergoing a multicenter clinical trial. Preliminary clinical results are reported as work in progress. The results in 44 patients at two centers are analyzed in detail, and major events are reported from 103 patients in 17 centers in the United States during a 10-month period. The filter was successfully inserted via the femoral or jugular route in all patients through a 9-F catheter. The placement procedure was easy and without significant complications. Follow-up studies included plain radiography, ultrasoundography, magnetic resonance (MR) imaging, and clinical evaluation. No filter migration or perforation occurred among the 103 patients. Symptomatic occlusions occurred in 7%-9%, comparable to other series, and some asymptomatic occlusions were detected with MR imaging only. The implications of occlusion of the filter are discussed.

**Index terms:** Embolism, pulmonary, 60.72 • Vena cavae, filters • Vena cavae, interventional procedure, 982.1299 • Vena cavae, stenosis or obstruction, 982.458

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**THE** Simon nitinol filter (SNF or filter) for the prevention of pulmonary embolism is currently undergoing clinical trial in a multi-institutional study in the United States, with 17 participating centers. At this time, a total of 103 filters have been placed in patients. This filter is presently classified as an investigational device by the U.S. Food and Drug Administration (FDA). The trial did not include randomization with any other vena cava filter in current clinical use, since extensive published data already exist regarding the safety and efficacy of these devices.

The SNF exploits the unique thermal shape-memory properties of nitinol, a nickel-titanium alloy that can exist as a soft, straight set of wires when cooled but is instantly transformed into a previously imprinted, complex rigid filter shape when warmed (1,2). Biocompatibility of this material has proved comparable to stainless steel in animal and human studies (3,4). A cold saline infusion allows it to pass easily through a standard 9-F catheter for delivery into the inferior vena cava (IVC). Here, it is warmed to body temperature, assumes its filter shape, and locks into place. It is designed to trap emboli from the lower limbs or pelvis and prevent the emboli from reaching the lungs. The filter is 3.8 cm long, has a 28-mm dome with seven overlapping loops, and has six diverging legs with terminal hooks to engage the vena cava wall (Fig 1). The legs serve as a coarse first filter, while the dome forms a fine second filter. The filter can adapt to a broad range of vena cava widths up to a maximum of 28 mm.

This preliminary progress report focuses on detailed early clinical results of placement of the SNF in 44 patients. We also report follow-up data of the major complications of filter placement that would be reportable to the study monitor in a total of 103 patients from all 17 centers participating in the clinical trial.

**PATIENTS AND METHODS**

**Patients**

The study population consisted of 26 men and 18 women, ranging in age from 19 to 96 years (median, 62 years). Eighteen patients underwent placement of the SNF at Beth Israel Hospital (BIH), and 26 underwent the procedure at Massachusetts General Hospital (MICH) between February and November 1988. Appropriate informed consent was obtained from all patients.

The clinical indications for filter placement were those generally accepted for IVC filter placement (5). The major indications were pulmonary embolism or extensive deep venous thrombosis when anticoagulant or thrombolytic therapy was contraindicated, resulted in complications, or failed to prevent recurrent embolism. The high proportion of filter placements in neurosurgical patients at MGH is noteworthy.

**Methods**

**Insertion procedure.**—Before the procedure is started, a 500 mL bag of normal saline is cooled in a bucket of ice chips for at least half an hour. The 9-F delivery catheter is inserted percutaneously into a

**Abbreviations:** BIH = Beth Israel Hospital, FDA = Food and Drug Administration, IVC = inferior vena cava, MICH = Massachusetts General Hospital, SNF = Simon nitinol filter.
common iliac vein via a standard femoral or jugular venipuncture, on either side, with the Seldinger technique. The catheter is first used to obtain a preliminary vena cavaogram to determine the position of the renal veins and to ensure that the vena cava does not exceed 28 mm in width, after correction for magnification. The presence of thrombi or significant anatomic anomalies is also shown. The catheter tip is then repositioned just below the lowest renal vein, the optimal location for the filter dome.

The filter comes ready to be delivered. It is received preloaded in the storage-tube section of the delivery system and is preassembled with a telescoping feeder-pump section and pusher wire. The cold saline is briefly infused through the storage tube via a sideport at the rate of about 10 drops per second to cool and soften the filter. The storage tube is then connected directly to the 9-F catheter so that the cold saline infuses into the IVC for a few seconds. Typically, less than 150 mL of saline is required for filter delivery, an insufficient amount to affect patient temperature. The filter is then advanced rapidly through the catheter until its tip aligns with the tip of the catheter. This requires about six forward strokes of the feeder pump handle. Finally, a single backward stroke of the storage tube and catheter unsheaths the filter and releases it into the IVC. It is instantaneously transformed into its expanded filter shape and locks into place. The catheter is then pulled back slightly, and a follow-up venogram is obtained to check the final positioning of the filter and whether there is any leg penetration. Finally, the catheter is removed and the puncture site is compressed in the usual manner. The procedure requires only routine angiographic skills and typically takes 30–45 minutes to complete, including both vena cavaograms, if cine or digital-subtraction imaging is used.

The femoral and jugular delivery systems are identical, except that the jugular catheter system is longer and its filter is preloaded for a feet-first delivery from above. After a jugular delivery, follow-up venography can be performed through the same catheter by means of a retrograde injection of contrast medium just above the filter.

Follow-up.—The initial and follow-up examinations were directed toward the detection of complications at the venu-puncture site, such as venous thrombosis and hemorrhage, and at the filter site, including filter migration, penetration, perforation of the vena cava wall, misplacement, filter tilting, or crossing of the filter legs. Possible recurrent pulmonary embolism and systemic effects of the nitinol material were also evaluated with clinical and laboratory methods. In addition, partial or complete occlusion of the filter due to trapped emboli, an anticipated sequel of filter placement, was also diagnosed clinically or by means of noninvasive imaging, including magnetic resonance (MR) imaging.

Protocol requirements included clinical history and physical examination, documentation of the placement procedure, and plain radiography of the filter shortly after placement and again at 3 and 6 months. Optional studies included ultrasound (US) imaging of the puncture site and filter region, computed tomography (CT), MR imaging, or digital-subtraction angiography. Chest radiography and ventilation/perfusion lung scanning were also optional studies. Vena cavaography enhanced with contrast material was performed only when clinically indicated. The clinical examination at 3 and 6 months included history, physical examination of the puncture site and lower limbs, plain radiography of the filter region, and laboratory tests of blood and urine for liver and kidney function and blood clotting. Autopsy examination of the vena cava and filter of patients who died during the course of the 6-month study or later, due to any cause, was encouraged but was not a protocol requirement.

The study protocol requires that major complications at all centers be reported immediately to the study monitor. These included filter migrations, recurrent pulmonary embolism, IVC occlusions, and filter-related deaths.

No follow-up medications or other therapies were prescribed. The use or withholding of anticoagulant or thrombolytic therapy at the time of filter placement or subsequently was based purely on clinical considerations and was not influenced by the protocol.

**RESULTS**

The trial is now in progress and data are incomplete; thus, only limited trends can be reported. Of the 103 patients at all 17 centers, there were no filter migrations and no deaths related to the filter (Table 1). There was one unconfirmed case of symptomatic recurrent pulmonary embolism, and two patients had confirmed asymptomatic pulmonary embolism. There were seven cases of confirmed symptomatic IVC occlusion and two possible IVC occlusions detected on the basis of clinical findings only.

Of the 44 patients studied in Boston, 10 have undergone a 3-month follow-up and four have completed a 6-month follow-up (Table 2). Initial abdominal radiographs of the filter were obtained in all 44 patients; seven underwent abdominal radiography at 3 months, and four at 6 months. Ultrasound studies of the puncture sites were performed in 18 patients soon after placement, five at 3 months and two at 6 months. US studies of the IVC and filter region proved technically difficult due to wide variations in build and bowel contents in individual patients but

### Table 1

**Summary of Preliminary Results of SNF Placement in 103 Patients at 17 Centers**

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migrations</td>
<td></td>
</tr>
<tr>
<td>Cranial</td>
<td>0</td>
</tr>
<tr>
<td>Caudal</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0 (1)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2</td>
</tr>
<tr>
<td>IVC occlusion</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
</tr>
<tr>
<td>Deaths related to filter</td>
<td>0</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses represent additional patients with clinically suspected findings only.

### Table 2

**Summary of Preliminary Results of SNF Placement in 44 Patients**

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative complications</td>
<td></td>
</tr>
<tr>
<td>Entry site thrombus</td>
<td>5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>Failure to introduce</td>
<td>0</td>
</tr>
<tr>
<td>Major misplacement</td>
<td>0</td>
</tr>
<tr>
<td>Leg penetration</td>
<td>0</td>
</tr>
<tr>
<td>Migration</td>
<td>0</td>
</tr>
<tr>
<td>Tilting of dome</td>
<td>24</td>
</tr>
<tr>
<td>Spindle formation</td>
<td>1</td>
</tr>
<tr>
<td>Leg crossing</td>
<td>4 (2)</td>
</tr>
<tr>
<td>IVC patency</td>
<td></td>
</tr>
<tr>
<td>Patient with thrombus</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Occlusion (symptomatic)</td>
<td>3 (2) [7-11]</td>
</tr>
<tr>
<td>Occlusion (asymptomatic)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Recurrent pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0 (1)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
</tr>
<tr>
<td>Related to filter</td>
<td>0</td>
</tr>
<tr>
<td>Unrelated to filter</td>
<td>7</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses represent patients with clinically suspected findings only. Numbers in brackets are percentages.

* Dome tilting of up to 30° occurs as a normal adaptation to a small IVC lumen. It does not affect filtering efficiency, since the dome hole sizes are unaffected.

1 Spindle formation is an intermediate stage of dome recovery that may occur in very small vena cavae.

2 Leg crossing occurred in the first four patients due to a pusher wire problem that has been corrected.
were attempted in nine patients in the early period after placement, in five patients at 3 months, and in two at 6 months. CT was performed in three patients. Twenty-five MR imaging examinations with nongated T1-weighted sequences or a new fast gradient-echo sequence were performed in 21 patients. MR imaging appears to be a promising noninvasive method for determining the patency of the vena cava and for documenting thrombi captured in the filter or complete occlusion of the vena cava (6). In seven patients, follow-up was only by telephone interview of the referring physician or patient. One patient refused all follow-up examinations.

Seven patients died of causes unrelated to the filter placement during the trial period. None of these patients died of pulmonary embolism. One autopsy study was obtained during the study period and showed no thrombus in the filter. A second autopsy was performed on a patient after the 6-month study period and showed an organized thrombus attached to the legs—a result that confirmed findings of an earlier follow-up MR imaging study—as well as a more recent thrombus captured in the filter dome.

Forty-one filters were delivered by the femoral route, 29 on the right and 12 on the left, and three were delivered by the jugular route, two on the right, and one via the left external jugular vein. The filter-placement procedure was well tolerated by all 44 patients. There were no failures of introduction. Some early problems with material caused difficulty in starting the filter movement out of the storage tube, and some leg crossing resulted in the first four patients, without clinical effect. These early problems were resolved by minor design changes of the feeder system. There was no clinical evidence of hematoma formation at the venous puncture site. Five of the 18 patients studied with US in the days following the procedure showed some local thrombosis. Three patients were symptomatic. This finding could represent local thrombus formation due to intimal injury, thrombus peeled off of the catheter surface during catheter withdrawal, or new development of venous thrombosis in patients not receiving anticoagulant therapy. Femoral thrombus was noted subsequently in one patient who developed disseminated vascular coagulation. No arteriovenous fistula formation or air embolism occurred.

The filter tip was properly positioned within 3 cm of the lowest renal vein in all patients, except three in whom it was delivered slightly lower than planned due to early operator inexperience. In two cases, the dome appeared to engage the inferior edge of the lowest renal vein without affecting renal venous return. It should be noted that in large vena cavae, the tip of the filter normally descends about 2 cm during dome formation as the catheter is being withdrawn. It is possible to readvance the filter upward to its optimal position before the legs are released, but this is not recommended because of the risk of damage to the venous endothelium. In smaller vena cavae, the filter dome commonly assumed a slightly tilted position.

Penetration of the vena cava wall by the filter legs did not occur. There was no clinical evidence of retroperitoneal hemorrhage, nor was any seen in patients followed up with MR imaging or CT. There were no instances of either cranial or caudal filter migration. The device appears to secure itself well.

DISCUSSION

It is now widely accepted that vena cava filters have become the method of choice for the prevention of pulmonary embolism for patients who cannot be given anticoagulant or thrombolytic drugs or for whom such drugs have failed (7). In the United States, the only device currently available for clinical use is the Greenfield filter (8). At the time of its introduction in 1973, placement of the Greenfield filter required surgical venotomy of the jugular or femoral vein in order to insert the large metal delivery capsule that houses the folded filter. In recent years, percutaneous insertion of the Greenfield filter has been performed with increasing frequency. However, this requires dilation of the venipuncture track to accommodate a 29-F (measured outside diameter) introduction sheath, about 9.6 mm in outside diameter (9). Questions have been raised about the mechanical efficacy of the Greenfield filter, which has been shown to allow the passage of large emboli once its apex has been filled with clot, a condition resulting in recurrent pulmonary embolism (10). Other problems included tilting, misplacement, caudal or cranial migration, perforation and fracture of the Greenfield filter, and thrombosis at the entry site (11,12). IVC occlusion is reported to occur in about 5% of patients (13).

For these reasons, a number of investigators have attempted to develop improved filter devices that are easier to insert, have lower complication rates, and produce a more effective mechanical filtering action. The SNF is one of these. Others include the bird’s nest filter, the Amplatz filter, and the Gunther filter (14–16). The SNF is distinguished by its ease of insertion and mechanical effectiveness. The device is preloaded to eliminate handling of the filter device, and the delivery system is pressembled. The delivery is accomplished through a 9-F (3-mm outside diameter) angiographic catheter; thus, local complications at the puncture site are minimized. The clinical experiments have documented an jugular vein approach on either side, but access to the central venous system may eventually be gained via a number of alternative peripheral veins. The external jugular vein has been used in one patient. The only special requirement is the infusion of a cold saline solution during the brief passage of the filter through the catheter.

During the clinical trial a number of new observations and insights have emerged about the filter placement and the capture of emboli en route to the lungs. These relate to tenting of the vena cava wall, tilting of the dome, and occlusion of the filter by thrombus.

Local tenting of the vena cava wall due to pressure by the rim of the filter dome was observed frequently, particularly in smaller vena cavae, but appeared to have no significant hemodynamic impact or ill effects. The tented portion fills in within a few months due to development of a slightly thicker neointima at the points of contact just within the outer rim so that the rim may appear to lie just outside the main column of contrast medium on follow-up venograms. Similarly, though rarely, the distal end of a filter leg may appear to lie alongside the lu men. Earlier animal experiments have documented that this effect is due to a longitudinal crease formed by the legs in the vena cava wall and covered with endothelium. The leg ends have not penetrated the vena cava wall.

The dome of the filter frequently was observed to be tilted about 20°–25° toward the wall of the vein, particularly in small vena cavae (Fig 2). This result is due to the dome geometry, which is more easily accommodated in a confined space if the dome is slightly inclined rather than perfectly transverse. However, such sloping does not impair the filtering efficiency of the filter because the size of the openings in the dome remain unchanged. Fewer openings of a given size are required to subdivide a smaller IVC cross section. This contrasts with the Greenfield filter, in which tilting enlarges the size of the openings between some of the legs and
Thus reduces the mechanical efficiency of the device, an effect well documented in in vitro studies (17). Portions of the dome loops or legs that are in contact with the wall of the vena cava become covered by a neointimal layer within 2 weeks (3).

Traditionally, occlusion of a vena cava filter has been regarded as a serious complication. However, the SNF is designed to trap emboli in the IVC in order to prevent them from reaching the lungs. We would therefore argue that filter occlusion should be considered an unfortunate but expected event in a small but significant percentage of the patients in our study. Occlusion is certainly preferable to pulmonary embolism, the potentially fatal alternative. Partial or complete occlusion may be associated with obstructive symptoms of variable severity, depending on the size of the emboli, the completeness of obstruction, and the state of the collateral venous return. The symptoms are usually transient, with recovery in weeks or months as lysis and recanalization of the IVC or enlargement of collateral vessels occur. We believe that the frequency of occlusion thus primarily reflects the recurrence rate of pulmonary embolism and the size of the emboli in a given patient population rather than any defect of filter design or performance.

The frequency of recurrent pulmonary embolism in patients such as ours who cannot receive anticoagulant treatment, and thus the potential clot capture rate of the filter, is difficult to determine and can be estimated only indirectly. Before the use of anticoagulants, mortality due to pulmonary embolism was reported to be about 30% (18), while the current mortality in patients treated with anticoagulant therapy is only 8% (19). This difference of 22% thus represents the probable fatal recurrence rate of pulmonary embolism, when anticoagulants are not used. Since less than one-third of significant pulmonary emboli are lethal, there must be at least three times this number of clinically significant recurrent emboli, or more than 66%. It seems clear that once a patient has had a single episode of embolism and remains untreated with anticoagulants, the probability of a recurrence is very high. This is supported by autopsy studies of pulmonary embolism (20, 21) and a clinical study of the Gunther filter with computed enhanced CT, which showed thrombi in 39% of the filters studied at an arbitrary point of time in the follow-up period (22).

Clinical reports of patients with filters in place indicate that 5%-10% experience symptoms and signs of IVC occlusion (22). In view of the estimated high embolism recurrence rate, it seems that some large single emboli or several smaller emboli can be massive enough to cause a symptomatic occlusion when captured in the filter. Furthermore, since improved imaging methods indicate that complete occlusion may occur without symptoms if good venous collaterals exist, the total number of complete occlusions is probably higher than previously reported. In the BIH/MGH subseries, five of the 44 patients (11%) had lower-limb swelling. MR imaging showed filling defects in the filters in these patients, which could represent captured emboli. Three of 44 patients (7%) showed complete occlusion (Table 2). In addition, two patients had clinical findings that may have been due to IVC occlusion, but this result was not confirmed with imaging studies. The symptomatic occlusion rate in the BIH/MGH series is thus 7%-11% (three plus a possible two of 44 patients), and the overall symptomatic occlusion rate is 7%-9% (seven plus a possible two of 103 patients in all 17 participating centers), findings comparable to those previously reported by other investigators. Another three completely asymptomatic patients also showed complete occlusion, which would not have been detected without a routine MR imaging follow-up study. To our knowledge, this is the first clinical study in which it has been possible to use noninvasive MR imaging to assess the presence of thrombus in a vena cava filter, since the SNF is nonferromagnetic (23). This suggests that the true total occlusion rate for other IVC filters may be greater than previously reported without MR imaging.

Partial or complete filter occlusion may cause various transient but nonlethal clinical problems. Small emboli, generally asymptomatic or associated with mild leg swelling, can be recognized as filling defects when imaged with contrast material-enhanced CT, digital-subtraction angiography, or vena cavography or with MR imaging or duplex US. Recovery occurs within days or weeks. In contrast, a large embolus or cluster of small emboli may cause complete occlusion of the vena cava with total absence of flow on MR or US images. A complete occlusion may also be asymptomatic if adequate collateral veins exist. Generally, collateral veins are multiple and small and will not allow passage of emboli. Occasionally, one or two collateral veins may be large. This large size could explain recurrent pulmonary embolism (24). However, if the collateral veins are compromised, there may be severe lower-limb swelling that can persist for weeks or months (25,26). MR images showed that three of our patients with no symptoms had complete occlusion. Five patients had clinical signs of occlusion that were confirmed in three with MR imaging. It is of interest that five of the eight patients with complete occlusion were neurosurgical patients. Such patients tend to be more prone to develop extensive venous thrombosis with obstruction of the collateral venous pathways (27).

Thus, it is likely that the rate of filter occlusion reflects the prevalence of recurrent embolism in the various populations of patients who receive the filters. Symptomatic occlusions at a rate of 5%-10% have been reported in various other studies of filters (22). We believe these occlusions do not indicate filter failure and thus cannot be used to compare filter efficiency. In fact, too low an occlusion rate should raise questions of patient selection or, perhaps, of significant clots being allowed to pass through the filter. These emboli may be missed clinically, and routine fol-
low-up ventilation/perfusion radionuclide studies are rarely used (28). Even deaths due to pulmonary embolism may be ascribed to the known underlying cardiac disease or malignancy, as autopsies are performed in only a small percentage of fatalities in hospitals.

The possibility of local thrombosis occurring on the filter itself as a reaction to a metallic device in the bloodstream is difficult to rule out with certainty. This would be difficult or impossible to distinguish from captured emboli from the veins of the lower limb or even from the catheter surface during withdrawal. The nitinol material of the SNF has been shown to have low thrombogenicity in animal experiments (3). Furthermore, since the majority of SNFs in humans remain clot-free, inherent thrombogenicity of the nitinol wire seems unlikely. In this population of patients with SNFs and without anticoagulation treatment, the high probability of recurrent embolism remains the most likely cause of filter occlusion.

All attempts to insert the filter were successful. There was no filter migration or significant misplacement. Only one filter dome failed to form completely in an extremely small vena cava, and its intermediate spindle shape was considered satisfactory. Crossing of the filter legs was extremely rare after an initial problem with the pusher wire was corrected. Some thrombus developing at the venipuncture site within a week of the procedure could represent venipuncture trauma, coincidental venous thrombosis, or stripping of the thrombus layer from the surface of the small-bore delivery catheter during withdrawal (29). The rate of recurrent pulmonary embolism was very low. Pulmonary embolism was suspected in one of 103 patients on the basis of clinical findings and a change in the pattern of abnormal findings on ventilation/perfusion scans. Another patient was asymptomatic, but new perfusion defects were observed on a routine follow-up perfusion scan at 2 weeks. A vena cavaogram demonstrated a thin thrombus extending above the filter from clot contained within it. No deaths were attributable to recurrent pulmonary embolism or any complication of filter placement.

In conclusion, our initial experience with the SNF is encouraging. The procedure for percutaneous filter insertion is simple, quick, and relatively free of significant complications at the venipuncture site due to the small size of the introducer catheter. The operator never handles the filter, and the delivery system requires no assembly. The only special requirement is the infusion of cold saline while the filter is being advanced through the catheter.

Partial or complete vena cava occlusion, which may be symptomatic or asymptomatic, is regarded by the authors as an expected effect of successful trapping of thromboemboli in the filter. In the larger series of 103 patients, symptomatic occlusion occurred in 7%–9%, a finding comparable to those in published series of other filters. All patients showed marked clinical improvement over a period of weeks or months. The use of MR imaging permits noninvasive demonstration of thromboemboli in the filter. In our detailed BIH/MGH series, we demonstrated filling defects or occlusions in 25%–29% (11) plus two possible that of autopsies in the presence of simple, recurrent, and fatal pulmonary embolism to site inferior vena cava interruption with the Greenfield filter. Vasa 1987; 16:84–85.


ADDENDUM

Since this article was submitted, one migration of a SNF has occurred and will be included in a future report.

The bird’s nest filter (Cook, Bloomington, Ind) has been recommended for clinical approval by an FDA panel since this article was submitted.

Acknowledgments: We are indebted to the many unnamed investigators currently participating in the clinical trial of the SNF at numerous centers in the United States. Their interest and dedication in the exploration of new interventional developments and in the pursual of the demanding protocols necessary to obtain meaningful data have been remarkable. We thank Anne Maloney, RT, Beth Israel Hospital, and Joseph DeBenedetto, RT, Massachusetts General Hospital, and their staff for technical assistance, and Claire Martinez, BA, for manuscript preparation.

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