EDITORIAL

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Tumor Angiogenesis

The Future Is Now

In this issue of *Annals of Surgery,* Frank and others have described measurement of tumor angiogenesis to determine prognosis in patients with node-negative colon cancer. The hypothesis was that the amount of angiogenesis will correlate negatively with prognosis, presumably because angiogenesis is necessary for tumor growth and metastases. The authors used a relatively simple technique to measure angiogenesis, immunoperoxidase staining with an antibody for endothelial cell factor VIII–related antigen. This technique could be readily applied in most pathology laboratories. The authors demonstrated that patients with higher angiogenesis scores had decreased 5-year survival rates and that the angiogenesis score and grade were better predictors of survival than tumor grade, size, and site.[1] Similar reports have been described recently by other groups for patients with lung, breast, and prostate cancer.[2–4] It appears from this work that the tumor angiogenesis score has prognostic importance and should be provided as part of the pathologic evaluation of tumor specimens from patients with these common cancer diagnoses.

The clinical significance of angiogenesis comes from important questions about the basic biology of tumor. Why do some tumors metastasize and others do not? What causes tumors to metastasize? Pioneering basic research by Folkman et al.[5] and Liotta et al.[6] independently demonstrated the importance of tumor angiogenesis for the metastatic potential of tumors. There is marked heterogeneity of tumors such that only a small portion (<10%) of the tumor develops angiogenic activity. The new vessels that are recruited support the growth of the angiogenic and nonangiogenic tumor cells alike. It is also probable that as neovascularization increases within a tumor, the surface area for potential escape of tumor cells into the systemic circulation and the propensity for the development of metastases increase.[7]

Experimental evidence has shown that angiogenesis supports expansion of a primary tumor and the development of metastases. Any significant increase in tumor mass must be preceded by an increase in blood vessels to provide access for the delivery of nutrients to the tumor cells. Recent studies have confirmed the hypothesis that tumor growth is dependent on angiogenesis. Some experimental tumors make specific substances, such as vascular endothelial cell growth factor, that are capable of mediating angiogenesis. If vascular endothelial cell growth factor is inhibited by a specific antibody, microvascular density is reduced and there is a dramatic inhibition of tumor growth.[8] Basic fibroblastic growth factor is another factor that is capable of enhancing angiogenesis of experimental tumors. Recent studies have demonstrated that antibodies against it will inhibit angiogenesis and tumor growth *in vivo,*[9] and administration of it will enhance angiogenesis, growth, and metastatic behavior of tumors.[7] Furthermore, recent evidence suggests that angiogenesis may not only enhance tumor growth by supplying more nutrients to the tumor, but also may work through paracrine effects of endothelial cells. Endothelial cells are capable of releasing growth factors that stimulate tumor cells. It appears that there may be a bidirectional paracrine relationship between tumor cells and endothelial cells. Tumor cells release substances that stimulate endothelial cells, and endothelial cells in return release substances that promote tumor cell growth.[7]

Modulation of angiogenesis is mediated by genes that can initiate angiogenesis as well as by genes that can turn off inhibitors of angiogenesis. One example of the latter is thrombospondin, which is an inhibitor of angiogenesis.[10] When cell lines are transformed to a malignant phenotype, the production of thrombospondin may be downregulated. Studies suggest that the control of thrombospondin is linked to the tumor suppressor gene p53 and that mutation of the p53 gene is associated with decreased production of thrombospondin, angiogenesis, and tumor formation. However, in one recent study of

patients with localized breast cancer, p53 and angiogenesis correlated with disease-free survival, but not in the same patients; that is, p53 mutation did not seem to enhance angiogenesis.[3]

The reproducible findings by different groups of investigators linking tumor angiogenesis to survival among cancer patients with similar disease stages suggest that the future is now for angiogenesis. Surgeons should insist that pathologists carefully grade angiogenesis as an important prognostic factor. Studies should be undertaken to treat patients with node-negative colon cancer with adjuvant chemotherapy based on the pathologic assessment of increased tumor angiogenesis. Similar studies should be performed in patients with node-negative breast cancer. Instead of treating all node-negative breast cancer patients with chemotherapy, chemotherapy can be administered to patients with a worse prognosis, as identified by assessment of angiogenesis. The research work of Folkman et al. has provided the experimental rationale and support for the investigation of angiogenesis in patients with cancer.[5] Future work may focus on reducing metastases or tumor size or controlling tumor dissemination at the time of surgery with the use of anti-angiogenesis factors.

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CL-32

Evolution of a New Device for the Prevention of Pulmonary Embolism

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The embolus trap (ET) is a new device that interrupts the inferior vena cava (IVC) for the prevention of pulmonary embolism. It has a central column from which six wires extend in two tiers. The adjacent wires are formed into loops with hooks at the distal ends that grip the vein wall. Each tier contains three wire loops, and the loops are staggered circumferentially between the tiers. The ET was implanted into the IVC in 26 dogs via a femoral or jugular venotomy. IVC patency was evaluated by venacavagrams. Autologous clots were embolized via the femoral vein to test the efficacy of the ET. The animals were followed for 1 to 4 months prior to postmortem examination. The ET remained patent in all animals and consistently trapped the thromboemboli while preserving blood flow. Lysis of the trapped emboli was observed in 4 to 6 weeks. There was no evidence of malpositioning, penetration through the vein wall, or migration of the ET.

The introduction of transvenous inferior vena caval interruption for the prevention of pulmonary embolism heralded a new era in technological advances in endovascular surgery.

The first of these devices was introduced in 1967 by Mobin-Uddin et al.[1] The Mobin-Uddin umbrella filter (UF) (**Figure 1A**) was an umbrella-shaped device with six spokes radiating from a central hub. The spokes were covered with a thin sheet of Silastic (Dow Corning Corp., Midland, Michigan) which had 18 perforations that were 3 mm in diameter. The UF was effective in trapping thromboemboli, but resulted in thrombosis of the inferior vena cava (IVC) in a large percentage of patients. This was largely due to the small size of the perforations in the filter that restricted blood flow.

A device that improved upon the UF was introduced in 1973 by Kim-Ray-Greenfield.[2] The Greenfield filter (GF) (**Figure 1B**) consisted of six stainless steel wires arranged in the shape of a cone. The spacing between the wires ranged from 2 mm at the apex of the cone to 11 mm at its base. This filter had a significantly higher patency rate than the UF because it did not restrict blood flow. Complications of the GF have included passage of small emboli through the filter, decreased effectiveness in larger IVC diameters, tilting within the IVC, crossing of its adjacent wires, penetration of wires through the vein wall, and migration of the filter.

Mobin-Uddin has recently developed a filter, the Mobin-Uddin embolus trap (ET) that improves upon the GF.

EMBOLUS TRAP DESIGN

The initial ET (prototype I) (**Figure 2**) consisted of a central column from which wires were arranged in three tiers. In each tier, two wires were crossed at the central column and angled downwards. The wires in each tier were staggered to cover the entire circumference, and their distal ends were shaped into a hook for fixation. The problem of vein wall penetration by single wires had not been solved at the time the first prototype was developed. As animal experimentation began, a simple discovery led to the solution of this problem. While the ET was being loaded into the catheter, the distal ends of two adjacent wires crossed. It was realized that if the wires were crossed into a loop with hooks at the distal ends, this shape would securely fix the device in the IVC and would prevent penetration of the wires through the IVC wall.

This loop-hook design of the wires was incorporated into the next three prototypes of the ET. To shorten the length of the ET, the wire loops were constructed in two tiers. Two options for wire configuration were available: four loops in two tiers or three loops in two tiers. Initial animal experiments were done using the four-looped design (prototype II). This was found to be thrombogenic secondary to there being many wires in close proximity. The three-looped design (prototype III) (**Figure 3**) was not thrombogenic and worked well; this became the final wire configuration.

The initial three prototypes of ET were made of a stainless steel alloy called elgiloy. The wire loops made of elgiloy did not expand well to fit larger IVC diameters. After a new material, nitinol (a nickel-titanium alloy) became available, the ET was manufactured from this (prototype IV) (**Figure 4**). The loop hooks made of nitinol expanded to fit all IVC sizes and maintained their shape. The Simon nitinol filter,[3] which is currently available, requires a cooled saline drip during insertion. The ET does not rely on the thermal shape memory properties of nitinol to maintain its shape and, therefore, does not require the cooled saline drip during insertion.

MATERIALS AND METHODS

Experimental Studies

Animal experiments were carried out using 26 mongrel dogs weighing 45 to 65 pounds. After being anesthetized with thiamylal sodium (20 mg/kg), the dogs were endotracheally intubated and were either allowed to breathe

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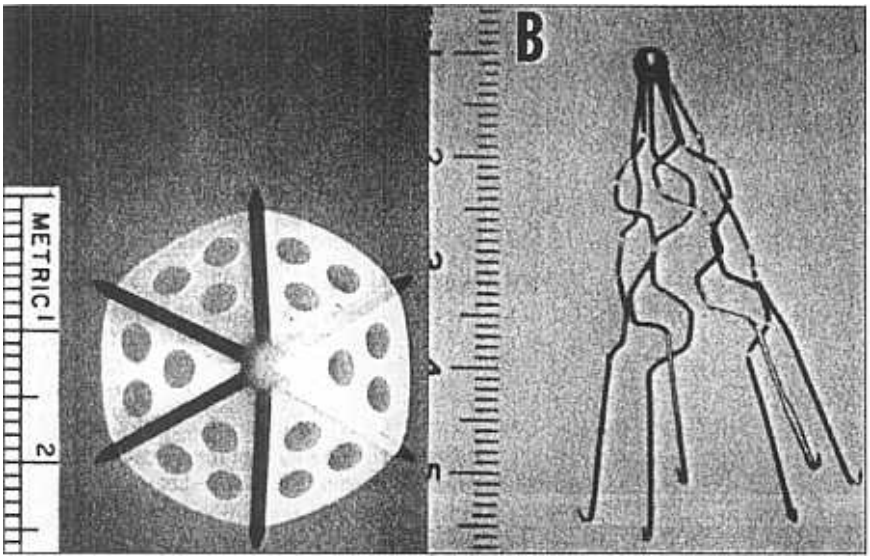

Figure 1. A. Mobin-Uddin umbrella filter. **B.** Kim-Ray-Greenfield filter.

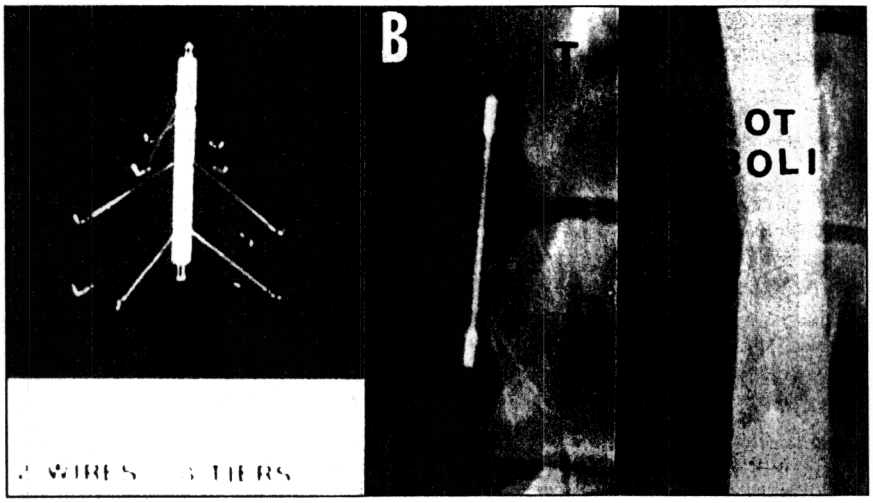

Figure 2. A. Embolus trap: prototype I (2 wires in 3 tiers, elgiloy) **B.** Radiograph of the abdomen in a dog showing the embolus trap within the inferior vena cava. **C.** Angiogram of an inferior vena cava in a dog immediately following clot embolization. Note trapped emboli within the embolus trap and that blood flow has been preserved. The distal wires of the embolus trap are penetrating through the inferior vena cava wall.

room air or placed on a ventilator. The ET was inserted into the infrarenal IVC.

Implantation Procedure

Using a loading cone, the ET is collapsed into a capsule attached to a catheter. The catheter is then inserted via the jugular or femoral vein and fluoroscopically guided into the IVC. A stylet within the catheter ejects the device into the IVC where the ET wire loops expand and grip the vein wall, fixing the ET into place. The catheter is then removed, and the vein is ligated. To prevent thrombus formation within the catheter, a heparinized saline drip is used during insertion. No systemic anticoagulants were given prior to or following ET insertion.

Acute Studies

The dogs were killed immediately after experimentation and then examined (**Table**). Acute studies were done to evaluate the ET's ability to trap emboli. Autologous clots were made by collecting the animals' blood in 5-mL syringes and refrigerating the clotted blood for 1 to 7 days. The autologous blood clots were transferred into a 60-mL toomey syringe containing saline solution and then embolized via a 14-Fr or 16-Fr Robinson catheter that had been inserted into the femoral vein.

The 1- to 3-day-old clots were mobile and were easily embolized through the syringe. The 7-day-old clots were firm and well formed, and these were dissected into 5-mm × 10-mm and 10-mm × 25-mm sizes and then embolized. Venacavagrams were done to assess the trapping of emboli by the ET. After the dogs were killed, postmortem examinations were conducted as follows: 4,000 units of heparin was given intravenously just before death to prevent postmortem clot formation prior to examination of the ET. The segment of the IVC that contained the ET was excised and examined to evaluate the ET's ability to trap the emboli. The lungs were also examined for any evidence of embolization.

Chronic Studies

After ET insertion, the dogs were followed for 1 to 4 months (Table). The dogs were followed to observe vein patency, wire-loop penetration through the vein wall, thrombus formation within the ET, and ET migration. The dogs that did not have autologous clots embolized had venacavagrams at 1 week and then at 4-week intervals. They

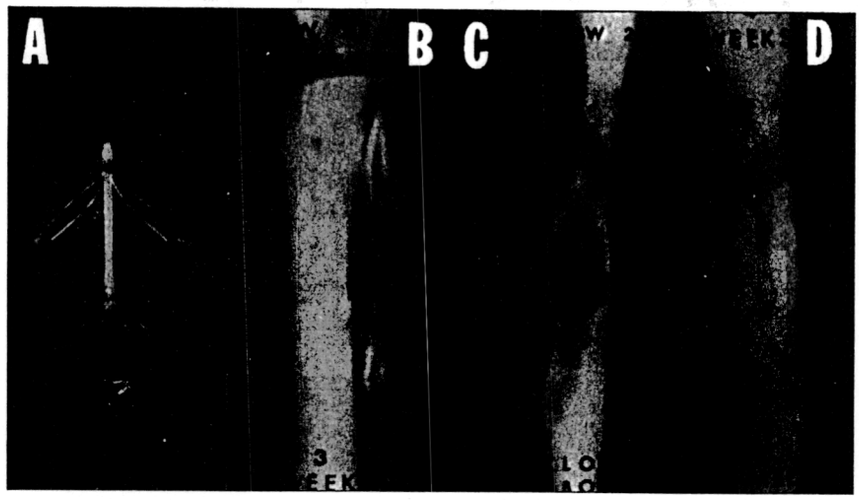

Figure 3. A. Embolus trap: prototype III (3 loops in 2 tiers, elgiloy) **B.** Angiogram of the inferior vena cava in a dog obtained 3 weeks after insertion of the embolus trap. Note free flow of blood through the embolus trap. **C.** Angiogram of the inferior vena cava in the same dog obtained immediately after embolization of autologous clots. Note that the contrast media flows around the trapped emboli within the embolus trap. **D.** Angiogram of the inferior vena cava in the same dog 4 weeks after clot embolization. Note lysis of trapped emboli with some remnant of organized thrombus within the embolus trap.

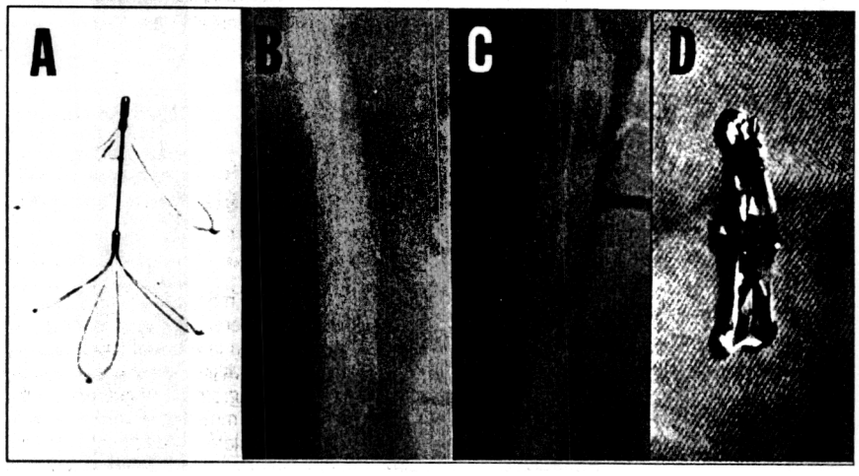

Figure 4. A. Embolus trap: prototype IV (3 loops in 2 tiers, nitinol). **B.** Angiogram of the inferior vena cava in a dog obtained 4 months after insertion of the embolus trap. Note free flow of blood through the embolus trap. **C.** Angiogram of the inferior vena cava in the same dog following embolization of autologous clots at 4 months just prior to death. Note contrast media flows around the trapped emboli in the lower and upper tier. There is no penetration of the wire-loops through the vein wall. **D.** Postmortem specimen of the inferior vena cava in the same dog obtained just after clot embolization. Note trapped emboli in the upper and lower tiers of the embolus trap.

also had postmortem examinations after death. The dogs that had autologous clots embolized had venacavagrams immediately after embolization to assess ET's trapping ability and then at 2-week intervals to observe resolution of the trapped emboli. During the postmortem examination, the lungs in these dogs were examined for any evidence of embolization.

In prototype III, 4 of the dogs were followed without having had clots embolized and were killed at intervals between 1 and 4 months. For the other 4 dogs, after the ET's patency had been confirmed by venacavagrams at 2 months, autologous clots were embolized. All of these dogs were killed and examined after being followed for 4 months.

In prototype IV, 1 of the dogs was followed without having had clots embolized. After the ET's patency was confirmed at 1½ months, this dog was killed. The other 3 dogs were followed for 4 months. In 1 of these dogs, autologous clots were embolized just prior to death. In the other 2 dogs, autologous clots were embolized at 2 months and then again at 4 months just prior to death.

Animal care complied with the "Principle of Laboratory Animal Care" (formulated by the National Society for Medical Research), and the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health Publication.

RESULTS

Acute Studies

All of the embolized autologous clots were trapped by the ET. Blood flow was preserved, and no pulmonary embolizations were found.

Chronic Studies

Prototype I. This prototype had the single wire design. The thromboemboli were trapped by ET; however, the ET's wires penetrated the vein wall.

Prototype II. The dogs did not have clots embolized. They were followed for up to 4 months prior to death. Thrombus formation was noted in 3 of the 4 subjects. In 1 dog, the 1-week venacavagram demonstrated a thrombus that had formed on the central column and extended to the upper tier. Blood flow was preserved, and significant lysis of the thrombus was seen at 2 weeks. In 2 other dogs after death at 4 months, postmortem examination demonstrated a small amount of organized thrombus on a portion of the central column. Because of the thrombogenicity of this four-looped design, no embolization studies were conducted, and a new prototype containing three loops was developed.

Prototype III. In the dogs that did not have autologous clots embolized, the ET remained patent in all subjects until death. No thrombus formation was found on post-

mortem examination. Of the dogs that did have autologous thrombi embolized, the ET consistently trapped the thrombi. Venacavagrams demonstrated lysis of the trapped emboli within 4 to 6 weeks. At postmortem examination, some remnants of organized thrombus were found within the device in 2 dogs. Blood flow was preserved, and there was no evidence of pulmonary embolization. In all of the dogs, there was no migration of the ET, and its wire loops had not penetrated the vein wall.

Prototype IV. In the dog that did not have autologous clots embolized, the ET remained patent. No thrombus formation was found on postmortem examination. Of the dogs that did have autologous clots embolized, the ET consistently trapped the emboli. Venacavagrams demonstrated lysis of the trapped emboli within 4 to 6 weeks. At postmortem examination, no thrombi other than the embolized clots were found, the device was securely fixed and well centered within the IVC, the wire loops had not penetrated through the vein wall, and there had been no migration of the ET.

TABLE

Methods and Results

	Prototypes			
	I	II	III	IV
Methods				
Design	2 W, 3 T	4 L, 2 T	3 L, 2 T	3 L, 2 T
Materials	Elgiloy	Elgiloy	Elgiloy	Nitinol
No. of dogs				
Acute studies	2	2	1	1
Chronic studies	4	4	8	4
Follow-up (months)	1–2	1–4	1–4	1–4
Results				
Patency in nonembolized dogs	100%	100%	100%	100%
Thrombus formation	0	1	0	0
Trapping (emboli ≥5 mm)	100%	—	100%	100%
Resolution of trapped emboli	Partial	—	Complete	Complete
Penetration vein wall	Yes	0	0	0
Migration	0	0	0	0

W = wire; T = tiers; L = loops.

COMMENTS

There has been an ongoing search for an ideal device to interrupt the IVC for the prevention of pulmonary embolism. The ideal characteristics of a new device would include: (1) device insertion through a small-diameter catheter to reduce insertion injury to the vein, which may result in venous thrombosis; (2) percutaneous placement via a jugular or femoral approach; (3) simplicity of insertion; (4) one size fitting all caval sizes; (5) secure fixation without injury to the vein wall; (6) use of nonthrombogenic materials; (7) efficacy at trapping thromboemboli of 5 mm or greater diameter with preservation of blood flow; and (8) resolution of trapped emboli. Many devices have been in use.[3-5] The GF is currently the gold standard for the devices in this category. It has a high patency rate and is effective in trapping large emboli, but many problems have also been associated with its use. The newly designed ET by Mobin-Uddin improved upon the design of the GF and has been able to solve many of the GF's problems. We will discuss some of these problems and how ET solves them.

When the GF is released, its cone shape often causes it to tilt to one side and assume an angled position in the IVC. Studies have shown that a tilted filter is less effective at trapping emboli.[6-9] The wire-loop design of the ET and two-tiered system centers the device within the IVC and prevents tilting.

Another complication resulting from tilting of the cone-shaped GF is that when the apex of the GF rests against the caval wall, it can become a nidus for thrombus formation. Proximal extension of thrombus from the apex of the GF has been reported.[10,11]

The single wire legs of the GF have been noted to penetrate the IVC, and penetration of several structures by the GF legs have been reported, including the duodenum,[11,12] small bowel,[13-15] ureter,[11] kidney,[16] lumbar ganglion,[17] vertebral body,[14] psoas muscle,[12,16] diaphragmatic crus,[12] lumbar artery,[18] and aorta.[19] Some of these cases required operative intervention.[17,18,13-15,20] The ET's design solves the problem of wire penetration. Its pairs of adjacent wires are crossed into loops that hook at the distal ends. The hooked ends grip the vein wall and secure the device within the IVC. The crossed wires in each loop prevent vein wall penetration.

The GF's adjacent single wires sometimes become crossed[9,21] when the filter is loaded into the catheter. When this complication occurs, large spaces are created through which thrombi can pass. The ET's wire-loop design and its two-tier system also prevent this complication.

The GF is not recommended in caval sizes greater than 28 mm in diameter because it does not expand to fit large diameters and is more likely to migrate.[22] Secondary to the characteristics of nitinol, the ET's wire loops expand to a maximum of 48 mm and will provide protection in large caval sizes.

The GF has been known to migrate proximally to the right ventricle[23,24] and the pulmonary artery,[25] and distally into the IVC and iliac veins.[11,13,26] The ET's hooks at the end of the wire loops grip the vein wall and secure the device and prevent any proximal or distal migration.

Characteristics of the GF wires have reduced its efficacy. GFs were originally made of stainless steel and required a 24-Fr insertion catheter.[27] To reduce insertion catheter size, new GFs were made of titanium, which required a 12-Fr catheter. Characteristics of titanium sometimes caused the filter to splay, thus increasing the chance of IVC perforation and injury to adjacent structures.[28,29] Teitelbaum and associates[29] reported splaying of the titanium GF in 3 patients. Perforation of the IVC and aorta occurred in 1 patient, and all 3 patients experienced back and abdominal pain. They conclude that the titanium GF possesses structural characteristics that may predispose it to splay, thus increasing the risk of IVC perforation and injury to paracaval organs and blood vessels. They also recommend that design modifications be instituted to reduce the risks of such complications prior to widespread use of the titanium GF. The ET is inserted through a 12-Fr sheath. No evidence of splaying has been observed in the experimental

studies on dogs using the nitinol ET. It is anticipated that the two tiers and the loop design will prevent splaying in patients.

The GF is not as effective in trapping smaller emboli (5 × 10 mm in diameter), which may also be clinically significant.[6,7] Experimental studies have shown the ET is effective in trapping emboli that are 5 mm or greater in diameter.

The ET is a new device that interrupts the IVC for the prevention of pulmonary embolism. The theoretical advantages of this device compared with the GF were confirmed in preliminary experimental studies in dogs. The ET is self centering, and it expands to fit the diameter of the IVC. It does not migrate or penetrate through the vein wall, and its materials are nonthrombogenic. Blood flow is preserved while emboli 5 mm or greater are trapped. Lysis of the trapped emboli within 4 to 6 weeks has been demonstrated. The clinical trials of the ET will begin shortly.

From one of the earliest workers in this field comes another new and improved device to protect the patient from sudden fatal pulmonary embolism. What we all need to know is in whom to apply them.

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