Factors involved in the migration of endoprosthesis in patients undergoing endovascular aneurysm repair

Fatores envolvidos na migração das endopróteses em pacientes submetidos ao tratamento endovascular do aneurisma da aorta abdominal

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Abstract

Migration of the endoprosthesis is defined as the misplacement of its initial fixation. To assess the migration, the position of the endoprosthesis regarding a certain anatomic region is verified. Considering the aneurysm of the infrarenal abdominal aorta, the proximal area of reference is the origin of the lowest renal artery and, at the distal region, it is located next to the internal iliac arteries. Patients should be monitored for long periods so that migrations can be identified; these migrations usually occur 2 years after the implantation. To avoid migrations, mechanical forces that enable fixation and that are determined by the characteristics of the devices and by the incorporation of the endoprosthesis should predominate over gravitational and hemodynamic forces, which tend to drag the prosthesis toward to caudal direction. Angulation, extension, and diameter of the neck, and transversal measure of the aneurysmatic sac are important morphological aspects related to migration. In relation to the technique, endoprosthesis implantation with excessive oversizing (> 30%) is not recommended because it leads to aortic neck dilatation, folds and proximal leakage that also contribute to migration. On the other hand, endoprosthesis with additional fixation devices (hooks, barbs and suprarenal fixation) seem to be less associated with migration. The process of endoprosthesis incorporation is partial and does not seem to be enough to prevent later migrations. In this sense, experimental studies with endoprosthesis of higher porosity, as well as the use of substances that allow higher fibroplasia and adherence of the prosthesis to the artery, have been conducted and are promising. Such aspects are discussed in the present review of the literature.

Keywords: Vascular prosthesis, migration, complications, aortic aneurysm.

Resumo

A migração da endoprótese é complicação do tratamento endovascular definida como deslocamento da ancoragem inicial. Para avaliação da migração, verifica-se a posição da endoprótese em relação a determinada região anatômica. Considerando o aneurisma da aorta abdominal infrarrenal, a área proximal de referência consiste na origem da artéria renal mais baixa e, na região distal, situa-se nas artérias ilíacas internas. Os pacientes deverão ser monitorizados por longos períodos, a fim de serem identificadas migrações, visto que estas ocorrem normalmente após 2 anos de implante. Para evitar migrações, forças mecânicas que propiciam fixação, determinadas por características dos dispositivos e incorporação da endoprótese, devem predominar sobre forças gravitacionais e hemodinâmicas que tendem a arrastar a prótese no sentido caudal. Angulação, extensão e diâmetro do colo, além da medida transversa do saco aneurismático, são importantes aspectos morfológicos do aneurisma relacionados à migração. Com relação à técnica, não se recomenda implante de endopróteses com sobredimensionamento excessivo (> 30%), por provocar dilatação do colo do aneurisma, além de dobras e vazamentos proximais que também contribuem para a migração. Por outro lado, endopróteses com mecanismos adicionais de fixação (ganchos, farpas e fixação suprarrenal) parecem apresentar menos migrações. O processo de incorporação das endopróteses ocorre parcialmente e parece não ser suficiente para impedir migrações tardias. Nesse sentido, estudos experimentais com endopróteses de maior porosidade e uso de substâncias que permitam maior fibroplasia e aderência da prótese à artéria vêm sendo realizados e parecem ser promissores. Esses aspectos serão discutidos nesta revisão.

Palavras-chave: Prótese vascular, migração, complicações, aneurisma da aorta.

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Introduction

Conventional treatment of abdominal aortic aneurysms consists of placement of a polyester tube graft, the ends of which are sutured to the arterial wall proximally and distally to the aneurysmal dilatation, preventing blood flow from straining the wall of the aneurysm. Development of this treatment modality was one of the finest achievements of vascular surgery, as it allowed modification of the natural history of the disease and reduction of rupture-associated mortality.[1] Endovascular repair of abdominal aortic aneurysms (EVAR)[2] is based on insertion of an endoprosthetic device through the femoral or iliac artery. The device is then deployed within the lumen of the aorta so its ends are anchored to normal artery, proximally and distally to the aneurysm. After the sheath is released, the elasticity of the stent graft provides radial strength, which keeps the device fixated to the aneurysm neck. The endoluminally deployed stent thus excludes the aneurysmal sac from circulation. Some stents have hooks or barbs to improve fixation to the arterial wall.

EVAR is associated with decreased transfusion requirements and avoids aortic cross-clamping, decreasing cardiac overload and the untoward effects of ischemia and reperfusion, all of which contributes to allow shorter postoperative recovery times.[3,4]. However, long-term follow-up of patients undergoing EVAR shows a permanent risk of graft migration and structural failure, even when treatment was successful. Close surveillance is therefore required to detect any relevant changes and, sometimes, establish the need for reintervention.[5-9] On the other hand, despite the need for continuous postoperative monitoring, EVAR carries the benefit of lower rupture-related death rates than with no treatment.[10]

Since the introduction of EVAR, expectations on short-, medium- and long-term outcomes has run high. Ten years and countless studies on, the ideal endoprosthetic device has yet to be developed. Despite progress in graft materials, endoprosthesis migration is still a major issue, as it may lead to type I endoleak and increased pressure within the aneurysm, culminating in rupture or collapse of the device into the aneurysmal sac, both of which indicate emergent open repair.[5,11]

The present article will discuss the clinical and pathophysiological factors involved in endograft migration.

Definition and criteria

Endoprosthesis migration is defined as displacement of the device from its original site of attachment. Assessment of migration consists of determining the position of the endoprosthesis relative to a predefined anatomical landmark. In infrarenal AAAs, the proximal landmark is the origin of the lowest renal artery, and the distal landmark is located next to the internal iliac arteries. The landmark for suprarenal fixation is the superior mesenteric artery (SMA). CT scanning is the imaging modality of choice for assessment of adequate placement or migration. Slices no larger than 3 mm should be obtained from the level of the SMA down to the common femoral arteries. The use of other anatomical landmarks, such as position of the vertebral bodies as observed on CT itself or on abdominal plain films, is unreliable, as any vertebral size changes due to osteoporosis or other bone conditions may lead to erroneous assessment of migration.[12]

The Society for Vascular Surgery (SVS) defines endograft migration as any displacement of 10 mm or more.[13] Caudal migration of the proximal stent is most common and poses the greatest risk in EVAR. The SVS definition is problematic in that, when the neck is small, 10 mm will correspond nearly to its maximum length, and diagnosis may only occur after the patient develops complications. In light of these considerations, current practice is to regard any migration >5 mm as clinically relevant.[14]

Regardless of endoprosthesis type, most migrations occur after the 13th month post-implantation, peaking at 19 months.[14-16] One key finding is that the risk of migration persists indefinitely after EVAR; complications have been reported as late as 4 years post-treatment. Follow-up studies seeking to assess graft migration must therefore extend for no less than 24 months after the procedure.

Although follow-up and observation for graft migration are essential, the absence of migration is no guarantee of treatment success. In some cases, perigraft leak may occur despite adequate proximal fixation of the endoprosthesis, leading to expansion of the aneurysm. Therefore, proper device positioning may only be interpreted as a positive treatment outcome if there are no perigraft leaks at the neck of the aneurysm.[17-19]

Current recommendations provide for CT follow-up at 1 month and 6 months post-procedure and annually thereafter. If migration is present, follow-up intervals are shortened for closer surveillance.[20] In some cases, arteriography (which allows endovascular repair if necessary) is indicated.

Importance of implantation technique

Implantation of the endograft body more distally than originally intended may be caused by erroneous operator

assessment due to parallax error, which is common in the tortuous aortic neck. Oblique views can minimize this issue and allow more accurate deployment.

Zarins et al.[21] assessed the importance of proper placement of the AneuRx stent graft at the origin of the renal artery. Isolated review of this factor showed that graft deployment below the intended site was directly correlated with greater risk of migration. The authors established that the greater the distance from the renal artery to the proximal end of the graft, the greater the risk of migration; each millimeter increase in distance below the renal arteries increased risk of migration by 5.8%. Likewise, each millimeter increase in length of the infrarenal neck covered by the graft decreased migration risk by 2.5%. Adequate placement of the distal end of the graft near the origin of the internal iliac arteries also correlates with a lower incidence of migration, as it reduces the risk of distal leakage and allows better longitudinal columnar support for the endograft, which tends to prevent proximal migration.[14]

Close attention to proper endograft placement at the proximal and distal neck of the aneurysm is therefore of the essence, as correct placement is positively correlated with lower risk of migration-related complications.

Biomechanical forces interacting with the device

Biomechanical forces produced by oversizing, the contact area between the device and the artery, and additional fixation such as hooks, barbs, or bare-metal suprarenal support extensions encourage fixation of the device to the aorta, as does the inflammatory process that occurs in the arterial wall.[22] Conversely, gravitational pull and hemodynamics tend to drag the device caudally. The balance of these forces determines whether migration will occur. Complex calculations performed both in vitro (in the biomechanics lab setting)[23] and in vivo, with computational analysis of the CT results of patients who underwent EVAR,[24,25] have provided important information on the dynamic interactions between the aortic wall, the endoprosthesis, and blood flow. Several authors have adapted mathematical formulae to experimental models of abdominal aortic aneurysms before and after stent graft deployment. These studies have concluded that, even in technically successful cases, certain areas of the endoprosthesis will always be more sensitive to hemodynamic changes, particularly at the aortic neck attachment site and at the bifurcation of the iliac extensions. In these areas, the endograft wall is subjected to strain, producing a 1- to 2-newton drag force that pulls the device distally.

These findings created a need for better understanding the forces involved in endograft fixation. Lambert et al.[26] assessed the mechanical behavior of endoprostheses implanted in cadaveric aortas and found that, the greater the extent of prosthesis oversizing and the contact area between the device and the artery, the greater the load required to dislodge it. In similar experiments, Malina et al.[27] found that hooks and barbs increase fixation even further. These studies have also provided important contributions by identifying the load required for dislodging endografts (3 N on average) and comparing it with mean hemodynamic drag forces (2 N). Despite their validity, however, these investigations failed to take into account several factors that interact with endoprostheses in the living body, as all experimental testing was conducted in cadaveric aortas.

Proper graft fixation to the proximal neck also reduces the risk of migration. Wolf et al.[18] reported a higher number of migration and type I endoleak events when there was poor apposition of the stent graft to the aortic wall. This is explained by decreased contact area and by leakage through folds in the graft fabric, leading to reduced friction and fixation forces.

Distal fixation was investigated by Volodos et al.,[28] who carried out in vitro assessment of straight and bifurcated polytetrafluoroethylene (PTFE) grafts in a specially designed model: a plastic cylinder mimicking an aortic aneurysm was connected to a pulsatile flow circuit powered by a cardiac pump, which subjected the system to different pressures. The authors found only minor changes in diameter, but significant changes in graft length and distal kinking, culminating in displacement of the device when load exceeded 208 g (approximately 2 N), thus demonstrating the importance of distal fixation. In fact, the importance of proper distal fixation is proven by the high rate distal displacement-related complications in patients receiving first-generation endoprostheses, which lacked adequate stent support in the iliac regions.

In addition to aneurysm- and endoprosthesis-related aspects, certain clinical changes may destabilize graft fixation forces and encourage migration. Mohan et al.[29] studied 2,862 post-EVAR patients included in the EUROSTAR registry. Using Massey's formula,[30] the authors analyzed significant (> 5 mm) migrations of the proximal end of stent grafts and their correlation with clinical features, and found that smoking and hypertension were associated with increased risk of migration.

Smoking is an important determinant of aneurysmal wall dilatation, with an added harmful effect in weakened arterial walls as a potentiator of protease activity.[31-33] Hypertension was significantly correlated with migration, as it increases the hemodynamic forces that push the graft caudally.

In short, an understanding of relevant biomechanical forces is a key element to be considered in the choice of endoprosthesis and EVAR technique.

Migration and device type

Table 1 shows differences in complication rates depending on the type of endoprosthetic device. These comparisons must be viewed cautiously, as they represent the work of different teams with varying levels of experience in EVAR and patients with heterogeneous aneurysm characteristics.

Differences in migration rates may be explained by stent design – namely, by the choice of material used in graft construction and by mode of fixation. Resch et al.,[34] for instance, used Dacron-covered, Gianturco stent-based graft prototypes with proximal fixation hooks in most cases, whereas other authors used third-generation commercial endografts, the design of which has been substantially perfected.[14,16,21,22,35,36]

The considerable variation in migration rates (1.8–45%) also reflects differences in study criteria, such as length of follow-up, choice of technique and operator experience.

Tonnensem et al.[22] found lower migration rates after use of Zenith devices. However, the authors already had extensive EVAR experience when they began using this model of endoprosthesis, which may have biased their results. At any rate, mid- and long-term assessment studies appear to support lower migration rates with use of endoprostheses that employ auxiliary fixation systems.[16] Longer follow-up studies should define whether this lower likelihood of migration is sustained over time.

Factors involved in migration

Aneurysm neck morphology

The shorter the length of the aneurysm neck, the smaller the contact area between endoprosthesis and artery, thus hampering device fixation. There is no objective definition of the minimal area required for adequate fixation, but most authors empirically recommend a length of 15 mm.[37]

Aneurysm neck angle appears to influence duration of surgery and post-EVAR complication rates. Sternberg et al.[38] measured aortic neck angulation (the angle formed between the aortic neck and the longitudinal axis of the aneurysm) and classified it as severe (≥ 70º), moderate (40 to 59º) or mild (< 40º). The authors found higher rates of complications (such as type I endoleak, aneurysm expansion and graft migration), endovascular reintervention, and conversion to open repair in patients with severe aortic neck angulation. Furthermore, procedure duration was longer in these patients due to greater difficulty in endograft placement. The authors concluded that EVAR should be discouraged in patients with aortic neck angles greater than 40º. Albertini et al.[19] assessed the risk of proximal type I endoleak and migration and their correlation with aortic neck size, shape, and angulation. The authors found neck angle

Table 1 – Migration rates and device type.

Authors	Sample size (n)	Follow-up (months)	Endoprosthesis	Definition (mm)	Migration rate (%)
Conners et al.[14]	91	33.2±1.1	AneuRx® (Medtronic)	≥5	16
England et al.[16]	55	41	Talent® (Medtronic)	≥10	16.6
Zarins et al.[21]	1119	30±11 (0.5-61)	AneuRx®	"Any distal displacement"	8.4
Tonnensen et al.[22]	77	39±2.3	AneuRx®	≥5	28
				≥10	18.8
	53	30.8±1.9	Zenith® (Cook)	≥5	7.5
				≥10	1.8
Resch et al.[34]	58	29 (1-49)	Ivancev-Malmo, Chuter	>5	45
Cao et al.[35]	113	28 (24-46)	AneuRx®	≥10	15
Sternberg et al.[36]	261	12	Zenith®	>5	2.3

to be the predominant factor associated with complications (Figure 1). Two major mechanisms explain this finding:

1) Tortuous proximal sites reduce the contact area between the device and the arterial surface, decreasing friction, which tends to anchor the device;
2) Hemodynamic studies show that the force exerted by blood flow against the vessel wall at a single point is proportional to the square of the velocity of flow at that point. Thus, flow velocity is increased in tortuous arteries, leading to increased drag forces. This, coupled with the fact that blood columns directly impact a larger surface of the kinked endoprosthesis, would increase the likelihood of distal displacement even further.[38,39]

Some authors have reported the use of endoprostheses in very large neck AAAs (> 28 mm diameter) as a predisposing factor for graft migration; other studies, however, have found no such correlation.[36] A greater likelihood of neck dilation 10 years after repair has also been reported when proximal cuff diameter at the time of EVAR exceeded 28 mm.[40] Considering that postoperative aneurysm neck expansion is a known predisposing factor for migration and that large neck are more likely to expand, one may infer that endovascular repair of large neck aneurysms would be inherently complication-prone.[14,41]

Thrombi, calcification, and other irregularities of the aortic neck wall are also associated with poor endoprosthesis fixation and increased likelihood of migration:

1) Thrombi found at the aneurysm neck have a friable surface, which decreases the area of friction between the device and the arterial wall;
2) Irregularities and calcification of the arterial wall lead to deformities or minor kinks and folds in the endoprosthesis. This reduces contact area, and type I endoleak may also occur through these points;[28]
3) Calcifications also harden the arterial wall, reducing complacency and decreasing device seating.

Aneurysm size and migration

Larger aneurysm size significantly correlates with parameters that predispose do endograft migration. Large aneurysms (> 55 mm) tend to have shorter, wider and more tortuous necks, which would thus increase the risk of migration.[42,43] Ouriel et al.[44] assessed 700 patients according to aneurysm size, classified as small (< 55 mm) or large (> 55 mm), and found a statistically higher rate of migration and type I endoleak in the latter group. Aneurysms with smaller diameters were deemed more anatomically suitable for EVAR, which may explain the lower rate of complications in narrower aneurysms. In their five-year follow-up of 923 post-EVAR patients, Zarins et al.[45] grouped aneurysm diameter into three size classes (small, < 50 mm; medium, 50 to 59 mm; large, > 60 mm) and found no significant differences in migration, leakage or aneurysm expansion rates. They did, however, report significantly higher rates of conversion to open repair and rupture-related mortality in patients with larger aneurysms. Interestingly, as conversion to open repair is usually prompted by leaks, migration or aneurysm expansion, higher conversion rates may correlate with these events.

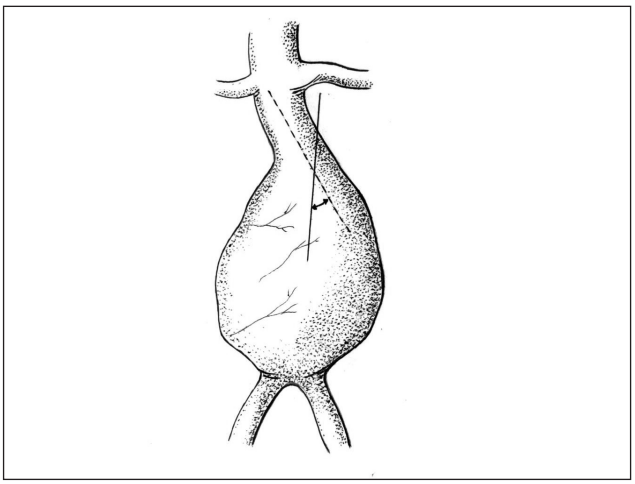

Figura 1 - Medida do ângulo do colo do aneurisma segundo Sternberg et al.[38]

Recent studies have shown improved outcomes and lower migration rates in patients with aneurysms smaller than 55 mm in diameter, which provide an anatomically favorable setting for EVAR.[46] However, it bears noting that patients with small aneurysms undergoing purely clinical treatment aimed at controlling blood pressure have a low risk of rupture (0.6% per year). Indications for EVAR must therefore take life expectancy and risk of the endovascular procedure (and possible reintervention) into account.[47]

Oversizing and migration

Mohan et al.[48] reported increased rates of type I endoleak when grafts were oversized less than 10%, and suggested 10 to 20% oversizing as adequate. Almeida & Yoshida[49] implanted 10- to 20%-oversized endografts in a swine aorta model. After 14 days, biomechanical assessment was

conducted to ascertain the displacement load required to dislodge the device from the aorta. In the 20% oversizing group, displacement load was statistically higher than in the 10% oversizing group. This may be explained by the increased radial strength of the stent struts, which would penetrate the wall of the aorta and reach deeper into the tunica media. Some authors[50] have posited that greater oversizing would produce a greater inflammatory response at the vessel wall, improving stent fixation and integration as well. In smaller vessels, such as the coronary arteries, greater oversizing would produce an even more intense inflammatory response, leading to intimal hyperplasia and early thrombosis.[51,52] In larger arteries, however, greater inflammation would increase prosthesis fixation, preventing graft migration. Histological examinations carried out in the Almeida & Yoshida study corroborate results reported elsewhere in the literature, showing that a fibroblastic reaction, with attending inflammation and areas of neovascularization, occurred only in the 20% oversizing group.

However, weakness of the aneurysmal aortic wall must be taken into consideration;[31-33] due to this factor, the additional strain of oversizing would produce a dilatation of the aortic neck over time.[53,54] This trend has been proven by Sternberg et al.,[36] who reported higher rates of type I endoleak and aneurysmal neck expansion in patients whose endografts were oversized more than 30%.

Excessive oversizing was also associated with worse aneurysmal sac outcomes, such as lower reduction rates and greater expansion, when compared with < 30% graft oversizing. Migration rates are also higher, probably due to aneurysmal neck expansion. Schurink et al.[17] carried out experimental studies of endograft implantation in an in vitro model using cadaveric aortic segments. After device deployment, the authors performed vascular ultrasound, angioscopy, angiography and CT scanning. Results showed a relationship between the presence of folds in the fabric and prostate diameter; the greater the degree of oversizing, the greater the number and size of graft fabric folds associated with significant perigraft leaks. Although this particular experimental study used water as a substitute for blood, which may have led to overestimation of leakage, the untoward effects of excessive device oversizing were clearly established.

Endograft incorporation

As mentioned above, the immediate success of EVAR is due to mechanical forces acting on the endoprosthesis and aorta. However, incorporation of the endograft fabric to the arterial wall, producing a permanent hemostatic seal, is desirable for medium- and long-term outcomes. The ability to obtain a healing process is absolutely critical in preventing migration and protecting against aneurysm rupture. Table 2 lists some studies of endoprosthesis incorporation.

Tissue incorporation varies depending on the material from which the device is made. Past studies have shown that tissue incorporation of PTFE devices is poor as a consequence of their hydrophobic surface, which would pose a limit to cell adhesion. Dacron-covered endografts have intermediate tissue incorporation capacity, whereas polyurethane devices induce a more intense inflammatory process and greater cell adhesion, which translate into better endothelialization and fixation to adjacent tissues. Limiting their use, however, is the fact that polyurethane endoprosthesis are mechanically weak and tend to degenerate.[55,56,59]

Studies investigating endografts removed from patients' bodies provide conflicting accounts of the tissue incorporation process. Some authors[59,60] have reported a good endothelialization response and good fixation into the artery, while others have reported little graft adhesion to the vascular wall.[55,56] These dissonant findings may be explained by differences in choice of material and by the low number of cases described in the literature. Furthermore, some patients mentioned in these reports had developed typical complications of EVAR, such as leakage or migration, which interfered with histological examination of the device. Analysis of uncomplicated grafts was thus limited to those removed from the small number of patients who died from non-EVAR-related causes, such as myocardial infarction or stroke,[55-59] further decreasing the number of useful cases.

In animal experiments, the tissue incorporation process has somewhat differed from that found in human studies. In swine and sheep – the most common animal models of endoprosthesis implantation – results were far more exuberant than those found in human studies due to interspecies differences. Furthermore, all experimental studies published in the literature were performed on normal arteries with none of the typical aortic wall changes, such as calcification and thrombi. Evidence suggests that inflammatory response and incorporation occur differently in the human aneurysmal aorta.[60,61]

In light of these results, studies assessing endografts after their removal from human patients and those conducted in animal models must be viewed and interpreted cautiously.

Medium- and long-term follow-up of EVAR patients has shown that risk of migration is permanent, and that

Table 2 – Tissue incorporation studies: gross and histological findings

Author	Sample	Time to explant	Device type	Gross appearance	Histological findings
McArthur et al.[55]	Grafts recovered from 11 patients	4 days–18 months (mean, 9 months)	Talent=7 Megs PTFE=3 Excluder PTFE=1	Translucent material covering graft ends, thrombi	Organized thrombus, absence of myointimal cells, poor tissue incorporation across all samples
Malina et al.[56]	Grafts recovered from 23 patients	1–31 months (mean, 9 months)	Dacron endografts and Gianturco stents	Little adhesion	Fibrin, organized thrombus In some samples, thin layer of cells, actin, and some collagen on the luminal surface
White et al.[59]	Single patient explant (67yo)	67 days	Dacron endografts and Palmaz® stent (J&J)	Moderate adhesion	Incipient healing, giant multinucleated cells and collagen surrounding graft
McGahan et al.[57]	Single patient explant (73yo)	7 months	EGS (Endovascular Grafting System) Dacron endografts, steel stent	Proximal end of stent covered by shiny material	Proximal end: good tissue incorporation, collagen, myofibroblasts, giant multinucleated cells Distal end: mild inflammation, less neointima
Shin et al.[59]	Two patient explants (76 and 77yo)	20 and 42 days	Polycarbonate urethane Corvita® bifurcated grafts at the iliac arteries, Elgiloy wire	Endograft firmly adhered to the arterial well	Good ingrowth of tissue into the proximal 2 cm of the graft, collagen, endothelialization, and smooth muscle cells present.
Lambert et al.[60]	Experimental animal study (13 swine)	Serial follow-up (1, 3, 6, 12 months)	Nitinol-mesh Dacron endografts	1 month: signs of ingrowth, neointima 3 months: proximal and distal ingrowth 6 and 12 months: significant adhesion of graft to artery	1 month: organized fibrin, intense inflammatory reaction, lymphocytes, giant cells 3 months: chronic inflammatory reaction, increased number of lymphocytes and giant cells, neointimal formation. 6 and 12 months: inflammatory cells replaced with myointimal and endothelial cells. Good incorporation
White et al.[61]	Experimental animal study (20 sheep)	Serial follow-up (1, 3, 6 months)	Bard® self-expanding nitinol mesh Dacron endografts	Graft firmly adhered at 1-month follow-up	1 month: graft completely covered by neointima, myoepithelial cells and collagen present. 3 months: more collagen, replacing myoepithelial cells in isolated areas. 6 months: complete incorporation with neointima, some giant cells and abundant collagen

PTFE = polytetrafluoroethylene

substantial complication rates persist for years after repair. These findings suggest that the tissue incorporation process occurs only partially and is not enough to prevent late complications, such as endograft migration.

Future prospects

Several recent studies have been conducted with the purpose of developing endoprosthetic devices that heal better into the arterial wall.[62,63]

Two basic factors prevent adequate tissue incorporation of stent grafts. The first is the use of PTFE or Dacron, which are inert materials and thus have little potential for tissue incorporation. The second is associated with a peculiar characteristic of the aneurysmal wall: depletion and decreased resistance to apoptosis of myointimal cells, which play an essential role in tissue incorporation.[62]

Studies have been conducted with the aim of improving the tissue incorporation process by adding coatings

that could potentially stimulate cell adhesion and proliferation, creating an environment conducive to the migration of fibroblasts and pluripotent smooth muscle cells. In addition to providing a more adequate microenvironment, this strategy would improve collagen production by fibroblasts, decreasing rates of myointimal cell apoptosis. Lerouge et al.[62] conducted tests using nitrogen-rich plasma- and chondroitin sulfate-coated stent grafts and found increased adhesion of fibroblast and myointimal cell cultures to these surfaces, as well as decreased apoptosis, as compared to controls. The chemical properties of Nitrile coated surfaces is believed to favor certain intracellular signaling pathways, modulating expression of integrin receptors, which are responsible for intercellular adhesion. Integrins also activate the integrin-linked kinase and phosphatidylinositol pathways, which are believed to play a key role in inhibiting apoptosis. Chondroitin sulfate would decrease apoptosis by acting on a similar kinase pathway (specifically, the P13K pathway). The authors conclude that the use of these substances may be an important option in manufacturing stent grafts with added capacity to incorporate into adjacent tissues.

Device porosity appears to influence the tissue incorporation process. Experimental studies suggest that, in lower-porosity grafts, the myointimal cells responsible for tissue ingrowth migrate from the ends of the graft and cover an intraluminal area of up to 20 mm. In microporous grafts, capillaries and vascular smooth muscle cells derived from the underlying granulation tissue have been found to penetrate the pores present throughout the device, producing improved graft coating. Studies are currently underway to improve graft porosity and cell adhesion as a means of increasing tissue incorporation.[64]

Van der Bas et al.[63] implanted collagen- and fibroblast growth factor-soaked Dacron endografts in the porcine aorta and found significant improvement in tissue incorporation at 8 weeks post-implantation. The authors observed neointimal growth and, on immunofluorescence studies, detected an increased number smooth muscle cells consistent with myofibroblast and myointimal cell proliferation. This study proved that in vivo induction of fibroplasia is possible, despite variables such as blood pressure and the blood flow effect, which were expected to "wash away" any substances impregnated into the graft.

Gene therapy studies are currently investigating alternatives for improving the tissue incorporation process. Eton et al.[65] implanted myointimal cells transduced with tissue plasminogen activator genes. Cells were suffused into a dual-layer Dacron endograft and implanted into dog aortas. According to the authors, grafts removed at 1, 2, 3, 4, 5 and 7 months were highly populated with genetically modified smooth muscle cells, with increased t-PA antigen levels and t-PA activity, both of which were desired outcomes of the transduction procedure. The authors concluded that endografts can serve as an important delivery vehicle for transduced cells. Although not its main objective, the Eton study revealed the possibility of inducing greater fibroplasias by employing cells transduced with genes that increase proliferation of vascular smooth muscle cells or fibroblasts, leading to improved graft incorporation and fixation.

Almeida & Yoshida[49] implanted Dacron-coated nitinol stent grafts in porcine thoracic aorta, applied fibrin glue to the interface between the graft and the endothelium, and compared the results to a control group in which no fibril glue was used. On the 14th postoperative day, biomechanical testing was conducted to measure the displacement load required for dislodging the device, as in the work of Malina et al.[27] and Lambert et al.[26] Displacement load was significantly increased in the fibrin glue group, and histological testing confirmed increased fibroplasia in the group. The authors concluded that application of fibrin glue to the endoprosthesis/aorta interface may become an important step in improving graft adhesion and tissue incorporation to prevent migration.

In conclusion, continuous improvement of endoprosthetic devices has led to the development of improved materials, with greater wear resistance and reduced cross-sections. Current progress is moving towards development of mesh coatings that improve tissue incorporation, so as to improve long-term results and prevent endograft migration, which is still a major hurdle to positive outcomes in EVAR.

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