Acquired abdominal aortic aneurysm

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Introduction

Acquired abdominal aortic aneurysms classically are characterized anatomically by an unparallelism of the aorta edges, resulting in an expanded and beating abdominal mass. The pathophysiology consists of a loss of vascular contention, including a risk of rupture. Indeed, the arterial wall fulfils several haemodynamic functions of blood tissue distribution, damping of the pulse wave, etc. The most elementary of these functions is containing high pressure blood within the arterial lumen. Arterial wall aneurysmal diseases are characterized by partial (dilation) or total (rupture) loss of integrity. In the wall of large arterial trunks, the extracellular matrix predominately contributes to containing blood inside vessels. The extracellular matrix of the arterial wall is essentially composed of collagen fibres and elastin, with proteoglycans and structural glycoproteins such as fibrillins as inter- and peri-fibre ligands. More simply, elastin is implicated mainly in arterial wall resistance to dilation whereas connection proteins, collagen and fibrillin, are involved mainly in resistance to rupture. Contrary to classical, stenotic atheroma, an essentially arterial intima pathology, large vessel acquired aneurysm is a disorder of the arterial wall media characterized by the destruction of the extracellular matrix components, elastin in particular, associated with a reconstruction phenomenon, essentially fibrous, and remodelling the vessel in an aneurysmal fashion under the effect of tensional stress.

Epidemiology

Contrary to the relatively rare thoracic aortic aneurysms whose incidence does not fluctuate, the incidence of abdominal aortic aneurysms has increased over the last 40 years [1]. When all aortic aneurysms are included, mortality increased steadily during the 1950–1970 period. The causes of that increase are not known and cannot be explained entirely by the increase in life expectancy or the introduction of echotomography. There was, therefore, a real increase in the incidence of abdominal aortic aneurysms. Smoking could be one of the risk factors. Auerbach [2] noted eight times more abdominal aortic aneurysms in smokers than in non-smokers. Abdominal aortic aneurysms are clearly predominant in men (sex ratio = 8/1). Also, popliteal or femoral aneurysms are found almost exclusively in men. The main determining factor of aneurysmal disease is age. The link between age and the incidence of aneurysms is probably related, among other factors, to the widening of the aortic lumen, equally observed in man and in animals [4]. This dilatation phenomenon of large arterial trunks is intrinsically linked to age, unrelated to blood pressure and probably related to modifications of the extracellular matrix composition.

A major factor controlling the choice of surgical treatment is the size of the aneurysm, because it was established, clinically and through autopsy studies, that large aneurysms rupture more often. Cronenwett’s study [5] defined the risk of rupture by multifactorial analysis of the incidence of rupture in relation to 18 variables. Diastolic blood pressure, baseline anteroposterior diameter and the existence of chronic obstructive airways disease are independent predictors of rupture.

Incidence of discrete aneurysmal disease

In Dent’s series [6] of 1488 patients with aneurysms of the abdominal aorta and its branches, 57 had multiple aneurysms. A patient with a peripheral aneurysm runs a 59% risk of carrying another peripheral aneurysm and a 71% risk of abdominal aortic aneurysm. Multiple aneurysms are essentially found in men (1/57) and predominantly in elderly subjects (mean age 66.2 years, range 47–82).

In a series of popliteal aneurysms, only 14% of patients had discrete aneurysmal disease affecting the aorta, iliac, femoral and popliteal arteries. In patients with abdominal aortic aneurysms, the frequency of femoral aneurysms is 3.2%.

The incidence of arteritis (46%) is greater in the presence of multiple aneurysms than with isolated abdominal aortic aneurysm (25%) but less than in...
Genetic determinism

The role of genetics in aneurysmal disease is strongly suggested by the existence of familial aggregation. There is a 15% probability of patients with aortic aneurysms having first-degree relatives also with aortic aneurysms. The risk in that case is thus multiplied by a factor of 11. In a recent linkage study [7] involving 91 patients with aneurysms, the authors proposed a recessive autosomal transmission with a major determining locus. In contrast, most acquired abdominal aortic aneurysms are characterized by their often unique localization and their association with aortic and iliac atheroma. Consequently, the atheroma is considered as the classic aetiology of acquired aortic aneurysms.

A recent analysis of a cohort of 8000 men in Hawaii has revealed a perfect similarity between risk factors of lower limb arterial stenosing atheroma and acquired aortic aneurysms [8].

There are also more discrete forms of arterial dilation: aneurysmal polydystrophy and arteriomegaly. René Leriche in 1942 described a clinical, radiographic and surgical entity characterized by discrete dilation and tortuositys (lengthening) of conductance vessels, then named dolichomega-arteries. Histologically, this entity was characterized by a discrete rarefying of the elastic mesh. It was the underlying origin of true aneurysms (66% of cases). This very discrete type of arterial dimensional abnormality might also be genetically determined.

In two sensational articles [9,10], the Philadelphia group identified a family where four members had dilating and/or dissecting vascular lesions of visceral arteries. In a 37-year-old homozygous woman with no aneurysm, a one-off mutation was evidenced, which transformed the glycine 619 codon of the alpha1 chain of type III procollagen into a codon for arginine. The same mutation was found in two young patients from the same family, who died of arterial rupture; the study was conducted from arterial fragments collected surgically. Likewise, from saliva DNA testing, the mutation was also revealed in other apparently asymptomatic members, of the same family. Mutation induces a functional impairment of the chain of amino acid-containing type III procollagen substituted at position 619: control procollagen resists protease digestion up to ~36°C whereas type III procollagen synthesized by the propositus’s fibroblasts was hydrolysed at 20°C and one of the fragments so obtained contained ~620 amino acids. That hypothesis, however, was subject to several serious criticisms with regard to its relevance to acquired abdominal aortic aneurysms classically observed in elderly men and associated with atheroma: (i) the patients in that family were young (~30 years old); (ii) the histological report of the article showed typical images of dissection, not aneurysms. This study raised the nosological issue of differentiating dissections (ruptures), often related to abnormalities in the collagen which ensures connection between elastic strips, from aneurysms (dilation) related to elastin rarefying. That working hypothesis on type III procollagen was re-assessed in a multicentre study [11] involving 54 patients with aortic aneurysms. Only two had type III collagen abnormality, including one 18-year-old male who was described as having a dissecting aneurysm. The other one was a 71-year-old man with a truly ‘classic’ aortic aneurysm and carrying a mutation of amino acid 501 of the type III procollagen chain. That mutation was also present in two of his brothers (68 and 73 years old) who did not have aneurysms. That mutation therefore was not considered as the cause of aneurysms.

Haemodynamic and mechanical factors

The classic pathophysiology of abdominal aortic aneurysms considers that haemodynamic stress increases the parietal atheromatous process and impairs the mechanical properties of the abdominal aorta.

The human abdominal aorta contains fewer lamellae than could be expected from its thickness and diameter. The lamellar unit is the basic structural unit of the media. It consists of elastic strips arranged as concentric fibrillar leaves separated by smooth muscle cells. A network of collagen fibres are associated. The human abdominal aorta only possessed ~30 lamella units, which increases the parietal stress on each lamella unit. Also, from its base to its bifurcation, the aorta narrows and rigidifies. Because of the deflection of the pressure wave on the aortic bifurcation, systolic blood pressure is increased and diastolic blood pressure is decreased, thus subjecting the abdominal aorta to wider pressure oscillations of the whole vascular tree (stress peak frequency). Therefore, fatigue, i.e. the stress peak frequency, could be increased on that site. Fragilization and fragmentation of elastic fibres enhance the increase in parietal stress per lamella unit. In Laplace’s formula, $T/P = h/r$, $T$ is the parietal stress, $P$ the intravascular pressure, $r$ the vessel radius and $h$ the wall thickness. Under the same pressure and as the aortic radius increases and pressure decreases, the parietal tensional stress increases, which theoretically continually increases the dilation and rupture tendency. So, from the mechanical standpoint, aggravated haemodynamic conditions and the incapacity of the aortic wall to withstand them would make the abdominal aorta aneurysmal. These alterations reflect a succession of injury and healing of the media under the effect of parietal haemodynamic stress.

The combination of local factors, atheromatous processes and aortic ageing helps us to understand the frequency of aortic aneurysms at the abdominal level. However, the reasons why this multifactor situation...
may lead to stenosis or aneurysm, as well as the reasons why some aneurysms occur without any atheromatous lesions, have not been determined. Abdominal aortic aneurysm can be clearly distinguished not only from ageing abdominal aorta but also from obliterating aortic atherosclerosis, by the incapacity to ‘physiologically’ restore the media. Ageing aorta is characterized by an increase in diameter, even and with maintained edge parallelism.

Rarefying of the structural elements of the aortic media was clearly demonstrated by a number of studies. The elastin concentration is reduced by 77% on average in the media of aneurysmal aortas. These measurements were confirmed by histology in abdominal aortic aneurysms: the aortic media is considerably atrophied and its normal architecture has disappeared. On the other hand, the aortic wall thickness can be preserved by compensatory collagen synthesis.

**Intraparietal protease activities**

In the early 1980s, it was suggested that proteases played a role in the pathogenesis of abdominal aortic aneurysms. Swanson et al. [12] were the first to underline the possible role of collagen in aneurysmal rupture by showing that laparotomy for another cause induced or precipitated aneurysmal rupture in a group of patients with abdominal aortic aneurysm, indicating increased collagenolysis during the post operative inflammatory period. It recently has been demonstrated that collagenolytic activity was low in stable aneurysmal walls and that it increased sharply in the case of aneurysmal rupture. This increase, however, was essentially due to an influx of inflammatory cells and it was not determined whether it was the cause or the consequence of aneurysmal rupture. Busuttil et al. [13] in 1982 measured elastase activity in aneurysmal aortic walls. It was demonstrated that this activity was significantly greater than in normal aortas and that it was linked to aneurysmal evolutiveness. A parallelism has been established between aortic aneurysm pathophysiology and that of pulmonary emphysema, in an attempt to demonstrate that there is a systemic protease–antiprotease unbalance. The molecule whose deficiency could induce extensive elastolysis could be the tissue inhibitor of metallo-proteases. However, the systemic presence of activated proteases capable of degrading insoluble proteins in the organism is inconceivable. The phenomena contributing to the presence of activated proteases in the media are evidently strictly restricted to the arterial wall. In contrast, loco-regional elastolysis will induce a systemic increase in circulating antiproteases (inflammation proteins of hepatic origin). A role for proteases in aneurysmal pathogenesis is very probable. Indeed, elastin and collagen are solid insoluble proteins and only significant enzyme activity could degrade them extensively. We developed an experimental model of abdominal aortic aneurysm in rats in vivo by infusing an elastase solution [14]. In human aneurysmal aortic walls, it is difficult to characterize elastases. It would appear, however, that they are closer to macrophagic elastases. Intra-parietal proteases are probably responsible for extensive protein degradation in the extracellular matrix of the aortic media. These hypotheses recently have been confirmed by the discovery, in the aneurysmal wall, of: (i) genes implicated in fibrinolysis such as plasminogen activators (U and T-PA) also involved in activating proenzymes like metalloproteinases [15]; and (ii) gelatinase-like zinc metalloproteinases (MPP-9) [16–18].

**Role of inflammatory cells**

Although several types of cells are capable of synthesizing elastases, in man only polymorphonuclear neutrophils (PMN) and macrophages can produce elastases in large amounts. It was demonstrated in vitro that macrophages were the most effective cells for insoluble elastin degradation. Beyond protease activities, there is the issue of their occurrence in the aortic wall. Elastase and collagenase in fact are part of an enzyme complex secreted under conditions of inflammatory cell activation. In that complex, plasmin plays a crucial role. Plasmin is an activator of pro-elastases and pro-collagenases, and elastin degradation is a cooperative phenomenon. We were able to confirm these results in vivo. Inducing an inflammatory reaction in the aortic media in rats induced significant elastase secretion and degradation of the extracellular matrix. Also, plasmin potentiates the effects of a sub-lesional dose of elastase and produces a true aneurysm. Similarly, plasmin potentiates the degrading activity of the extracellular matrix, induced by macrophages [14]. The role of plasmin appears to be especially important, not only in generating aneurysmal lesions but also in evolving towards rupture. Indeed, parietal thrombus is, by definition, a source of plasmin and if it does not have any protecting effect by not reducing parietal stress, it may nevertheless play an aggravating role in the areas where fibrinolysis is predominant on fibrogenesis.

Few authors have investigated the presence of inflammatory cells in aneurysmal walls: Beckman [19] in 1986, from a series of 156 abdominal aortic aneurysmal walls, identified 31 media inflammatory infiltrates and 106 adventitial inflammations. Medial and adventitial inflammation has been found recently in abdominal aortic aneurysm walls, suggesting a possible involvement of these cells in aortic wall degradation. Recent studies have shown that macrophages and T lymphocytes were present in human atheromatous plaques as well as in experimental atheromatous lesions and were expressing MPPs. There is, therefore, a close relationship between atheroma and inflammation. Also, circulating lipoproteins could activate atheromatous plaque macrophages and stimulate protease secretion. Lastly, elastic fibre fragmentation products have a chemotactic effect in vitro on inflammatory cells, and this might constitute an aggravating factor of aortic elastolysis. The atheromatous plaque thus contains all the necessary ingredients to establish a preferential
Therapeutic future: endovascular treatment of aneurysms

The ultimate purpose of aneurysm treatment is to bypass the aneurysm without any occlusion of lower-limb or visceral circulation. The expected benefits of aneurysm endovascular treatment would be the ability to use local or regional anaesthesia, to avoid a surgical approach to the aneurysm, to avoid clamping the aorta, to avoid the risk of inducing transient lower-limb, renal or hepatic ischaemia, reduce bleeding, reduce the risk of secondary aortic–digestive fistulae and to reduce treatment costs.

These specifications are not without technical difficulties. Prosthesis is definitive. Once fitted via the endovascular channel, it cannot be removed. Hence the necessity to define precisely and accurately the dimensions before fitting (length and diameter) by additional tests: echo-Doppler, arteriography and CT scan. An arterial approach, preferably via the femoral artery, is mandatory. The iliofemoral axis should be permeable, stenosis-free and not too tortuous. Approach ‘from the top’ is always possible.

The volume required for the diameter of the equipment (i.e. anchoring system and above all prosthetic cladding) should be reduced to a minimum (miniaturization), its rigidity and especially its progress through tortuous arteries requires using a fitting and releasing sheath. This releasing sheath helps lead the prosthesis to the lesion site while preventing it from rubbing against the atheromatous arterial wall. It permits working without blood shedding in a high pressure arterial environment. The sheath could also permit the use of prosthesis positioning control systems other than arteriography (endovascular echography, etc.) [20,21]. There is a risk of distal embolization during the endoluminal procedures.

Prosthesis anchoring is an essential part of the method. The purpose of solid anchoring is to prevent prosthesis migration. This currently is ensured by using a stent. There are two types of stent: expandable with balloons and self-expandable (relying on their own elastic force at release). Expandable stents with balloons are precise when fitted: the balloon accurately positions the stents where the operator chooses. They are anchored solidly: they will not move later. It is a simple endoprosthesis system. On the other hand, it is very cumbersome. Self-expandable systems are less precise at release, they are unstable and can move later; but they can be fitted with hooks providing greater anchoring strength. Three mechanisms help to maintain implant deformation: plastic deformation (expandable on balloon), intrinsic elastic load (self-expandable) and thermal memory (Nitinol).

Anchoring problems are linked to the very nature of the arterial wall. The arterial wall at the neck level may be aneurysmal. Ideally, the stent should be capable of anchoring on a lesioned wall. A study conducted on human cadaver aortas demonstrated the good anchoring performance of the prosthesis, resisting a lengthwise traction of > 1300 g (self-expandable stents fitted with anchoring hooks). There are major experimental limitations to the assessment of prosthetic anchoring: animal aneurysm models have healthy subjacent and superjacent necks. Does the neck, in human aneurysmal disease, continue to evolve once the prosthesis has been set in place? Tight cladding is mandatory for aneurysmal bypass. Two types of material are currently available: dacron and nylon. The advantages of dacron are linked to its long known use and the effectiveness of aneurysmal exclusion. The material is not porous and is non-expandable. Its disadvantages are its thrombogenic potential and its difficult unfolding, carrying risks of picatures. Its volume is the main drawback, even with thin-wall dacron. The advantages of nylon are the possibility of secondary endothelialization and its restricted volume. Its disadvantages are its porous structure, not ensuring good permeability, its fragility and long-term expanding potential. However, it could be reinforced by a metal frame which would increase its long-term strength.

The ideal cladding should be an impermeable structure capable of excluding an aneurysm while being as small in volume as possible in order to pass through a small artery, and above all, before release, a small gauge material (femoral) capable of adapting to large gauge vessels (aorta) without lengthwise deformation and marked widening.

Despite endoprosthes fitting, the aneurysm may continue to progress, through a variety of mechanisms. Prosthesis radius elongation may occur, especially when using thin, compliant, supple and soft wall material, of small volume but barely resistant in the long term (nylon). The stent–arterial wall interface must be totally impermeable. A blood leak at that level would jeopardize aneurysmal exclusion. This prerequisite again poses the crucial problem of precise and accurate stent release and anchoring. In total, if endovascular fitting of an impermeable endoprosthesis is the choice treatment of aneurysms for the future, many points of the specifications are yet to be resolved. However, it is under way and human application is also in progress.

References
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