Eur J Vasc Endovasc Surg (2010) **40**, 468–474

Aortic Length Changes During Abdominal Aortic Aneurysm Formation, Expansion and Stabilisation in a Rat Model

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Submitted 7 January 2010; accepted 5 May 2010
Available online 15 June 2010

KEYWORDS
Abdominal aortic therapy;
Aneurysm length;
Cell therapy;
Extracellular matrix;
Matrix metalloproteinase

Abstract *Background:* Determinants of extracellular matrix (ECM) destruction/reconstruction balance influencing abdominal aortic aneurysm (AAA) diameter may impact length.
Objective: Document aortic lengthening, its correlation to diameter, and determine how treatments that impact diameter also affect length.
Methods: Three hundred and fifty-five diameter and length measurements were performed in 308 rats during AAA formation, expansion and stabilisation in guinea pig aortas xenografted in rats. Impact of modulation of ECM destructive/reconstructive balance by endovascular Vascular Smooth Muscle Cell (VSMCs) seeding, TIMP-1, PAI-1 and TGF-beta1 overexpression on length has been assessed.
Results: Length increased in correlation with diameter during formation (correlation coefficient (cc): 0.584, $P < 0.0001$) and expansion (cc: 0.352, $P = 0.0055$) of AAAs. Overexpression of TIMP-1 and PAI-1 decreased lengthening ($P = 0.02$ and 0.014, respectively) demonstrating that elongation is driven by matrix metalloproteinases and their activation by the plasmin pathway. Overexpression of TGF-beta1 controlled length in formed AAAs (17.3 ± 9.6 vs. 5.9 ± 7.4 mm, $P = 0.022$), but not VSMC seeding, although both therapies efficiently prevented further diameter increase. Length and diameter correlation was lost after biotherapies.

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doi:10.1016/j.ejvs.2010.05.001

Conclusion: Length increases in correlation with diameter during AAA formation and expansion, as a consequence of ECM injury driven by MMPs activated by the plasmin pathway. Correlation between length and diameter increases is not universally preserved.

The definition of arterial aneurysms is based on diameter, but aneurysmal aortas are also increased in length. Although the clinical importance of aneurysmal lengthening is increasingly recognised,[1,2] its relation to diameter and its determinants are poorly characterised.

In vitro, Dobrin et al. has demonstrated the respective roles of elastase and collagenase activities in arterial elongation, dilatation and rupture.[3] The mechanical behaviour of human aneurysmal wall is altered both longitudinally and circumferentially,[4] more severely in ruptured abdominal aortic aneurysms (AAAs).[5] These data provide support to the concept that aortic elongation is determined by extracellular matrix (ECM) injury.

The xenograft model of AAA has been used to unravel the role of proteases in aneurysm formation and rupture,[6,7] and to validate concepts of endovascular cell[8] and gene therapy[9] in already formed, expanding lesions. Human atherosclerotic AAAs and the xenograft model share common determinants of aortic ECM injury, for example, inflammation (T and B lymphocytes, macrophages),[10,11] possibly triggered by immunity/auto-immunity,[12] and involvement of matrix metalloproteases (MMP-2, -3 and -9) activated by the plasmin pathway.[6,7,13–15] Because the segment of xenogeneic aortic ECM undergoing aneurysmal degeneration is topographically delimited by two end-to-end suture lines, we thought to use the xenograft model in rats to better characterise length changes during AAA formation and expansion, and their correlations to diameter. Our hypothesis was that determinants of ECM destructive/reconstructive balance influencing AAA diameter would impact length.

Material and Methods

Data sources

Length and diameter of experimental aneurysms have been recorded in studies using the aortic xenograft model of AAA in rats. Published data regarding diameter are summarised in Table 1.[6–9,16] Data regarding length have not been published previously.

Xenograft implantation

Animal care complied with the European Union and United State of America regulations. Sub-renal aortas from male guinea pigs decellularised with sodium dodecyl sulphate,[15] and grafted as 10-mm-long segments after removal of 9-mm segments of native rat aorta (Lewis or Fischer 344) using two end-to-end anastomoses.

Preventive treatments

Three different cell seeding approaches aimed at preventing aneurysmal degeneration by blocking ECM injury were applied endovascularly through a catheter in the lumen, at the time of xenograft implantation, for example, in a non-aneurysmal vessel: (1) non-genetically engineered syngeneic vascular smooth muscle cell (VSMCs),[16] (2) VSMCs transfected with a retrovirus encoding tissue inhibitor of matrix metalloprotease-1 (TIMP-1), a natural inhibitor of MMPs,[6] (3) VSMCs transfected with a retrovirus encoding plasminogen activator inhibitor-1 (PAI-1), a natural inhibitor of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).[7] Controls were xenografts receiving VSMCs transfected with a retroviral vector with no gene of interest, for TIMP-1 and PAI-1 experiments, or culture medium without cell for experiments with non-genetically engineered VSMCs (summarised in Table 1).

Curative treatments applied to already formed AAAs

Percentage changes are calculated in reference to the length or diameter value for each vessel at the entry in the observation interval, that is, at implantation for AAA formation and at day 14 for AAA expansion. Implanted xenografts complying with AAA definition on diameter criteria 2 weeks after implantation were included in treatment protocols aimed at controlling AAA diameter expansion by modulating ECM destructive/reconstructive balance (summarised in Table 1). Syngeneic, non-genetically engineered VSMCs,[8] or a suspension of adenoviruses encoding simian, mutated active transforming growth factor-beta1 (TGF-beta1)[9] have been delivered endovascularly. Controls were culture medium or a suspension of an adenovirus with no gene of interest, respectively. AAAs were measured at time of treatment, and a second time at various delays thereafter.

Measurement method

Graft length and diameter were measured with a grid in the eyepiece of an operative microscope under beating heart, before vessel treatment or harvest. Length was defined as the distance between the two suture lines of the xenograft. Grafts/aneurysms remained linear, for example, with no tortuosity, even after very significant diameter expansion. The rat aorta at vicinity of suture lines was never dilated. Diameter was measured at the level of maximum dilatation. Length changes were expressed as percentages and calculated as follows: for AAA formation experiments: (length at evaluation − length at implantation) × 100/length at treatment; for AAA expansion experiments: (length at evaluation − length at day 14 endovascular injection) × 100/length at endovascular injection. Similar formulas were used to calculate diameter percent changes.

Table 1 Summary of treatment studies.

	Injected material	Control	Main outcome on diameter criteria
Preventive treatments			
VSMC seeding	Isogenic VSMCs	Culture medium	Prevention of AAA degeneration
PAI-1 overexpression	PAI-1 overexpressing isogenic VSMCs	VSMCs transfected with no gene of interest	Prevention of AAA degeneration
TIMP-1 overexpression	TIMP-1 overexpressing isogenic VSMCs	VSMCs transfected with no gene of interest	Prevention of AAA degeneration
Curative treatments			
VSMC seeding	Isogenic VSMCs	Culture medium	Suspension of AAA diameter expansion
TGF-beta1 overexpression	Adenovirus with cDNA encoding activated TGF-beta1	Adenovirus with cDNA encoding beta galactosidase	Suspension of AAA diameter expansion

Statistical analysis

Data were recorded for each xenograft/AAA, in treated and control groups when appropriate, and were expressed as means $\pm$ standard deviation. Using StatView 5.0 for PC, treated and control groups for evaluation of treatment were compared with the non-parametric Mann—Whitney *U*-test (less than 10 AAA per group). An paired *t*-test was used to compare percent changes of length or diameter of a same xenograft/AAA between two time points during AAA formation or expansion, or in response to treatment. An analysis of variance (ANOVA) followed by a protected least significant difference (PLSD) Fischer test was used for comparisons between more than two time points during AAA formation and expansion. A correlation coefficient between diameter and length for each graft was calculated. $P < 0.05$ was accepted as significant.

Results

There was no difference between Lewis and Fischer 344 rat strains, nor between operators (EA or JD), regarding length and diameter at engraftment and at 14 days (not shown). Shapes of formed AAAs in the model varied widely, from fusiform, to 'sausage like' and saccular, pretty much as in human atherosclerotic AAAs.

Length during AAA formation and expansion

Percentage changes are calculated in reference to the length or diameter value for each vessel at the entry in the observation interval, for example, at implantation for AAA formation and at day 14 for AAA expansion.

During AAA formation, percentages of length changes were $14.7 \pm 15.1\%$ at 1 week ($n = 11$) and $36.8 \pm 27.8\%$ at 2 weeks ($n = 164$), respectively, in reference to value at implantation ($P = 0.013$). Diameter changes were $43.4 \pm 26.5\%$ at 1 week ($n = 11$) and $107.2 \pm 43.5\%$ at 2 weeks ($n = 164$) ($P = 0.01$). Diameter and length increase were correlated (correlation coefficient (CC): 0.584, 95%, confidence interval (CI): 0.493—0.662 $P < 0.0001$).

During AAA expansion, length continued to increase: $11.6 \pm 12.3\%$ at 1 week ($n = 14$), $11.9 \pm 15.3\%$ at 4 weeks ($n = 38$) and $11.9 \pm 15.3\%$ at 8 ($n = 18$) weeks (Fig. 1(A)). Diameter also increased: $21.3 \pm 13.1\%$ at 1 week ($n = 14$), $34.5 \pm 46.3\%$ at 4 weeks ($n = 38$) and 92.2 ± 143.3, $34.1 \pm 18.0\%$ at 8 ($n = 18$) weeks (Fig. 1(A)).

Length-to-diameter ratio, calculated from the values of lengths and diameters expressed in mm, were 3.7 ± 0.8 at 1 week and 3.4 ± 1.1 at 8 weeks ($P = 0.59$).

The correlation between diameter and length percent changes during AAA expansion was strong (analysis pooling vessels at the three delays) (CC: 0.832, 95% CI:

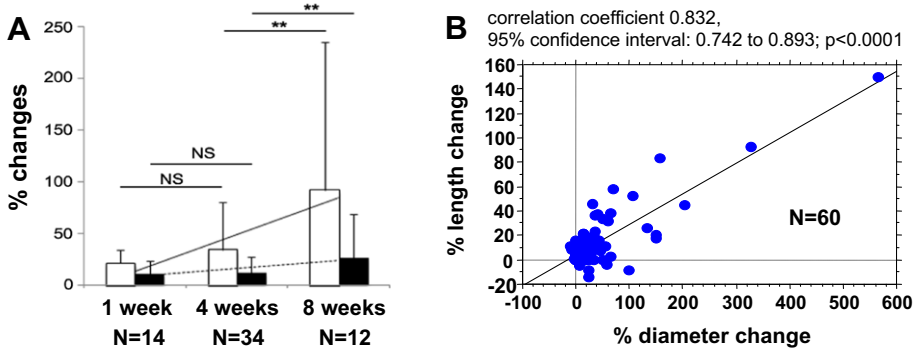

Figure 1 Length and diameter during expansion of experimental AAAs. (A) Relative length and diameter changes during AAA expansion. (B) Correlation between relative length and diameter changes during expansion. $^{**}P < 0.01$. NS: non-significant.

0.742—0.893; $P < 0.0001$) (Fig. 1(B)). A second correlation analysis has been performed after exclusion of 10 AAAs with extreme length and diameter changes, for example, over 40% and 100%, respectively. After exclusion of these outliers, the correlation was maintained (CC: 0.352, 95% CI: 0.108—0.556; $P = 0.0055$) (Fig. 1(B)).

Length in treatment studies

Comparisons between treated and non-treated vessels

Data comparing untreated vessels and vessels after preventive or curative treatments at latest observation time point are summarised in Table 2.

Analyses of length over time within treated vessel groups

Length evolution in preventive treatments (applied before AAA degeneration)

The experimental design of studies is presented in Fig. 2(A).

Length of non-aneurysmal vessels seeded by VSMCs was stable over time (percent of length changes at: 1 week: $-1.2 \pm 2.4\%$ ($n = 4$); 2 weeks: $-3.2 \pm 3.8\%$ ($n = 6$); 8 weeks: $4.4 \pm 16.2\%$ ($n = 8$) (NS); conversely, the diameter of the same vessels had increased at 1 week ($45.3 \pm 19.4\%$, $n = 4$). It remained unchanged at 2 ($46.8 \pm 8.6\%$, $n = 6$) and 8 weeks ($42.0 \pm 16.6\%$, $n = 8$) after treatment (NS)). As a consequence of discrepancies between length and diameter, correlation was lost (CC: 0.381, 95% CI: −0.104—0.720; $P = 0.12$) (Fig. 2(B)).

To test the impact of ECM degradation on AAA formation, TIMP-1 and PAI-1 were overexpressed in Fischer 344 rat VSMCs with a retroviral vector. Compared with their respective controls, both TIMP-1 and PAI-1 overexpression were followed by length stability over 4 weeks (Table 2).

Length evolution in curative treatments (applied to already formed AAAs)

In these experiments, length and diameter percent changes were calculated in reference to values in AAAs at time of treatment injection (day 14 after xenograft implantation) (see experimental design in Fig. 3(A)).

(1) *VSMCs seeding in already formed AAAs*. Length of AAAs seeded by VSMCs was stable over time ($6.0 \pm 7.0\%$ at 1 week ($n = 15$) and $4.5 \pm 4.7\%$ at 8 weeks ($n = 12$) (NS)). Diameter was also stabilised ($3.0 \pm 17.1\%$ at 1 week ($n = 15$) and $-5.2 \pm 8.0\%$ at 8 weeks ($n = 12$) (NS)). However, there was no correlation between diameter and length percent changes after VSMCs seeding: CC: −0.019, 95% CI: −0.396—0.363; $P = 0.93$) (Fig. 3(B)).

(2) *TGF-beta 1 overexpression in already formed AAAs*. Length of AAAs was stable over time after TGF-beta1 overexpression ($2.5 \pm 4.1\%$ at 2 ($n = 10$) and $5.9 \pm 7.4\%$ at 4 weeks ($n = 10$) ($P = 0.496$)). Diameter was also stabilised ($1.8 \pm 4.1\%$ at 2 ($n = 10$), and $11.9 \pm 20.6\%$ at 4 weeks ($n = 10$) ($P = 0.321$)). As for cell therapy, gene therapy failed to maintain a correlation between length and diameter changes, after excluding an outlier AAA with a major diameter increase: CC: 0.150, 95% CI: 0.119—0.223, $P = 0.223$).

Discussion

Measuring length of AAA in humans is difficult, technically and conceptually.[17,18] Moreover, AAA length may expand not only by elongation of the initial aneurysmal segment, but also by disease extension at the expense of necks.[19] In the xenograft model, it is possible to quantify the consequences of proteolysis-driven destruction of a defined segment of aortic ECM on aortic elongation. We demonstrate that length increases in correlation with diameter during AAA formation and expansion, as a consequence of ECM injury driven by MMPs activated by the plasmin

Table 2 Impact of treatments on length and diameter, in comparison with control groups.

	Diameter (% of change)			Length (% of change)		
	Control	Treated	P [c]	Control	Treated	P [c]
Preventive treatments						
VSMC seeding[a]	275.2 ± 279.7 ($n = 6$)	42.0 ± 16.7 ($n = 8$)	0.0002	38.9 ± 51.0 ($n = 6$)	4.4 ± 16.2 ($n = 8$)	0.011
PAI-1 overexpression[b]	395.8 ± 137.1 ($n = 6$)	60.1 ± 15.4 ($n = 6$)	0.014	56.5 ± 18.2 ($n = 6$)	7.3 ± 10.2 ($n = 6$)	0.014
TIMP-1 overexpression[b]	395.8 ± 137.1 ($n = 6$)	43.0 ± 8.3 ($n = 6$)	0.02	56.5 ± 18.2 ($n = 6$)	0.12 ± 4.1 ($n = 6$)	0.02
Curative treatments						
VSMC seeding[a]	261.3 ± 236.9 ($n = 5$)	-10.6 ± 9.4 ($n = 12$)	0.014	58.5 ± 76.2 ($n = 5$)	8.9 ± 0.3 ($n = 12$)	NS
TGF-beta1 overexpression[b]	66.0 ± 37.9 ($n = 8$)	11.9 ± 20.6 ($n = 10$)	0.0015	17.3 ± 9.6 ($n = 8$)	5.9 ± 7.4 ($n = 10$)	0.022

[a] At eight weeks.
[b] At four weeks.
[c] Mann—Whitney *U*-test.

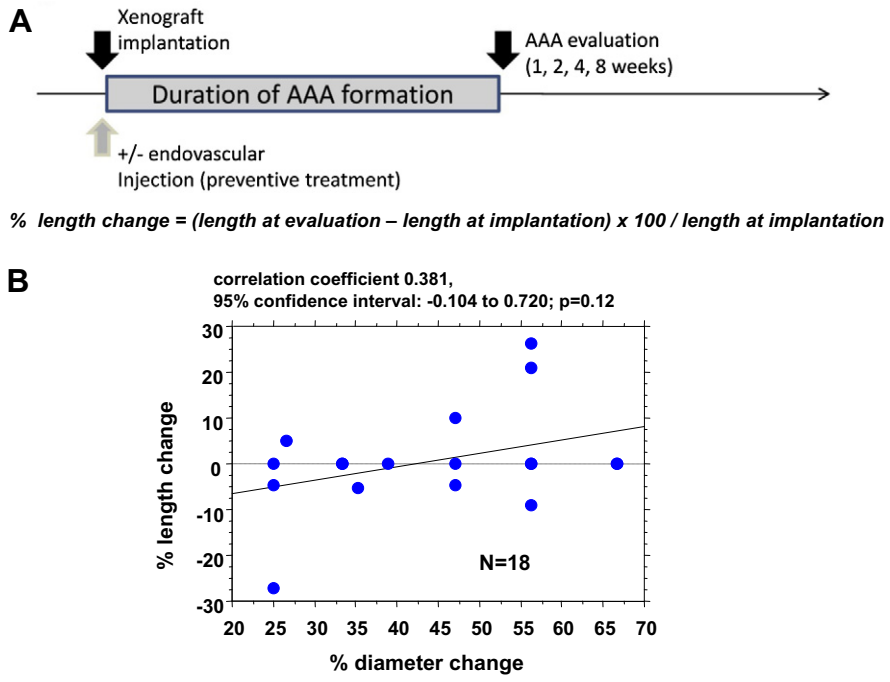

Figure 2 Length and diameter after preventive treatments of AAA formation. (A) Experimental design of preventive studies. (B) Impact of endovascular seeding of VSMCs with no genetic manipulation on correlation between relative length and diameter changes of already formed AAAs.

pathway. We also show that correlation between length and diameter increases is not universally preserved.

The magnitudes of length increase (14.7% and 36.8%) during experimental AAA formation compares to the 27% length increase of the sub-renal aorta in human AAAs in reference to non-aneurysmal aortas.[20] The mean length-to-diameter ratio of human AAAs is fairly constant (1.39—1.67),[21] as in our study, although ratios in the experimental model, calculated from values in millimetres, are different (3.4—3.5). The formation of the AAA was

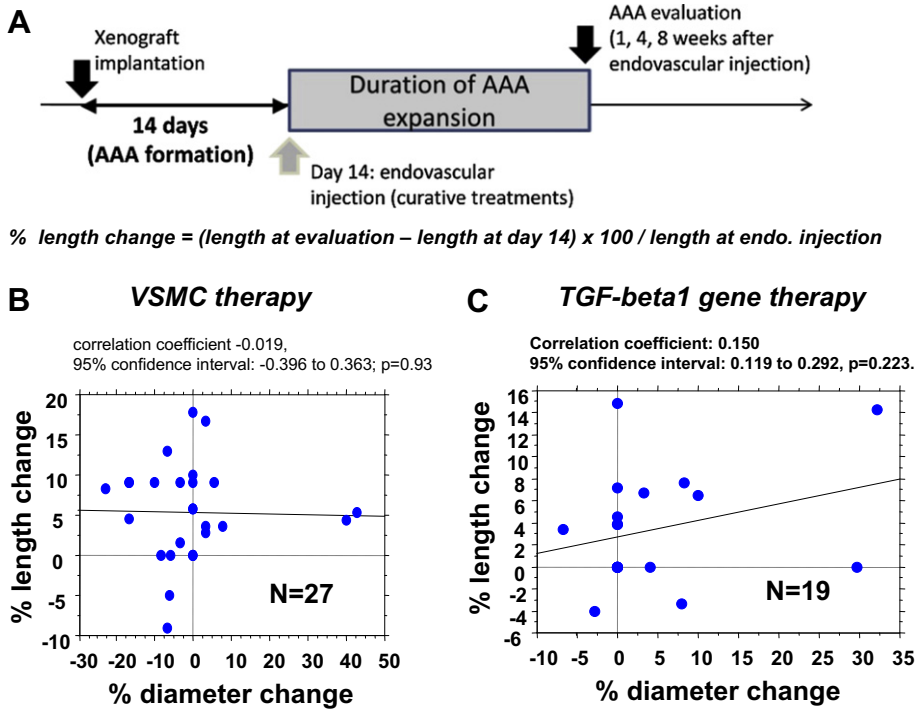

Figure 3 Length and diameter of already formed AAAs treated by endovascular biotherapies. (A) Experimental design of curative studies. (B) Impact of endovascular VSMCs therapy on correlation between relative length and diameter changes. (C) Impact of TGF-beta1 gene therapy on correlation between relative length and diameter changes of already formed AAAs.

studied from initial length and initial diameter of the guinea pig aorta. Sub-renal rat and guinea pig aortic diameters were similar (data not shown).

We demonstrate *in vivo* that aortic elongation during AAA formation is the consequence of a MMP-driven proteolysis, since it can be inhibited by TIMP-1 overexpression. We also show that activation of MMPs by enzymes of the plasmin pathway is instrumental, since the blocking of tPA and uPA by PAI-1 overexpression prevents aortic elongation. Our results demonstrate the role of ECM integrity in maintaining aortic length *in vivo*, and the destabilising role of MMPs activated by the plasmin pathway.

We provide the first demonstration that aortic ECM degradation by inflammation and proteolysis has a convergent impact on length and diameter changes. However, our data also show that, depending on local factors used to modulate the ECM destruction/reconstruction balance, the correlation between diameter and length increases is not always maintained. This finding is concordant with the clinical observation that patients may have particularly tortuous aorto-iliac vessels, independently of the diameter of their aneurysms. We have identified two mechanisms whereby correlation is lost. One is heterogeneous evolution of vessels with regard to length and diameter within one group of treatment, for example, VSMC seeding into already formed AAAs. Some vessels within one group clearly expand in length, not in diameter, and *vice versa*. This is also the case after endovascular gene therapy, although in a lesser extent. The other mechanism is divergent evolution of diameter and length for all vessels within one treatment group, for example, preventive seeding at 1 week. Collectively, these data suggest that under some circumstances, AAA remodelling does not happen simultaneously in all three directions in space. One reason may be that the endovascular seeding results into an uneven accumulation of VSMCs along the vessel, with ensuing local heterogeneities in ECM destructive/reconstructive balance. We have observed that after 48 h, accumulation of seeded cells sticking to the lumen of the aortic ECM is heterogeneous, with clusters of cells in discrete areas (E. Allaire, unpublished result). In addition to our data, it has been reported that the repartition of MMP activity along human AAAs is heterogeneous.[22] The maximum diameter of an AAA is the consequence of a very focal destruction of ECM along the aorta. Conversely, lengthening results from the addition of multiple focal degradations of ECM on the longitudinal axis.

Study limitations

Our study has limitations. The xenograft model does not reproduce aorto-iliac tortuosity, wall calcifications and extension of atherosclerotic disease to other arterial segments. All these characteristics of the human disease may have an impact on aortic remodelling, and, therefore, may have an additional impact on the relationship between length and diameter increase. In addition, shapes of formed AAAs were not recorded in this study. The lack of accounting for this variable may have induced more variability in the regression results.

Clinical relevance

Angulation modulates the risk of rupture of AAAs.[1,2] Feasibility and complexity of endovascular aneurysm repair (EVAR) are modulated by aortic and iliac angulation, presence of hostile necks characterised by shortness and severe angulation, all related to elongation.[23,24] Short necks are risk factors for limited durability of EVAR because of per-procedure and long-term type I endoleaks,[25] and increase rates of re-operation[26] and aneurysm-related death.[27]

Length changes contribute to EVAR durability. Longitudinal shrinkage causes stent-graft kinking and limb failure.[28,29] Post-EVAR neck shortening is associated to neck diameter increase, another illustration of the tri-dimensional aspect of aortic enlargement, and causes type I endoleak,[30] a major mechanism leading to secondary AAA rupture.[27] Whether entire coverage from neck to end of common iliac by stent graft may help controlling proteolysis and length changes is another important issue for EVAR durability.

In contrast to EVAR, results of open surgery may not be affected by aorto-iliac length and tortuosity. A better appreciation of aorto-iliac lengthening may help to stratify risks and benefits, and, for identified patients, may shift the balance towards one technique or the other. This is particularly relevant since mortality related to re-operation after EVAR failure likely contributes to the decline of the benefit of EVAR over surgery.[31,32]

Conclusion

When a segment of aortic ECM is exposed to a proteolytic injury together with longitudinal and radial strains *in vivo*, length increases in correlation to diameter. Length expansion is driven by MMPs activated by the plasmin pathway, and can be suspended by selective inhibition by TIMP-1 or PAI-1. Under some circumstances, heterogeneity of aortic wall remodelling may occur along the AAA and disrupt correlation between length and diameter evolution.

Conflict of Interest

None.

Acknowledgements

We thank Anne-Marie Guinault for technical support, Philippe Druelle and Philippe Mario for animal care and Nicole Sauvant for administrative support.

We thank the Fondation de l'Avenir pour la Recherche Médicale, the Fondation de France, the Fondation pour la Recherche Médicale and the European Union (P.C.R.D. 7, ≪Fighting Aneurysmal Disease≫ programme) for financial support.

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