Intrasac Pressure Changes and Vascular Remodeling After Endovascular Repair of Abdominal Aortic Aneurysms: Review and Biomechanical Model Simulation

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In this paper, we review existing clinical research data on post-endovascular repair (EVAR) intrasac pressure and relation with abdominal aortic aneurysm (AAA) size changes. Based on the review, we hypothesize that intrasac pressure has a significant impact on post-EVAR AAA size changes, and post-EVAR remodeling depends also on how the pressure has changed over a period of time. The previously developed model of an AAA based on a constrained mixture approach is extended to include vascular adaptation after EVAR using an idealized geometry. Computational simulation shows that the same mechanism of collagen stress-mediated remodeling in AAA expansion induces the aneurysm wall to shrink in a reduced sac-pressure after post-EVAR. Computational simulation suggests that the intrasac pressure of 60 mm Hg is a critical value. At this value, the AAA remains stable, while values above cause the AAA to expand and values below cause the AAA to shrink. There are, however, variations between individuals due to different cellular sensitivities in stress-mediated adaptation. Computer simulation also indicates that an initial decrease in intrasac pressure helps the AAA shrink even if the pressure increases after some time. The presented study suggests that biomechanics has a major effect on initial adaptation after EVAR and also illustrates the utility of a computational model of vascular growth and remodeling in predicting diameter changes during the progression and after the treatment of AAAs. [DOI: 10.1115/1.4003134]

Keywords: vascular mechanics, stress-mediated growth and remodeling, constrained mixture model, endoleak

1 Introduction

An abdominal aortic aneurysm (AAA) is a localized dilation of the aorta below the diaphragm. The rupture potential of AAAs increases with increasing diameter of the aneurysm, and thus the recommended treatment for aneurysms larger than 5.5 cm is open surgical repair of the aneurysm with aortic graft placement or placement of an aortic endograft to exclude the aneurysm. Over the last decade, the technology of endovascular repair (EVAR) has been developed, improved upon, and has become the preferred treatment of AAAs. Clinical experience with EVAR during the past decade, however, suggests that the many advantages of EVAR, such as a reduction in operative mortality, come at a price. EVAR has its own unique set of complications and risks after endovascular repair such as endoleaks and endovascular stent migration [1,2]. Detecting early signs of endoleaks and risk assessment after EVAR is now an active research area. Although there is significant variability in the data, there is increasing evidence that a high intra-aneurysm (or intrasac) pressure is associated with post-EVAR expansion. In this paper, we summarize existing clinical research data on post-EVAR intrasac pressure and relation with AAA size changes, and then test the prediction capability of a computational model of an AAA and its utility in increasing our understanding about biomechanical effects on vascular adaptation after EVAR.

Although the physiopathogenic mechanism of AAA enlargement is not completely understood, it is generally accepted that loss of elastin and smooth muscle is responsible for the weakening of the aortic wall. Nevertheless, the degradation of elastin and the loss of smooth muscle alone does not explain the large dilatation of aneurysms. On the other hand, collagen turnover is continuous and at a relatively fast rate (half-life of 70 days in normal conditions) and the continuous process of degradation and deposition of collagenous fibers is believed to be the main process in the enlargement of an aneurysm. Therefore, by accounting both elastin degradation and collagen turnover, computational models of AAA enlargement have been developed by multiple groups [3–6]. Using the finite element method, these models describe how changes in the microstructure of the aortic wall may lead to the development of an AAA. Although the detail forms of constitutive relations and parameters are different, their parameter studies suggest that the rate of collagen production should increase with the stress (or strain) of the arterial wall in order for a model to predict the rate of AAA expansion found in the clinical studies. The sensitivity of the rate of stress-mediated collagen turnover, however, may be different for individuals, which may also affect the rate of AAA enlargement [4,5]. In order to model vascular adaptation of the arterial wall after EVAR, we employ the computational model of

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AAA enlargement developed by Zeinali-Davarani et al. [5] but use an idealized axisymmetric model and simulate vascular adaptation under the reduced pressure after EVAR.

In Sec. 2, we first review the clinical research on changes of intrasac pressure over time and association with vascular adaptation after EVAR, and we hypothesize that intrasac pressure has a significant impact on post-EVAR AAA size change and that post-EVAR remodeling depends not only on the value of the intrasac pressure but also on how the pressure has changed over a period of time. In Sec. 3, a biomechanical model for vascular adaptation based on a constrained mixture approach is presented. Finally, in Secs. 4 and 5 we will present the computational simulation results that test the hypotheses suggested from the literature review and discuss the results, their clinical relevance, and limitations.

2 Intrasac Pressure and Endotension After EVAR

EVAR is a minimally invasive method of repairing an AAA that is associated with less blood loss, less risk of infection, shorter hospital stay, lower mortality, and other advantages compared with open surgery. During this operation, a stent graft is introduced through the femoral arteries and is deployed with the proximal portion below the renal arteries. Once in place, the stent graft excludes blood flow from the aneurysm sac. There are two main types of stent graft configurations: aorto uni-iliac and bifurcated. The aorto uni-iliac stent graft extends from the infrarenal aorta into only one iliac artery, whereas a bifurcated stent extends into both iliac arteries. Due to its associated advantages, EVAR has become the treatment of choice for AAA and is now used for over 50% of AAA repairs. However, EVAR is not always perfect and several issues with the technique have arisen.

After EVAR, the aneurysm sac should ideally be completely excluded from aortic blood flow resulting in a much lower intrasac or intra-aneurysm pressure than the systemic pressure. In reality, this pressure is not zero but varies from case to case [7–14]. A multitude of variables affect the intrasac pressure after EVAR including time-elapsed from repair, location within the aneurysm, and presence of endoleaks, which can result in a wide range of post-EVAR intrasac pressures.

Endoleaks are a significant disadvantage of EVAR. Significant endoleaks can result in near-systemic pressures within the aneurysm sac, potentially leading to aneurysm rupture. An endoleak is defined as the persistence of blood flow outside the lumen of the endoluminal graft but within the aneurysm sac. There are four types of endoleaks. A type I endoleak occurs when blood flows through an inadequate or incomplete seal of the graft against the artery at the proximal or distal ends of the endograft. Subscripts are used to indicate where the inadequate seal is. The subscripts *a* and *b* indicate the leaks at the proximal and distal ends of the endograft, respectively, while the use of the subscript *c* indicates a failing iliac occluder plug with use of an aorto uni-iliac graft. Type II endoleak, by far the most frequent type, suggests that collateral vessels connected to the aneurysm result in blood flow in the area. Type II endoleaks most commonly result from lumbar arteries or the inferior mesenteric artery. Type III and type IV endoleaks are due to stent malfunction. A hole in the graft, separation between graft components, or a tear in the graft results in a type III endoleak, which uses the subscripts *a* and *b* to further classify the endoleak. The subscript *a* suggests a module disconnection, while the subscript *b* indicates a fabric tear. Increased blood flow in the aneurysm due to the porosity of the graft within the first 30 days after EVAR is indicative of a type IV endoleak. Any one of these types of endoleaks can lead to a heightened intrasac pressure.

While type I and type III endoleaks are deemed as signs of EVAR failure and repair of these leaks is essentially mandated, management of type II endoleaks remains more controversial. Type I endoleaks can be repaired through extension grafts with aortic cuffs or large balloon expandable stents, reinflation of large diameter balloons, or open surgery. Type III endoleaks are repaired by extension of grafts more distally or with the use of stent grafts for relining of the previously placed stent graft. The significance of type II endoleaks is not agreed upon although most clinicians would agree that an enlarging aneurysm sac in the presence of a type II endoleak should be treated. Type II endoleaks are generally repaired through embolization with coils or other embolic material. Type IV endoleaks usually resolve spontaneously within 30 days and therefore do not generally require treatment. More detailed information on endoleaks and their management can be found elsewhere [15,16].

The intra-aneurysm or intrasac pressure can be measured using two different methods: a direct, catheter pressure measurement or an implantable pressure transducer. The implantable pressure transducer is a relatively new method but its accuracy has been shown [13,17].

One of the biggest questions regarding intrasac pressure is how time elapsed after EVAR affects the value of the pressure (see Table 1 for the summary). Chuter et al. [7] found an immediate decrease in intrasac pressure after EVAR using a catheter and a pressure transducer. Eight patients were included in the study with six out of eight patients seeing an immediate decrease in pressure. Average aneurysm pressures were significantly lower than average arterial pressures. In one of the patients that did not have an immediate decrease in pressure, the aneurysm pressure was 95/45 mm Hg while the arterial pressure was 150/60 mm Hg. A leak was found but after reorientation of the stent, the aneurysm pressure dropped to 25/25 mm Hg. The second patient without an immediate drop in pressure had an aneurysm pressure of 95/55 mm Hg and an arterial pressure of 160/80 mm Hg. No endoleak could be found but by the time they had finished searching, the aneurysm pressure had already decreased to 27/27 mm Hg. While this study shows a clear reduction in pressure immediately after EVAR, there are a couple of facts to note. The number of patients included in this study was small, which could lead to a misinterpretation of the overall trend of post-EVAR intrasac pressure. In addition, the author describes the presence of type II endoleak among some of the patients, which we will discuss later. Interestingly, Baum et al. [18] stated that they found an immediate decrease in pressure like in Chuter et al. [7]. However, the longer they left the catheters in, the higher the pressure rose and actually exceeded the radial artery pressure at times. No explanation for this behavior was found. Further work by Ohki et al. [13] showed a significant drop in pulse pressure immediately after EVAR using a wireless pressure measurement system. This pulse pressure though is significantly higher than the values found by Chuter et al. [7].

In more recent studies, Ellozy et al. [11,17] did not find such a dramatic decrease in pressure immediately after stent placement but instead found a gradual decrease of pressure over time. They recorded arterial and intrasac pressures initially at 1 month and at 3 months [17]. Mean values are shown as well as the maxima and minima, which are important to consider due to the low number of patients and high variability in pressures. A significantly higher initial intrasac pressure is seen compared with the value from Chuter et al. [7] but after 3 months, this pressure decreases to a value that is comparable. It is also stated that initially, the diastolic pressure in the sac increases while the systolic pressure decreases. The cause for this increase in diastolic pressure is unknown. In a separate study from Ellozy et al. [11], a relatively low intrasac pressure is present for shrinking aneurysms at 6 months and later and states that intrasac pressure decreases gradually.

AAA size change corresponds very well with intrasac pressures. With an aneurysm that is increasing in size, intrasac pressures are found to be relatively high. With an aneurysm that is decreasing in size, intrasac pressures are relatively low. It makes sense then that aneurysms that have remained stable in size usually have pressures in between the two extremes. Many authors have shown this to be true (Table 2). Therefore, a change in pressure could indicate whether EVAR was successful. Dias et al. [8]

Table 1 Intra-aneurysm pressure with respect to time elapsed after EVAR. MPI is the ratio of mean sac pressure to mean systemic pressure.

		Intra-aneurysm pressure				
	Time after EVAR (month)	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)	MPI (%)	Pulse (mm Hg)
Chuter et al. [7]	0	36.5	33.8	34.7		1.7
Ellozy et al. [17] (minimum, maximum)	0	122.73 (85, 188)	77.27 (52, 105)	92.42		47
	1	109.64 (83, 167)	74.45 (57, 103)	86.18		37
	3	63 (18, 151)	47.17 (11, 104)	52.44		15.5
Ellozy et al. [11]	Shrinking					
	6	18	15	16	14	3
	12	33	24	27	24	9
	Final	34	17	22.7	22	17
	Stable					
	6	82	63	69.3	58	19
	12	69	49	55.67	53	20
	Final	72	54	60	54	18
Sonesson et al. [14]	19	19	18	19	20	1
Dias et al. [9]	32	46	43	44	46	3
		48	43	45	49	5
Ohki et al. [13]	Before EVAR					59.34
	After EVAR					27.5

also stated that there may be a delay in aneurysm size change in response to the intrasac pressure. Four patients initially had an unchanged aneurysm diameter but had pressures similar to patients who had shrinking aneurysms. Eventually, these unchanged aneurysms shrank. In concordance, two patients with initially unchanged aneurysms but had pressures corresponding to those found in patients with expanding aneurysms were found to have expanding aneurysms after some time.

Type I and type III endoleaks can lead to near-systemic pressure in the sac, and as mentioned previously, are signs of EVAR failure. Dias et al. [10] saw a pressurization of the sac in the presence of type I or type III endoleaks, mentioning the case of one patient who underwent direct intra-aneurysm sac pressure measurements (DISP) after 15 months and had a near-systemic pressure in the nidus (mean pressure index, MPI 93%) with a type I endoleak. This patient saw an increase in aneurysm diameter soon after. Ellozy et al. [17] observed a patient with a type I endoleak and surprisingly found a higher sac pressure (108/78) compared with the simultaneous systemic pressure (105/60) directly after EVAR. After 1 month, the sac pressure (141/94) was near systemic (157/66).

Type II endoleaks are more unclear (Table 3). It has been

Table 2 Intra-aneurysm pressure with respect to AAA size change

			Intra-aneurysm pressure				
	Change	Time (month)	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)	MPI (%)	Pulse (mm Hg)
Ellozy et al. [11]	Decrease	6	18	15	16	14	3
		12	33	24	27	24	9
		Final	34	17	22.7	22	17
Sonesson et al. [14]	Decrease	19	19	18	19	20	1
Dias et al. [8]	Decrease	19	19	18	19	19	2
Dias et al. [10]	Decrease	19			40	35	7
Ellozy et al. [11]	Stable	6	82	63	69.3		19
		12	69	49	55.7		20
		Final	72	54	60		18
Dias et al. [10]	Stable	15			86	78	21
Dias et al. [8]	Stable	18	32	26	29	30	6
Dias et al. [10]	Increase	22			76	74	17
Dias et al. [8]	Increase	38	67	60	63	59	10

Table 3 Intra-aneurysm pressure in presence of type II endoleaks

	Patients (n)	Diameter change	Time after EVAR (months)	Diameter change (mm)	Intra-aneurysm pressure: Mean (mm Hg)	Intra-aneurysm pressure: Pulse (mm Hg)	Intra-aneurysm pressure: MPI (%)
Dias et al. [10]	4	Shrinking	19 (7–43)	−6 (−9, −5)	40 (24–47)	7 (6–10)	35 (25–38)
	11	Stable	15 (13–16)	2 (0, 3)	86 (53–97)	21 (12–22)	78 (47–85)
	6	Expanding	22 (20–31)	7 (6, 10)	76 (59–109)	17 (11–31)	74 (58–87)
Ellozy et al. [11]	1	Shrinking	6	−7			17

shown that even with type II endoleaks, the aneurysm can decrease in size and can have a low intrasac pressure. Dias et al. [10] found aneurysms in patients with type II endoleak that shrank, remained stable, and expanded. However, other papers show that with an initially high MPI, embolization or sealing of the collateral vessels (whether natural or artificially induced) can decrease MPI significantly [17,10] (Table 4). Ellozy et al. [11] observed a separate patient that did not need embolization to repair a type II endoleak. In this patient, MPI decreased to 0.17 and diameter decreased to 7 mm 6 months after EVAR without embolization or natural sealing. It is significant to note that for the two patients that saw a significant decrease in MPIs in Dias et al. [10], initial MPIs were relatively high, perhaps creating a higher probability for them to decrease after embolization. The patients with relatively lower initial MPIs did not see such a sizable decrease. Ellozy et al. [17] also stated that while the patients with type II endoleak also experienced a decrease in sac pressures over time, the reduction in pressure was not as significant as the decrease within patients without endoleak. In this study, only three patients with type II endoleak were studied.

From the literature, it is seen that time elapsed and endoleaks have a major influence on the intrasac pressure. A final pressure reading of around 20–40 mm Hg after a successful EVAR seems to be the norm. However, there is a high variability of the rate at which this pressure decreases. In addition, intrasac pressure is indicative to the size change of the aneurysm; a relatively low intrasac pressure leads to a decrease in aneurysm diameter, while a relatively high intrasac pressure may cause an increase in aneurysm diameter. Intrasac pressure has a significant impact on post-EVAR AAA size change. Additionally, post-EVAR remodeling depends not only on the value of the intrasac pressure but also on how the pressure has changed over a period of time.

3 Computational Model of an AAA

For simulation of AAA enlargement and post-EVAR adaptation, we employ a computational model of an AAA by Zeinali-Davarani et al. [5]. The aortic wall is assumed to consist of elastin, multiple families of collagen, and vasoactive smooth muscle cells. Collagen fibers and smooth muscle continuously turn-over with their own rates and with prestretches. The material parameters are obtained using the parameter estimation method presented by Zeinali-Davarani et al. [19] using a biaxial test data of nonaneurysmal tissue sample from Vande Geest et al. [20]. The rate of mass production for kth collagen fiber family $m_R^k(t)$ is a function of a scalar measure of intramural stress $\sigma^k(t)$ given by

$$m_R^k(t) = \frac{M_R^c(t)}{M_R^c(0)} m_{\text{basal}}^k \left[K_g^c \frac{(\sigma^k(t) - \sigma_h^c)}{\sigma_h^c} + 1 \right] \tag{1}$$

where $M_R^c(t)$ is an areal mass density of collagen, m_{basal}^k is the basal rate of mass production of the collagen fiber family, and K_R^c is a cell sensitivity parameter that controls the stress-mediated turnover rate. Similarly, for smooth muscle, the rate of mass production is given by

$$m_R^{\text{SM}}(t) = \frac{M_R^{\text{SM}}(t)}{M_R^{\text{SM}}(0)} m_{\text{basal}}^{\text{SM}} \left[K_g^{\text{SM}} \frac{(\sigma^{\text{SM}} - \sigma_h^{\text{SM}})}{\sigma_h^{\text{SM}}} + 1 \right] \tag{2}$$

The coefficients K_R^c and K_R^{SM} are related to mechanosensitive cellular activities and assumed to be varying with individuals depending on the patient's state of health, age, and other parameters (e.g., smoking). To simulate arterial growth and remodeling, we employ an axisymmetric finite element model based on the principle of virtual work

$$\delta I = \int_S \delta w dA - \int_s P(t)\mathbf{n} \cdot \delta\mathbf{x} da = 0 \tag{3}$$

where $\mathbf{x}$ and $\mathbf{n}$ are the position and out normal vectors, respectively, and $P(t)$ is the transmural pressure. To simulate arterial growth and remodeling, the strain energy of the vessel wall is assumed at a given time (viz. Refs. [5,21])

$$w(t) = \sum_i \left\{ M_R^i(0) Q^i(t) \Psi^i(C_{n(0)}^i(t)) + \int_0^t m_R^i q^i(t,\tau) \Psi^i(C_{n(0)}^i(t)) d\tau \right\} \tag{4}$$

where $Q^i(t)$ is the fraction of the constituent i that was presented at time 0 and still remains at time t, and $q^i(t,\tau)$ and $\Psi^i(C_{n(0)}^i(t))$ are the survival fraction and the stored energy of constituent i that

Table 4 Intra-aneurysm pressure related to sealing of type II endoleaks

	Patient	Type of seal	Intra-aneurysm pressure: MPI before (%)	MPI after (%)	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)	Follow-up after embolization (month)	AAA diameter change after embolization
Dias et al. [10]	1	Embolization	70	31	34	28	30	44	−7
	2	Embolization	NA	13	22	19	20	72	−18
	3	Embolization	67	19	25	18	21	50	−6
	4	Embolization	NA	42	53	40	45	39	−1
	5	Embolization	45	44	45	38	40	11	1
	6	Embolization	39	37	60	57	58	9	−1
Ellozy et al. [17]	1	Natural	72	3.1				6	−7

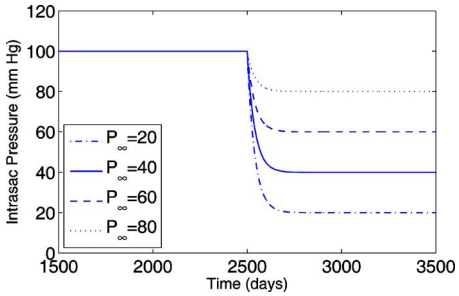

Fig. 1 Intrasac pressure with respect to time varying the final pressure P_∞ for a constant $k=1/40$

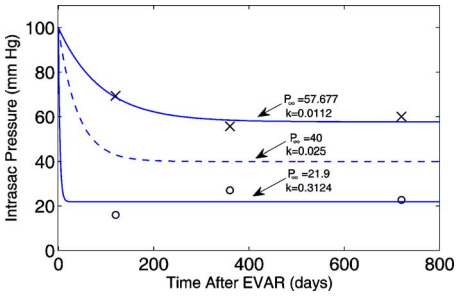

Fig. 2 Best-fit pressure curves after EVAR using clinical data from Ellozy et al. [11] compared with the pressure-time curve using the control values for simulation (dotted line)

has been produced at time τ, respectively. More details about constitutive forms for constituents and numerical simulation are available in Zeinali-Davarani et al. [5].

For AAA simulation, we assume healthy aorta to be an ideal cylinder with a mean diameter of 2 cm and thickness of 1 mm under the in vivo pressure. In normal physiological conditions, production and removal of each constituent are balanced and the intramural stress for each constituent remains a preferred homeostatic state. Then AAA growth is initiated by prescribing axisymmetric damage (a mass reduction) in the middle of the aorta [5]. Simulation of the AAA enlargement is continued until the prescribed time of endovascular repair, namely, t_s. Until the time of EVAR, the mean pressure is kept to a constant pressure, 100 mm Hg. However, after placing a stent graft, for $t \geq t_s$, the pressure decreases in the sac and the pressure is prescribed as a function of time. Also, the constrained force due to the stent graft with the radius r_s is imposed from the proximal to distal area of the AAA by

$$\delta I = \int_S \delta w dA - \int_s P(t)\mathbf{n} \cdot \delta \mathbf{x} da + \int_s \delta \left[\frac{k_p}{2} < r_s - r(t) >^2 \right] da = 0 \quad \text{for} \quad t \geq t_s \tag{5}$$

where t_s is the time when EVAR is done, k_p is a parameter for the penalty method, and $<x>=x$ only if $x \geq 0$ otherwise zero. The time course of the pressure after EVAR is modeled by an exponential decay function of time $\tilde{t}=t-t_s$ given by

$$P(\tilde{t}) = (P_{\text{sys}} - P_\infty)\exp\{-k\tilde{t}\} + P_\infty \tag{6}$$

where P_{sys} is the mean systemic pressure set to 100 mm Hg, P_∞ is the stabilized final intrasac pressure, and k is the rate parameter for the pressure change.

Figure 1 plots the time course of the pressure used in simulation of AAA enlargement and shrinkage after EVAR.

4 Simulation Results of Post-EVAR AAA Changes After Stent Placement

For computational simulation, the change of intrasac pressure is modeled with two parameters, P_∞ and k, to see the impact on post-EVAR remodeling including diameter and thickness change. To estimate the range of these two parameters, clinical data from patients with shrinking aneurysms and patients with stable aneurysms [11] was plotted with the best-fit lines (Fig. 2). These lines provided loose bounds for the k value, the rate of intrasac pressure decay, and the final pressure value. From the best-fit curves, the k value of 1/40 and the final pressure P_∞ of 40 mm Hg were chosen to be the control values that used in general parameter studies and otherwise, the values are specified. The EVAR operation time was set to be 2500 days (6.85 years), allowing the aneurysm to grow for this period of time before the EVAR operation.

Even though aneurysm growth rate depends on aneurysm size, clinical data show average growth rates of around 2.6–4 mm per year [22,23]. The sensitivity parameter for stress-mediated growth and remodeling $K_R^c=K_R^{\text{SM}}$ from 0.06 to 0.08 yielded growth rates similar to average growth rates found in patients (Fig. 3). A cell sensitivity of 0.08 had an AAA growth rate slightly smaller than the aforementioned average growth rates, while a sensitivity of 0.06 gave a slightly higher AAA growth rate than the norm. After the initial damage, thickness gradually increased for these values. A control value of 0.06 was used for later simulations. Using this value, after 2500 days, the aneurysm was larger than 50 mm in diameter, close to the value for an AAA to be operated on. However, growth rate can be as extreme as 6.1 mm/year, which suggests a large variation between patients [23]. For cases such as this, where the AAA grows faster than normal, a value of 0.05 could be utilized. The thickness decreased for a small aneurysm for this sensitivity value after initial damage, mainly due to the rapid increase of the aneurysmal area, but eventually increased to a level similar to the thickness obtained from 0.06 and 0.08 due to the stress-mediated adaptation.

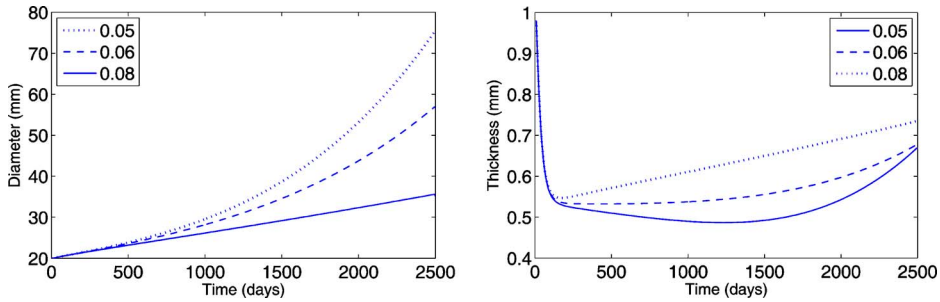

Fig. 3 AAA diameter growth and thickness change before EVAR, varying cell sensitivity parameters

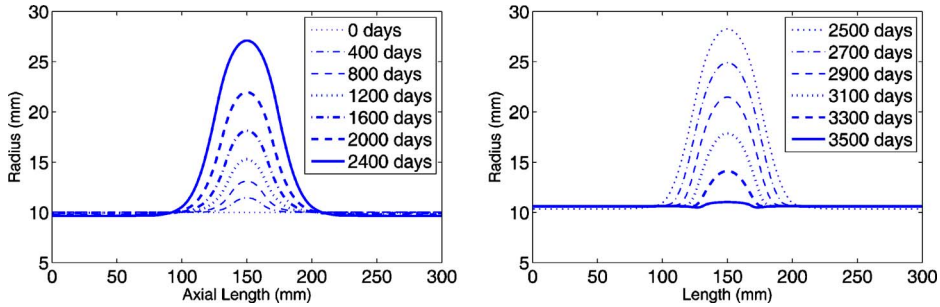

Fig. 4 AAA radius with respect to axial length showing growth of AAA before EVAR (left) and shrinking after EVAR (right)

Before EVAR, the simulation showed that the aneurysm increased in radius over a period of time. In a similar fashion, after EVAR, the simulation showed that the aneurysm radius decreased alongside a decrease in intrasac pressure (Fig. 4). For these simulations, the control k value of 1/40, a sensitivity of 0.06, and pressure at time infinity of 40 mm Hg were used. A clear difference was seen when using different final pressures P_∞ (Fig. 5). The diameter of the AAA decreased faster and more extensively with lower final pressures. When the final pressure was set to 20 mm Hg, the diameter of the AAA decreased quickly and seemed to stabilize. The circumferential and axial components of the stress rapidly decreased after EVAR but increased again for $P_\infty=80$ mm Hg, remained constant for $P_\infty=60$ mm Hg, and continuously decreased for $P_\infty=40$ and 20 mm Hg. When the diameter of the AAA reaches that of the stent, it cannot shrink further because of an increased reaction force from the stent, which also caused an increase of circumferential stress.

The thickness increased as the AAA shrank, and it continued to increase even after it seemed the diameter had stabilized. With the final pressure set to 40 mm Hg, the diameter did not decrease as quickly and stabilized after 1000 days post-EVAR. As this diameter decreased, the thickness increased at an exponential rate. With the final pressure of 60 mm Hg, the AAA diameter increased slightly but remained relatively stable. Accordingly, the thickness also remained stable but seemed to decrease slightly after initially increasing. At 80 mm Hg, the increase in AAA diameter seen during AAA growth persisted at nearly the same rate.

Cell sensitivity parameters also affected the remodeling of the AAA after EVAR (Fig. 6). At 0.08 stress-mediated cell sensitivity, the AAA quickly shrank too close to its original diameter while the thickness stabilized as the diameter stabilized. At 0.06, the AAA diameter shrank but no stabilization was seen while the thickness increased exponentially. For 0.05, the AAA diameter

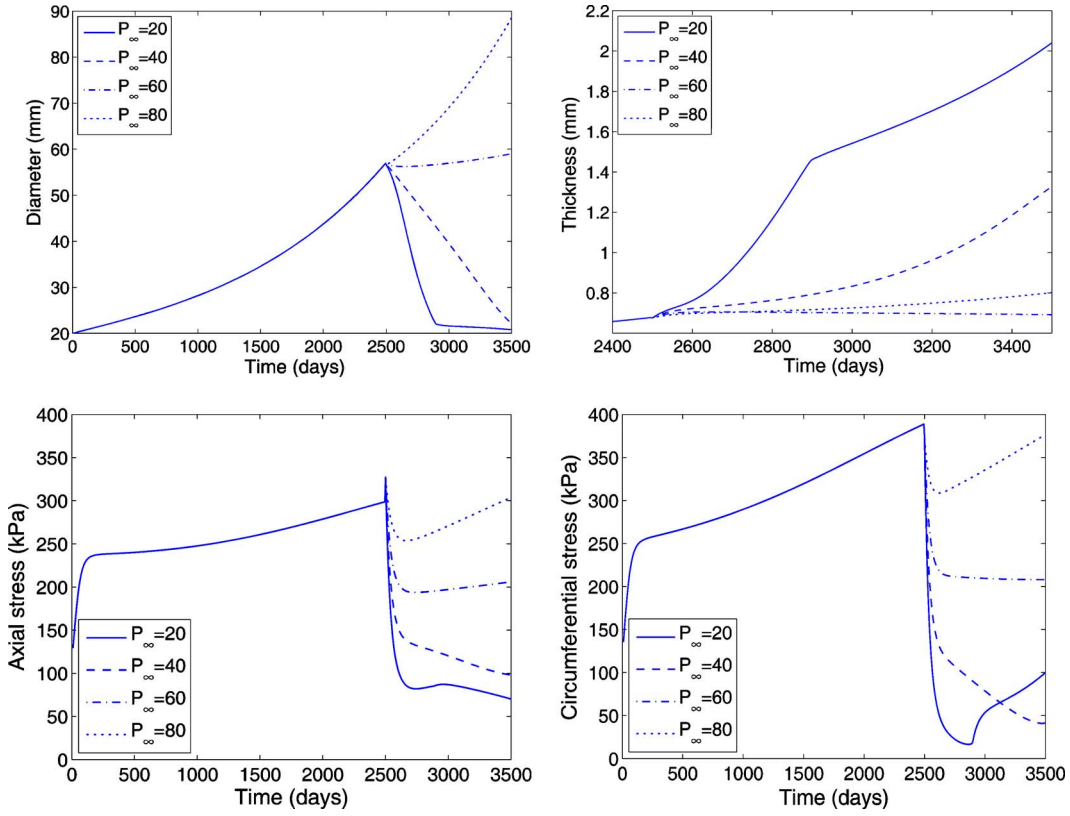

Fig. 5 AAA diameter, thickness, the circumferential component, and the axial component of the stress at the middle point of the wall with respect to time for different final intrasac pressure P_∞

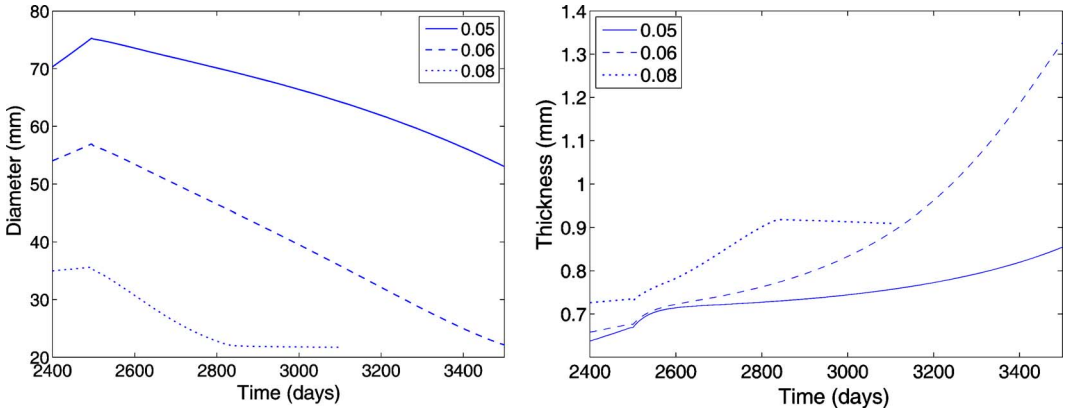

Fig. 6 AAA diameter and thickness with respect to time, showing the effects of changing cell sensitivity

shrank a small amount but at a delayed rate compared with the other values. The thickness also increased at a relatively high exponential rate.

Figure 7 shows that the simulation results are consistent with the clinical data we used, further validating our model. The intrasac pressure curve obtained from the shrinking aneurysms in Ellozy et al. [11] produced a shrinking AAA diameter after EVAR. For this pressure curve, the thickness increased as the diameter decreased, then continued to increase but at a different rate after the diameter had stabilized. Accordingly, the intrasac pressure curve from stable aneurysms in Ellozy et al. [11] resulted in a relatively stable AAA diameter after EVAR. The AAA diameter increased very slightly but could be classified as being stable because the diameter did not change by more than 5 mm. The thickness also remained relatively stable.

From the literature review, it is speculated that the change in the size of an AAA depends not only on the value of the final intrasac pressure but also on how the pressure has changed over a period of time. To test this with computer simulation, we simulate a case where the intrasac pressure initially decreases rapidly but increases again after a certain amount of time after EVAR (possibly due to type II endoleak) and compared with the case of a constant P_∞ (Fig. 8). This change exhibited drastically different results. An AAA that has an intrasac pressure that decreases to 40 mm Hg at first, then increases back to 60 mm Hg, continues to shrink. Comparatively, an AAA that has an intrasac pressure that decreases to 60 mm Hg will stay relatively stable and even expand a small amount.

In summary, computational simulation shows that the same mechanism of collagen remodeling in AAA expansion induces the aneurysm wall to shrink in a reduced sac-pressure. The simulation results also suggest that vascular adaptation after EVAR depends on the time history of the sac-pressure and the ability (sensitivity) of the vessel wall to react on the change of the mechanical state.

5 Discussion

The presented literature and the results from computational simulation suggest that intrasac pressure plays a major role in how an AAA remodels after EVAR. The value at which the pressure stabilizes can determine whether an AAA shrinks, grows, or remains stable. A lower pressure will lead to a contracting AAA, a higher pressure will lead to an expanding AAA, and a pressure in between will generally lead to a stable AAA. However, this intrasac pressure is affected by other factors such as endoleak. Clearly, changes in intrasac pressure over a period of time have a major impact on the behavior of an AAA after EVAR (Fig. 8). It appears that the initial drastic decrease in intrasac pressure helps the AAA shrink even if the pressure increases after some time. This finding, hence, supports the hypothesis that the vascular adaptation after EVAR depends on the time history of the sac-pressure. It probably explains wide variations of diameter changes in patients with type II endoleak in Dias et al. [10].

Intrasac pressure at around 60 mm Hg seems to be of particular importance, a sort of tipping point important to AAA remodeling. At this value, the AAA remains stable while values above cause the AAA to expand and values below cause the AAA to shrink. It is important, however, to note that stress-mediated cell sensitivity may play a large role in vascular adaptation after EVAR as well as during the progression of an AAA. Cell sensitivity may vary from patient to patient, something essential to consider due to its substantial influence on AAA behavior. Not only does it affect the

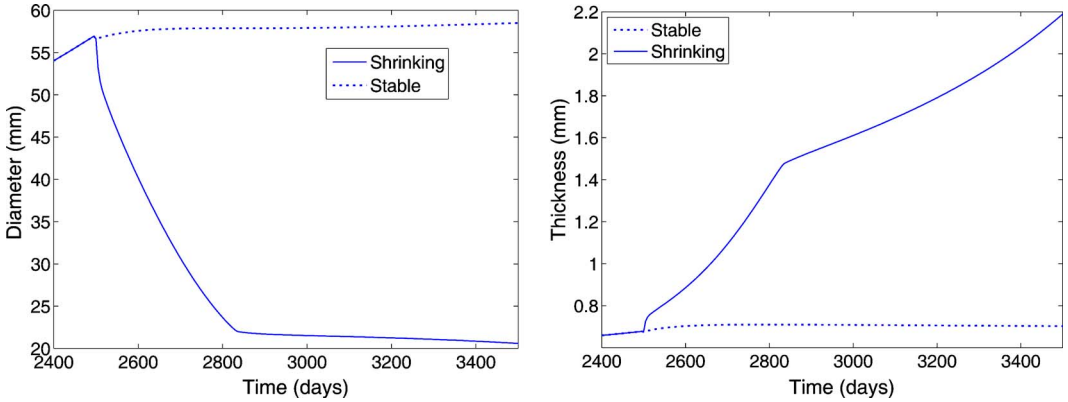

Fig. 7 Changes of AAA diameter and thickness for the intrasac pressure curves obtained from the shrinking and stable aneurysms in Ellozy et al. [11]

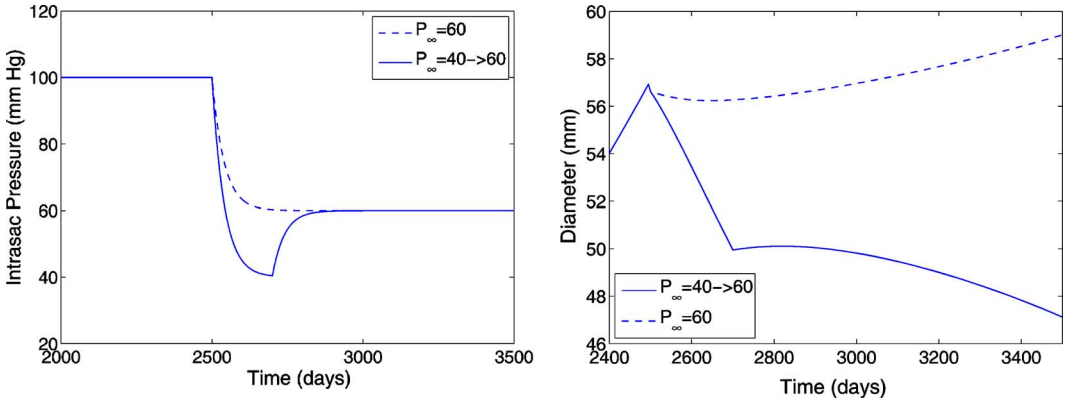

Fig. 8 AAA pressure and diameter with respect to time, demonstrating the affect of making the intrasac pressure inconsistent

rate of growth of an AAA, it also affects AAA change after EVAR. The simulation results show that if the sensitivity for stress-mediated cellular activities is high, then an AAA expands slowly but shrinks faster after EVAR for the similar time history of the pressure changes (Fig. 6).

During stress-mediated adaptation, in general, wall thickness increases in high stress and decreases in low stress [24,25]. After EVAR, however, thickness of aneurysmal wall continues to increase even with the decrease in stress. The thickening occurs due to the prestress of newly produced collageneous tissues, which causes in-plane shrinkage of existing tissues and hence a relative thickening in the out-of-plane. Different from adaptation during aneurysm expansion, the thickening after EVAR associates with more undulation of existing tissues, which is evident from the very low circumferential stress right after the stent replacement (Fig. 5). Hence, the initial thickening does not necessarily mean a strengthening of the wall but continuous vascular adaptation process after EVAR will remove the old undulated constituents, replace with new constituents, and improve the structural integrity. Recent studies suggest that both the proteolytic activity and the susceptibility of collagen molecules to enzymatic degradation in a vascular tissue increase in low stretch conditions [26–28]. Hence, it is likely that the turnover of the collagenous tissue is accelerated as the remodeling after EVAR progresses.

The simulation presented in this paper certainly has many limitations. The aneurysm growth is currently assumed to be symmetric, which is not the case in saccular aneurysms. An asymmetric AAA, customized to the actual shape of a patient's AAA, would lead to a better, patient-specific and possibly more accurate model. Asymmetric AAA growth may lead to a potentially dangerous bulging on one side of the AAA, which would not be present in our symmetric model. Patient specificity must be considered if we want to use this simulation to predict the success of EVAR for patients. We also used an ideal assumption that the stress-mediated vascular growth and remodeling under the change in pressure is the only mechanism during AAA enlargement and remodeling after EVAR. Especially, we did not incorporate other important factors such as change in proteolytic cellular activities, cellular apoptosis, and biochemomechanical influence of intraluminal thrombus during aneurysm growth and after EVAR [29,30]. Even with these limitations, however, the computational simulation presented in this paper captured the biomechanical impact well through the effect of intrasac pressure shown in the literature. It strongly suggests that the biomechanical factors play important roles in initial period of vascular adaptation after EVAR. Other biomechanical and biochemical factors may have a significant effect, especially some time after EVAR [31], and we need more data to build a better model and predict long-term vascular adaptation and its failure.

6 Conclusion

The reviewed literature and biomechanical model simulation suggest that AAA remodeling after EVAR depends on the intrasac pressure. More specifically, not only is the value of the intrasac pressure important but the time history of the intrasac pressure plays a major role as well. A continuous assessment of intrasac pressure is more useful in determining the success of EVAR rather than a singular measurement of the pressure at one time. In addition, sensitivity may play a significant role in post-EVAR remodeling, which provides an explanation why success after EVAR varies between patients.

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