CHAPTER 9

Summary and general discussion
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Endovascular aneurysm repair (EVAR) is nowadays a globally applied treatment of abdominal aortic aneurysms (AAAs). During EVAR under fluoroscopy a stentgraft is placed via the femoral and iliac arteries inside the abdominal aortic aneurysm. The Achilles heel of EVAR is the incomplete seal of the aneurysm sac (endoleak) or the persistence of significant pressure in the aneurysm sac without detectable endoleak (endotension) [1, 2]. Endoleaks and endotension are associated with increased risk of aneurysm rupture due to persistence of high aneurysm sac pressures [3]. Therefore, follow-up is needed after EVAR. However, the relation between endoleak and aneurysm sac pressure is less clear. Much research has been conducted to evaluate aneurysm sac pressure after EVAR. A review of literature demonstrates that the mean pressure index (MPI), i.e. the ratio between mean aneurysm sac pressure and mean systemic pressure, is not specific to the type of endoleak (Chapter 2). This implies that the same type of endoleak does not necessarily pose the same MPI and by this the same hazards of aneurysm rupture.

Why do the MPIs differ so widely between studies?

Aneurysm sac pressure is multifactorial. As mentioned, endoleaks and the presence of efferent side branches influence the aneurysm sac pressure. Furthermore, the size of endoleak, the type of graft, the mechanical properties of the aneurysm wall and the aneurysm volume have been investigated as determinants of aneurysm sac pressure [4–10]. The size of the endoleak only affects the aneurysm sac pressure in the presence of outflow form the aneurysm sac [5, 8, 9]. In this situation, the endoleak size is positively correlated to the aneurysm sac pressure (the larger the endoleak, the higher the aneurysm sac pressure) [8, 9].

Greater aneurysm sac pressure reduction was demonstrated after deployment of an aorto-mono-iliac stent-graft than after deployment of a bifurcated stent-graft [6]. This could be an explanation why Chuter et al. and Gawenda et al. published a lower MPI immediately after aneurysm exclusion than others [4, 6]. They deployed aorto-mono-iliac stent-grafts instead of bifurcated stent-grafts. One might speculate that less time is needed before depressurization of the aneurysm sac will take place after deployment of an aorto-mono-iliac stent-graft than after deployment of a bifurcated stent-graft. Before occlusion of one common iliac artery (CIA) during mono-iliac procedure, this CIA might act as a large efferent vessel. This could result in an immediate aneurysm sac pressure drop after stent-graft deployment. As can be understood, there is no large efferent vessel after deployment of a bifurcated stent-graft.

Differences in MPIs between studies are probably also caused by difference in aneurysm wall compliances and aneurysm size. The aneurysm wall compliance
was inversely correlated to the aneurysm sac pressure in an in-vitro model [10]. A decrease in compliance resulted in an increase in aneurysm sac pressure. Gawenda et al. measured during an in-vitro study lower aneurysm sac pressures in larger excluded aneurysms. Therefore, they concluded that the influence of aneurysm volume needs to be considered when aneurysm sac pressures are measured [7].

Differences in experimental set-up between studies also contribute to a wide range of MPIs. The low MPIs after successful EVAR in in-vitro studies, in comparison to the MPIs in in-vivo studies, could be explained by differences between the in-vitro experimental set-up and the in-vivo situation. In-vitro models are only appropriate to evaluate aneurysm sac pressure after successful EVAR if the stent-graft is deployed in a running artificial circulation. However, during some in-vitro studies the aneurysm sac was separately filled after deployment of a stent-graft [5, 11, 12]. Of course, the aneurysm sac pressure in this set-up depends on the amount of liquid injected in the aneurysm sac and misrepresents the in-vivo aneurysm sac pressure after successful stent-graft deployment. In the other in-vitro studies, it is not clear if the aneurysm sac was filled after stent-graft deployment or if the stent-graft was deployed in a running artificial circulation [8, 9, 13, 14]. Anyway, the MPIs of these studies are lower than those of in-vivo studies.

**Follow-up after EVAR**

The follow-up after EVAR is focused on the prediction of aneurysm rupture. Aneurysm rupture occurs if the aneurysm wall stress exceeds its strength. The aneurysm wall stress is directly related to the aneurysm sac pressure [15]. CT is the golden-standard for follow-up after EVAR. However, during follow-up by CT neither the aneurysm wall stress nor the aneurysm sac pressure is measured. The extent of the aneurysm sac exclusion from the systemic circulation is determined by either imaging the endoleak or indirectly by imaging the aneurysm size. Shrinking aneurysms are assumed to be excluded from the systemic circulation. Expanding aneurysms are considered as non-excluded aneurysms [3]. However, CT scans are not unambiguous to predict the risk of rupture of stable aneurysms. Is the aneurysm size stable because of a stiff aneurysm wall or because of a high aneurysm sac pressure? Furthermore, the absence of an endoleak on CT does not exclude the possibility of high pressure in the aneurysm sac and the persistent risk of rupture.

The EUROSTAR registry published a rate of aneurysm rupture after EVAR of 1% per year over a 5-year follow-up [16]. They emphasized the difficulty in predicting failure of endovascular repair. Most aneurysm ruptures occurred without warning. Only a few patients had an increase in aneurysm size before rupture occurred. Therefore, improved techniques for diagnosis of endoleaks and particularly endotension are required.
Aneurysm sac pressure monitoring after EVAR

Aneurysm sac pressure monitoring as follow-up method after EVAR receives a lot of attention, because (I) it can reduce the number of CT scans and (II) it can be used to predict the optimal moment of re-intervention since the aneurysm sac pressure is directly measured. This will probably reduce the economical, hospital and patient burden during follow-up after EVAR.

In literature, pressure sensors are introduced in aneurysm sacs without wondering if the measured pressure values are correct or artifacts. Unfortunately, there has been no attention for the probable pitfalls of aneurysm sac pressure monitoring. The studies in this thesis contribute to the investigation of these pitfalls.

Experimental set-up of in-vitro studies

Several studies with in-vitro models of the human circulation have been performed [11, 14, 17, 18]. No validation data of the in-vitro models of these studies has been published. However, investigators should be aware that it is appropriate to compare results obtained from different in-vitro models only if the fidelity of each system is known and preferably identical.

In this thesis special attention has been paid to the construction and the validation of an in-vitro model of the human systemic circulation (Chapter 3). Our model has several advantages relative to other in-vitro models. Firstly, all parameters of pulse and mean pressure can be adjusted independently from each other. Secondly, different compliances can be adjusted by using a windkessel to mimic the stiffening of the arteries. Thirdly, a dicrotic nodule is mimicked by a ball valve. It is not clear if the dicrotic nodule is simulated in other models. Last but not least our model is CT and MRI compatible.

The mechanical properties of thrombus were measured (Chapter 4). With the use of these data special thrombus analogues for in-vitro studies were developed and validated. To our knowledge, the mechanical properties of thrombus analogues for in-vitro studies have not been validated before.

Pitfalls of aneurysm sac pressure measurements

The remaining studies of this thesis demonstrate that aneurysm sac pressure monitoring in fibrinous thrombus is not straightforward. The findings of these studies probably contribute to the explanation of variation between the reviewed studies in Chapter 2.

Fluid-filled pressure devices did not yield accurate pressure measurements in fibrinous thrombus (Chapter 5). Artifacts may occur because of dampening of the signal caused by occlusion of the pressure needle. Therefore, non-fluid pressure
devices rather than fluid-filled devices are superior to study the pressure in the aneurysm sac.

Ellozy et al. reported the first clinical experience with the use of wireless stent-graft attached pressure sensors [19]. However, pulsatile wall motion of the stent-graft results in sensor motion. This pulsatile sensor motion can influence the accuracy of the pressure measurement (Chapter 6). Pressure measurements may be falsely high. Sensors attached to compliant grafts are more sensitive to motion than sensors attached to less-compliant graft.

Pressure reduction occurs through aneurysm sac thrombus (Chapter 7). This reduction depends on the thrombus itself, on the elastic property of the aneurysm wall and on the distance from lumen to sensor. Therefore, it seems difficult if not impossible to accurately measure pressure in the entire sac at a single location. This conclusion agrees with the findings by Vallabhaneni et al.[20] They performed in-vivo measurement of pressure transmission through sac thrombus. Significant variation in the pressure was recorded within aneurysm thrombus both in different patients and within the same aneurysm. Their ex-vivo analysis of pressure transmission through sac thrombus confirmed the variation noted in the in-vivo experiments. There was a significant correlation between matrix density and pressure transmission across thrombus. Higher matrix density was associated with lower pressure transmission [20].

Finally, the direction of the pressure measurement in fibrinous thrombus in relation to the force must be taken into account during aneurysm sac pressure measurement (Chapter 8). Pressure measurements are only similar to the applied pressure if the pressure sensor is positioned at a right angle to the applied force. It is impossible to interpret single pressure measurements since the angle between the endoleak and the sensor is unknown during measurement.

What are the strong points and what are the limitations of this thesis?

The studies of this thesis are performed with in-vitro experimental set-ups. The advantage of these set-ups is that experiments can be performed in a controlled way, because different research parameters can be changed on demand and independently from each other. For example, in the in-vitro model of the human circulation the cardiac output, peripheral resistance and the compliance can be changed. Furthermore, it is easier to position the pressure sensors, to maintain and to control its positions.

The fact, that the experiments are performed in-vitro, is at the same time a limitation. The in-vitro studies are a simplified simulation of the in-vivo situation. However, before performing the experiments it has been considered whether the simplifications of the set-up could conflict with the objectives of the studies.
Will aneurysm sac pressure monitoring be valuable during follow-up after EVAR to reduce the number of CT scans (I) and to predict the optimal moment of re-intervention (II)?

Aneurysm sac pressure measurement is not straightforward (Chapter 5, 6, 7, 8). The problem of sensor obstruction and sensor motion can be easily avoided by using non-fluid filled pressure sensors attached to less-compliant stent-grafts (Chapter 5, 6).

The main problem of aneurysm sac pressure measurement is the fibrinous aneurysm sac thrombus. It is probably impossible to accurately measure pressure in the entire sac at a single location since pressure reduction takes place through the thrombus (Chapter 7) and the direction of measurement influences the pressure read-out (Chapter 8). However, in spite of the mentioned problems pressure changes are detectable (Chapter 7, 8). The pressure trend is probably the most appropriate parameter to follow up. An essential condition to follow up pressure trends is that the sensor has to maintain in its original position relative to the direction of the measured pressure.

Regular CT scans during follow-up protocol are probably not necessary when aneurysm sac pressure trends are followed. This could reduce the number of CT scans (I). A pressure decrease will be associated with a successful EVAR. Regular CT scans can possibly be omitted in this situation. However, when the aneurysm sac pressure increases, the endovascular treatment is probably not successful. Additional CT scans are necessary to diagnose and to treat possible endoleaks. Stable aneurysm sac pressures will remain a point of discussion. In this case it can be considered to make a CT scan. If an endoleak is detected it can be treated. However, the need for treatment will probably depend on the physician’s philosophy since it will be impossible to determine at which aneurysm sac pressure intervention is needed (Chapter 7, 8). When no endoleak is detectable pressure trends need to be followed. However, further research will be required to determine whether recognition of a pressurized aneurysm sac will change patient outcomes in a significant manner and will not lead to over-treatment.

What are the drawbacks of aneurysm sac pressure monitoring?

A possible shortcoming of aneurysm sac pressure monitoring as follow-up method after EVAR is that migration of the stent-graft is not detected. There is still a need for imaging modality to detect migration since early diagnosis of stent-graft migration is not possible with only pressure monitoring. CT is the gold-standard to detect stent-graft migration [21]. However, plain abdominal radiography is used
as an alternative to CT [22]. Roentgen Stereophotogrammetric Analysis (RSA) has been proposed as a new technology to detect stent-graft migration [23, 24]. The first results of RSA to detect stent-graft migration are very promising. RSA combines high accuracy with low cost in terms of radiation, healthcare costs and logistics and is more accurate than CT to detect stent-graft migration in a non-pulsatile in-vitro study [24]. However, further research is necessary.

Aneurysm sac pressure monitoring is probably not valuable to predict the optimal moment for re-intervention (II). As mentioned, the interpretation of absolute pressure levels is hampered by pressure reduction and by the influence of the direction of pressure measurement in the thrombus. Therefore, it will probably be impossible to determine a cut-off value when re-intervention is needed.

Another limitation is that device related complications could occur, such as infection, migration, mal-position and device failure. In this situation the pressure sensor should be replaced. An invasive intervention will be needed, which implies an extra burden for the patient without direct benefit. Furthermore, the sensor replacement may also hamper the follow-up of the pressure trend, because the position of the new sensor will be different.

In conclusion, this thesis demonstrates that aneurysm sac pressure measurement is not straightforward. Pressure measurements are hampered by the fibrinous thrombus of the aneurysm sac. Therefore, it seems impossible to make predictions about the risk of rupture based on absolute pressure levels. A pressure trend seems more appropriate to follow. Further research is needed to determine whether aneurysm sac pressure monitoring is valuable to decrease the number of CT scans and will change patient outcomes in a significant manner.
Future aspects

- Long-term in-vivo studies with wireless pressure sensors are needed to determine whether indeed the number of CT scans can be reduced.

- Knowledge about the biological behavior of fibrinous thrombus after EVAR is essential with respect to the possibility of liquefaction.

- The development of better pressure sensors is desirable. The problem of direction of measurement could theoretically be avoided by incorporating a wireless pressure sensor in a bubble filled with liquid.

- The long-term accuracy of wireless pressure sensors needs to be investigated. It is unknown if wireless pressure sensors will retain their function in an organized thrombus.

- Computer analysis of the biomechanical behavior of an aneurysm will contribute to the prediction of the risk of rupture. Special attention has to be paid to the permeability of thrombus.
References


