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Arterial Stiffness Alterations and Inflammatory Response Following Endovascular Aortic Repair

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Abstract

Endovascular abdominal aortic aneurysm repair (EVAR) and thoracic aortic aneurysm repair (TEVAR) have been widely incorporated into clinical practice. However, changes in arterial stiffness and post-implantation syndrome after aortic endografting remain important issues under investigation. The aneurysm sac wall motion after successful EVAR and TEVAR reflects complex interactions between all the components of the excluded aneurysm, including true compliance of the aneurysm wall itself, intra-aneurysm sac pressure, remodeling of the thrombus, and mechanical characteristics of the endograft. Experimental and clinical studies have shown that aortic endografting results in increased arterial stiffness in animal models. It can be assumed that the alterations of aortic mechanical properties can have a direct impact on heart output. The long-term impact of these mechanical changes on cardiovascular outcomes and the potential effects of different endografts on hemodynamics are important issues under investigation. Post-implantation syndrome (PIS) is a systemic inflammatory response frequently observed after endovascular treatment of aortic pathologies. The main features of PIS include fever, leukocytosis, elevated C-reactive protein levels, and coagulation disturbances. Endograft design appears to influence this inflammatory response following aortic endografting; woven polyester endografts have been shown to be associated with greater inflammatory response compared to polytetrafluoroethylene (PTFE) stent grafts. The purpose of this paper is to review the literature to elucidate arterial stiffness alterations and inflammatory response after EVAR and TEVAR and the impact of endograft design on aortic stiffness and the post-inflammatory response.

Key Words:

Stiffness • Mechanical properties • Aorta • Post-implantation syndrome • Pulse wave velocity (PWV) • EVAR • TEVAR

Introduction

Evolution in the endovascular area has influenced the management of aortic pathologies. Since Parodi and coworkers [1] performed the first endovascular abdominal aortic aneurysm repair (EVAR) in early

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1990, substantial progress has been made in treating patients with abdominal aortic aneurysms (AAAs). Endovascular aortic repair of AAA is widely accepted as a safe, effective and less invasive treatment as an alternative to open AAA surgical repair. Thoracic endovascular aortic repair (TEVAR) for descending thoracic aortic aneurysms was first reported by Dake in 1994 [2]. The benefits of TEVAR regarding operative morbidity and mortality, as documented in numerous trials and registries, have led to widespread acceptance of this less invasive modality for the management of thoracic aortic aneurysms. Although EVAR and TEVAR have been widely incorporated into clinical practice, changes in arterial stiffness after aortic endografting and post-implantation syndrome remain important issues under investigation. The effect of different endografts on aortic stiffness and compliance has not been evaluated. The purpose of this paper is to review the literature to elucidate these issues and also to investigate the impact of endograft material on arterial stiffness and inflammatory response after aortic endografting.

Arterial Stiffness after EVAR and TEVAR and the Impact of Endograft Type

Although endovascular techniques for the repair of aortic pathologies have emerged as an effective alternative treatment modality to conventional open repair, limited data exist concerning the biomechanical changes induced by endograft implantation. Experimental studies have shown that aortic endografting results in increased arterial stiffness in animal models [4]. Also, it can be assumed that the alterations of aortic mechanical properties can have a direct impact on heart output.

Mechanical parameters that have been used to analyze and describe the mechanical properties are the elastic modulus and the pulse wave velocity (PWV). The elastic modulus is the most common mechanical parameter used to describe the behavior of elastic material and its behavior (deform or break) when subjected to a force or stress. Therefore, aortic elastic modulus corresponds to the range of stresses occurring during the change of blood pressure. The initiation, growth, and eventual rupture of an aneurysm are prompted by changes in elasticity of the aortic wall. Knowledge of the elasticity of the aorta is also important for the design of aortic endografts because their stability, once inserted, depends to a large degree on the elastic behavior of the segment of the aorta to which they are attached [4, 5]. The pulse wave velocity (PWV) is accepted as the most simple, robust, and reproducible method to determine the regional arterial stiffness. There is a linear correlation between the speed of travel of pulse along an arterial segment and arterial stiffness. To calculate PWV, the distance between the two sites at which the pulse wave is being recorded is divided by the time of travel of the wave from the first to the second site [4, 5].

Contrary to open AAA surgical repair, the aneurysm sac remains intact after aortic endografting, and intrasac pressure may often persist following successful endovascular exclusion [6]. In addition, AAA wall motion after successful EVAR reflects complex interactions between all the components of the excluded aneurysm which evolve over time, including true compliance of the aneurysm wall itself, intra-aneurysm sac pressure with possible different effects for peak, mean, and pulse pressures, remodeling of the thrombus, stiffness characteristics of the graft, and systemic pressure [7].

Several studies have shown that vascular compliance in AAA patients is increased by EVAR at the level of the aneurysmal sac. Elastic modulus and aortic stiffness as indices of wall compliance following EVAR and the influence of different endografts have been determined using dynamic magnetic resonance angiography (MRA). In the study by Van Herwaarden et al. [8], EVAR resulted in increased aneurysm sac aortic stiffness and elastic modulus. Elastic modulus and aortic stiffness measurements at the aneurysm neck were 94% and 60% higher in PTFE endografts (Excluder, Gore Medical, Flagstaff, Arizona, USA) compared to those with a woven Dacron graft (Talent, Medtonic, Minneapolis, Minnesota, USA). The authors concluded that the presence of an endoleak did not seem to have an effect on wall compliance following EVAR. However, the design of the stent-graft did influence compliance at the level of the neck the level at which proximal sealing of the endograft in the aorta occurs. A similar study by Long A et al. [7] analyzing AAA wall motion using tissue Doppler imaging (TDI) showed a significant decrease in AAA compliance

after successful EVAR, which remained stable during later follow-up.

Pulse wave velocity (PWV) optimizes the assessment of vascular elasticity, quantifies artery wall parameters, and thus is considered an ideal index for comprehensive assessment of patients with cardiovascular diseases [9]. In a recently reported prospective study from our Department, we assessed changes in carotid-femoral PWV (c-fPWV) in patients undergoing EVAR [8]. Patients with AAA appeared to have significantly elevated c-fPWV levels compared to age- and sex-matched controls. The composition of the arterial extracellular matrix plus its spatial organization may predominantly explain the increased arterial stiffness in AAA patients. In addition, we found an association between stent-graft implantation and c-fPWV increase. An important regulator of arterial compliance following endografting is the engineering characteristics of stent grafts. In a subsequent prospective study we evaluated the effects of different types of endografts on PWV in patients undergoing EVAR [9]. One hundred eighteen consecutive men with AAA undergoing elective EVAR were enrolled in the study. Our study revealed that the endograft type was an independent predictor of c-fPWV change in the AAA group. The latter effect was independently associated with the endograft type. In particular, a greater increase of c-fPWC was recorded after implantation of a woven endograft when compared to ePTFE endograft. These results are, however, inconsistent to the study by Herwaarden et al. [8]. Thus, the need for further investigation of the impact of the endograft design on the arterial stiffness is underlined.

Preliminary data of an ongoing trial in our Department suggest that stent-graft implantation in the thoracic aorta leads to PWV increase. The impact of the endograft design on these hemodynamic changes is under investigation.

Clinical Implications of Altered Arterial Stiffness after EVAR and TEVAR

The influence that different aortic repair modalities exert on central hemodynamics depends widely on the site of intervention. It can be assumed that the hemodynamic impact exerted by a vascular prosthesis in the descending aorta may be more severe than implanting the endograft in the abdominal aorta. Ioannou et al., in an experimental study, showed that the aortic arch contributes about 50% of total arterial compliance and as a consequence endograft implantation in the ascending aorta results in significant decrease in aortic compliance, which has been shown to cause systolic hypertension through augmentation of both the running and the reflected waves [12-14]. The authors concluded that development of a more compliant prosthesis, which matches the host artery compliance, may be expected to reduce the hemodynamic changes induced after their implantation. Tzilalis et al. [15] in a clinical study concerning 11 young patients treated with TEVAR for thoracic aortic transection noticed that 9 patients had postoperative arterial hypertension after TEVAR, and four had persistent hypertension during the follow-up period. The aortic endografts produced a discontinuation of the pulsatile waves with a subsequent increase of aortic PWV. The authors concluded that increased PWV is an important risk factor for future cardiovascular events and should be evaluated in all patients after TEVAR.

A recent study by Takeda Y. et al. [16] investigating the mechanical changes in 40 patients undergoing EVAR found that endografting raised aortic vascular stiffness, induced left ventricular (LV) hypertrophy, and impaired LV diastolic function. The heart adapts to higher systolic loads via both hypertrophy and ventricular systolic stiffening (increased end-systolic pressure-volume relationship), which can severely affect cardiovascular reserve function. The authors concluded that low LV distensibility at baseline may be related to the impairment of exercise tolerance after EVAR; thus it is necessary to evaluate LV diastolic function and aortic stiffness before and immediately after EVAR in order to improve the cardiovascular outcome and longer term overall survival after EVAR. The long-term impact of these mechanical changes on cardiovascular outcomes requires further investigation.

Notably, a nonsignificant tendency toward cardiovascular deaths was apparent in the EVAR trial in the endovascular group during the 24-month interval [17, 18]. Although cardiovascular mortality was primarily due to the poor general health status of those patients or the required secondary interventions, a harmful effect of even slight alterations in aortic stiff-

ness induced by endografts should be considered. Whether this subtle hemodynamic impact represents an increased risk factor for patients with already impaired cardiac compensatory mechanisms needs to be investigated.

Post-Implantation Syndrome and Type of Endograft

Post-implantation syndrome (PIS) is a systemic inflammatory response frequently observed after endovascular treatment of abdominal (EVAR) and thoracic aortic aneurysms (TEVAR). The main features of PIS include fever, leukocytosis, elevated C-reactive protein and coagulation disturbances. This systemic inflammatory reaction is also associated with increased serum levels of cytokines, such as interleukin IL-6, IL-8, IL-1 and tumor necrosis factor-alpha (TNF-a). Mechanisms that have been proposed to explain this systemic inflammatory reaction include injury to the vascular endothelium and manipulation of the introducer catheters and sheaths inside the aneurysmal thrombus during the endovascular procedure, resulting in white cell activation and release of various cytokines [19]. Recently, the role of procalcitonin (PCT) has also been investigated [20].

The intramural thrombus, which remains in situ after EVAR, has previously been reported to be a source of proteases and speculated to be involved in development of late complications after EVAR. However none of these hypotheses have been confirmed. In a recently published study from our Department, we found that the volume of new-onset thrombus is associated with the development of PIS after EVAR, whereas chronic mural thrombus appears to be an inert material. In addition, inferior mesenteric artery (IMA) patency and contrast medium volume were irrelevant to the inflammatory response after EVAR [21].

Furthermore, endograft type appears to influence the inflammatory response following EVAR. Results of a recently reported study from our institution, based on 88 patients followed clinically and by cytokines perioperatively, support the hypothesis that implantation of stent grafts based on woven polyester are associated with a stronger inflammatory response compared to PTFE stent grafts. The inflammatory response was transient during the early postoperative phase and was not associated with adverse clinical events [22]. Voûte et al. [23] confirmed the same hypothesis, reporting that PIS occurred almost exclusively in the first 3 days after woven polyester endograft implantation and the first 2 days after PTFE endograft implantation.

An ongoing prospective trial in our department, evaluating the inflammatory response and renal function after elective thoracic endovascular aortic repair, suggests that endograft implantation in patients with TAAs may stimulate the inflammatory response during the early postoperative period. However, renal function does not seem to be deteriorated and influenced by the inflammatory response [24].

Clinical Implications of PIS after EVAR and TEVAR

The clinical manifestation of PIS includes fever and lumbar back pain. This biological response following EVAR is not always spontaneously attenuated and could lead to the development of SIRS even several days after the operation [19]. This issue raises concerns of postoperative morbidity, especially in patients at high risk, including the elderly with several comorbidities. Although previous studies have reported that PIS may result in severe complications, such as pulmonary dysfunction, cardiovascular events, and renal insufficiency, leading to prolonged hospitalization, according to our experience in 88 patients, PIS was not associated with perioperative adverse clinical events. Although transient pyrexia and patient discomfort may be present, PIS usually follows a benign course [22]. However, close surveillance of patients developing an excessive inflammation response postoperatively or patients with severe comorbidities is suggested. In addition, a further theoretical concern could be that the post-implantation syndrome may be associated with late complications such as endoleaks, stent graft migration and aneurysm rupture. However, this hypothesis remains to be validated in future studies.

Conclusions

Cardiovascular mortality remains the main cause of death among AAA patients treated with endovascular repair. Increased arterial stiffness observed after

EVAR and TEVAR represents a concern. The negative impact of endografting on aortic compliance would be expected to increase left ventricular after-load and myocardial energy requirements and may be related to adverse long-term outcomes. The long-term impact of these mechanical changes on cardiovascular outcomes and the potential differential effects of different endografts on central hemodynamics require further investigation. Post implantation syndrome usually is transient during the early postoperative phase and follows a benign course. The clinical impact of the PIS has been diminished during recent years. We suggest a close surveillance of patients—especially those at high risk, including the elderly with several comorbidities—who may develop an excessive inflammation response postoperatively.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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EDITOR'S COMMENTS

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This is an outstanding "translational" review, bridging basic science and biomechanical concepts into the clinical scenario--demonstrating that the implantation of an endograft subtlely changes arterial hemodynamics. These changes can be measured by pulse wave velocity. These adverse changes lead to increased afterload on the heart. In patients with impaired cardiac reserve, these changes may be a risk factor for cardiovascular adverse events and even mortality. The authors present suggestive data to this effect.

The authors also pinpoint the inflammatory Post Implantation Syndrome, more frequently seen with Dacron grafts. Although in vulnerable patients this Post Implantation Syndrome can lead to Systemic Inflammatory Response Syndrome, the majority of patients manifest a short-lived, benign course.