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Pulmonary Embolism After Endovascular Aortic Repair, a Retrospective Cohort Study☆

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WHAT THIS PAPER ADDS

This is the first study to assess pulmonary embolism after endovascular aortic repair using routinely performed aortic computed tomography angiographiess. This paper shows that, despite routine thrombo-embolism prophylaxis, pulmonary embolism occurs frequently after endovascular aortic repair, and thoracic endovascular aortic repair, respectively.

Objectives: Endovascular aortic repair (EVAR) is associated with an increased risk of pulmonary embolism, which is often clinically silent and therefore difficult to recognise. The aim was to investigate the incidence of pulmonary embolism after EVAR using routinely performed pre- and post-operative aortic computed tomography angiography (CTA), and the association between pulmonary embolism and mortality.

Methods: This single centre retrospective cohort study included adult patients who underwent EVAR in the University Medical Centre Utrecht between January 2010 and July 2015 and who had a total aortic, thoracic aortic, or pulmonary CTA within one month post-operatively. Baseline and mortality data were obtained by reviewing hospital and general practitioner records. The primary outcome was pulmonary embolism within one month after surgery. Secondary outcomes were 30 day and six month mortality.

Results: During the study period, 526 EVARs were performed. Seventy-four of these procedures were included in the analysis of which there were 40 thoracic and 34 abdominal EVARs. In nine patients (12%, 95% CI 7—22) pulmonary embolism was observed of which one was central, two were segmental, and six were subsegmental. Seven were clinically silent and two were present on the pre-operative CTA. Thirty day mortality was significantly higher in patients with pulmonary embolism (relative risk 14.4, 95% CI 1.4—143, $p = .037$) though none of the deaths seemed directly attributable to it.

Conclusions: This study, although preliminary, suggests that silent pulmonary embolism after EVAR occurs in approximately one in 10 patients, despite routine thrombo-embolism prophylaxis. Pulmonary embolism was associated with a higher 30 day mortality risk yet it was not the cause of death in any of these patients.

Keywords: Pulmonary embolism, Endovascular, Aorta, Thrombo-embolism, Surgery
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INTRODUCTION

Endovascular aortic repair (EVAR) overtook open surgery for the treatment of aortic aneurysms as a result of its lower invasiveness and less post-operative morbidity and 30 day mortality. The mortality advantage however, declines with long-term follow up.[1,2] Of note, EVAR is associated with an increased risk of (venous) thrombo-embolism because of hypercoagulability due to increased thrombin generation, thrombin activity, and fibrin turnover in aortic aneurysm and EVAR.[3] Surgery and immobilisation are also well known thrombo-embolism risk factors.

The incidence of pulmonary embolism (PE) after EVAR has been reported to be approximately .4%.[4,5] This estimate is primarily derived from small studies that only assessed symptomatic PE. Most PEs in the post-operative phase however, are clinically silent due to masking of symptoms. For

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instance, thoracic complaints may be misinterpreted in the presence of post-operative pain whereas dyspnoea and low oxygen saturation may be attributed to post-operative anaemia.[6] As some PEs may consequently have been missed, the incidence of PE after EVAR could be underestimated.

In the University Medical Centre Utrecht, an aortic computed tomography angiogram (CTA) is routinely performed after EVAR, preferably within one week, to assess graft position and endoleak (i.e., blood leakage between the prosthesis and the aneurysm wall). Because these CTAs include the chest, they are potentially suitable for assessment of PE. In addition, it is possible to distinguish a new PE from a pre-existing or chronic PE, since pre-operative CTAs are also routinely performed. The aim of this study was to investigate the incidence of PE within one month of EVAR placement and its association with 30 day mortality.

METHODS

Study design and population

This retrospective, single centre cohort study included patients $\geq$18 years old who underwent a CTA of the thoracic aorta or of the pulmonary artery within one month after EVAR in the University Medical Centre Utrecht, a tertiary referral centre, between January 2010 and July 2015. Pre- and post-operative CTAs were routinely performed as part of the standard of care in this hospital to assess the location and dimensions of the aneurysm and graft position/endoleak, respectively. Post-operative CTAs were performed preferably within one week after EVAR. Exclusion criteria included a CTA with insufficient contrast in the pulmonary artery (i.e., impossible to assess for PE) and a complicated EVAR that required multiple procedures (in which case only the first EVAR was included). Of note, if an EVAR was performed after $>$6 months because of a different aneurysm (e.g., thoracic EVAR after a prior abdominal EVAR), patients could be included more than once. The need for informed consent for this analysis was waived by the local medical ethics committee (reference number WAG/mb/16/001927).

EVARs were stratified into abdominal and thoracic EVAR and graded on complexity. Abdominal EVAR was defined as an endovascular stent graft in the abdominal part of the aorta (i.e., below the level of the diaphragm) and a thoracic EVAR as an endovascular stent above the level of the diaphragm (i.e., in the thoracic part of the aorta). If a stent covered both the abdominal and the thoracic part of the aorta, the procedure was defined as an abdominal EVAR. Non-complex EVARs were bifurcated stent grafts with ipsilateral or contralateral leg extensions, or both. Complex EVARs were defined as all procedures in which fenestrated or branched stent grafts were used or a chimney technique was applied.

Routine intra-operative antithrombotic therapy consisted of 5000 IU heparin in total until July 2014, after which it was changed to 100 IU heparin/kg. In complex EVAR procedures, activated clotting time (ACT) was measured after 30 min and every hour thereafter; heparin was administered when ACT was $<$250 s. Post-operatively, low molecular weight heparin 2500 IU or 5000 IU (dosage based on body weight) was administered daily until hospital discharge. Therapeutic doses of low molecular weight heparin were given if indicated (e.g., in case of a thrombo-embolism prior to surgery or mechanical heart valve prosthesis). Platelet inhibition was continued peri- and post-operatively. Patients that had a complex EVAR were given dual antiplatelet therapy for three months and lifelong single antiplatelet therapy thereafter. Peri-operative heparin was not administered in ruptured aneurysm cases.

Data collection

Patient demographic data, comorbidities, and operative details were extracted from electronic patient records. Relevant peri- and post-operative characteristics were peri- and post-operative use of anticoagulation and antiplatelet drugs. Also, clinical signs and symptoms of PE (dyspnoea, thoracic pain, signs of deep venous thrombosis [DVT], tachycardia (heart rate $>$ 100/min), and haemoptysis) and signs of myocardial injury were assessed. The clinical signs and symptoms were assessed by reviewing electronic medical records from the procedure day to the day of the CTA. Of note, in intubated or severely delirious patients, the clinical signs “dyspnoea” and “thoracic pain” were scored as absent if not clinically overt. Data on peri- and post-operative anticoagulation and antiplatelet drugs were derived from peri-operative anaesthesia documentation and hospital drug prescription records. To ensure accuracy, a triple check was performed by additional assessment of hospital records, surgical reports, and intensive care unit (ICU) documentation (if admitted pre- or post-operatively). Myocardial injury was assessed using routine post-operative troponin I measurements. Troponin I was routinely measured on the first three post-operative days using a third generation AccuTnI assay (Beckman Coulter, Brea, CA, USA) with a clinical cut off value of 60 ng/L. The highest troponin I value was used in analysis. An electrocardiogram (ECG) was only carried out in the case of troponin elevation above the clinical cut off or for a clinical indication (e.g., angina or suggestion of an arrhythmia). ECGs made within three post-operative days and within two days before or after the post-operative CTAs were assessed retrospectively and compared by an experienced investigator, who was blinded to the outcome.

Access to the research data are unavailable because of confidentiality.

Outcomes

The primary outcome was PE within one month after surgery, which was defined as a sharply marginated pulmonary artery filling defect on at least two consecutive CTA images, located either centrally within the vessel or with acute angles at its interface with the vessel wall. All CTAs were performed on a 256 slice CT scanner (Brilliance iCT, Philips Healthcare, Best, The Netherlands). To diagnose PE, an experienced reviewer assessed all total aortic, thoracic aortic, or pulmonary CTAs that were performed within one month after surgery without knowledge of the clinical findings (i.e., baseline characteristics, clinical signs and symptoms, laboratory and ECG values).

The degree of PE was scored as central, segmental, and subsegmental. All PEs were confirmed by an experienced radiologist (T.L.). To observe whether (chronic) PE was present prior to surgery, pre-operative CTAs that were performed up until a year earlier were assessed likewise. Secondary outcomes were 30 day and six month mortality. Mortality data were obtained by linking the database to the municipal registry, a high quality registry that registers all deaths in The Netherlands. Causes of death were obtained by consulting the electronic patient record of the centre. For an out of hospital death, the patient's general practitioner was contacted.

Statistical analyses

Categorical data are presented as number count and percentage. Continuous data are presented as mean ± standard deviation, or median and interquartile range as appropriate. The incidence of PE was expressed as number with percentage, accompanied by a 95% confidence interval. Subsequently, peri-operative characteristics were compared for patients with and without PE. Levene's test for equality of variances was used to test continuous variables for normality and the Student *t*-test or the Mann Whitney test was used for parametric and non-parametric distributions respectively. Categorical variables were compared using the Pearson chi-square test or the Fisher exact test. Survival was compared between patients with and without post-operative PE using a Kaplan—Meier survival curve and differences were tested using the log rank test. Statistical significance was defined as $p \leq .05$. All statistical analyses were performed using SPSS 21.0.

RESULTS

During the study period, 526 EVARs were performed including 464 abdominal and 62 thoracic EVARs. Forty-five procedures were excluded because no post-operative CTA was available within one month, 391 because the pulmonary arteries were not fully visible on CTA (i.e., for abdominal CTA after abdominal EVAR) and 14 because of insufficient contrast in the pulmonary artery on CTA. Furthermore, two cases were excluded because of a re-EVAR within the study period. Consequently, 74 procedures were included in the analysis: 34 abdominal EVARs and 40 thoracic EVARs (Fig. 1). Two patients were included more than once. Baseline characteristics and indications for surgery are shown in Table 1 and in Appendix 1, respectively, and procedure and hospitalisation characteristics are shown in Table 2. Furthermore, baseline characteristics for first operation only are provided in Appendix 2; results were highly similar to characteristics of the entire population and therefore not analysed additionally.

PE was observed in nine patients (12%, 95% CI 7—22): six after abdominal EVAR (18%, 95% CI 8—34) and three after thoracic EVAR (8%, 95% CI 3—20). One PE was central, two were segmental and six were subsegmental (Appendix 1). Two of these PEs were present on the pre-operative CTA

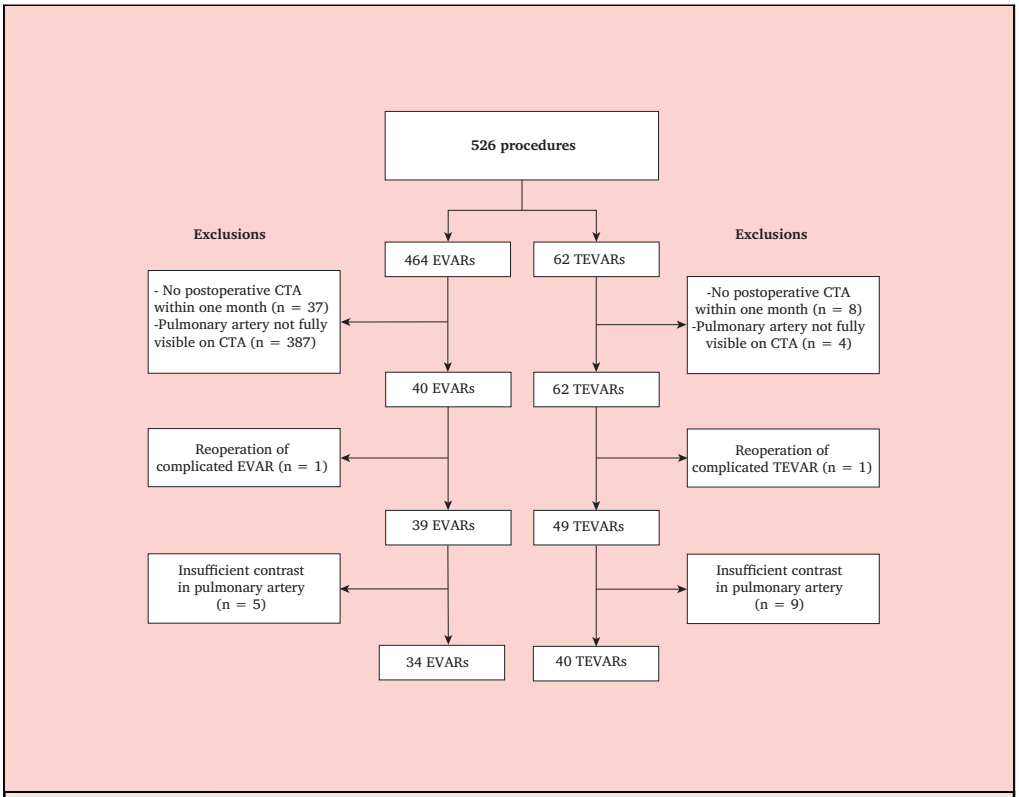

Figure 1. Flowchart of inclusion and exclusion criteria. EVAR = Abdominal endovascular aortic repair; TEVAR = thoracic endovascular aortic repair; CTA = computed tomography angiography.

Table 1. Patient characteristics

	PE (n = 9)	No PE (n = 65)	p
Age in years, mean (SD)	72 (6)	69 (12)	.57
Male sex	6 (67)	49 (75)	.69
BMI, mean (SD)	26 (3)	26 (4)	.96
ASA class			
I or II	3 (33)	42 (65)	.14
III or higher	6 (67)	23 (35)	
Medical history			
Current smoking	3 (33)	14 (26)	.69
Hypertension	6 (67)	41 (63)	>.99
Diabetes	2 (22)	9 (14)	.62
Current angina	0	5 (8)	>.99
Coronary revascularisation	1 (11)	16 (25)	.68
History of myocardial infarction	2 (22)	17 (26)	>.99
Peripheral artery disease	1 (11)	17 (26)	.44
Congestive heart failure	1 (11)	4 (6)	.49
Atrial fibrillation	0	10 (15)	.35
Pacemaker	0	0	–
Prior stroke or TIA	2 (22)	15 (23)	>.99
COPD	4 (44)	7 (11)	.024
History of VTE	0	2 (3)	>.99
Active malignancy[a]	0	7 (11)	.59
Pre-operative medication			
Aspirin	4 (44)	43 (66)	.24
Other platelet inhibitor	0	6 (9)	>.99
Oral anticoagulation	2 (22)	10 (15)	.91
NSAIDs other than aspirin	0	3 (5)	>.99
Statin	3 (33)	38 (59)	.18
Inhaled bronchodilators or steroids	4 (44)	9 (14)	.047

Data are presented as absolute numbers (%) unless stated otherwise. ASA class = American Society of Anesthesiologists Class; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drugs; PE = pulmonary embolism; SD = standard deviation; BMI = body mass index in kg/m;[2] TIA = transient ischaemic attack; VTE = venous thrombo-embolism; defined as pulmonary embolism or deep venous thrombosis.

[a] Defined as a malignancy treated <6 months or palliative treatment.

(one segmental and one subsegmental PE), showing similar size as the post-operative PE. One segmental and one central PE were diagnosed clinically on the first and second post-operative day, respectively, as a result of dyspnoea, low oxygen saturation, and tachycardia. In retrospect, the segmental PE (Appendix 1, Patient 2) was already visible on the pre-operative aortic CTA but was clinically silent at the time. The second segmental PE was clinically diagnosed on the thirtieth post-operative day in a patient with persistent chest pain and dyspnoea after surgery (Appendix 1, Patient 3). In retrospect, the PE in that patient was already present on the aortic CTA on the fifth post-operative day and showed progression in size over time. All six subsegmental PEs were clinically silent. Therapy of patients with PE is shown in Appendix 1.

Post-operative troponin I values and clinical signs and symptoms of PE did not differ significantly between patients with and without PE, as shown in Table 2. Patients with PE were more often admitted to the ICU and more often had chronic obstructive pulmonary disease (COPD), with the higher numbers of inhalation steroids or bronchodilators used (Table 1). Post-operative thrombo-embolism prophylaxis was routinely administered in all except one patient with a subsegmental PE, in whom anticoagulant therapy was withheld because of a ruptured aorta (Appendix 1).

Death within thirty days occurred in two patients (22%) with PE versus one (1.5%) patient in the group without (relative risk 14.4, 95% CI 1.4—143, p = .037), and six month mortality occurred in two (22%) versus four patients (6%), respectively (relative risk 3.6, 95% CI 0.8—17, p = .15). Both deaths in the PE group were patients with a subsegmental PE. The causes of death in these patients were sepsis/bowel ischaemia and massive haemorrhage after aortic rupture, which was confirmed by autopsy in both patients (Appendix 1, Patients 6 and 7). In the group without PE, the causes of death were post-operative myocardial infarction, multi-organ failure, malignancy, and sepsis. The Kaplan—Meier survival curve is shown in Fig. 2 (log rank test p = .073).

DISCUSSION

Despite routine thrombo-embolism prophylaxis, PEs occurred frequently after EVAR and a third were central or segmental. One central and one segmental PE were symptomatic at the time of the aortic CTA while one segmental and six subsegmental PEs were clinically silent. PE was associated with a higher risk of death yet it was not the primary cause of death in any of these patients. Despite small numbers, these results may have implications for patient management.

Prior studies have suggested that the incidence of PE after EVAR is approximately .4%, which is considerably lower than the 12% that was found in this study.[4,5] This discrepancy can be explained by the fact that most of these studies focused on symptomatic PE. However, interpretation of signs and symptoms suggestive of PE can be challenging in the early post-operative period because pleuritic pain can be mimicked by “normal” post-operative pain and dyspnoea can easily be attributed to (post-operative) anaemia. This notion is underlined by the diagnostic delay of almost four weeks that resulted from misinterpretation of minor dyspnoea and thoracic complaints in a patient with a segmental PE in this study (Appendix 1, Patient 3). Furthermore, the presence of factors such as anaemia (which occurred slightly more often in patients with PE in this study) may also induce symptoms such as dyspnoea and thoracic pain. Finally, it should be noted that two of the PEs (i.e., one segmental and one subsegmental) were present prior to surgery and that the segmental PE turned symptomatic after surgery. In these patients, clinical signs may be triggered by vasoconstriction in the presence of peri-operative stressors.[7]

The peri-operative diagnostic difficulties warrant further identification of risk factors. In this study, the most relevant

Table 2. Procedure and hospitalisation characteristics of 74 analysed patients

	PE, n = 9 (12%)	No PE, n = 65 (88%)	p
Procedure characteristics			
Stent type			.27
Abdominal EVAR			
Non-complex[a]	3 (33)	16 (25)	
Complex[b]	3 (33)	12 (19)	
Thoracic EVAR			
Non-complex[a]	2 (22)	35 (54)	
Complex[b]	1 (11)	2 (3)	
Emergency procedure	3 (33)	16 (25)	.69
General anaesthesia	8 (89)	64 (99)	.23
Duration of surgery in minutes, median (IQR)[c]	231 (111–317)	126 (101–241)	.23
Antithrombotic therapy			
Peri-operative heparin use	7 (78)	57 (88)	.60
Peri-operative heparin dosage, median (IQR)	5000 (2500–16,750)	5000 (5000–10,000)	.89
Post-operative LMWH			.92
Prophylactic dosage	7 (78)	51 (78)	
Therapeutic dosage	1 (11)	9 (14)	
No LMWH	1 (11)	5 (8)	
Peri- and post-operative antiplatelet therapy			.80
Aspirin only	5 (56)	38 (58)	
Other antiplatelet drug only	0	3 (5)	
Dual antiplatelet therapy	2 (22)	16 (25)	
No antiplatelet therapy	2 (22)	8 (12)	
Hospitalisation characteristics			
Clinical symptoms			
Dyspnoea	2 (22)	12 (19)	.68
Thoracic pain	0	8 (12)	.58
Clinical signs of DVT[d]	1 (11)	4 (6)	.49
Tachycardia (>100/min)	4 (44)	17 (26)	.26
Haemoptysis	0	0	–
Hospital stay in days, median (IQR)	12 (7–15)	7 (4–11)	.14
ICU admission	7 (78)	24 (37)	.03
Duration of ICU admission in days, median (IQR)	2 (1–5)	2 (2–3)	.98
Post-operative haemoglobin (g/dL), mean (SD)	10.1 (2)	11.1 (1)	.07
Post-operative myocardial infarction[e]	0	8 (12)	.27
Routine post-operative troponin I assessment	8 (89)	49 (75)	
Troponin elevation (>60 ng/L)	3 (38)	19 (39)	>.99
Peak troponin, median (IQR)	36 (25–767)	40 (21–207)	.66

Values are presented as n (%) unless stated otherwise. DVT = deep venous thrombosis; EVAR = endovascular aortic repair; ICU = intensive care unit; IQR = interquartile range; LMWH = low molecular weight heparin; PE = pulmonary embolism; SD = standard deviation.

[a] Non-complex EVARs: bifurcated stent grafts with ipsilateral or contralateral leg extensions, or both.

[b] Complex EVARs: use of a chimney, fenestrated, branched or custom made stent graft.

[c] Time between first incision and closing suture.

[d] Objectively measured leg swelling and pain with palpation in the deep vein region.

[e] Post-operative myocardial infarction defined by elevated troponin I combined with new onset electrocardiogram (ECG) changes suggestive of ischaemia.

factors associated with PE were ICU admission and COPD (with consecutive use of inhalation steroids/bronchodilators), as shown in Tables 1 and 2. Also, a trend was observed for higher ASA score and post-operative haemoglobin level (Tables 1 and 2, respectively). The association between PE and ICU admission is attributable to prolonged immobilisation and a higher likelihood a hypercoagulable state in case of a ruptured aneurysm or peri-operative or intraluminal haemorrhage, relevant comorbidities such as COPD, and more complex procedures (i.e., branched or fenestrated stent grafts).[8–10] Of note, a higher prevalence of silent PE in patients admitted to the ICU has been documented by prior observational studies, which may justify a lower threshold for PE assessment in patients admitted to, or recently discharged from the ICU, although current guidelines do not endorse routine assessment for venous thrombo-embolism.[11,12] The second factor associated with PE in this study was COPD, which has been reported as a minor risk factor in observational studies.[13] It should be recognised that a timely diagnosis in that population is difficult because of the similarity between PE and COPD symptoms. Like the association with ICU admission, the trend for ASA score is probably attributable to a higher risk of prolonged immobilisation and a hypercoagulable state due to comorbidities and transfusions. The latter could also explain the lower haemoglobin level in patients with PE, that is, chronically anaemic patients due to comorbidities and bleeding in case of a ruptured aneurysm, respectively.

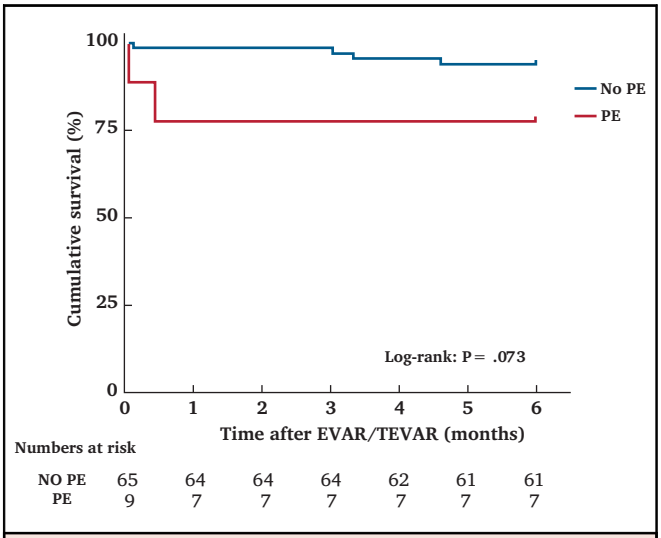

Figure 2. Kaplan Meier survival estimates up to 6 months after endovascular aortic repair. PE = pulmonary embolism; EVAR = abdominal endovascular aortic repair; TEVAR = thoracic endovascular aortic repair.

The incidence of subsegmental PE has risen strongly over recent decades as a result of the increase in spatial and temporal resolution of multidetector CTA.[14] These subsegmental PEs often have a mild clinical presentation and are frequently an incidental finding. Adequate therapy is uncertain in this population, since a clear benefit of anticoagulation has not yet been established due to a significant risk of (major) bleeding.[15,16] It is plausible that a subsegmental PE is a contributing factor in death or an expression of comorbidities/prolonged immobilisation rather than the primary cause of death.[17] Therefore, in the absence of conclusive evidence regarding anticoagulant therapy, physicians should carefully weigh the benefits of anticoagulation against the risk of bleeding when confronted with a clinically silent subsegmental PE in especially haemodynamically stable post-operative patients.

The overall 30 day mortality in this study was 4% which is higher than the .5—2.3% mortality that is generally reported after EVAR.[18] This discrepancy is probably explained by the fact that most studies were designed to compare simple EVAR with open surgery and therefore included patients who were physically eligible for open repair. Of note, the population in the tertiary centre consisted predominantly of patients with complex pathology and comorbidities, some of whom were unfit for open surgery.

Limitations

A number of limitations have to be acknowledged. First, selection bias cannot be eliminated due to the large number of exclusions, particularly in the abdominal EVAR population. It is possible that patients who were more severely ill or who had a more complicated abdominal EVAR procedure were more probably to undergo a CTA that included the thorax, which may have led to an overestimation of the PE incidence in the abdominal EVAR group. To address this issue, baseline characteristics and mortality data of excluded patients were assessed, which showed a higher percentage of males and TEVAR in the included patients (Appendix 3). A trend towards a higher ASA class and pre-operative statin use was also observed in included patients. Although statin use has been suggested to reduce the risk of deep vein thrombosis and recurrent PE, evidence of a reduced risk of developing a first PE is lacking.[19] Second, the CTAs were primarily intended to assess the aorta rather than the presence of PE, which resulted in insufficient contrast in the pulmonary artery in 14 of 88 CTAs (16%) (Fig. 1). It is believed that this occurred at random and it is thought unlikely that it affected the validity of the results. The perfusion defects observed in the CTAs were assessed by an experienced radiologist and are highly likely to be attributable to PE. Despite this, other causes of the perfusion defects (e.g., flow artifacts) could not be excluded with certainty. Third, multivariable analysis was not possible due to a small and heterogeneous sample size. Finally, pre-operative CTA was absent for one patient with a post-operative PE and the time between the pre-operative CTAs and surgery was more than one month in half of the cases. In these patients it is uncertain whether the PE occurred after EVAR. Fourth, due to the retrospective study design, the proportion of symptomatic patients may be underestimated. Of note, “dyspnoea” and “chest pain” were scored in intubated and severely delirious patients as absent in order to provide “real life” clinical data which could have led to under reporting of these symptoms. However, because these patients were monitored continuously and only constituted for a small part of the study population they are not expected to be a significant influence.

CONCLUSION

The study, although preliminary, suggests that silent PE after EVAR occurs in approximately one in 10 patients. PE was associated with a higher risk of 30 day mortality yet it was not the cause of death in any of these patients.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.08.054.

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