

Peer Review File

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Reviewer A

This is a retrospective study by Ibrahim et al., Münster dealing with data on patients who had the FET, and it analysed the relationship between the inflammatory markers and mural thrombosis. They concluded that post-implantation syndrome can trigger non-infectious fever after the FET. I have several questions and comments.

Comment 1: The mechanisms of postoperative thrombosis are varied in many situations, such as aortic dissection or non-dissection aneurysm, the presence of atherosclerosis, local haemodynamics inside the aorta, or blood coagulation and haemolysis. They do not have any data regarding these subjects.

Reply: Thank you very much for your comment.

Unfortunately, we do not have any specific supportive data regarding these subjects.

It is certainly challenging to ascertain which of the mentioned mechanisms may have triggered the occurrence and extension of postoperative thrombosis. In the opinion of the authors, a combination of them rather than a single mechanism activates the thrombotic reaction after the FET and endovascular treatment in general.

We have now addressed the topic by adding the following text to the manuscript:

Change in the text:

Discussion: We added some data in the Discussion (Page 8, line 267)"

The mechanisms behind the thrombosis of the false lumen in the case of aortic dissections are varied. The so-called “aortic remodelling” consequent to the endovascular exclusion of the false lumen has been seen as the most relevant factor triggering the occurrence and extension of postoperative thrombosis [19, 20, 21, 22]. However, the extension of concomitant atherosclerotic lesions, the changes of local

haemodynamics inside the aorta, as well as the activation of or blood coagulation and haemolysis can be seen as concurrent factors in activating the thrombotic reaction after the FET and endovascular treatment in general [24, 26].

Comment 2: They did not show the coagulation and fibrinolysis data.

Reply: Thank you for your comment. We added some of the above-mentioned data in the Results and in tables 1 and 2.

Change in the text: (page 6, line 190)

The partial thromboplastin time PTT value was significantly higher in the PIS group preoperatively and on the seventh postoperative day. There were no statistically significant differences between the PIS and non-PIS groups in terms of residual known coagulation and fibrinolysis data (Table 1 and 2).

Reviewer B

The authors addressed the issue of post-implantation syndrome after endovascular procedures, especially the frozen elephant trunk approach. This study involves 38 patients with acute aortic type A dissection, post-dissection aortic aneurysm or aortic aneurysm; from a single-centre. The authors performed a multivariable statistical regression in order to identify risk factors associated with post-implantation syndrome. This study identified an association between the volume of new-onset thrombus and the incidence of post-implantation syndrome after frozen elephant trunk procedures. The novelty of this article consists of the analysis of this issue in a cohort of patients undergoing a frozen elephant trunk procedure, as the volume of mural thrombus has already been studied as an inflammatory marker in endovascular aortic repair procedures. As the indications for frozen elephant trunk in this series are multiple, the results have to be interpreted with caution. Indeed, a post-dilatation aneurysm differs from an acute aortic type A dissection or from a native aortic aneurysm by the timing of presentation, the urgent versus elective setting of the procedures and so far. Nevertheless, this article points out an important aspect post-cardiovascular surgery, that is to say the assessment of an underlying inflammatory status in these patients and their possible consequences.

Major comments

Comment 1: As the definition for post-implantation syndrome may be variable in the literature, it is important to specify the method of assessment you used. In case of discrepancies between bladder temperature and tympanic temperature, which did you register? The highest? The lowest? And Why?

Reply: Thank you very much for your comment.

As you pointed out, there is a variety of definitions of post-implantation syndrome in the literature. We decided to use the definition of the presence of fever ($>38^{\circ}\text{C}$ lasting over at least one day) and leukocytosis (white blood cell count $> 12000/\mu\text{l}$).

Furthermore, we used preferentially the temperature of the bladder, since it is considered more accurate and because the bladder measurements were taken more frequently than the tympanic measurements, reducing the risk of missing possible peaks. Only in cases where bladder measurements lacking did we use the tympanic temperature.

The temperature we used was the highest measured on that particular examined day accordingly to what usually reported in the literature dealing with post-implantation syndrome (Moulakakis KG, Sfyroeras GS, Papapetrou A, Antonopoulos CN, Mantas G, Kakisis J, Alepaki M, Mylonas SN, Karakitsos P, Liapis CD. Inflammatory response and renal function following endovascular repair of the descending thoracic aorta. J Endovasc Ther. 2015 Apr;22(2):201-6).

Change in the text (page 7, line 234):

The definition of post-implantation syndrome is variable in the current literature[8,11-14]. In the remaining cohort, the occurrence of PIS was hypothesised by the presence of fever ($>38^{\circ}\text{C}$ lasting over at least one day) and leukocytosis (white blood cell count $> 12000/\mu\text{l}$). In the present study, a substantial quote of the patients met the criteria for postoperative PIS, with an estimated incidence of 44.7% (n=17). In the literature referring to endovascular procedures, PIS incidence varies from 14 to 60 % after endovascular aortic repair (EVAR) and from 15.8 % to 34 % after thoracic EVAR (TEVAR). This variability is due to the different diagnostic criteria and definitions used [8,11-14]. Some authors use as criteria the development of fever ($> 38^{\circ}\text{C}$) and CRP elevation using the cut-off value of 10 mg/dl, while most use as

criteria the occurrence of fever ($> 38^{\circ}\text{C}$) and leucocytosis ($> 12000/\mu\text{l}$) [9,10,15-18]. In the current study, PIS was defined by the presence of leucocytosis ($> 12000/\mu\text{l}$) and fever ($> 38^{\circ}\text{C}$) lasting longer than one day, with onset in the first 24 hours after surgery.

Comment 2: In the limitation sections, the authors mentioned that concomitant pathologies cannot be documented. It would be interesting to assess also the status of chronic kidney disease, smoking and other baseline characteristics which may influence an underlying inflammatory status.

Reply: Thank you for your comment. The occurrence of chronic kidney disease as well as the smoking status and concomitant pathologies such as diabetes mellitus may have influenced the occurrence and extension of the inflammatory reaction post-FET. We now support the missing data on chronic kidney disease and diabetes mellitus in table 1.

We have revised the text accordingly.

Change in the text (page 5, line 172):

There were no significant differences between the PIS and non-PIS group regarding known atherosclerotic risk factors, **status of chronic kidney disease, smoking and other baseline characteristics.**

Change in the text (page 9, line 309):

Even if the two study groups did not differ in terms of occurrence of concomitant pathologies such as chronic kidney disease, active smoking and diabetes mellitus, the possible influence of these proinflammatory factors in determining a postoperative inflammatory reaction cannot be completely excluded.

Comment 3: The Discussion section has to be improved. Please provide a short summary (3 lines) of the study to begin. The main findings of this study are the association of age and a greater volume of new-onset thrombus with post-implantation syndrome. As you didn't provide information about the baseline level of interleukine and other inflammatory biomarkers, please shorten this part. Also, state more clearly why post-implantation syndrome is an important

issue after cardiovascular surgery. Ideally, the Discussion section should not be more than two pages.

Reply: Thank you for your suggestions. We have modified and shortened the Discussion accordingly.

Change in the text (page 7, line 224):

In the current study we detected a positive association between increased volume of new-onset thrombus and the occurrence of post-implantation syndrome in patients undergoing the FET.

Change in the text (page 7, line 227):

Postoperative fever after cardiac surgery can result from an infectious or non-infectious aetiology. Previously described causes of non-infectious postoperative fever include surgical trauma, cardiopulmonary bypass, bleeding, transfusion reaction and drug reactions [28]. PIS as a source of fever of non-infectious aetiology after the FET has not yet been investigated. **To identify patients with PIS could reduce the possible empirical use of antibiotics and of invasive imaging in order to rule out possible infectious processes.**

Comment 4: To further strengthen the analysis, it would be better to have a control group with no false lumen and consequently no thrombus formation. Do you have such patients? I presumed in the patients undergoing the FET for aortic aneurysm, there was no false lumen present? How did you did with the measures in this case?

Reply: Thank you for your comment.

Unfortunately, we do not have any control group of patients without a false lumen or aneurysm sack to support.

In patients treated due to a primary aneurysm, a thrombus formation occurred postoperatively. The volumetric measurement of thrombus material in the FET for aneurysms was based on the same principles as in patients with dissection.

To confirm your comment, the volume of thrombus material which developed in patients with pure aortic aneurysms was smaller with and the median value was only

6 mm³. Accordingly, patients with the FET for aneurysms experienced a PIS less frequently than patients with an aortic dissection.

Comment 5: Overall in the text, it should be mandatory to provide revision by a native English speaker.

Reply: A native English speaker has revised the manuscript. (Anchor English, Inchnacardoch, Fort Augustus, Inverness-shire, UK, PH32 4BN)

Minor comments

Comment 6: Page 2 line 42-43. What does “Clinical charts” mean? Is there another specific flow chart?

Reply: Thank you for your question. The expression “clinical chart” was related to the records of the patients’ key clinical data and medical history, such as demographics, vital signs, diagnoses, medications, treatment plans, radiology images, and laboratory and test results.

Comment 7: Page 4. Line 114. Please include the number of the reference cited.

Reply: We apology for the missing reference, which is now cited in the text.

Comment 8: Page 4, Line 133-136. Please rephrase.

Reply: Thank you for your comment. We have rephrased the sentence.

Pre- and postoperative ECG-gated computed tomography angiograms (CTAs) were used to perform thrombus volumetric measurements.

Comment 9: Page 9, Line 276-277. Please include a reference number for Kakisis et al. and Lee et al.

Reply: We apology for the missing reference, which is now cited in the text.

Comment 10: Page 9, Line 291. Please rephrase “Amaoutoglou reported...”

Reply: We have rephrased the above mentioned sentence.

Change in the text (page 9, line 286):

Arnaoutoglou et al. found that the use of polyester endograft independently predicted PIS and was correlated with an above 10 times higher risk for an inflammatory response [8].

Comment 11: Page 9, Line 293. Please include a reference number for Ker et al. (2014).

Reply: We apology for the missing reference, which is now cited in the text.

Comment 12: Page 9, Line 297-298. “Interestingly, an association between PIS and other predictors such as female gender and type of aortic pathology has also not been described in the literature” What do you mean exactly?

Reply: Thank you for your comment. The sentence does not provide any meaningful information and is therefore deleted from the text.

Tables and Figures.

Comment 13: Table 2. This is not clear when you write the number of patients involved in the section thrombus volume measurements, and-new-onset thrombus. Please put this more clearly in the table or put this information in the text and not in the table.

Reply: Thank you for comment. As suggested, we have put this information in the text and deleted it from table 2.

Change in the text (page 6, line 182) :

For the thrombus volume, 62 measurements were obtained, starting from the left subclavian artery and ending just proximally to the celiac trunk. Twenty-eight patient CTAs were evaluated for acute dissection, 18 for chronic dissection/post-dissection aneurysm and 16 for non-dissection aneurysm.

Comment 14: Table 3. As you begin the line with “3 POD”, “5 POD”, “7 POD”, it’s a little bit confusing. You should present these results in a graphic for more clarity.

Reply: We agree with you about the lack of clarity of the presented data. These are now provided in graphic 3 and removed from table 3.

- Table 5.

Comment 15: Why did you not assess the odds ratio and the confidence interval for the variables female gender and type of aortic pathology in the table?

Reply: We now support these data in the table 5

Comment 16: Type of aortic pathology: can you please provide the univariable analysis for each subgroup of pathology?

Reply: We now provide the univariate analysis for each subgroup of pathology (aneurysm, acute dissection, chronic dissection) in table Nr. 5.

Change in the text:

Table5: Multivariate analysis						
	<u>Univariable analysis</u>			<u>Multivariate logistic regression</u>		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)	0.901	0.831 - 0.978	0.012	0.734	0.54 - 0.980	0.036
volume of new-onset thrombus	1.056	1.015 - 1.099	0.007	44.440	1.01 - 1.18	0.028
Femal gender	0.147	0.027 - 0.808	0.027	0.61	0.01 - 960	0.7
Type of aortic pathology	1.358	0.631 - 2.919	0.434	17	0.03 - 850	0.531
Aneurysm	0.102	0.011 - 0.920	0.042			
Acute dissection	1.23	0.344 - 4.454	0.744			
Chronic dissection	4.2	0.884 - 19.94	0.71			

CI: confidence interval; OR: odds ratio ; Statistically significant *p*-values are marked in bold

Comment 17: Figure 3. Please define the additional middle line.

Reply: The additional middle line (Red line) refers to the cut-off value of 12.000 WBCC (B) and 38 C° temperature (A). We changed the figure legend as follows:

Figure 3: Graphic representation of the median measures of body temperature (A), White blood cell count (WBCC) (B) and C-reactive protein (CRP) (C) in the PIS and

non-PIS groups. Middle line (Red line) shows the cut-off value of 12.000 WBC (B) and 38 C° temperature (A) * Significant difference between groups ($P < 0.05$), ** high significant difference between groups ($P < 0.001$)