

## Peer Review File

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### Reviewer A

**Comment 1:** I congratulate the authors for the interesting article. TEVAR is a well established treatment for FID in the arch or descending aorta, and demonstrating its utility in solving secondary ascending aorta IMH is of high value. The article is in general well written, precise and concise, but in my opinion is too long, with unnecessary description (like surgical details or extended patient data details). I recommend the authors to summarize it: shorter articles are easier to read and the message is better delivered to the reader.

*Reply: Many thanks for the comments and appreciation of our manuscript. We have modified the text as advised and tried to made it shorter (less than 4000 words including refs).*

However, I would like to focus on some items:

**Comment 2:** The article is in general too long. It is not necessary to describe all technical operative details, as TEVAR is a widespread technique. Only the general materials or if you use special techniques (as chimneys or in-situ fenestrations, which could be described better). You also describe your tables; if data is in the tables, it is not necessary to rewrite it in the text, only the most interesting parameter.

*Reply: Thanks for the constructive suggestions. We have shortened the text accordingly about the operative details and baseline characteristics.*

**Changes in the text:** *We have deleted the description of technical operative details (see Page 7, Para 2), and the repeated description of baseline characteristics (see Page 9, Para 2).*

**Comment 3:** You don't use open debranching (carotid-subclavian bypass), but chimneys in the subclavian. Why?

*Reply: Thanks for the question. In our case series, 21 patients underwent standard*

*TEVAR, but 1 patient received chimney technique and 2 received physician modified fenestration to preserve LSA. Though open debranching is a feasible strategy for aortic arch repair, it still shows significant surgical risks and might be not suitable for patients with poor conditions. Our center has abundant experience of chimney technique and physician modified fenestration in aortic arch repair (as reported in a previous study J Thorac Dis 2020, 12:1437-48). And these minimally invasive techniques are usually preferred.*

**Comment 4:** The informed consent was approved to be included in the article or for the surgery?

*Reply: Thanks for the question. Informed consent was initially for the surgery, but every patient was also told the possibility of including their clinical data for research use and it was also approved.*

**Comment 5:** How many of all ascending IMH were treated with TEVAR? It could be interesting to know how many cases meet the inclusion criteria

*Reply: Thanks for the question. From January 1st 2015 to December 31st 2020, a total of 42 patients with type A IMH were admitted in our center. And a consecutive of 24 patients met the inclusion criteria and were treated with TEVAR*

**Comment 6:** In the methods section you state that you will describe means and standard deviations, but afterward you describe medians and ranges. Please, include medians and ranges in your methods section (statistical analysis)

*Reply: Thanks for the helpful suggestion. We have revised the text accordingly.*

**Changes in the text:** The sentence was revised as “The values were expressed as mean  $\pm$  standard deviation or as medians (ranges)”. (see Page 9, Para 1)

## **Reviewer B**

Introduction and discussion

Although IMH doesn't present as overt false lumen, focal intimal disruptions (FIDs) could be detected in 70% of 59 IMH with high resolution computed

tomography<sup>2</sup>. The FIDs include ulcer-like projection 60 (ULP), penetrating atherosclerotic ulcer (PAU), intramural blood pool (IBP) and 61 localized dissection, which are regarded as risk factors for the deterioration of IMH<sup>3-5</sup>.

Discussion: One important feature of IMH is FID. <sup>202</sup> Although the definition of IMH is the crescent or circular aortic wall thickening without <sup>203</sup> the presence of detectable blood flow, FID could be found in 70% of IMH<sup>2</sup>. The FID has <sup>204</sup> prognostic value for IMH, and may provide guidance for clinical decision-making. Moral <sup>205</sup> et al reported that FID development in the acute phase of IMH indicates a poor prognosis <sup>206</sup> and necessitates surgical or endovascular repair<sup>5</sup>. The patients in our series presented <sup>207</sup> different types of FIDs (IBP in 5, ULP in 15, PAU in 2, LD in 5). <sup>20</sup> patients had FIDs in<sup>208</sup> the CT angiography at admission, while 4 patients showed late developed FIDs in the <sup>209</sup> secondary CT angiography.

**Comment 1:** I think author refer these descriptions to the type B IMH. However, we are looking at the data for retrograde type A with focal intimal defect in DTA. If any defect in the ascending aorta, these are not cases that we are discussing, author may consider delete these words, and the point in this article should be to cover the FID in the DTA, the ascending aorta IMH can re repaired. It doesn't matter the DTA is dissection, IMH or PAU. Please describe this more clearly

**Reply:** *Thanks for the comments and helpful suggestions. In the current manuscript we want to present two key points. The first is that covering the intimal tear in DTA could cure the retrograde IMH in ascending aorta and favorable clinical outcome and aortic remodeling could be obtained, just as what other two recently published papers conveyed (Eur J Vasc Endovasc Surg 2020, 60:386-93; J Vasc Interv Radiol 2020, 31:1334-41). The second key point is that IMH is quite different from aortic dissection, as the intimal tear is usually fixed for AD but quite unpredictable for IMH. Our paper also tries to put an emphasis on the dynamic changes of FID and different types of FIDs presented in DTA, which might be the unique parts of our manuscript. So the introduction of FID in the beginning of the paper is essential. But in the discussion part, we indeed should describe more concisely.*

**Changes in the text:** *We have deleted the sentences “One important feature of IMH is FID. Although the definition of IMH is the crescent or circular aortic wall thickening without the presence of detectable blood flow, FID could be found in 70% of IMH”, “Moral <sup>205</sup> et al reported that FID development in the acute phase of IMH indicates a poor prognosis <sup>206</sup> and necessitates surgical or endovascular repair”. (see Page13,*

Para 2)

#### Discussion

The application of regular TEVAR in aortic 227 dissections or IMH involving the ascending aorta (mainly retrograde type A aortic 228 dissections with an entry tear in descending aorta) was also reported.

**Comment 2:** This description may require some modifications. In this manuscript, all the TEVAR was landed in Zone 2-3, it is different from this description landing in Zone 0

*Reply:* Thanks for the comments and helpful suggestions. We are sorry for the blurry description. Actually here we didn't mean landing in Zone 0, but using standard TEVAR to cover entry tear in descending aorta to treat retrograde type A aortic dissection (as what reported in *J Vasc Interv Radiol* 2012, 23:453-60, 60 e1, *J Vasc Surg* 2019, 69:1685-93, *J Vasc Surg* 2001, 34:1023-8). We have revised the sentence and tried to make it clearly.

**Changes in the text:** The sentence is revised as "Previous studies have demonstrated that the application of regular TEVAR to cover the entry tear in descending aorta is a feasible strategy to treat retrograde type A aortic dissection." (see Page14, Para 2)

#### Reviewer C

The authors performed a retrospective observational study to evaluate their initial experience with TEVAR for retrograde type A IMH. There was no mortality but one retrograde type A dissection.

I would like to make a couple of comments.

**Comment 1:** In type A IMH, those with localized intimal injury in the descending aorta do better. Therefore, such a watch-and-wait strategy to see if the descending pathology progresses over time or not seems to be a wise one. Having said that, one third of the patients in this study underwent TEVAR without having a repeated CTA. Please comment.

*Reply:* Thanks for the comments. For those patients with stable conditions and

*presenting small FIDs or even no FID, we strongly advocate a watch-and-wait strategy, and recommend the patients to take a repeated CTA to see whether the descending pathology progresses over time or not. But for those with uncontrollable chest pain or presenting with large FIDs or even localized dissection in the first CTA, we think there is no need to take a repeated CTA before TEVAR.*

**Comment 2:** 4% incidence of RTAD is significant. The authors may want to further investigate the case that developed RTAD.

**Reply:** *Thanks for the comments. In our case series, there was one patient developing RTAD 3 months after TEVAR and received open surgery. RTAD is a serious complication of TEVAR, however, for the patient, we don't know what are the exact causes. Other studies also reported the occurrence of RTAD, but the incidence still remains unknown for retrograde type A IMH. So in the discussion part, we give 3 possible mechanisms. Firstly, as the stent grafts deployed on the aorta segment with IMH, the intima could potentially be injured, especially when there is too much oversizing or a "bird-beak" formed. Secondly, the manipulation of wires and catheters during TEVAR could possibly cause damage to the intima of ascending aorta which already presented with IMH. Thirdly, there may be tiny and unrecognizable intimal tear in the IMH of ascending aorta, which could gradually enlarge and lead to the development of RTAD.*

#### **Reviewer D**

This manuscript is a single center retrospective study of TEVAR for IMH at ascending aorta with focal intimal disruption in descending aorta.

It is an interesting research, and also, I think it can contribute for daily clinical practice.

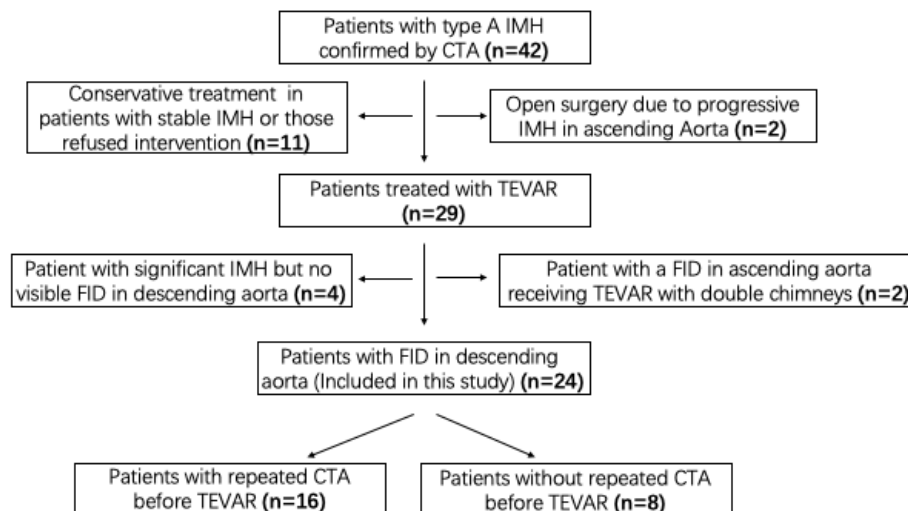
However, several points need to be discussed in considering for publication.

**Comment 1:** Study design and patient enrollment (Page5, line 83-88):

“Patients who met the following criteria were considered to be candidates for TEVAR : ...”

How many patients were excluded by this criterion? And, I find it easier to understand if there is a figure like a decision tree considering the indication of TEVAR.

**Reply:** Many thanks for the appreciation of our manuscript and constructive suggestions. During the period of our study, a total of 42 consecutive patients with type A IMH were admitted in our department. We included 24 patients in the current study. The flow chart of patient enrollment is as follows.



**Changes in the text:** We have added the above figure as Figure 1 “flow chart of patient enrollment”.

**Comment 2:** Study design and patient enrollment (Page5, line 86-87):

“maximum diameter of ascending aorta was no more than 55mm”

I think that the exclusion criteria for an ascending aorta diameter of less than 55 mm need to be reconsidered in terms of a risk of RTAD. Is 54mm diameter ascending aorta safe when considering TEVAR for retrograde type A IMH?

Please provide the manuscript if there is evidence that the risk of RTAD is low if the diameter of the ascending aorta is less than 55 mm. A careful discussion is needed in this point, as it can mislead the readers.

**Reply:** Thanks for the comment and question. There are still no generally accepted criteria to for type A IMH. But as a previous publication pointed out, aorta diameter and hematoma thickness are independent predictors for development of adverse events in patients with type A IMH receiving initial medical treatment, and the best

*cutoff values are 55 and 16 mm respectively (Outcomes of Patients with Acute Type A Aortic Intramural Hematoma. **Circulation**. 2009 Nov 24;120(21):2046-52). In our center, if the patient presented with maximum hematoma thickness of ascending aorta more than 15mm or maximum diameter of ascending aorta more than 55mm, he would be considered more suitable for open surgery.*

**Comment 3:** Operative Details and Device Selection (Page 7, line119-120):

“The selected diameter size of the stent graft was 10%-15% greater than the diameter of the aorta at the proximal sealing zone measured in aortic angiography.”

How was the proximal sealing zone selected in this study?

For the treatment of retrograde type A IMH, how to choose the proximal sealing zone is extremely important. Please describe in detail in this point.

**Reply:** *Thanks for the comment and question. The proximal sealing zone is generally distal to LSA, but it is dependent on the location of FID. As the treatment goal is to cover FID in descending aorta, there should be at least 2cm of proximal and distal sealing. This is similar to what described in a recent published paper (Eur J Vasc Endovasc Surg 2020, 60:386-93).*

**Changes in the text:** *We have added a sentence in the Operative Details and Device Selection part, “As the treatment goal is to cover FID in descending aorta, there should be at least 2cm of proximal and distal sealing” (see Page13, Para 2).*

**Comment 4:** Operative Details and Device Selection (Page 7, line120-121):

“Three types of commercially available stent grafts were implanted in the 24 patients.”

Please describe the characteristics of each device simply and provide the criteria for selecting the device.

**Reply:** *Thanks for the question. In the current study, three types stent grafts were used in the 24 patients: the Medtronic Valiant, the MicroPort Hercules and the Lifetech Ankura. Valiant is a tubular stent, and in some occasions a smaller restrictive stent might be needed to prevent distal stent graft-induced new entry. While Hercules and Ankura were tapered stents. The delivery system of Valiant is softer than Hercules and Ankura, so is easier to delivered in the steep aortic arch. But in China, Hercules and*

*Ankura are domestic and are cheaper than Valiant. The choice of device largely depends on the preference of surgeons and the economic status of patient, as well as the aortic lesions sometimes. So we actually couldn't provide a certain criteria for selecting the device.*

**Comment 5:** Perioperative results (Page 9, line 167-169):

“1 patient underwent TEVAR as long as 11 months since the first admission, as he had recurrent chest pain and CT angiography revealed a newly developed ULP.”

The onset of this patient is described to be 11 months ago, but if it has already been cured by conservative treatment, isn't it a new onset? Please tell us the opinions of the authors.

***Reply:** Thanks for the question. We think the patient develop ULP based on the previous IMH, rather than a new onset. As in the 6 month follow up CTA, though the IMH in ascending aorta is largely re-absorbed, IMH in descending aorta still existed. The lately appeared ULP might be caused by the enlargement of progress of a previously tiny intimal tear in IMH.*

**Comment 6:** Follow-up outcome and aortic remodeling (Page 10, line 179-180):

“1 patient developed retrograde type A aortic dissection (RTAD) and underwent open surgery 3 months after TEVAR.”

As the authors describe, RTAD is a serious complication.

What factors do you think caused RTAD in this case?

Was it the effect of oversizing or bare stents? Or was it influenced by the type of FID?

It is a very important point in this research, so I think it should be discussed in the Discussion section.

***Reply:** Thanks for the questions. In our case series, there was one patient developing RTAD 3 months after TEVAR and received open surgery. RTAD is a serious complication of TEVAR, however, for the patient, with a 34\*26\*200 Ankura stent implanted with about 10% oversizing in proximal landing zone, we don't know what are the exact causes. Other studies also reported the occurrence of RTAD, but the incidence still remains unknown for retrograde type A IMH. So in the discussion*



*section, we give 3 possible mechanisms. Firstly, as the stent grafts deployed on the aorta segment with IMH, the intima could potentially be injured, especially when there is too much oversizing or a “bird-beak” formed. Secondly, the manipulation of wires and catheters during TEVAR could possibly cause damage to the intima of ascending aorta which already presented with IMH. Thirdly, there may be tiny and unrecognizable intimal tear in the IMH of ascending aorta, which could gradually enlarge and lead to the development of RTAD.*

**Comment 7:** Follow-up outcome and aortic remodeling (Page 10, line 189- Page 11, line 192 ):

“Complete resolution of IMH in the ascending aorta was found in 18 patients (75%), and complete resplution of IMH in the descending aorta occurred in 13 patients (54%).”

In this study, I understand that TEVAR was performed at descending aorta for the treatment of retrograde type A IMH.

However, the results show that the healing rate of the descending aorta is lower than that of the ascending aorta.

What do you think is the reason for this result? Is it due to the type of FID?

Please discuss about this point in the Discussion section.

**Reply:** *Thanks for the questions. As in the case series, the 24 patients generally had significant more severe and thicker IMH in descending aorta than in ascending aorta (11.7±2.8mm vs. 8.3±1.8mm). That might explain why the healing rate of the descending aorta is lower than that of the ascending aorta. Similar results were also reported by a previous study (Novel insights into the mechanisms and treatment of intramural hematoma affecting the entire thoracic aorta. Ann Thorac Surg 2008, 86:453-6), in which the healing rate of ascending aorta was 100%, while 75% in descending aorta.*

**Changes in the text:** *We have added in the discussion section “IMH in both ascending aorta and descending aorta were significantly decreased. The ascending aorta seemed to have a higher rate of complete resolution of IMH, possibly due to the fact that IMH in ascending aorta was generally milder than descending aorta.”(see Page 11, Para 1)*