Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-688

Reviewer A

Thank you for this interesting case report. Mechanical hemolysis is difficult to diagnose and treatment options can be limited due to the patient's anatomy and comorbidities. Description of endovascular solutions are rare in the literature. You have presented a case with thorough explanation of the work-up and outcome. Some questions remain to be answered however:

Comment 1: Did you have any functional functional flow-measurement test eg TEE (you already mentioned that there were no pressure gradient readings)? As the kink visually is quite similar on the CT-A it would be interesting to see if the stenosis/flow velocoties changed significantly.

Reply 1: Thank you for the insightful question. Prior to the procedure, we attempted to assess the pressure gradient through a preoperative transthoracic echocardiogram (TTE). However, evaluating the blood flow within the kinked ascending aortic graft proved challenging due to poor echo view, resulting in a failed attempt. This made the diagnosis even more difficult. Nevertheless, through multidisciplinary discussions, we ruled out alternative medical diagnoses and treatments, ultimately concluding that the cause lay within the kinked aortic graft. Indeed, as you suggested, performing a transesophageal echocardiogram (TEE) would have provided clear diagnostic evidence. However, considering the patient's comorbidities, we deemed TEE, which requires sedation, to carry risks. In fact, even the main procedure we performed, stent insertion, was conducted under local anesthesia, as the use of sedative agents solely for diagnostic purposes posed concerns.

We acknowledge that the absence of a pressure gradient was a significant limitation in our case. However, in retrospect, the patient's hemolysis improved as a result of our intervention. Above all, our goal was not to achieve complete correction of hemolysis but rather to improve the condition through a less risky stent procedure. We believe that sharing our attempt with readers will be helpful and interesting, as it aimed to bring about any degree of improvement in the hemolytic condition.

Changes in the text:
Page 8, line 164~173:
"Prior to the procedure, we attempted to assess the pressure gradient through a preoperative transthoracic echocardiogram. However, evaluating the blood flow within the kinked ascending aortic graft proved challenging due to poor echo window resulting in a failed attempt. Performing a transesophageal echocardiogram would have provided clear diagnostic evidence. However, considering the patient's comorbidities, we deemed transesophageal echocardiogram, which requires sedation, to carry risks. In

fact, even the main procedure we performed, stent insertion, was conducted under local anesthesia, as the use of sedative agents solely for diagnostic purposes posed concerns. Nevertheless, through interdisciplinary discussions, we eliminated other potential medical diagnoses and treatments, ultimately determining that the kinked aortic graft was the underlying cause of hemolysis."

Comment 2: Line 53. This patient is described to have been bed-ridden for over a year with vascular dementia. While beyond the scope of presenting a mechanical hemolysis case solved with endovascular techniques, it raises some very relevant and current ethical questions regarding endovasular therapies in complex multi-comorbid patients. Given the outcome, could you explain the ethical reasoning when offering further surgical interventions in this case?

Reply 2: Thank you for pointing out the important aspect. Through discussions with the patient and her family, we decided to pursue minimally invasive treatment options rather than riskier surgical interventions. Therefore, we attempted stent insertion under local anesthesia instead of general anesthesia. It was originally intended as an effort to improve the hemolytic condition rather than achieve complete correction. We provided sufficient explanation of the advantages and disadvantages of the procedure to the patient and her family, and obtained their consent. Therefore, we believe there are no ethical concerns regarding this intervention.

Changes in the text:
Page 8, line 173~178:
"Through discussions with the patient and her family, we decided to pursue minimally invasive treatment options rather than riskier surgical interventions. Therefore, we attempted stent insertion under local anesthesia instead of general anesthesia. It was originally intended as an effort to improve the hemolytic condition rather than achieve complete correction. We provided sufficient explanation of the advantages and disadvantages of the procedure to the patient and her family, and obtained their consent."

Comment 3: Line 59. Could you explain the reasoning behind the choice of stent? What where the properties in terms of radial strength etc? What kind of balloons were used - high pressure PTA balloons?

Reply: We appreciate your important question. The stent product we utilized is a unique option in the domestic market as it is approved for customization according to individual patient needs. To mitigate the risk of arch vessel occlusion resulting from stent migration, we chose to use a bare metal stent. The product company provided information that the patient-specific stent has a radial force of approximately 3.5 $kg \cdot m/s^2$. However, there is no practical method to directly confirm the extent of force applied within the kinked aortic graft in vivo.

We used a 46 mm Reliant stent graft balloon catheter (Medtronic Inc., 710 Medtronic Parkway N. E. Minneapolis MN 55432 USA). This balloon catheter is not applied with

a predetermined pressure, but rather, it is a product that allows manual control of the shape of the contrast agent inside the balloon, where the desired amount of ballooning is achieved by applying pressure with the hand. In practice, we performed inflating the balloon several times while observing the gradual unfolding of the contrast agent's shape within the kinked graft.

Changes in the text:
Page 6, line 127~128:
"To mitigate the risk of arch vessel occlusion resulting from stent migration, we chose to use a bare metal stent."
Page 5, line 108~111:
"Using a 46 mm Reliant stent graft balloon catheter (Medtronic Inc., 710 Medtronic Parkway N. E. Minneapolis MN 55432 USA), we performed balloon inflation while observing the shape of the contrast agent inside the balloon, which was initially bent and then straightened, while manually adjusting the pressure."

Comment 4: What was the total flouro time and volume of contrast used?

Reply: m The fluoroscopic procedure lasted for 23 minutes, and a total of 120 ml of contrast agent (Iodixanol) was used.

Changes in the text:
Page 5, line 111~113:
"The fluoroscopic procedure lasted for 23 minutes, and a total of 120 ml of contrast agent (Iodixanol) was used."

Reviewer B

At first, I congratulate the authors for the success of difficult intervention in such serious case.
I have experienced some cases of hemolytic anemia thought to be cased by graft kinking, however my case did not need blood transfusions. In my case of graft re-replacement, preoperative LDH level was the same as authors, however Hb was around 9.5g/dL without blood transfusion. After the graft re-replacement, anemia was corrected soon.
It is important to know that hemolytic anemia by graft kinking is not rare and additional intervention is necessary to resolve severe hemolytic anemia.

I have some questions.
Comment 1: Why this patient needed blood transfusion even after stent deployment? Is there any other cause of anemia?

Reply: Thank you for the insightful question. Since it was not a complete replacement

of the graft through a redo sternotomy, even if we were to partially correct the kinked graft by inserting a stent, we do not believe that the hemolytic condition would improve completely. In conclusion, it would be considered an incomplete correction.
Our goal was not to achieve complete correction of hemolysis but rather to improve the condition through a less risky stent procedure. Taking into consideration the patient's underlying conditions and after adequate discussion with both the patient and her family, we proceeded with the explanation that even with the insertion of the stent, the correction of the hemolytic condition might be incomplete.
Furthermore, in fact, case reports of mechanical hemolysis caused by kinked graft origin indicate that even after correcting the underlying cause, hemolysis improves gradually over times. It would be helpful to consider this information as a reference.

Changes in the text:
Page 8, line 171~178:
"Nevertheless, through interdisciplinary discussions, we eliminated other potential medical diagnoses and treatments, ultimately determining that the kinked aortic graft was the underlying cause of hemolysis. Through discussions with the patient and her family, we decided to pursue minimally invasive treatment options rather than riskier surgical interventions. Therefore, we attempted stent insertion under local anesthesia instead of general anesthesia. It was originally intended as an effort to improve the hemolytic condition rather than achieve complete correction. We provided sufficient explanation of the advantages and disadvantages of the procedure to the patient and her family, and obtained their consent."

Comment 2: Has infection been controlled in preoperative state? Please show the information about infection.

Reply: This case involved a patient with chronic hemolytic condition, for which multidisciplinary discussions and internal medical treatments, including the use of antibiotics, had already been attempted. The patient was referred to 'cardiovascular surgery department' specifically for the treatment of the kinked aortic graft, with internal medical issues, including infections, ruled out.

Changes in text:
Page 8, line 171~173:
"through interdisciplinary discussions, we eliminated other potential medical diagnoses and treatments, ultimately determining that the kinked aortic graft was the underlying cause of hemolysis."

Comment 3: Do you have any parameters which indicate severity of graft kinking? How about cardiac echo or hemodynamics data before and after operation? Gain of afterload caused by graft stenosis is known to induce cardiac dysfunction.
Reply: Prior to deciding on stent insertion, we attempted to confirm the presence of hemolysis with a mechanical origin due to the kinked graft by assessing the pressure

gradient through transthoracic echocardiography (TTE). However, due to poor echo views, the measurement was not possible. Although performing a transesophageal echocardiography (TEE) would have provided more conclusive evidence for diagnosis, we decided not to proceed with the invasive TEE that requires sedation. As we described, the main procedure of stent insertion was also performed under local anesthesia. Consequently, we did not confirm the change of the pressure gradient even after stent insertion, and we acknowledge that this is a clear limitation of the case. However, considering the significant improvement in the patient's hemolytic condition, we believe that our attempt could be helpful to readers.

Changes in the text:
Page 8, line 164~173:
"Prior to the procedure, we attempted to assess the pressure gradient through a preoperative transthoracic echocardiogram. However, evaluating the blood flow within the kinked ascending aortic graft proved challenging due to poor echo window resulting in a failed attempt. Performing a transesophageal echocardiogram would have provided clear diagnostic evidence. However, considering the patient's comorbidities, we deemed transesophageal echocardiogram, which requires sedation, to carry risks. In fact, even the main procedure we performed, stent insertion, was conducted under local anesthesia, as the use of sedative agents solely for diagnostic purposes posed concerns. Nevertheless, through interdisciplinary discussions, we eliminated other potential medical diagnoses and treatments, ultimately determining that the kinked aortic graft was the underlying cause of hemolysis."

Comment 4: I think redundant inside structures at proximal or distal anastomosis site, for example graft or felt, could also cause hemolytic anemia. How do think about this? In your case, how proximal and distal anastomosis site was constructed? Did your bare stent cover there?

Reply: Thank you for the important question. In fact, this patient had previously undergone aortic surgery at a different hospital, and the records, including the referral letter, did not provide detailed information regarding the presence of felt or similar materials. While it is possible, as you pointed out, that hemolysis could have been caused by felt, it would have been highly speculative and impractical to assume the presence of felt and attempt to cover it with a stent without detailed information about the site of aortic anastomosis in the patient.
Therefore, ultimately, we applied the stent only to the kinked graft area, and as a result, there was a significant improvement in the hemolytic condition.

Comment 5: Please teach me the technical pitfall of this case.

Reply: As this is the first case of endovascular treatment for hemolytic anemia caused by a kinked graft at our institution, we cannot confidently speak about specific technical pitfalls. However, in our opinion, it is important to appropriately select the size of the

stent. In our case, we decided to use a stent size approximately 15% larger than the existing artificial aortic graft. Nevertheless, due to the absence of clear guidelines in this regard, we believe that further attempts and reporting in the medical community, similar to this case, are necessary.
In addition to placing a stiff wire in the ascending aorta, we also inserted a stiff wire into the left ventricle to provide support during the insertion of the main body of the stent. During this process, it is crucial to ensure that the stiff wire passes through the aortic valve without causing any damage to it.
Additionally, we chose a bare metal stent to prevent any potential blockage of the entrance to the arch vessel in case of stent migration.
We hope that our efforts will be helpful to readers in determining the approach to treating patients with hemolytic anemia caused by a kinked graft.

Changes in the text:
Page 6, line 124~128:
"Tips and Pearls
It is crucial to ensure that no damage is inflicted upon the aortic valve when placing the stiff wire in the left ventricle.
To mitigate the risk of arch vessel occlusion resulting from stent migration, we chose to use a bare metal stent."

Reviewer C

The authors are presenting interesting case study which supports the use of bare-metal stent for mechanical hemolytic anemia following aortic surgery. The study is nicely written, I just have a few comments and suggestions which might improved the case study.

Comment 1: The authors should review the pre-operative echo or MRI at the time of the transfer for detection of accelerated turbulent flow which induce mechanical hemolysis. And also post-operative follow-up echo after stenting is needed.

Reply: Thank you very much for your advice. Unfortunately, we did not perform an MRI prior to the endovascular treatment, and the TTE was inconclusive due to poor echo views, preventing us from confirming turbulent blood flow within the kinked graft. Similarly, even in the postoperative TTE, we were unable to measure the pressure gradient for the same reasons.
We acknowledge that these limitations are inherent to this case. However, through interdisciplinary discussions and after thoroughly evaluating all internal medicine diagnoses, the patient was referred to the cardiovascular surgery department. We had consultations with the patient and her family, considering the patient's comorbidities, and it was decided to pursue the least invasive treatment under local anesthesia. Of course, we thoroughly explained that the improvement of the hemolytic condition may be incomplete. As a result, considering the significant improvement in hemolysis, we

believe that our efforts should be reported in the academic community.

Changes in the text:
Page 8, line 164~173:
"Prior to the procedure, we attempted to assess the pressure gradient through a preoperative transthoracic echocardiogram. However, evaluating the blood flow within the kinked ascending aortic graft proved challenging due to poor echo window resulting in a failed attempt. Performing a transesophageal echocardiogram would have provided clear diagnostic evidence. However, considering the patient's comorbidities, we deemed transesophageal echocardiogram, which requires sedation, to carry risks. In fact, even the main procedure we performed, stent insertion, was conducted under local anesthesia, as the use of sedative agents solely for diagnostic purposes posed concerns. Nevertheless, through interdisciplinary discussions, we eliminated other potential medical diagnoses and treatments, ultimately determining that the kinked aortic graft was the underlying cause of hemolysis."

Comment 2: Line 58: How did you determine the bare-metal stent size by 15%.

Reply: Thank you for the valuable input. The selection of the size for the bare-metal stent was not based on an absolute criterion but rather on choosing a size approximately 15% larger than the artificial aortic graft. The recommended range of oversizing varies depending on the type of stent product and the pathology of the aorta (dissection or aneurysm). In our institution, when performing TEVAR for aortic dissection, the stent size is typically selected to be about 10% larger than the native aorta, while for aortic aneurysms, oversizing of approximately 20% is common. Therefore, empirically, we decided on a value of 15% as a middle ground for determining the bare-metal size in the case of a kinked graft. This choice was made because there are no specific guidelines providing an absolute criterion for selecting the size in the context of a kinked graft. It is anticipated that many more cases or clinical trials will be necessary to address the issue of selecting the appropriate size in the future.
We selected the size of the stent to be approximately 15% oversized compared to the existing artificial aortic graft. However, it should be noted that there is no objective evidence supporting this specific choice. It is anticipated that many more cases or clinical trials will be necessary to address the issue of selecting the appropriate size in the future.

Change in the text:
Page 9, line 190~193:
"We selected the size of the stent to be approximately 15% oversized compared to the existing artificial aortic graft. However, it should be noted that there is no objective evidence supporting this specific choice. It is anticipated that many more cases or clinical trials will be necessary to address the issue of selecting the appropriate size in the future."

Comment 3: Line 95–97: Please describe possible mechanism for delayed (after a few years) onset of mechanical hemolysis following aortic surgery.

Reply: According to the review article summarized by Davision et al. (1), it can be observed that many cases of graft kinking or graft stenosis manifest as delayed mechanical hemolysis. Although the precise mechanism of this delayed hemolysis is not fully understood, it can be speculated that graft kinking itself may occur gradually due to progressive growth of the surrounding tissues, or that stenotic portions within the graft worsen over time. In the case of this patient, since CT images from immediately after the previous aorta surgery were not available, it was impossible to determine when the graft kinking became severe. Serial examinations of individual patients may serve as a key to uncovering the mechanism of delayed onset hemolysis.

Changes in the text:
Page 7, line 151~155:
"Although the precise mechanism of this delayed hemolysis is not fully understood, it can be speculated that graft kinking itself may occur gradually due to progressive growth of the surrounding tissues, or that stenotic portions within the graft worsen over time. In the case of this patient, since CT images from immediately after the previous aorta surgery were not available, it was impossible to determine when the graft kinking became severe."

Comment 4: Line 106–109: If hemolytic anemia is occurring, I think the replaced aorta should exhibit accelerated turbulent flow whether it is a kinking or a inverted felt. So, there must have been a pressure gradient. How was the angiography? Wasn't there a jet turbulent flow? The author should describe the possible reason why there was no pressure gradient although the patient developed mechanical hemolysis.

Reply: I agree with your statement. In order to obtain a definitive diagnosis, we also attempted to confirm turbulent flow and pressure gradient within the ascending aortic graft through transthoracic echocardiogram (TTE). However, due to poor echo view, we were unable to confirm these parameters. Performing a transesophageal echocardiogram (TEE) would have provided clear diagnostic evidence. However, considering the patient's comorbidities, we deemed TEE, which requires sedation, to carry risks. In fact, even the main procedure we performed, stent insertion, was conducted under local anesthesia, as the use of sedative agents solely for diagnostic purposes posed concerns.
During angiography, the use of a power injector to inject contrast through the Pigtail catheter prevented the observation of turbulent flow. We acknowledge that these factors represent clear limitations of our case. However, through thorough interdisciplinary discussions, we were able to differentiate internal medical conditions, leading to the case being referred to the cardiovascular surgery department. We could not predict how much improvement our stent insertion would bring to the hemolysis phenomenon, but we proceeded after providing sufficient explanation to the patient and her family.

Taking into account the patient's comorbidities and after consulting with the guardian, we opted for the least invasive treatment possible. Ultimately, the partial improvement in the hemolysis phenomenon holds significance. I believe that our attempt should be reported in the academic community and could assist someone in making decisions regarding mechanical hemolysis caused by a kinked graft.