

Peer review file

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Reviewer A

Comment 1: The authors narratively reviewed the synthesis of multidimensional pathophysiological process leading to TAAD.

The manuscript was grammertically well written in correct English and this work is worth be published in JTD.

Reply 1: Thank you for your kind words.

Changes in the text: None.

Comment 2: I just would like to say minor revision.

1) The abbreviation for CTD was not listed in the P.2, which was supposed to be connective tissue disease. CTD was found in Firure 3.

Reply 2: The figure 3 has been completely reformed and the abbreviation for CTD has been removed from the manuscript.

Changes in the text: Figure 3 has been reformed.

Reviewer B

Comment 1: Good review on the dynamic progress of type A dissection

Reply 1: Thank you for your words.

Changes in the text: None.

Reviewer C

Comment 1: This is an interesting and comprehensive review on the pathophysiological aspects involved in aortic dissection, it is of great interest as a result of the recent publication of a European registry.

The work is well structured and written, with a very exhaustive literature review addressing all aspects related to aortic dissection. It is also accompanied by very interesting diagrams and an updated bibliography.

Reply 1: Thank you for your kind words.

Changes in the text: None.

Reviewer D

Comment 1: Although the author tried to summarize the pathophysiological process leading to type A aortic dissection from current evidence. The whole manuscript is poor organized and the pathway diagram is too busy. The authors should try to make it more concise and make some important points from the published literatures.

Reply 1: Thank you for your effort with this manuscript. I would be pleased to improve the manuscript if the reviewer would like to give suggestions.

Changes in the text: None.

Reviewer E

Comment 1: Thank you for giving me the opportunity of reviewing this manuscript. This is a well-written narrative review that summarizes the anatomy, physiology, histopathology of the healthy aorta, and the progression to type A aortic dissection. The author has put a considerable amount of work into this manuscript. This manuscript does add to the body of knowledge in the field of aortic diseases and summarizes all the important points.

Reply 1: Thank you for your kind words.

Changes in the text: None.

Comment 2: Minor comments:

- Certain areas in the manuscript are too wordy and (if possible) I would either try to cut down on the number of words by simplifying the sentence. I totally agree with the use of subsections as you have done for ease of reading in the histopathology and biomechanical section. Can consider applying the same for the anatomy and dynamic

continuum section and underlying the subsections.

Reply 2: Thank you for pointing this out. The anatomy section has been divided into subsections. However, the dynamic continuum section could not be divided sensibly.

Changes in the text: Subheadings has been added to the anatomy section. Sentences have been simplified as the reviewer advised.

Comment 3: - I would avoid using those (histopathology/histopathological vs. pathology/pathological) or (biomechanical vs. mechanical) terms interchangeably too often and stick to either one for simplicity and ease of understanding for the readers.

Reply 3: Thank you for pointing this out.

Changes in the text: The manuscript has been checked for inappropriate use of the terms and corrected when necessary.

Comment 4: Some of the sentences are too wordy and I have offered some suggestions:
- page 5 line 122 I would say “Inflammation in the aortic wall has been shown to play a key role in the....”

Reply 4: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 5: - page 5 line 126, I would say “Chronic arterial hypertension has consistently been found to be associated with an...)

Reply 5: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 6: - page 5 line 132, I would say “ascending aorta due to hypertensive blood pressure in the...”

Reply 6: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 7: - page 5 line 133, I would say “Since the perfusion of vasa vasorum is focused on diastole in the physiological state, the vas perfusion is....”

Reply 7: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 8: -page 5 line 137 “play a part in the compromised perfusion during arterial hypertension.”

Reply 8: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 9: - page 7 line 198 “ECM and functions in tissue remodeling.”

Reply 9: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 10: -page 9 line 247 “the middle section of the ascending aorta convexity is found to be more prone to...”

Reply 10: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 11: -page 10 line 305, please define the abbreviation of TAV that was not described in the manuscript.

Reply 11: Thank you.

Changes in the text: This has been corrected as suggested.

Comment 12: -All the figures are very informative. However, for figure 3, I would add abbreviations at the end of the sentence to state what BAV, VSMC, CTD, and TAAD (e.g., BAV: bicuspid aortic valve) is for ease of the readers although the abbreviations have been stated in the body of manuscripts. If possible, arrows should be colored differently for the respective sections to facilitate better understanding. E.g., aortic blood flow dynamics and associated factors should be colored in red, vasa vasorum malfunction and associated factors in blue, CTD and branching processes in green, etc.

Reply 12: Thank you for the excellent suggestions.

Changes in the text: The figure 3 has been completely reformed and colors have been added to improve readability. Abbreviations have been replaced by whole words. The caption has been amended accordingly.

Comment 13: - If possible, short paragraph consisting of 3-5 sentences at most, at the

end (after dynamic continuum of aortic disease and before summary) on how our understanding of TAA may impact future medical or surgical therapies and what therapies (if any) is available that utilized the etiological process as discussed comprehensively by the author.

Reply 13: Thank you for this suggestion. The Summary section already included a short review on the clinical perspectives of the etiological process of TAAD.

Changes in the text: Discussion on the clinical perspectives has been extended.