Peer review file

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Reviewer A

This is an interesting MS based on a retrospective analysis of 3 groups of patients attempting to find better predictors of type A dissection than the GL parameter of mere dimension (55mm). With the limitations of a retrograde analysis the authors show that diameter is not enough, but extended length and a certain volume may better predict dissection (which needs to be consolidated in prospective trials). But the presented observation is valid and important hypothesis generating information.

Comment 1: The title should probably be more specific, mentioning finding rather than questioning diameter!

Reply: Thank you for pointing this out. We changed the title from "Ascending aorta's morphological parameters, beyond the diameter, to prevent Acute Aortic Dissection Type A" to "3D morphometric analysis of Ascending Aorta as an adjunctive tool to predict type A Acute Aortic Dissection".

Comment 2: Introduction: Dissection is not a medical emergency but rather a surgical in the ascending anatomy.

Reply: As suggested by reviewer, we changed the sentence. See Page 2, line 30 and page 4, line 61.

Comment 3: The authors got valid point highlighting that GL are a bit dated and decisions should not be based only on diameter from the old New Haven data (with some updates). Page 4, lines 97-99: the mentioned recent publications should be quoted!

Reply: Thank you for this suggestion. References has been added. See Page 4, line 72.

Comment 4: Discussion: The observations are indeed not new; there are already similar finding in the public domain and the authors should quote them all (particularly on length as a predictor). Unfortunately, they have no access to pre-dissection dimensions of the aorta to support their conclusions, but only the retrospective estimation based on ref. 16. Obviously, however, all patients' aortas would have been measured at sub-threshold.

Reply: We agree with this. In fact, before beginning our study, we made an accurate revision of literature and all studies concerning length, aortic area or volume as predictors of acute aortic dissection had been quoted.

Comment 5: The role of a bicuspid AV needs to be discussed to some extent as the authors have included such patients in their analysis!

Reply: Thank you for highlining this out. More discussion to the role of bicuspid AV and histological changes in the ascending aorta in BAV patients had been added.
See page 10, line 216-217 and Page 12, line 259-272.

1) Conclusion: Functional imaging incl 4D MRI and FDG-PET has already been performed and subsequently should be quoted.

Reply: Thank you for this suggestion. Reference has been added. See Page 15, line 345.

Reviewer B

Comment 1: While all the parameter for assessment of aortic morphology was noted to be larger for AAAD and aneurysm disease compared to control, there was no threshold for surgical decision making mentioned. Please identify the thresholds for surgical intervention for the parameters (aortic length, aortic volume, etc) described.

Reply: You have raised an important point here. However, this was not intended in the study design; the study was meant to provide a vision into the topic of aortic elongation, volume and area and their possible correlation to TAD. On the other hand, we cannot predict how many people out of the aneurysms/control groups will develop an AAAD because of the retrospective nature of our study and the fact that pre-dissection CT scans were not available. Therefore, it is not possible to quantify the risk or to identify thresholds for surgical decision based on our initial data. Further investigations are needed to assess the pathophysiological role and diagnostic value of aortic elongation, aortic volume and aortic area.

However, the length of the ascending aorta, in the control group, did not exceed 100 mm in both, frontal and sagittal, views and aortic volume did not exceed 60 cm^3.

Comment 2: Does aortic length correlate with aortic diameter/area? I assume it correlated with aortic volume.

Reply: Thank you for this suggestion. In our analysis, we did not perform a correlation between these variables. No correlation was described in literature. Talking about physics, in the description of the morphology of a cylinder, these variables are independent, while the length and the volume, as you say, are dependent on each other.

Comment 3: Are you able to normalize the diseased aortic dimensions (e.g. diameter) to the predicted based on patient gender, weight and height, and then describe how large

the aorta has grown? This will help fine tune the relative aortic size at which intervention should occur prior to complications.

Reply: We believe that this is a very valid proposal of which we share the usefulness. In fact, it would have been interesting to explore this aspect and it may represent the subject of future works. However, in the case of our study, it seems slightly out of scope. On the other hand, in case of aortic dissection, this type of evaluation could be misled due to the changes that occurs to aortic geometry.

Reviewer C

Comment 1: Introduction:

- in addition to the 3D acquisition, nowadays measurements of aortic diameter are performed on aortic cross-sectional images perpendicular to the center-line, allowing precise measurements of diameter. Previous measurements (amongst others, Elefteriades et al.) relied on axial images, which overestimates the diameter. Therefore, with current technology, we measure (for example) 5.3cm, where in an actual axial plain, 5.5cm would be measured. So we 'underdiagnose' aneurysms at the moment.

overall, the introduction is too elaborate and should be shortened. Many aspects of the introduction are more 'discussion-material'. Please just state some background, 'the problem' and the aim.

Reply: Thank you for pointing this out. The introduction was shortened and discussion was revised, as kindly suggested.

Comment 2: Methods: how is the diagnosis of hypertension established? By medication? by blood pressure measurements?

Reply: Thank you for this suggestion. Hypertension was diagnosed on the basis of the presence of one or more antihypertensive drugs in the chronic medications: central and peripheral vasodilators and calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers but not diuretics.
We have incorporated your suggestion throughout the manuscript. See Page 5, lines 93-96.

Comment 3: if you measure at the prespecified levels, it is possible that you miss 'maximal' aortic diameter

Reply: Thank you for highlining this point of which we agree. In fact, while measuring the diameters, in all CTA studies examined, we had measure diameters in other levels of ascending aorta (data non-shown). And in our cohort, these diameters were stackable

to the maximal aortic diameter. Therefore, we decided not to show these results in order to simplify the analysis of values over all the paper.

Comment 4: Is diameter measured inner-inner, outer-outer or outer-inner?

Reply: Thank you for this suggestion. Diameters were measured using the inner edge to inner edge technique.

We have incorporated your suggestion throughout the manuscript. See Page 5, line 103.

Comment 5: In which cardiac phase did you measure the diameter and length? especially when you measure aortic length, starting from the aortic valve, the valve-to-STJ distance is influenced notably by the cardiac cycle, as the aortic root is lengthening and shortening during the cycle.

Reply:

You have raised an important point here.

In our cohort, we included CTA studies dated back up to 15 years. This meant that the studies were not standardizable, basing on the phases of the cardiac cycle. First of all, none of them was EKG-gated.

Another important element, that limited the implementation of such a standardization, is represented by the fact that, in the case of aortic dissections but also in the control group or ascending aortic aneurysms, most of the CTA exams were performed in peripheral centers and patients were transferred to our center to undergo emergency surgery.

These limitations had been added in the manuscript. See Page 15, lines 357-358.

Comment 6: in dissection data, many times data is not normally distributed. Did you test for normality?

Reply: Thank you for pointing this out. For the analysis of continuous quantitative and qualitative variables we did not test normality of distribution and therefore these variables are presented as mean and SD. Though, before comparing groups, we

performed Levene's test to verify the homogeneity of the variables within the three groups of patients instead of Bartlett's Test.

Comment 7: Results: please see the last comment of methods. All data are presented as mean and SD, but many data seem not to be distributed normally --> later on, you state that 85% of patients are >60 years.

Reply: Please see comment above.

Comment 8: Are patients with severe aortic stenosis an honest control? It is possible that they suffer from post-stenotic dilatation.

Reply: We believe that this comment is a very a fair comment of which we want to thank the reviewer. First of all, the mean +/- standard deviation of observed in the control group 3,4 ± 0,3 cm. We did not observe in our evaluation, values of diameters > 4 cm.
On the other hand, severe aortic stenosis was present in 45,3% of all control patients. Since post-stenotic aortic dilatation does not appear to be related to the degree of AS*, we do not believe it has a major impact on our results.

*Crawford MH, Roldan CA: Prevalence of aortic root dilatation and small aortic roots in valvular aortic stenosis. *Am J Cardiol* 2001, 87(11):1311-1313
*Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, John Sutton MG St: Bicuspid Aortic Valves Are Associated With Aortic Dilatation Out of Proportion to Coexistent Valvular Lesions. *Circulation* 2000, 102:35-39.

Comment 9: were there patients with AAD with previous CT-scans? This would potentially be interesting to investigate.

Reply: We agree. In fact, the initial aim was to match healthy aortas with pre-dissection values of aorta. However, we were not able to find any pre-dissection CT scans also due to external referral of the patients.

Comment 10: Discussion: many of the aspects mentioned in the introduction pass here again. I would advise to significantly shorten the introduction and mention these aspects in the discussion for the first time.

Reply: The introduction was shortened and discussion was revised, as kindly suggested.

Comment 11: please add a reference to the statement that tears in aortic dissection are often transverse/horizontal, implying elongation to play a role.

Reply: Thank you for this suggestion. Reference had been added. See Page 12, line 283.

Comment 12: If elongation is associated with dissection, and age is associated with elongation, perhaps age-specific cut-offs should be proposed?

Reply: We agree. However, in our cohort, and for the limitations exposed in the manuscript, no correlation was found between elongation and age. Therefore, we could not analyze these aspects based on our data. However, we believe that any cut-off proposed should consider age-specific impact, since such correlation had been described in other and similar scientific investigations.

Comment 13: An additional limitation is that you probably do not possess of pre-dissection CT's/measurements of AAD-patients.

Reply: We totally agree with the reviewer. Please see comments above.

Comment 14: In general, throughout the manuscript there are several spelling and grammar mistakes

Reply: Thank you for this suggestion. We rechecked carefully for any spelling and grammar mistakes.

Reviewer D

The authors tried to show the alternative determinants of the indication of aortic surgery to prevent type A AAD. The result showed that aortic diameter was not enough to determine the surgical indication to prevent dissection. Although this paper is interesting, there are a lot of factors to be solved.

Comment 1: Firstly, this paper is redundant. Introduction is too long to read. Conclusion is very ambiguous. Thus, please simplify the article and focus on the important things.

Reply: Thank you for this suggestion. The introduction was shortened and discussion was revised, as kindly suggested.

Comment 2: Secondly, this paper does not suggest the alternative determinants for surgery. Aortic diameter is widely accepted because it is very simple and acquired easily. Thus, if the authors want to change the determinants, they should suggest the alternative determinants from this study.

Reply: Thank you for pointing this out. Our study aims to describe morphological parameters of ascending aorta, by comparing the three groups of patients. In fact, we proposed that an algorithm-based risk scores that contemplate all these variables would allow for prompt identification of patients at risk and to prevent Aortic Dissection. This tool needs to be validated with further prospective clinical trials. With the limitations of a retrospective study and without pre-dissection parameters in all the patients, we are not still able to identify independent risk factors for AAAD, to quantify the risk or to suggest thresholds but we encourage a prospective study with this target.

Comment 3: Please rewrite the paper to simplify and more readable one and provide the alternative determinants for surgery from your data.

Reply: As kindly recommended by the reviewer, we have revised our paper.