Author's response to reviews

Title: Augmentation index assessed by applanation tonometry is elevated in Marfan Syndrome

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Author's response to reviews: see over
Response to reviewers’ reports.

We would like to take the opportunity to thank both reviewers for their extremely helpful comments and criticisms. We have made extensive revisions in line with the two reviews, and have addressed the various comments/issues raised on a point-by-point basis below. Changes to the manuscript are highlighted in red. In particular we have:

1. decided to pair the patient and control data – this has resulted in subtle changes only to results.
2. performed multivariate analyses of the determinants of augmentation index (AIx), pulse wave velocity (PWV) and aortic root size.
3. reanalysed the transfer function data, identifying subtle differences between Marfan patients and controls.

Segers:

• Matching of controls and patients
  o Our original analysis used unpaired comparisons. Given the comments of both referees, we have elected to drop the oldest subject from the Marfan population, and match patients and controls on a one-to-one basis for age, sex and height. The data analysis has been performed using paired comparisons. This change has resulted in no major changes in the results.

• Age and PWV/AIx
  o A multivariate analysis has now been performed (page 7/8), to ascertain the determinants of carotid AIx and PWV (Table 3). Marfan Syndrome was the strongest independent determinant of variation in carotid AIx, followed by age and height. Age and mean arterial pressure were the strongest independent determinants of PWV, although the presence of Marfan Syndrome nonetheless had an independent (albeit weaker) association. We have also referred to the different findings of Segers et al (page 10).

• What was the correlation between aortic root size and age/AIx/PWV?
  o Table 4 did indeed show univariate correlations, and did not distinguish patients and controls. We have therefore performed a multivariate analysis (page 8), reported in a revised Table 3. Presence of Marfan Syndrome was the strongest determinant of aortic root size. Both PWV and AIx were additional independent predictors of aortic root size. Age, sex, mean arterial pressure and carotid pulse pressure did not have a significant effect.

• Method of calculation of augmentation index?
  o Wave inflection points were found on ensemble-averaged waves, using an automated computer algorithm to determine the zero-crossing points of the fourth derivative. Signal analysis was indeed performed blinded to clinical details. These details have been added to the text (page 5).

• Time-alignment of the signals when calculating transfer functions?
  o Signals had originally been aligned using the intersection of the signal baseline with the tangent through the maximum slope. We have redone the analysis by synchronising to the maximum slope itself, resulting in an average time lag of 10.9ms in the radial signal (relative to the carotid wave). The revised GTFs no longer demonstrate positive phase at lower frequencies. We have also reanalysed the data and have identified subtle differences between Marfan patients and controls. The method of time-alignment has been added to the text (page 5) and the Figure updated accordingly.
What distance was used to calculate carotid-femoral PWV?
- The straight-line distances between the sternal-notch and both carotid and femoral sites was determined, and path length taken as the difference between the two distances. This has been added to the text (page 4).

Boutouyrie:

- Are the data sound and well controlled?
  - As suggested by the reviewer, we have paired the data, based on age, sex and height. Making this change has resulted in no major changes in the results.
- Conclusion that AIx is more sensitive to vascular abnormalities in MFS is not justified
  - We have toned down the conclusion and other relevant parts of the discussion, and emphasised that AIx should be employed in addition (rather than as an alternative) to established measurements such as pulse pressure and PWV.
- Effect of beta-blockers in MFS may have increased AIx
  - We agree that this is a possibility, although we feel that the lack of a significant difference in heart rate or in maximum dP/dt makes this less likely. We have added a note to this effect in the discussion (page 9/10).
- Effect of pulse pressure on aortic root size, and correction for body surface area.
  - We have now performed a multivariate analysis of the determinants of aortic root size. We found both PWV and carotid AIx to be predictors of aortic root size, independent of the presence of MFS. We did not find pulse pressure to be associated, although as previously stated in the discussion this may reflect lack of power. We have added comments on the revised analysis to the results (page 7 and table 3). We also performed the analysis using aortic root size measurements corrected for BSA, but did not find any association with different haemodynamic parameters.
- Although statistically the transfer function does not differ between MFS and controls, this is not evident in the graphic
  - We agree that subtle differences appeared to be present on the graphic. We have therefore reanalysed the transfer functions by quantifying the lowest frequency at which a trough in the phase shift and gain occurs. We have also recreated the transfer functions to improve the time alignment of the signals (see above). This has indeed identified subtle differences in transfer function between the two groups. Although no differences were found in derived waveforms, we have reworded our discussion and conclusions, emphasising that caution should be employed when using non-MFS transfer functions in MFS patients.
- The title/abstract/conclusion do not completely convey what has been found.
  - We have left the title unchanged, as we feel this still reflects the findings of the study. However, we have reworded the conclusion both in the abstract and the main discussion.
- Plot of PWV/AIx/aortic root size
  - 2 scatter plots showing the relationship between these parameters are now included (figure 1).