Peer Review File

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Comment 1: The title in this manuscript seems very promising at first, but content does not really match it. Discussion really focuses only on differences in PWV and aortic reservoir function in patients with CHD.

Reply 1: Thank you for your comment. The PWV is the most useful biomarker evaluating vascular aging. However, the second half of the title is too strong, as you said. I changed the title.
Changing in the text: Vascular aging in adult congenital heart disease.

Comment 2: Missing data on constellations regarding quality of life, nutrition, sport and school education in these patients. It would be great to have more this information.

Reply 2: Thank you for your comment. The items you listed are interesting. However, this review has focused on the vascular physiology.

Comment 3: Discussion is lacking about operated patients with CHD, for example after valve sparing aortic root replacement or TEVAR.

Reply 3: Thank you for your important comment. However, there are limited studies concerning the vascular physiology in patients with CHD. We have presented some data about postoperative patients with CHD (aortic coarctation, etc.).

Comment 4: And in general, there is not enough concrete specific data in manuscript, despite the large amount of cited reference.

Reply 4: Thank you for your comment. I have added real pressure waveform (Figure 6).
Changing in the text: Figure 6.

Comment 5: Moreover, some illustrations are not very informative, and need, in my opinion a description.

Reply 5: Thank you for your comment. I have added new figure and explanation in the text.

Comment 6: P.9, 3. Possible mechanism of EVA in CHD: The 1st paragraph is for aortic coarctation repair; the 2nd paragraph is for systemic-pulmonary shunt. The authors can explain more clearly about their relation with CHD based on the effects on the pulse waveform.

Reply 6: Thank you for your advice. We consider that, mainly, there are two pathological conditions which cause the discontinuity of the stiffness gradient: aortic arch repair and systemic-pulmonary shunt. We added sentences below.
Changing in the text: In patients with CHD, surgical management and hemodynamics can influence the aortic aging process and induce EVA. judging from the study concerning pressure wave reflection.

Comment 7: Conclusion: Since the discontinuity of the stiffness gradient is important to evaluate EVA as mentioned by the author, the author can suggest any feasible method to evaluate the discontinuity of the stiffness gradient.

Reply 7: Thank you for your comments. We added some sentences about method to evaluate the discontinuity of the stiffness gradient.
Changing in the text: Magnetic resonance imaging is one of the noninvasive methods evaluating the stiffness gradient of the aorta.

Comment 8: p. 2 “The aging process causes hypertension and cardiovascular disease, which results in a degenerative change in the systemic arterial system characterized by the stiffening of elastic arteries (known as arteriosclerosis) and the enlargement of aorta.” The causality might also be reverse. The sentence should be adapted.

Reply 8: Thank you for your advice. I agree with you. I corrected the sentence.
Changing in the text: The aging process leads to hypertension and cardiovascular disease, which is caused by a degenerative change in the systemic arterial system characterized by the stiffening of elastic arteries (known as arteriosclerosis) and the enlargement of aorta.

Comment 9: p. 3 The phrase “… and cardiovascular disease is common in adults with CHD” needs a better definition of ‘cardiovascular disease’. I think that what is meant here is acquired disease, as a contrast to congenital disease.

Reply 9: Thank you for your comments. I have added the concrete conditions
Changing in the text: cardiovascular disease (e.g., ischemic heart disease, cerebrovascular disease, and renal disease).

Comment 10: ‘overloaded in some form’ sounds somewhat vague. Please define.

Reply 10: Thank you for your comment. I have added the concrete conditions.
Changing in the text: overloaded in some form since birth (e.g., cyanosis, volume overload, and systemic right ventricle).

Comment 11: ‘The cause of hypertension in CHD patients is unknown; however, other factors may play a role, given…’ The term ‘other factors’ has no comparative term.

Reply 11: Thank you for pointing this out. I have corrected the sentence.
Changing in the text: however, renal factors may play a role, given that cyanosis and cardiac surgery can both impair renal function.

Comment 12: ‘there is not much research targeting functional aspects of large arteries...’, define ‘functional’.

Reply 12: Thank you for your advice. I have changed the sentences.
Changing in the text: n the definition of the EVA, the stiffness of large arteries is generally evaluated and referenced. The enhancement of aortic stiffness impairs the reservoir function of large arteries.
Concerning large arteries in CHD, morphological evaluation is commonly performed. However, there is not much research targeting reservoir function of large arteries in patients with CHD.

Comment 13: Maintain the term “EVA” consistently where appropriate. Better not alternate with ‘aged aorta’ (p. 3, bottom of page) or other terms.

Reply 13: Thank you for your advice. However, in this sentence, “aged aorta” does not mean “EVA”.

Comment 14: p. 4 ‘This histological changes of the aorta’ should be ‘These histol…

Reply 14: Thank you for pointing this out. I have corrected the sentence.
Changing in the text: These histological changes.

Comment 15: “The functional aspects of aortic aging…”. Perhaps ‘markers’ is better than ‘aspects?

Reply 15: Thank you for pointing this out. I have corrected the sentence.
Changing in the text: The functional markers of aortic aging.

Comment 16: Also, on p. 4 it can be mentioned that pulse pressure is one of the strongest risk markers for CVD.

Reply 16: Thank you for your comments. It is true especially in aged persons. However, the adults with CHD are still young, and it is important that pulse pressure amplification is strong in young population. Therefore, it is difficult to simply apply the pulse pressure to a risk marker for CVD.

Comment 17: On p. 5 the role of the reflective wave is explained. I do not fully understand the sentence “...and runs off to the heart during diastole. However, as the aorta loses elasticity with age, its role as a functional reservoir is diminished.” I think what is meant here is that the reflective wave feeds the coronary perfusion during diastole, and that this is disturbed if vascular stiffness is too high. Please clarify.

Reply 17: Thank you for your comment. I have changed the sentence.
Changing in the text: However, as the aorta loses elasticity with age, its role as a functional reservoir is diminished, because the reflected pressure wave returns to the heart during systole due to the increased PWV.

Comment 18: Augmentation Index should be shortly explained / defined in the text. Also shortly explain the ‘technical difficulties’ when measuring augmentation index, and what consequences this has that are relevant for this review.
It is important that the reader understands what is measured, and where. The pulse wave can be studied at different distances from the heart, and depending on the position the forward and reflective waves are differentially positioned toward each other. It would help if this can be explained, and if this is integrated in Figure 1 to shown where the

augmentation index is derived. In following figures, the effects of vascular stiffening on augmentation index can be explained with the use of a similar presentation.

Reply 18: Thank you for your opinion. I have added the explanation about augmentation index.
Changing in the text: Figure 1 shows ascending aortic pressure waveforms in young (Figure 1A) and old (Figure 1B). Because of the low PWV in adolescents, the reflected pressure wave (arrow) returns to the heart during diastole (Figure 1A). However, PWV elevates with age, and the reflected pressure (arrow) wave returns to the heart during systole (Figure 1B)

The augmentation index is defined as the ratio of augmentation pressure to pulse pressure, and the index becomes negative when the peak systolic pressure precedes the inflection point (Figure2). The augmentation index is important parameter in evaluating aortic reservoir function, however, the measurement of the augmentation index has technical difficulties (identification of inflection point) compared to PWV measurement. It may be one of the reasons why the PWV is commonly used in clinical practice.

Comment 19: Explain subendocardial viability, comparing a healthy with a diseased condition in the same figure showing the representative pulse waves for both conditions.

Reply 19: Thank you for your comments. The “abnormal” subendocardial viability ratio is difficult to define, because it may be preferentially maintained. I have added the below sentence.
Changing in the text: The subendocardial viability ratio (Fig.3) is an important biomarker or aortic reservoir function. In Figure 1, the subendocardial viability ratio of the pressure waveform A is higher than that in the pressure waveform B. We previously measured the subendocardial viability ratio in pediatric patients with repaired aortic coarctation [30], repaired tetralogy of Fallot [31] and transposition of great arteries after arterial switch operation [32]. In comparison with age-matched controls, the subendocardial viability ratio was preserved in each study.

Comment 20: PART 2. Shortly explain the types of congenital heart diseases and the intervention modes that are relevant for this review.

Reply 20: Thank you for your advice. I have added the sentence.

Changing in the text: especially aortic arch disease, tetralogy of Fallot, Fontan candidates,

Comment 21: The discontinuity of the gradual stiffness increase (actually compliance decrease?) from the proximal toward the distal aorta is the proposed mechanism that causes workload increase and loss of myocardial perfusion during diastole. I think it might be good to explain this right after mentioning of the types of CHD. After explaining these mechanisms, the results that support this paradigm can be summarized, followed by exceptions and the explanation of the contrasting findings. Lastly, the recommendations for further studies can be given.

Reply 21: Thank you for your comment. Concerning the discontinuity of the gradual stiffness, I added new figure in part 3 section. The figure demonstrated the real pressure waveforms in patients after aortic arch repair, that is one of the easiest cases to understand the difference of pressure waveform, I think.

Comment 22: Average age and post-procedure survival time might be factors that explain contrasting results described at p. 6 and 7. It is perhaps worthwhile to mention the value of these variables observed in the studies that are quoted in the text, because it should support these explanations.

Reply 22: Thank you for your comment. I completely agree with you. However, there are variations in the age (and post-procedure survival time) of the patients depending on the disease. For example, there are only child data in patients with HLHS. Therefore, it is difficult to simply compare the data between each disease., I think.

Comment 23: For the relevant CHD's, a subdivision can be made in those marked by preserved left ventricle (1), or those requiring recruitment of the right ventricle to perfuse both the pulmonary and body circulation (2). Please explain for which of the two categories the disturbance of augmentation index is most likely to be relevant. I would expect categories 2 perhaps, because myocardial under perfusion might have a stronger impact there?

Reply 23: Thank you for your comment. I agree with you, because the elastin fracture progresses with a large strain and cyclic number.

Changing in the text: This procedure increases ascending aortic blood flow without affecting descending aortic blood flow. The elastin fracture progresses with a large strain and cyclic number [12].

Comment 24: p. 7: ‘reginal’ should be ‘regional’.
On p. 9 a ‘in a dissociation between aortic stiffness and augmentation index’ is mentioned. This entire section is not very clear, and I think that Figure 4 can be more optimally used to explain this phenomenon, e.g., by showing the effect on the wave form when measured at different aortic positions.

Reply 24: Thank you for your comment. I agree with you. I have corrected the word.
The dissociation between aortic stiffness and augmentation index is observed in aged aorta. The reason why I mention it is to tell the fact that the importance of the stiffness gradient has been recently pointed out. I have changed the sentence and Figure 4.
Changing in the text: Regional (Figure 4A) [42]. By the study in aortic aging, the importance of “normal” stiffness gradient has been recently come to light.

Comment 25. Was the gradual increase and the discontinuity in the aortic stiffness gradient actually ever measured in elderly vs. CHD patients? It might be good to explain (graphically) how this was demonstrated with measurements.

Reply 25: Thank you for your comment. As I have just said in reply 17, the discontinuity of aortic stiffness is not aged change. In this review, I would like to the effect of aortic stiffness discontinuity in CHD patients. Therefore, I have added one more figure (Figure 8). The figure demonstrates the real pressure waveforms in patients after aortic arch repair. (Changing in the text: Figure 6)

Comment 26: Objective
Lines 29-30: “In this review, we consolidate studies on systemic vascular physiology in patients with congenital heart disease and discuss their vascular aging".
Lines 29-30: "In this article, we will review vascular aging in the general population, and discuss vascular aging in patients with CHD".
The " general population" as I understand it includes normal people, which may be inconsistent with the objective in the Abstract.

Reply 26: Thank you for your comments. I have changed the sentence.

Changing in the text: In this article, we will review the studies on systemic vascular physiology in patients with CHD and discuss vascular aging.

Comment 27: Lines 90-91: "From the theory mentioned above, the high PWV enhances pressure wave reflection". I only understand that the two are correlated, how did the author arrive at the causal relationship?

Reply 27: Thank you for your comment. The high PWV makes the reflected pressure return fast. Therefore, the high PWV is one of the causes of the enhancement of pressure wave reflection.

Comment 28: Lines 105-106: "In some studies, researchers measured the PWV at the proximal and distal aorta, although there were variations in the measurement sites (Table)". Please specify "Table1".

Reply 28: I have attached the Table.

Comment 29: Lines 113-114: "A recent study in a dialysis cohort has shown that the evaluation of the arterial stiffness gradient can predict the mortality superior to the carotid–femoral PWV measurement [46]".
It is suggested the authors could analyze the findings of the literature in the context of the data (e.g., what is the accuracy of each of the two in assessing mortality), which would also facilitate the reader's reading (without having to find the original literature for confirmation). Please re-check and revise it.

Reply 29: Thank you for your comment. I have changed the text as below.
Changing in the text: A recent study in a dialysis cohort has shown that the aortic-brachial arterial stiffness mismatch was strongly associated with increased mortality [46].

Comment 30: Possible mechanism of EVA in CHD
It is suggested the authors could first list all the possible mechanisms and then reflect the importance of this mechanism through literature discussion (instead of discussing only "one of the possible mechanisms - the enhancement of pressure wave reflection").

Reply 30: Thank you for your comment. I have changed the sentence as you pointed out.

Changing in the text: One of the possible mechanisms of EVA in CHD – the enhancement of pressure wave reflection.