Peer Review File

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Reviewer Comments:

Comment 1. This review lacks focus, giving vague details in every section described. How PHTN can affect the onset of different cardiovascular diseases? What is, specifically, its effects on the myocardium and the vessels? Which cells are principally involved in this process?

Response:

Thank you for your comment.

We have refocused part of our review to examine the possible pathogenic mechanisms of prehypertension (PHTN). We have renamed the title to 'Prehypertension and the cardiovascular system: effects and potential pathogenic mechanisms' . We have discussed that PHTN can affect the cardiovascular system via the inflammatory response, endothelial damage, insulin resistance, sympathovagal imbalance, RAS, ROS and so on.

For example, vascular endothelial function is mainly regulated by the production of nitric oxide (NO). Diminished NO-mediated endothelium-dependent vasodilation is linked to an increased risk of future cardiovascular disease (CVD). The dysfunctional NO synthesis in PHTN may be a source of oxygen free radicals or ROS, which may be an additive factor for developing overt hypertension (HTN). Endothelial progenitor cells (EPCs) are markers of cardiovascular health. In PHTN, senescence of EPCs is substantially increased while NO production is markedly reduced. This pathophysiological process leads to impaired endothelial function, and thus represents an early event in the development of arterial HTN (1). The endothelial repair capacity of EPCs is also impaired in subjects with PHTN compared with healthy subjects ($p < 0.05$) (2). Furthermore, EPC colony formation is impaired in adults with an SBP >130 mmHg ($p < 0.05$) (3). The autonomic nervous system (ANS) controls the major functions of the body. The ANS exerts its functions via the sympathetic and parasympathetic nervous systems. As ANS activity contributes to the regulation of cardiac output and blood pressure (BP) during rest, exercise, and in CVD, abnormalities in autonomic physiology, especially increased sympathetic activity, attenuated vagal tone and delayed heart rate recovery, have been associated with increased mortality. In that study, the heart rate recovery was significantly lower in subjects with PHTN compared with a normal BP group ($p < 0.05$), proving that ANS dysfunction developed

in patients with PHTN (4).

Changes in the text: Page 13-19, Lines 234-363.

2. In the section 3.4, the authors have described the effect of PHTN on vascular vessels, in particular on atherosclerosis, without taking into consideration the importance of a controlled-blood pressure to prevent, for example, aneurysmal rupture or arterial stiffening. It is well known that elevated pulsatile pressure due to hypertension leads to vessel structural disorganization, elastin fragmentation and thus contributing to aneurysmal rupture. What about PHTN? Are there pharmacological treatments able to slow down the onset of these pathologies in PHTN patients?

Response:

We appreciate this helpful comment.

Firstly, we have added studies examining the influence of PHTN on arterial stiffening into the revised manuscript. Increased aortic stiffness was reported to be more common in subjects with PHTN compared with those with optimal BP.

Secondly, the level of 'normal BP' and the advantages of more intensive BP control remain unclear. When BP exceeds 140/90 mmHg, there are definitive adverse effects on the cardiovascular system and benefits of reducing BP below 140/90 mmHg. However, for people with PHTN, it remains controversial whether to take measures to lower BP. The PHARAO study(5) suggested early intervention((ramipril at a dose of 1.5mg qd in the morning for 3 days, then 2.5mg for 7 days, and thereafter 5 mg) in patients with PHTN could help to prevent the progression to HTN. The TROPHY study(6) used the candesartan (16 mg daily) to treat PHTN, and the results indicated pharmacologic treatment of PHTN could postpone the development of HTN. However, clinical trials have raised doubts about the long-term benefits of drug intervention and not all antihypertensive medications for more intensive BP control provide benefits. The ACCORD study(7) found that for patients with type 2 diabetes at high risk for cardiovascular events, achieving an SBP < 120 mmHg compared with SBP < 140 mmHg did not reduce the rate of a composite outcome of fatal and nonfatal major CVDs. The HOPE-3 study(8) determined that candesartan (16mg per day) plus hydrochlorothiazide (12.5mg per day) were not associated with a lower rate of major CVDs than placebo among persons at intermediate risk who did not have CVD. Brunström M et al.(9) found that treatment was associated with reduced risk for major cardiovascular events (RR 0.90; 95% CI 0.84–0.97), but was not associated with

survival (RR 0.98; 95% CI 0.89-1.07) in people with previous CHD. In trials conducted on patients with a baseline SBP below 140 mmHg, treatment was not associated with mortality (RR, 0.98; 95% CI, 0.90–1.06) or major cardiovascular events (RR, 0.97; 95% CI, 0.90–1.04). More studies are needed to determine the effects of pharmacological treatment on cardiovascular-related morbidity and mortality or other target organs damage. Further studies are needed to determine the cost-effectiveness of medical interventions and whether a particular drug is more effective in PHTN group.

Current studies of PHTN are largely focused on the risk of morbidity of PHTN. Thus, there are few large-scale studies exploring the impact of PHTN on the risk of aneurysm rupture. Further, the molecular and cytological mechanisms underlying the effects of PHTN on the cardiovascular system remain unclear.

Changes in the text: Pages 11-12, Lines 200-212 ; Page 20-21, Lines 365-388.

3. The risks associated with PHTN are in part related to the tendency of blood pressure to increase with age. Most of the possible etiological factors proposed by the authors concerns healthy life-style and diet, suggesting that a non-pharmacological management of the PHTN could be enough to prevent hypertension and its correlated cardiovascular risks. This seems to be an important concept that is left out in the review.

Response:

Thank you for your comment.

Some etiologies of PHTN, such as high-fat diet, high-sodium diet, electrolyte disorder, or sympathetic/parasympathetic disorder, may be controlled by lifestyle adjustments. Lifestyle adjustments are also recommended as the first step to control PHTN in later guidelines (10, 11). Although lifestyle modifications can effectively lower BP and have favorable effects on reducing cardiovascular-associated morbidity, a healthier everyday lifestyle may be difficult to maintain in the long term. Some clinical trials have suggested the use of drug therapies for more intensive control of BP. The ACC/AHA 2017 guidelines (12) suggest assessing the 10-year ASCVD risk for patients with a BP ≥130/80 mmHg. Further, drug therapies should be initiated immediately for high-risk patients with an ASCVD risk ≥10%, while non-pharmacological treatments such as lifestyle intervention should initially be used for patients with an ASCVD risk <10%. There is some evidence to support this suggestion. For example, the SPRINT group (13) showed a significantly lower rate of the primary

composite outcome (MI, acute coronary syndromes, stroke, heart failure, or death from CVDs) in the intensive-treatment group (SBP target of <120 mmHg) compared with the standard-treatment group (SBP target of <140 mmHg) (1.65% per year vs 2.19% per year, respectively; HR with intensive treatment: 0.75; 95% CI: 0.64–0.89; p < 0.001). All-cause mortality was also significantly lower in the intensive-treatment group (HR: 0.73; 95%CI: 0.60–0.90; p = 0.003). Further, the rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure were higher in the intensive-treatment group. However, some clinical trials have raised doubts about the long-term benefits of short-term drug intervention, while not all antihypertensive medications for more intensive BP control provide benefits (7) (8) .

Finally, regarding the controversy around interventions for PHTN, we have added a new section titled 'Is it appropriate to treat PHTN?' into the revised manuscript.

Changes in the text: Page 20-21, Lines 365-388.

4. Since the manuscript contains many syntactic and grammatical errors and misused words (e.g. line 135 "scarce", line 136 "heart quality"), I recommend authors to edit for proper English. The use of "more likely to" is redundant.

Response:

Thank you for your comment. The manuscript has been extensively edited for language and spelling by native English speakers at a professional editing company. The editing certificate is attached.

理文编辑

Certificate of Editing

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While this certificate confirms the authors have used Edanz's editing services, we cannot guarantee that additional changes have not been made after our edits.

Changes in the text: All of the review.

5. Finally, I suggest adding figures/tables summarizing the important key points of the review.

Response:

Thank you for your comment. We have added a figure summarizing the important key points of the review into the revised manuscript.

Changes in the text: Page 32, Line 585-588.