Response to Reviewers

Thank you for the reviewers’ comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our manuscript. We have studied comments carefully and made revise which we hope to meet with approval. The English-language speaker has copyedited our manuscript for language usage, spelling, and grammar. The main corrections in the manuscript and the responds to the reviewer’s comments are as following:

Answer to Evren Ustuner (Reviewer 1):

Q: In the conclusion section of the abstract, the findings related to leukocytes (Relationship between IPN and peripheral leukocyte count and CEUS should be worded better.

A: It was revised into “The variation in the perivascular leucocyte is significantly related to intraplaque inflammatory activities, CEUS is a feasible monitor of intraplaque neovascularization, so CEUS combined with perivascular leucocyte could be helpful as a warning for vulnerable plaques.”
Q: 45 plaques were measured in the external carotid artery (ECA). It is generally accepted that plaques in the ECA system are not related to cerebrovascular events and they are of superfluous importance with respect to cerebral circulation since they are considered not to embolize into the intracranial system. It would be better if these plaques were not measured and included in the study.

A: It was revised into “Though forty-five plaques were detected in the external carotid artery, they were not included in this study because the plaques in this site were not related to cerebrovascular events.”

Q: Page 10 line 17. "An obvious plaque was successfully selected to perform CEUS". This plaque selection criteria must be stated in detail because selection criteria (especially anatomical location) is relevant to acute cerebral infarction risk (ACI).

A: The selection criteria was added” those located at the far wall of carotid bifurcation or the initial part of the internal carotid artery; those thicker than 2mm, choosing the largest; no calcification or the least calcified plaque; and cerebral infraction ipsilateral to the side of the carotid plaque”.

Q: The reasons that cause decreased lymphocyte count and increased ACI risk need to be described better.

A: Leukocytes include neutrophils and lymphocytes, and it is an indicator of the overall inflammatory status of the body. Besides, Inflammation plays a fundamental role in the development and progression of atherosclerosis. So, we added:” Asuman et al [31] demonstrated that the neutrophil to lymphocyte ratio (N/L ratio) was highest in patients with ACI compared with transient cerebral ischemia and control subjects. Inflammation plays a fundamental role in the development and progression of atherosclerosis, and leukocytes participate in the plaque formation and destabilization, thereby inducing acute thrombotic events. Therefore, the variation in the perivascular leucocyte could be a novel noninvasive marker for cerebrovascular events.”

Answer to Yonggui Yang (Reviewer 2):

Q: This study evaluates carotid vulnerable plaques using contrast-enhanced ultrasound (CEUS) and explores the relationship between vulnerable plaques and leukocytes. The quality of Article is better; it's clarity of presentation clarity of figures and tables. The research content has certain innovation, and has the feasibility. It's suitability for journal. However, part of the discussion is not deep enough, especially for the advancement of the method, and its comparison with other
currently more reliable inspection methods. The suggestion is published after minor amendments by the author.

A: There are many methods for assessing vulnerable plaques, and it is difficult to discuss in limited worlds. Besides, the subject of this study is “relation between carotid vulnerable plaques and peripheral leukocyte assessing by multi-parametric CEUS”. So, we briefly added” Though prospective observational data is still lacking, more advanced modalities have been introduced, including intravascular ultrasound (IVUS), virtual-histology IVUS, optical coherence tomography (OCT), et al. They can better delineate microstructures of plaques, and may potentially lead to a major shift in the management of millions of patients with ACI.”