Author’s response to reviews

Title: Measuring the Palpable Pulsatility Length as a Physical Examination Test in Defining the Severity of Inflow Stenosis for Hemodialysis Fistulas

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Dear Editor,

We would like to thank you for your comprehensive review of our manuscript and we appreciate the careful reading and high-quality, constructive comments from the Editor and the reviewers. In this revised version of the manuscript, we did our best to address all issues pointed-out by the reviewers. We included a point-by-point response to reviewers’ comments and the changes in the text were highlighted in blue. The revision has been developed in consult with all coauthors and each author has given the approval for the final form of the manuscript.

Sincerely,

Matt Chiung-Yu Chen, MD.

Editor Comments:

1: Please expand the limitations section to include limitations noted by reviewers 2 & 3. The data regarding the PPL and API techniques presented only applies to AVF monitoring after 6 months of use for hemodialysis.

The major shortcoming of the AVF is failure to mature, which cannot be addressed using this method. In addition, the examiners in this study are likely to be relatively expert compared to the community hemodialysis staff in most countries. These limitations make the study generalizability of relatively small scope and require that the conclusions be modified.

A1: The limitation section has been extended by including the limitations noted by the reviewers and the related descriptions have been revised as the following: “... 3) PPL and API measurements were performed only in mature AVFs. Their clinical application and usefulness in immature AVFs need further validation. “

The definition of mature AVF in the Method section has also been revised as the following: “1) a mature AVF (after 6 months of use for hemodialysis) with a single trunk available for cannulation.”

2: Accordingly, please revise the conclusions of the manuscript. "PPL and API are useful tools with high sensitivity and specificity for detecting critical inflow stenosis in the hands of trained examiners. applies to AVF monitoring after 6 months of use for hemodialysis These findings
support expanding the current population studied to refine the tool and, ultimately, to design prospective intervention studies."

A2: The conclusion has been revised according to your kind comment as the following: “PPL and API are useful tools in defining the severity of pure inflow stenosis for mature AVFs in the hands of trained examiners with high sensitivity and specificity. .....“

3: In the background section, the description of the arm elevation test and augmentation test description needs revision. Describing the arm elevation test as the excessive collapse sign is confusing as pointed out by reviewer 3, since that only applies to the inflow defect, which is probably often subtle. The arm elevation test is probably more important and better known for outflow stenosis detection with no or partial vessel collapse as a detection sign.

In addition, the statement that "diagnostic accuracies are lacking in the literature" for these tests is incorrect. Please cite studies 2 studies that evaluated the augmentation and arm elevation tests with impressive correlations compared to angiographic findings.


A3: Thanks for your kind comments. To avoid confusion and keep brevity of this manuscript, the following paragraph in the Background section has been deleted: “Currently available physical examination (PE) tests for assessing the AVF inflow is include the augmentation test and the excessive collapse sign in the arm elevation test, however, the diagnostic accuracies for the above mentioned two tests are lacking in the literature. “

Prof. Anthony M. Valeri (Reviewer 1):

5: Under Definitions, the vascular access pump (aPump), you state "It is not necessary for the whole length of an AVF to be capable of providing a high volumetric flow..." My understanding is that unless there are significant draining collaterals, then the volumetric flow must be constant along the entire length of the AVF proximal to any draining collaterals. Please comment.

A5: Thanks for your comment. Dr. William Paulson’s article in 2004 was referenced to answer your question. (1) In the absence of viscosity friction, total fluid energy would be constant anywhere in the AVF by Bernoulli’s law and your understanding would be correct. However, in reality, friction causes the dissipation of energy as blood flows through the AVF from anastomosis to the central veins. Thus, the fluid energy in the inflow artery is greater than
in the outflow vein. The energy loss can be estimated by pressure drop, which is proportional to the length of blood flowing along AVF and can be described by Poiseuille’s law. Therefore, it is not an abnormal finding as to the pulsatility in the venous cannulation site being absent or weaker than that in the arterial cannulation site.


6: You should state, though it is obvious from your results, that this method will only work for a pure/isolated inflow stenosis.

A6: The Conclusion section has been revised as the following: “PPL and API are useful tools in defining the severity of pure inflow stenosis for mature AVFs in the hands of trained examiners with high sensitivity and specificity. “

7: Do you have clearance data (URR or spKt/V) before and after intervention on these cases? This would be interesting as it provides additional data on the clinical significance (in the absence of blood flow limitation) of the inflow stenoses that you identified.

A7: In this study, no patient was referred for treatment because of abnormal clearance data, which might imply the clearance data for these patients were within normal limits before intervention. Therefore, we didn’t probe into this issue because the authors assumed a comparison of clearance data before and after intervention might not have significance. Thanks for your valuable comments, we will consider this issue in our further study design.

8: Comment on how long it took for the observers to be trained on measuring/recording the PPL consistently.

A8: The examiners (trained dialysis nurses) were trained by the interventional radiologist (IR, M. Chen) in our angiographic suite. Regardless of the referral indication, the pre-PTA PPL of an AVF to be treated was measured by the IR and the trained dialysis nurse, respectively. During the treatment, the trained dialysis nurse could see the location of AVF stenosis on the angiogram and then make a correlation with the measured PPL. After treatment, the PPL was measured again and the dialysis nurse would get a picture on how long could the PPL be for a robust AVF. It was usually easy for an examiner to learn the principle of how to measure PPL but it took some time to achieve a consensus on the measured between examiners. In our experience, it usually requires at least 30-40 cases for a trained dialysis nurse to achieve a fairish consensus with the IR.
Prof. Anatole Besarab, MD (Reviewer 2):

Major

9. Due to spasm 4 cases could not have pre-post comparisons but it is not clear whether the 4 cases were included in Hypothesis 1.

   A9: The 4 cases were included in Situation 1 and 2 but not included for comparisons in Situation 3. To avoid ambiguity, Figure 3 and 4 were revised by adding the case numbers for each group compared.

10. I am not convinced that a residual stenosis of > 30% at the completion of treatment is exclusionary. These could have been analyzed as a subgroup.

   A10: Thanks for your valuable comment. We excluded AVFs with a residual stenosis >30% after PTA because we defined a robust AVF as "full dilatation of a culprit stenosis...". We will include such AVFs as a subgroup for analysis in the future study design.

11. The paper is too long for the average reader. The discussions on rheologic blood flow and kinetic energy can be shortened

   A11: A total of 4 paragraphs in the manuscript have been deleted because they are of relatively low importance. The discussion on rheologic blood flow and kinetic energy has been shortened as the best as we can do.

12. Reason for referral is not stipulated in 32 cases. Are these the asymptomatic cases and if so what was the reason for referral.

   A12: The reasons for referral have been reviewed again and stipulated in the Result section.

Minor

13. The authors stipulated that only AVF that has matured and were in use for at least 6 months were studied. Also, any AVF with more than one main early trunk, or which was deep was excluded. This limit generalizability.

   A13: We have reworded the Limitation section as the following:
“…… (3) PPL and API measurements were performed only in mature AVFs and their clinical application and usefulness in immature AVFs need further validation. (4) Only selected AVFs with a main trunk and a visible and palpable aPump were eligible for PPL measurement, which limited the method’s generalizability. ….”

14. I am not sure that one needs to define 3 types of inadequate inflow.

A14: Thanks for your careful review. The following sentences in the Results section have been deleted, “There were five flat aPumps (three pure inflow stenosis, two I/O stenosis), two thrill aPumps (two I/O stenosis), and one balanced aPump (pure outflow stenosis). “

15. The absence of a significant difference in the API between subjects with hypotension and those with "normal BP" is limited by sample size (n=8). It is an observation which should be followed up!

A15: Thanks for your valuable comment. We will consider this factor in the future study design.

Ms. Deborah Brouwer-Maier (Reviewer 3):

A16. Immature fistula listed as excluded from the study due to the need for the the distance measurement from the anastomosis and the arterial needle cannulation sites. This is a significant limiting factor for the clinical application of the inflow stenosis detection method. Inflow stenosis at the JAS location commonly occurs after the AVF creation and prevents the maturation of the AVF.

A16: For mature AVFs, the arterial needle-stick sites were always obvious on the skin after repeated cannulations for at least 6 months of use for hemodialysis. Therefore, in our experience, it was usually not a problem for an examiner to define the aPump as we defined in this study. However, as your comment, it would be a problem to define the aPump for an immature AVF without a visible main trunk, which would be a significant limiting factor for the clinical application of our method.

17. The augmentation test referenced in the article was developed to help identify non-maturing AVF's prior to unsuccessful cannulation attempts. This will exclude wide clinical adoption of the PPL and API method.
A17: We agree with your comments. Based on the current study, the PPL and API method was validated only for mature AVFs and its clinical application and usefulness for immature AVFs need further study.

18. Under definitions of an inflow stenosis, symptomatic inflow stenosis and a critical inflow stenosis the suction or tubing shaking during hemodialysis - do the hemodialysis machines used monitor the pre-pump Arterial Pressure and if so can a pressure range be used to replace the current description? The Augmentation test is used in the identification of any inflow stenosis.

A18: For the dialysis machines currently used in Taiwan, measurement of the pre-pump arterial pressure was not available by default because of reimbursement issues for the pre-pump tubing and transducer protector.

19. Concern of the measurement of lengths may have wider variability when used beyond the limited staff in this study setting. It is also impacted by the cannulation practice patterns for needle placements that is not related to the aPump as described in the paper.

A19: We agree with your concern. Our study unveiled the potential usefulness for measuring PPL and API as PE tools in defining inflow severity of mature AVFs. Further study performed other than our institution by examiners with different training background is of no doubt needed to validate the value of our method.

20. The impact form blood pressure is referenced but not pulse rate- Cardiac Output changes will alert the access flow independent of stenosis.

A20: Thanks for your valuable comment. We will consider this factor in the future study design.

21. Excessive collapse sign upon arm elevation is very unclear as to the meaning. This is not part of the augmentation test typical description. Can that please be clarified?

A21: To avoid confusion and keep the manuscript short, the descriptions related to “excessive collapse sign” in the manuscript have been deleted.
22. The use of a tourniquet between the arterial and venous needles is not an acceptable practice and in itself is a clinical indication of a low flow AVF. Concern this might not be clear to the reader.

A22. I am sorry for the ambiguity. To make it clear, the paragraph has been reworded as the following: “In our daily practice, it is not uncommon for a dialysis nurse to place a tourniquet around an AVF, as a temporary measure, when the arterial cannulation site is not providing an adequate volumetric flow for hemodialysis but angioplasty was, for example, scheduled one week later because of a long waiting list for our angiographic lab.”