Author's response to reviews

Title: Systemic Vascular Function, Measured with Forearm Flow Mediated Dilatation, in Acute and Stable Cerebrovascular Disease: a Case-Control Study

Authors:

Christopher D Beer (christopher.beer@uwa.edu.au)
Kathleen Potter (kathleenpotter@yahoo.com)
David Blacker (david.blacker@health.wa.gov.au)
Leonard Arnolda (Leonard.Arnolda@act.gov.au)
Graeme J Hankey (gjhankey@cyllene.uwa.edu.au)
Ian B Puddey (puddeyib@cyllene.uwa.edu.au)

Version: 2 Date: 30 September 2010

Author's response to reviews: see over
Dear Dr. Picano,

Re: Manuscript ‘Systemic Vascular Function, Measured with Forearm Flow Mediated Dilatation, in Acute and Stable Cerebrovascular Disease: a Case-Control Study’

Thank you for your letter of 3 September and the opportunity to respond to the reviewer’s comments. We have addressed the reviewers’ comments, and revised the manuscript accordingly.

Reviewer 1: Rosa Sicari
1. Include more data/results in the abstract session of the manuscript. The abstract now includes the actual FMD values, and results for endothelium independent FMD.

2. Please clarify in the methods section of the manuscript if patients underwent brain imaging to support diagnosis. The methods now clarify that all participants underwent brain imaging.

3. The case-control study is correct, however a normal study group would strengthen the results. This point is acknowledged, and the rationale for the control group chosen further explained in the discussion by adding the text “The endothelial marker E-selectin is elevated in acute stroke and returns to normal concentrations within 3-6 months. [6] However it is not known if endothelial function is impaired in subjects with acute stroke (compared to those who have suffered a remote stroke)” and “Our aim was to determine the association of acute stroke with vascular function, and we thus chose to control for background cerebrovascular disease. However the study would have been furthered strengthened by the simultaneous inclusion of a healthy control population.”

4. The major limitation of the study is related to the lack of an operator-independent and automatic system of measurement of FMD. This should be acknowledged. We have clarified in the methods that a single operator made all measurements using custom-designed edge-detection and wall-tracking software designed to reduce observer bias. This software has been validated in a previous publication referenced in our paper. The intra-observer CV for FMD measured by our method is 6.7%.”

Dr E Picano, MD PhD
Editor-in-Chief
Cardiovascular Ultrasound

30 September 2010
5. In the results section of the manuscript 18 patients are the study population where the actual population is of 17. This is a little confusing. We have removed description of the patient who was excluded to avoid potential confusion.

6. Medical therapy at time of FDM evaluation may modulate the response. Provide data on the possible effect of medical therapy. We have expanded discussion by adding the text “given that commonly used medications, such as statins, may improve vascular function and reduce the risk of stroke....” and providing two additional references.

7. Due to the nature of the journal images should be uploaded with sample cases. Our methods have been described in detail previously, including images. We would thus like to offer two videos, which we believe readers will find more informative.

8. You may be interested in citing Takase et al. Cardiovascular Ultrasound 2008, 6:61. We have cited this article in the discussion and added the text: “FMD has been found to be associated with survival free from cardiac events (Takese 2008)....”.

Reviewer 2: Lucia Venneri
1. The study hypothesis posed by Authors is not well described. We have re-written the hypothesis statement to clearly state our hypothesis: “We hypothesised that acute ischaemic stroke would be associated with impairment of systemic endothelial dysfunction.”

2. Inclusion and exclusion criteria are not clearly defined. The diagnostic criteria we used are now described in more detail, rather than simply providing a reference.

3. The studied population is very small and definite conclusions cannot be drawn. We have re-worded the study conclusion to “Despite the small size of this study, these data indicate that recent acute stroke may not necessarily be associated with a clinically important reduction in FMD” in order to further emphasise this limitation.

4. The clinical implications of the study are not clear. We have added the sentence “These data suggest that subjects with stroke more than two years previously have similar vascular function to subjects with recent stroke. The clinical utility of assessment of FMD in subjects with recent acute ischaemic stroke thus remains uncertain” to the conclusions.

5. There are still a number of methodological limits regarding ultrasound-assessed systemic endothelial function. It would be interesting to know author’s opinion on why FMD evaluation is not considered to have a role outside research laboratories. We have added the sentence “Currently, concern regarding the safety of administration of GTN to people with acute ischaemic stroke precludes full measurement of FMD in acute stroke patients outside research
protocols” to the discussion. We acknowledge that there are still issues of reliability and reproducibility associated with the measurement of FMD, but many investigators do accept FMD as a functional bio-assay for endothelial-dependent NO production and we have used the most rigorous and objective methods currently available to assess FMD in our subjects. Our data, if published, will tend to support the argument that FMD is of limited clinical utility. Our data show that individuals with a proven recent ischemic vascular event, in whom endothelial function might be expected to be severely impaired, do not show any evidence of reduced FMD.

We would like to take this opportunity to again thank the reviewers for their thoughtful comments, which we believe have improved the quality of the paper. We hope you will find the revised version suitable for publication in ‘Cardiovascular Ultrasound’.

We look forward to hearing from you.

Christopher Beer