LETTER TO THE EDITOR

Cerebral vasoreactivity in white coat hypertension – response to comments written by V.K. Sharma

I and A.K. Sinha

B. Fülesdi^a and D. Páll^b

^aDepartment of Anaesthesiology and Intensive Care and ^bDepartment of Medicine, Medical and Health Science Centre, University of Debrecen, Debrecen, Hungary

Correspondence: Béla Fülesdi, Department of Anaesthesiology and Intensive Care, Health and Medical Science Centre, University of Debrecen, H-4032, Debrecen, Nagyerdei krt 98, Hungary (fax: + 3652255347; e-mail: fulesdi@dote.hu)

Keywords: Cerebrovascular diseases and cerebral circulation, neurological disorders

Received 31 May 2011 Accepted 3 June 2011

Sir

We were pleased to read the comments on our manuscript entitled 'Impaired cerebral vasoreactivity in white coat hypertensive adolescents [1]' written by Sharma and Sinha. There were two main concerns that were raised in their letter:

First, the regulation of the arterial tone by sympathetic and parasympathetic nervous system and its influence on cerebral vasoreactivity and autoregulation. In fact, there are numerous factors that may contribute to the cerebral arteriolar tone, and amongst them, the balance between parasympathetic and sympathetic innervation plays also a role. However, this role is not exclusive and may not explain flow-metabolism coupling of the brain parenchyma in all details. In recent decade, more and more observations came

into light supporting the role of nitric oxide-endothelin balance as main actor in determining cerebral vascular tone. It is believed that both the resting tone and vasodilatory and vasoconstrictory reactions occur through alterations in activation of the NOS by different stimuli. At present, there are three main known subtypes of NOS, amongst them iNOS (produced by the vascular endothelium)

2 (produced by the vascular endothelium) and nNOS (produced by the nitrargic nerves) are believed to play a pivotal role in determining cerebral vascular tone, vasoreactivity, and autoregulatory reactions. Metabolic changes (such as hypercapnia, altered cGMP, hyperoxia, or hypoxia) as well as neurogenic activities are thought to exert their vasoregulatory actions through this system. This concept may entirely explain flow-metabolism coupling, autoregulatory, and vasodilatory reactions of the cerebral vasculature [2]. In a previous review of acetazolamide tests, our group provided a simplistic description of these underlying mechanisms [3]. The role of nitric oxideendothelin imbalance in determining hypertension has been also proven previously in adolescent hypertensives [4,5]. The present study just aimed to underline the fact that decreased baseline nitric oxide concentrations are already observed in white-coat hypertensives compared with healthy persons.

In their second comment, Sharma and Sinha raised their concern about the formula used to evaluate the vasodilatory response. In fact, fixed time of breath holding may not represent a similar challenge in differently aged adults with different lifestyle and comorbidities. However, in the Debrecen Hypertension Study, young adults aged between 14 and 19 years with average lifestyles (no divers or professional swimmers) were included. We hypothesized that lung functions and vital capacities were normal in these

young subjects. Despite this, in some cases, it was necessary to repeat the breath-holding tests because of improper cooperation. To overcome this, we elaborated a technique that facilitates the cooperation of the subjects as described in a previous article in detail [6] and used the method also in the present study. However, in fact, breath holding index described by Markus and Harrison [7] may be a more sophisticated option for assessing cerebral vasoreactivity in elderly people and in patients with comorbidities.

Again, thank you very much for your excellent comments on our article.

References

- Páll D, Lengyel S, Komonyi E, et al. Impaired cerebral vasoreactivity in white coat hypertensive adolescents. Eur J Neurol 2011; 18: 584–589.
- Toda N, Ayajiki K, Okamura T. Cerebral blood flow regulation by nitric oxide: recent advances. *Pharmacol Rev* 2009; 61: 62–97.
- Settakis G, Molnár C, Kerényi L, et al. Acetazolamide as a vasodilatory stimulus in cerebrovascular diseases and in conditions affecting the cerebral vasculature. Eur J Neurol 2003; 10: 609–620.
- Páll D, Juhász M, Lengyel S, et al. Assessment of target-organ damage in adolescent white-coat and sustained hypertensives. J Hypertens 2010; 28: 2139–2144.
- Katona E, Settakis G, Varga Z, et al. Targetorgan damage in adolescent hypertension. Analysis of potential influencing factors, especially nitric oxide and endothelin-1. J Neurol Sci 2006; 247: 138–143.
- Settakis G, Lengyel A, Molnár C, Bereczki D, Csiba L, Fülesdi B. Transcranial Doppler study of the cerebral hemodynamic changes during breath-holding and hyperventilation tests. J Neuroimaging 2002; 12: 252–258.
- Markus HS, Harrison MJ. Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus. *Stroke* 1992; 23: 668–673.



Author Query Form

Journal: ENE

Article: 3483

Dear Author,

During the copy-editing of your paper, the following queries arose. Please respond to these by marking up your proofs with the necessary changes/additions. Please write your answers on the query sheet if there is insufficient space on the page proofs. Please write clearly and follow the conventions shown on the attached corrections sheet. If returning the proof by fax do not write too close to the paper's edge. Please remember that illegible mark-ups may delay publication.

Many thanks for your assistance.

Query reference	Query	Remarks
1	AUTHOR: Please check the title, authors' names and Affiliations.	—
2	AUTHOR: Please suggest whether the spelling of the term 'nitrargic' can be edited as 'nitrergic' with reference to net sources in the following sentence 'At present, therethrough this system'.	=

USING E-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required Software

Adobe Acrobat Professional or Acrobat Reader (version 7.0 or above) is required to e-annotate PDFs. Acrobat 8 Reader is a free download: http://www.adobe.com/products/acrobat/readstep2.html

Once you have Acrobat Reader 8 on your PC and open the proof, you will see the Commenting Toolbar (if it does not appear automatically go to Tools>Commenting>Commenting Toolbar). The Commenting Toolbar looks like this:



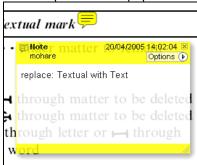
If you experience problems annotating files in Adobe Acrobat Reader 9 then you may need to change a preference setting in order to edit.

In the "Documents" category under "Edit – Preferences", please select the category 'Documents' and change the setting "PDF/A mode:" to "Never".



Note Tool — For making notes at specific points in the text

Marks a point on the paper where a note or question needs to be addressed.



How to use it:

- Right click into area of either inserted text or relevance to note
- Select Add Note and a yellow speech bubble symbol and text box will appear
- 3. Type comment into the text box
- 4. Click the X in the top right hand corner of the note box to close.

Replacement text tool — For deleting one word/section of text and replacing it Strikes red line through text and opens up a replacement text box.



How to use it:

- 1. Select cursor from toolbar
- 2. Highlight word or sentence
- 3. Right click
- 4. Select Replace Text (Comment) option
- 5. Type replacement text in blue box
- 6. Click outside of the blue box to close

Cross out text tool — For deleting text when there is nothing to replace selection Strikes through text in a red line.

substitute part of one or more word(s)
Change to italics
Change to capitals
Change to small capitals

How to use it:

- 1. Select cursor from toolbar
- 2. Highlight word or sentence
- 3. Right click
- 4. Select Cross Out Text



Approved tool — For approving a proof and that no corrections at all are required.



How to use it:

- Click on the Stamp Tool in the toolbar
- Select the Approved rubber stamp from the 'standard business' selection
- 3. Click on the text where you want to rubber stamp to appear (usually first page)

Highlight tool — For highlighting selection that should be changed to bold or italic. Highlights text in yellow and opens up a text box.



How to use it:

- Select Highlighter Tool from the commenting toolbar
- 2. Highlight the desired text
- 3. Add a note detailing the required change

Attach File Tool — For inserting large amounts of text or replacement figures as a files. Inserts symbol and speech bubble where a file has been inserted.

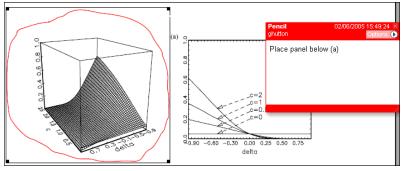
matter to be changed matter to be changed matter to be changed matter to be changed

How to use it:

- 1. Click on paperclip icon in the commenting toolbar
- 2. Click where you want to insert the attachment
- 3. Select the saved file from your PC/network
- 4. Select appearance of icon (paperclip, graph, attachment or tag) and close

Pencil tool — For circling parts of figures or making freeform marks

Creates freeform shapes with a pencil tool. Particularly with graphics within the proof it may be useful to use the Drawing Markups toolbar. These tools allow you to draw circles, lines and comment on these marks.



How to use it:

- Select Tools > Drawing Markups > Pencil Tool
- 2. Draw with the cursor
- 3. Multiple pieces of pencil annotation can be grouped together
- Once finished, move the cursor over the shape until an arrowhead appears and right click
- 5. Select Open Pop-Up Note and type in a details of required change
- 6. Click the X in the top right hand corner of the note box to close.



Help

For further information on how to annotate proofs click on the Help button to activate a list of instructions:

