Author's response to reviews

Title: The Effect of Ventricular Assist Devices on Cerebral Autoregulation: an Observational Study

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Author's response to reviews: see over
To the Editor-in-chief of BMC Anesthesiology Journal

RE: The Effect of Ventricular Assist Devices on Cerebral Autoregulation: an Observational Study

We write in response to the recommended modifications received on the 16\textsuperscript{th} November 2010.

We would be obliged if you could pass on our thanks to the reviewers for their time, effort and constructive criticism; which we believe will result in a more instructive article. In essence, we agree with the comments made by the reviewers and hope we have altered them sufficiently that it meets their approval.

We attached the modified manuscript as well as the answers to the reviewers’ requests. We hope these clarifications answer the concerns raised in the review and would be more than happy to answer any questions should the reviewers feel they are required.

Yours Sincerely

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Reply to the Editorial requests

1. **Ethics:** please specifically name the body that gave approval for your study. The Prince Charles Hospital Ethics Committee gave approval to this study.

2. **Authorship:** please review our guidelines for authorship and your authors' contributions section, as currently written, several authors do not fulfil our criteria for authorship.

   ... JB and JFF conceived and designed the study; JB undertook patient screen and data acquisition; JB drafted the manuscript which was reviewed and amended by all other authors. GC and Y-C T undertook data analysis and contributed to its interpretation. AGB undertook statistical analysis. KRD also facilitated patients’ and devices availability offering an invaluable technical support. RB and PA reviewed and amended the manuscript....

According to the guidelines for author’s contributions, KRD seems not to accomplish such conditions. However, without KRD’s contribution, this study had not been feasible, as KRD designed and conceived the technical components of this study. Please find the corresponding amendments in the text.
Major Compulsory Revisions:

1. The conclusion of disrupted autoregulation by pulsatile VAD does not seem fully warranted by the data: a) Both phase shift and gain as widely used parameters of dynamic cerebral autoregulation remain unaltered between VAD patients and controls. A higher coherence might be a sign of impaired autoregulation in some instances, but it is difficult to use this criterion alone as a sign of disrupted autoregulation. b) The study size of n=5 patients versus n=5 controls means that this is a pilot study with preliminary findings.

Dear reviewer:

a) The parameters used within this study do not show the statistical significance that makes results unarguable. Instead, only coherence within LF ranges shows statistical difference between cases and controls. However, other indicators that define the state of cerebral autoregulation are found in this study, these are: a high-pass filter property (evidenced by the finding of higher gain at high frequency ranges) among controls; negative phase among controls for VLF and HF ranges. The author states this fact in the discussion paragraph as well as in the methodological limitations paragraph, hence suggests that a possible cause could be the sample size, although this is not demonstrated.

b) The author agrees with the reviewer that the sample size is small, however the rarity of patients supported with Ventricular Assist Devices (around 10-15 per annum in our centre) allowed patients’ recruitment to be achieved within a year,
adding to this study a realistic view of patients’ conditions; therefore, the author states within the methods paragraph that it is a “convenience” sample. Furthermore, although a bigger sample could offer more solid results, power and sample size calculation was not targeted for this observational study.

Finally, in the original conclusion paragraph, the author does not state that cerebral autoregulation is preserved but that it is better. The author agrees that this is a confusing term which perhaps could not be supported by the data results. For this reason the author has modified the conclusion hoping to be in the reviewer’s agreement.

2. Patients & Controls: Cerebrovascular obstructive disease looked for? Stroke ruled out by neuroimaging?

Cerebrovascular disease or Stroke were not ruled out a priori, as all patients recruited were in their acute phase of the disease and some patients were not stable enough to be transferred to a scanner. Furthermore, the Ethic Committee would have most likely refused to perform a transfer as a study protocol, in such unstable patients. However, none of the patients who survived showed signs of neurological complications. Two of the patients who died, had remained with a low level of sedation in order to optimise therapy, therefore a fine neurological assessment was not reliable.

3. Controls: to define whether autoregulation is disturbed or not particularly with VAD, a control population without structural heart disease and without dopamine infusion (probably affecting BP variability) would be more appropriate.
The author agrees with the reviewer, however in order to match patients and to identify or isolate the CBF effects of VAD, patients with vasoactive drugs were required.

4. Given the small number of subjects and the high variability of spontaneous dCA measures, an autoregulation method with a better reproducible BP stimulus might have been considered.

Specific interest was in assessing cerebral autoregulation using a frequency domain analysis; in order to distinguish the frequency ranges that have been previously described for some authors, as more complex and relevant for CBF. For this reason the authors were in agreement that Transfer Function Analysis was a feasible method.

In regards of BP stimulus, it is precisely the use of VAD what the authors targeted, as current tendencies are based in the long term use of these devices, hence, few information is available of their effects in cerebral hemodynamics.

In regards of the apparent variability in BP and CBF: a simultaneous study (currently under review) using the same cohort of patients was performed by the same group; focussing on the assessment of BP and CBF variability (measured as fractality and using Detrended Fluctuation Analysis –DFA). In this study, minimal fractality was found in BP waveform of both groups (cases and controls) despite the apparent high degree of variability. Instead both groups maintained a significant degree of fractality in CBF.
5. Results of mean CBFV are not reported.

The author did not add mean CBFV in the original manuscript, as they were all normal and did not add novel information. In the amended manuscript, the author has modified table 2 introducing mean CBFV.

6. Phase shift is reported to be negative among controls (consistent with previous studies) in the Discussion section (p. 15, para 2). Results in Table 2 show different values: in LF range there is a positive phase in 4 of 5 subjects. Please check and clarify this point.

The author has modified the discussion section being more precise in the phase shifts results.

7. What is the clinical significance of the present findings in the authors’ opinion?

Please discuss.

The author acknowledges that this is a study with a specific scope of interest. Currently, invasive and bridging cardiovascular therapies are prolonging survival, mainly among elderly population. Many studies have revealed neurological complications amongst patients supported with these therapies, some related to worsen cerebral autoregulation. Although preliminary, these findings are an effort to describe further, cerebral hemodynamics in the setting of very aggressive cardiovascular strategies. The author believes that this study should lead to a more extensive one, also with a bigger sample. This study is the third of a series of studies (made by same author) focused in cerebral autoregulation in patients with cardiovascular instability.
Minor Essential Revisions

1. Page 6, para 2: Rider and coworkers: citation number does not match

The author apologizes and corrects the reference list in the revised manuscript.

2. Page 8, para 3: Transcranial Colour Coded Sonography does not allow determination of the vessel diameter.

The author refers to either color-coded or color-powered technology, with which visualization of the circle of Willis is possible as well as the cross-sectional area of the insonated vessel (please see amendment).

3. Table 1: Abbreviations should be named in legend

The author has added two abbreviations. Table 1 corrected.

4. Table 2: VAD number: could this allow identification of patients? I would suggest omitting numbers

The author has removed the clinical files number. Tables 1 and 2 corrected.

5. Analysis of autoregulation from time series of 10 minutes contrasts to page 7, para 3: 30 minutes.

What the author means with the sentence: “implied a 30 minutes period of data collection” is that total time dedicated by the main investigator at the bedside, was of 30 minutes; 10 of these 30 minutes were TCD recordings. The author has corrected this sentence in the manuscript.
6. Some sentences in the Discussion are difficult to follow.

Some modifications are located as follows: Page 13, line 19- col 18; Page 14, line 8-col 5; line 10- col 25. A revision of the revised manuscript has been undertaken by the other authors without identifying further misleading sentences. The author will modify further if necessary.
Reply to Reviewer 2

Reviewer's report
Title: The Effect of Ventricular Assist Devices on Cerebral Autoregulation: an Observational Study

This is an interesting study of dynamic pressure-flow relation in patients with and without ventricular assist device (VAD). With transfer function analysis, the authors concluded that cerebral autoregulation was impaired in patients with VAD when compared to those without VAD. This conclusion was based on a finding that coherence at low frequencies was increased in patients with VAD. This reviewer has two major concerns.

1. Fig 1 showed blood pressure (BP) as well as CBFV fluctuations in patients with VAD. However, spectral power was not calculated in each of specific frequency ranges. Mean CBFV’s for each patient, throughout the study are shown in table 2. The original table 3 was a summarised version of the updated table 3 (see manuscript); in this table, MCAv corresponds to the spectral powers (cm/s)^2, so they represent variability / fluctuations rather than the actual MCAv.

Also, BP and CBFV variability were not presented in patients without VAD. These data are important for this study and should be presented.

The author would like to clarify that figure 1 was a graphic representation of how pressure waveform is normally modified during the use of VAD. In this study, the ‘apparent’ BP variability (the one that clinicians can observe from bedside) was actually not translated into mathematical variability, when this was defined with fractal scales (the topic of a simultaneous study); this conclusion is the result of another study performed over the same cohort, currently under review.

2. The authors should appreciate that with the presence of nonlinearity of the cerebral circulation, estimation of coherence may be sensitive to the power of the input signal and may not be related to any change in cerebral autoregulation. This is the case especially when transfer function gain and phase remained unchanged as showed in this study.

The reviewer’s observation is a very important consideration and it is well taken by the author; the author has put less weight in gain and phase measures where the coherence is very low.

Specific comments:
Page 3, line 6 - The only significant change in coherence was at low frequencies, not in the very low frequency range.
Amended.

Page 9, line 10 - typo “though” should be “through”.
Text has been amended.
Page 10, line 11 - “the relation between two signals is either inverse or non-linear”, why should an “inverse” relation change coherence?

The expression “inverse” refers to “indirectly related”; the author has amended the text.

Page 11, line 3-4 - “Sxy(f), was computed as the product of Sxx*(f) and Syy(f)”
please make it clear whether Sxx and Syy represent Fourier transform of the time series or are the estimates of power spectral density of the time series?

Sxx and Syy are power spectral density (or autospectrum – Fourier Transform of autocorrelation sequence).

Page 14, line 11-13 - “In addition, it is also documented…on CBF”. This is a very confusing sentence.
The author has corrected this sentence.

Page 15, line 1 – “small” should be “low”.
Amended.

Page 15, whole second paragraph – The discussion of “negative value among controls throughout all frequency ranges” needs to be carefully reconsidered.
The author apologises as mean negative values were only present for VLF and HF ranges. The author has modified the text.

Table 3 showed that at very low frequencies, 3 out of 5 controls had positive phase (the mean negative value is likely due to one patient with -1.71).
The author agrees with the reviewer in that “the mean negative value is likely due to one patient with -1.71” and has amended the text.

Phase was positive at low frequencies.
Finally, phase at high frequencies is likely to be no significantly different from zero.
Most studies the authors cited in this work showed a positive phase between changes in BP and CBF velocity which has been well accepted if a correct algorithm for cross-spectral estimation is used.

Page 22 – References 21 and 22 are the same?
These are different references (different journals and years, by the same first author).

Page 24, Fig Legends. “TFA average” what does the term “average” mean herein?

Legend amended.