Author’s response to reviews

Title: Estimation of central arterial pressure from the radial artery in patients undergoing invasive neuroradiological procedures

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Author’s response to reviews:

Dear Editor in Chief of BMC Anesthesiology Prof. Guangde Tu,

We appreciated very much the opportunity we had to resubmit a revised version of our manuscript. We thank you and the Reviewers for the helpful comments and suggestions, which helped us to improve our article.

We revised it following the Reviewers’ suggestions and provided a point-by-point description of how we responded to the comments and concerns of the Reviewers. All the changes we made in the text are highlighted in red color.
We hope that our manuscript is now suitable for publication in BMC Anesthesiology.

Sincerely
Sabino Scolletta

Editor Comments:

Dear authors,

As you will see below, our reviewers and myself find your manuscript very interesting and very timely. The clinical reviewers just have a few comments to help you improve your manuscript. This is very achievable, and I look forward to receiving your revised manuscript.

We thank the Editor and the Reviewers for appreciating the manuscript and providing us with comments and suggestions that helped us to improve the article. All the changes we made in the manuscript are highlighted in red. Below are the point-by-point answers to all the queries.

1) I just have one important comment: Please address why the study was not registered, approved by the Ethic Committee in 2011 and only submitted now because readers may wonder why such a long delay? Especially because your team (JL Vincent & Daniel De Backer) has probably the best track record of publications in the world.

Answer: Indeed, Prof. Scolletta conducted the study during his fellowship at Erasme University Hospital in Brussels under the supervision of Profs. Vincent and De Backer. On his return to Italy, institutional and academic concerns unfortunately meant that he was unable to finalize the manuscript as quickly as he would have wished. Because it was a purely observational study, we did not register it.

R1#

The larger concern for this manuscript is what you stated just prior to your discussion of limitations: "In the present study, we were not able to clearly demonstrate that the reconstructed pressures obtained by PRAM were closer to central pressures than were the peripheral measurements. In fact, we found similar correlations and biases between central and reconstructed, and central and peripheral pressures.". If your function did absolutely nothing but
copy the peripherally measured pressures your correlations would be just as strong to Aortic pressures… This unfortunately significantly diminishes the validity of your novel multiple linear regression model derived transfer function… You need to think of better ways to validate your PRAM software, and this requires patients with larger differences between Aortic and peripheral pressures (which is also a good idea because this software is most clinically relevant is people with comorbid cardiovascular conditions as opposed to healthy patients such as those measured here). Potential areas of focus could be vascular surgical or diabetes patients moving forward. As long as the differences between measure peripheral and measured aortic pressures is small, no validation of your function can occur.

2) I recommend significantly changing the conclusion to indicate this less decisive result.

Answer: We thank the Reviewer for this comment. We have changed the conclusion as follows: “...central arterial pressure values reconstructed from the radial artery pressure wave using PRAM were similar to those measured directly in the aorta; however, given the small differences between measured peripheral and measured aortic pressures, we were unable to demonstrate conclusively that the PRAM technique could reconstruct the central arterial pressure. Further studies are warranted in patients with larger differences between measured peripheral and aortic pressures (e.g., vascular surgical or diabetes patients) to confirm validity. In addition, studies should also assess whether this method could be helpful in critically ill patients with different conditions that may affect the pressure wave shape (e.g., sepsis, cardiac failure, trauma, hemorrhage) and may increase the risk of bias between measured and estimated pressures.”

3) Assuming that values over a 2 minutes period, even without stimulation or changes in ventilation/anesthetic, can be averaged may not be completely accurate. Some short of deviation measurement should take place when reporting blood pressure values measured over a 2 minutes period

Answer: We agree with the Reviewer. Averaging the values of the pressure recorded and over a 2-minute period may not be completely accurate. We cannot provide a standard deviation of the mean values of pressure registered over a 2-minute period for each patient; however, we acquired the data during hemodynamic stability, defined as mean arterial pressure and heart rate variations < 5%. As a consequence, we believe that any deviations would be extremely small and not clinically significant.
4) Make the abstract and introduction more clear to explain that the PRAM method used here only uses peripherally obtained arterial pressures and the central led obtained pressures are only used for "gold standard" comparison to evaluate the efficacy of the PRAM method

Answer: We thank the Reviewer for this suggestion. We have modified the abstract and introduction accordingly.

5) Discuss the approach used to create the transfer function of taking peripheral arterial pressures and deriving central aortic pressures (how many patient values were used to validate this function? What type of patients? Where? When? Errors?)

Answer: We thank the Reviewer for this comment and have tried to better explain how the PRAM method works. The mathematical model to reconstruct aortic pressure was the result of a multi-linear regression analysis performed on a dataset of 123 measurements of 41 cardiac patients underwent heart catheterization (Romano SM et al. IEE transection 1999). The age of the patients ranged from 32 to 81 years; 16 patients had dilated cardiomyopathy, and 25 had valvular pathology. Peripheral and central pressure waves were recorded simultaneously in each patient (three pulsations each separated by 30 seconds). To work in the time domain, the single pulsations from peripheral and central records were interpolated linearly. The two signals were put in phase and the pressure and pulsation waveforms were analyzed. From each beat, samples were interpolated on a 1024 point grid. For each point a linear multiple regression was computed to obtain the single aortic waveform from the peripheral one. The ranges of error and relative standard deviations were: range from -20.27±2.82 mmHg to 2.38±16.4 mmHg; mean error 1.16±5.67 mmHg. The most important novelty of this transfer function is that it works in the time domain and not in the frequency domain, as for other transfer functions described in the literature. We have described this in more detail in the main text.

6) The section of the results describing the differences greater than 10 mmHg is confusing and hard to read, I would summarize it more succinctly and create a table (or something else that is easier to interpret).

Answer: We have tried to summarize the first part of the results more clearly, as follows:

“In eight patients, the difference between SAPao and SAPPeripheral was > 10 mmHg; in 4 of these patients, SAPao > SAPPeripheral, while in the remaining 4 patients SAPPeripheral was > SAPao. In 7 measurements (made in 6 patients) the difference between DAPao and DAPPeripheral was > 10 mmHg; in six of these measurements DAPao was > DAPPeripheral.”

For the differences between central and reconstructed pressures, we have now added a Table (new Supplemental Digital Content Table S4) and summarized as follow: “SAPrec
overestimated SAPao by > 10 mmHg in 5 patients and underestimated it by > 10 mmHg in 3 patients. DAPrec underestimated DAPao by > 10 mmHg in 2 patients. MAPrec overestimated MAPao by > 10 mmHg in 1 patient and underestimated it by > 10 mmHg in 2 patients (Supplemental Digital Content Table S4).”

7) Bland Altman analysis could be useful for comparing your peripherally derived aortic pressures to centrally derived

Answer: This is an interesting point. During the preparation of the manuscript, we discussed at length what would be the most suitable statistical approach. Our Statistician commented that: “The Bland Altman (BA) was designed to assess the degree of agreement between two methods that measure the same quantity (the true value) with errors. The aim is to assess the degree of agreement and not to estimate the bias versus the “true value”, which is unknown. When comparing a method giving the true value or a highly accurate method with a new one, BA should be avoided. The question here is not whether the two methods are in agreement but if the new method measure is unbiased. Statistical methods for Calibration are regularly used. In your case, regression analysis could be used.” We therefore used a linear regression analysis. Nevertheless, although we have not reported the classic Bland Altmann plots and the limits of agreement, the differences (“bias”) between the measured and reconstructed pressure values are clearly reported in table 2.

R2#

I appreciate the opportunity to review the manuscript "Estimation of central arterial pressure from the radial artery in patients undergoing invasive neuroradiological procedures". It reports the results of an open, monocentric, observational study which compared the measured central arterial pressure, the measured peripheral arterial pressure and, generated by a pressure recording analytical method (PRAM), the estimated central arterial pressure in 21 patients undergoing invasive neuroradiological procedures. The accurate, non-invasive measurements of peripheral and especially central pressures is clinically highly relevant. Your study is a pragmatic and well-conceived approach to this topic, the manuscript very well scripted and the conclusions substantiated by the results are dissected delicately and put into the context of current literature. I only have some, mainly minor, comments.
Comments:

8) Was the 20G peripheral arterial line inserted just before the procedure or already in place? Could an arterial line placed hours or days before the procedure have affected the quality of the measurements?

Answer: We thank the Reviewer for this important comment. We placed the 20G peripheral arterial line on the day of the procedure. This has been clarified in the methods.

9) Does the current literature give insight how the difference in catheter size could affected the measurements?

Answer: Thanks for this interesting comment. It has been demonstrated that when increasing the internal radius of the catheter, the damping coefficient decreases significantly as it varies inversely to the cube of the radius according to the formula: \( \beta = \frac{4\mu r^3 \rho L}{\pi E^{1/2}} \), where \( \beta \) is the damping coefficient (entity of friction forces), \( \mu \) is the viscosity of the fluid, \( r \) is the internal radius of the catheter, \( \rho \) is the density of the fluid, \( L \) is the length of the catheter, and \( E \) is the elasticity of the system (Romagnoli et al. Critical Care 2014, 18:644. “Accuracy of invasive arterial pressure monitoring in cardiovascular patients: an observational study”). In that study, arterial catheter diameter (20- versus 18 gauge) was one of the five parameters independently associated with underdamping/resonance. The smaller the diameter of the catheter, the greater the damping coefficient of the catheter-transducer system. We have now mentioned this in the revised text.

10) Were patients excluded if they showed exclusion criteria (e.g. arrhythmias) during the measurement? You state that the measurements were collected during periods of hemodynamic stability. You also eliminated values from the average measurements if extrasystolic heart beats affected the blood pressure values. Did you use a predefined cut-off for the number of extrasystoles during the measurement to exclude patients?

Answer: As the reviewer noted, measurements were collected during hemodynamic stability. No hemodynamic instability occurred during data acquisition and there was no need to repeat the measurements. In addition, as reported in the Methods, “blood pressure values affected by extrasystolic heart beats (if any) were excluded from the averages”. We did not use a predefined cut-off of extrasystoles to exclude patients.

11) Was the general anesthesia maintained with Propofol infusion pumps?
Answer: General anesthesia was maintained with Propofol infusion pumps in all patients. This is now stated in the revised text.

12) Repeated measurements were performed in single patients. Did you account for multiple measurements per subject when calculating the mean of the differences with SE and 95%-CI?

Answer: We did not adjust the results for multiple repeated measurements, as only three patients had more than one angiography and more than one data acquisition.

13) You state that the central arterial measurements are exact measurements of the "true" pressure (without intrinsic error), therefore you refrained from performing a Bland-Altmann-Analysis and calculated the correlation coefficient instead. Bland and Altmann state, that the correlation coefficient r measures the strength of a relation between two variables, not the agreement of them (Bland & Altmann, 1986). One may argue, that two methods that were designed to measure the same quantity (pressure) are by definition related. Thus, how much the new method differs from the old one cannot be derived from the correlation coefficient. Did you consider that the central pressure measurements with the established technique in itself are already indirect measurements, transduced into a signal we collect externally of the patients' body? One might argue that the measurements actually display the "true quantity" of the pressure (Bland & Altmann, 1986). Is there more literature to back up the use of the correlation coefficient in comparing PRAM with central arterial pressure measurements instead of using Bland-Altman analyis? (In doubt, a statistical reviewer might need to be consulted).

Answer: This is an interesting point. During the preparation of the manuscript, we discussed at length what would be the most suitable statistical approach. Our Statistician commented that: “The Bland Altman (BA) was designed to assess the degree of agreement between two methods that measure the same quantity (the true value) with errors. The aim is to assess the degree of agreement and not to estimate the bias versus the “true value”, which is unknown. When comparing a method giving the true value or a highly accurate method with a new one, BA should be avoided. The question here is not whether the two methods are in agreement but if the new method measure is unbiased. Statistical methods for Calibration are regularly used. In your case, regression analysis could be used.” We therefore used a linear regression analysis. Nevertheless, we would like to underline that, although we did not report the classic Bland-Altmann plots and agreement limits, the differences ("bias") and standard errors between the measured and reconstructed pressure values are reported in table 2.