Supplemental Material

More Details Can Be Found At: http://www.neurosurg.cam.ac.uk/pages/ICM/about.php

Autoregulation Signal Acquisition and Processing Methods

Transcranial Doppler (TCD) monitoring (DWL, Compumedics DWL, El Paso, TX) of the right and left MCA was performed with two 2.5-MHz transducers fitted on a headband and positioned over the temporal bone windows to obtain bilateral continuous measurement of baseline velocity. Depth of insonation was varied between 35 and 52 mm until representative spectral MCA flow is identified then the transducers are locked in that position. Arterial pressure data (from an indwelling cannula placed for clinical purposes) was obtained from the operating room hemodynamic monitor via the analog output port. The arterial blood pressure data and the TCD signals were sampled at 58 Hz with an analog-to-digital converter and then imported into a laptop computer using ICM+ software (University of Cambridge, Cambridge, UK).[1-7] This proprietary software collects and integrates high resolution, multimodal data for real-time analysis of intracranial pressure, arterial pressure, brain oxygenation, blood flow, and other signals allowing for calculation of various physiological indices include autoregulation metrics (https://www.enterprise.cam.ac.uk/opportunities/icm-software-for-brain-monitoring-in-neurological-intensive-care-research/).

Blood pressure and TCD signals are time-integrated as non-overlapping 10-sec mean values, equivalent to applying a moving average filter with a 10-sec time window and resampling at 0.1 Hz. This operation eliminates high-frequency noise from the respiratory and pulse frequencies, according to the Nyquist theorem, allowing detection of oscillations and transients that occur below 0.05 Hz. A continuous, moving Pearson's correlation

coefficient is calculated between MAP and TCD cerebral blood flow velocity, rendering the variable mean velocity index (Mx). Consecutive, paired, 10-sec averaged values from 300 sec duration are used for each calculation, incorporating 30 data points as we have reported.[8, 9] Mx values for each patient are placed into 5 mmHg MAP bins and displayed on the laptop computer (**Fig 1**). When MAP is within the limits of CBF autoregulation Mx approach zero; when MAP is outside the limits of autoregulation, Mx approaches 1, indicating that CBF is blood pressure dependent.

Based on our prior studies, we designate the LLA as the highest blood pressure associated with Mx $\geq$ 0.4. These values are within the range found to be associated with poor outcome after traumatic brain injury and adverse outcomes after cardiac surgery.[10-13] In about 20% of patients, impaired autoregulation is observed when Mx are $\geq$0.4 at all MAPs during CPB. An attenuated autoregulation plateau is usually observed. Thus, the "optimal" MAP, defined as the MAP with the lowest Mx, as this point is observed in patients with functional and impaired autoregulation. As blood pressure varies during the usual course of surgery, including during the initiation of CPB, no specific interventions are needed to establish autoregulation indices.

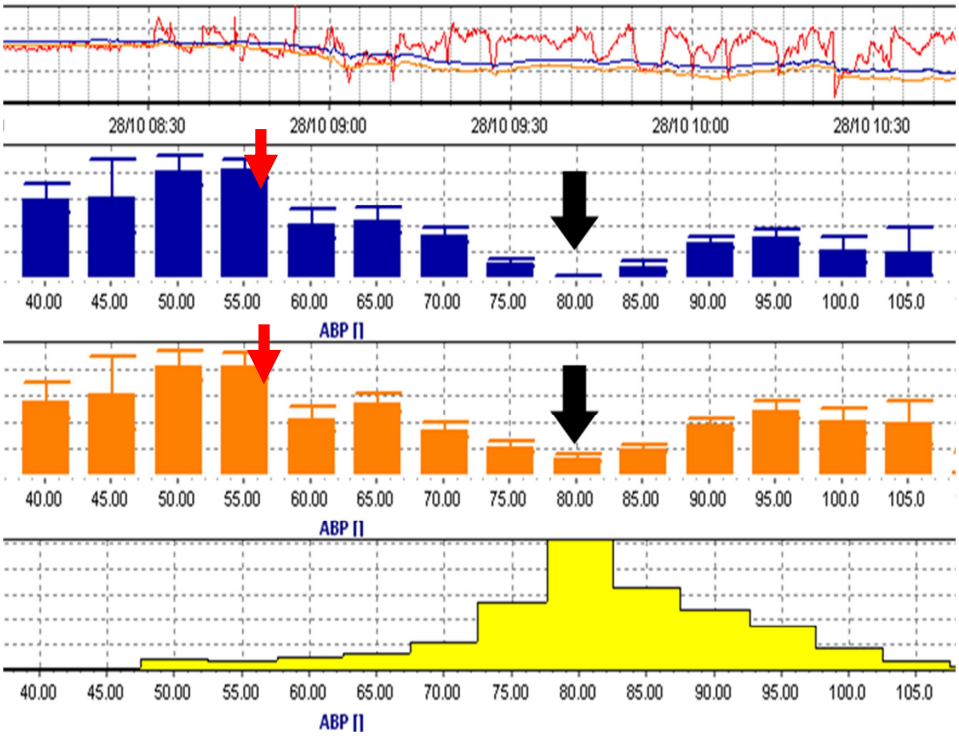

Figure. Graph of autoregulation data obtained in the operating room during cardiopulmonary bypass. The top graph is the time series of blood pressure. The middle two bar graphs represent autoregulation data from the left and right sides, respectively, placed into 5 mmHg arterial blood pressure (ABP) bins. The bottom histogram represents the percentage of the time of the recording spent at each ABP bin. The autoregulation variable is a dimensionless correlation coefficient between cerebral blood flow velocity and ABP, mean velocity index (Mx). An Mx approaching 1 represents impairment of autoregulation while Mx close to zero represents functional autoregulation. The red short arrow represents the lower limit of autoregulation defined in this analysis as that ABP were Mx increases from < 0.4 to ≥ 0.4. The thick black arrow indicates optimal ABP defined as that ABP with the lowest Mx.

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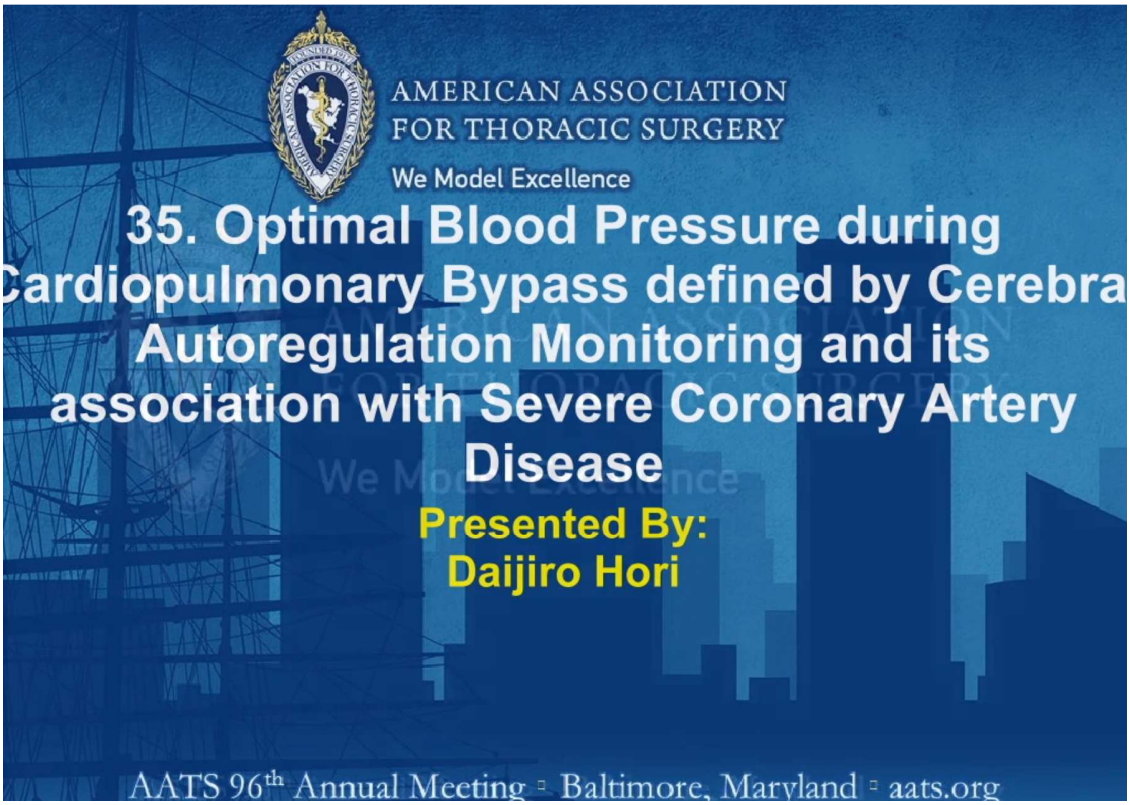
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35. Optimal Blood Pressure during Cardiopulmonary Bypass defined by Cerebral Autoregulation Monitoring and its association with Severe Coronary Artery Disease
Presented By:
Daijiro Hori
AATS 96th Annual Meeting ▫ Baltimore, Maryland ▫ aats.org

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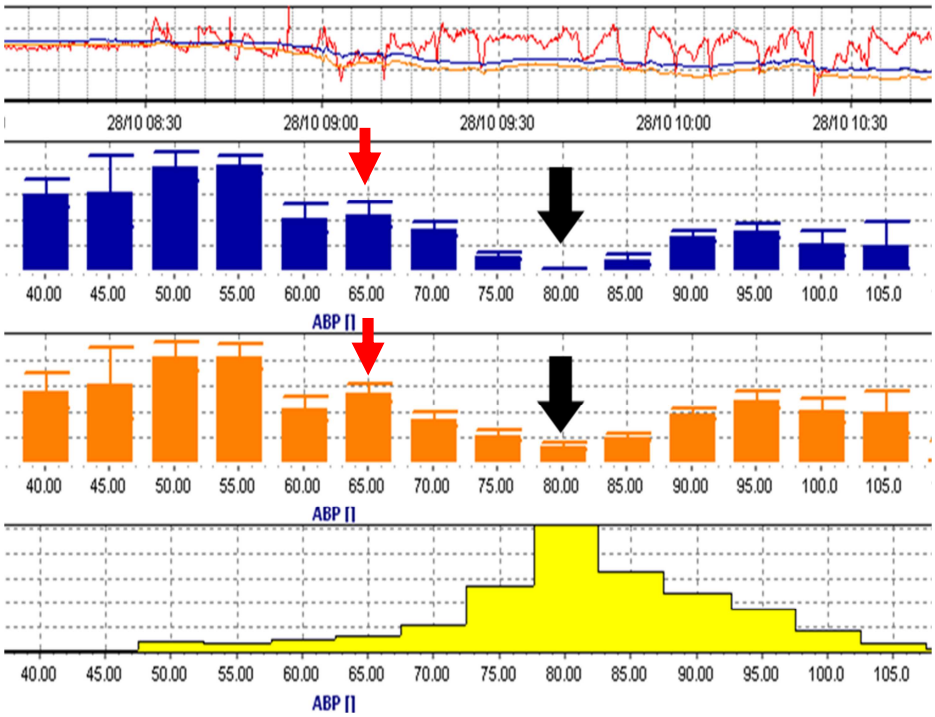

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35. OPTIMAL BLOOD PRESSURE DURING CARDIOPULMONARY BYPASS DEFINED BY CEREBRAL AUTOREGULATION MONITORING AND ITS ASSOCIATION WITH SEVERE CORONARY ARTERY DISEASE. Paper presented by Daijiro Hori, M.D., Baltimore, Maryland.

E-mail: dougskgh05@gmail.com

Discussion by Kenneth G. Shann, CCP, LP, Boston, Massachusetts.

E-mail: kshann@partners.org

Mr. K. Shann (Boston, Massachusetts):

Good afternoon. I would like to begin by thanking the Association for the invitation to be the discussant for this abstract presentation. I'd also like to thank you, Dr. Hori, for allowing me to review your manuscript prior to this session.

I'd also like to congratulate you and your colleagues for a well-designed and well-executed study. Intensive intraoperative cerebral monitoring or brain monitoring in 614 patients is a significant achievement. I'd also like to recognize that this work compliments a very large series of work from the group at Hopkins now focused

on the topic of cerebral autoregulation during cardiopulmonary bypass. This study does importantly highlight the differences in the autoregulation range between patients with coronary artery disease and those without and gives us insight into optimal targets for blood pressure management during cardiopulmonary bypass.

Ten days ago we celebrated the 63rd anniversary of the heart-lung machine, and after all this time we still have very limited data regarding the optimal blood pressure during cardiopulmonary bypass. So this work is also timely with the recent interest in creating strategies for goal-directed therapy for cardiopulmonary bypass.

So I have three questions for you. You've identified optimal blood pressure targets of 80 and 75 for patients with and without coronary artery disease. In addition, your work identified an additional 14% of patients whose lower limit of autoregulation was higher than 75 mmHg.

In some patients we know undergoing cardiopulmonary bypass, it is challenging to maintain empirical target arterial pressures from

our protocols and either elevated flow rates, elevated levels of vasopressors, or perhaps even transfusion is considered if not required.

I noticed in your methods you maintain CPB flow rates at 2.0 to 2.4 liters per minute per meters squared which are pretty consistent with common practice. I did not, however, see any context in your manuscript regarding the use of vasopressors to maintain a patient's pressure within their autoregulation range.

My first question is therefore related to vasopressor use. We know from previous laboratory work that phenylephrine may redirect blood flow away from the bowel and muscle and direct it to the brain and the liver.

In clinical practice, do we know whether strategies to maintain a patient's pressure within cerebral autoregulation range such as using increased pressors will ultimately improve outcome, or is it possible it causes other unwanted complications such as gut ischemia?

35. OPTIMAL BLOOD PRESSURE DURING CARDIOPULMONARY BYPASS DEFINED BY CEREBRAL AUTOREGULATION MONITORING AND ITS ASSOCIATION WITH SEVERE CORONARY ARTERY DISEASE. Response by Daijiro Hori, M.D., Baltimore, Maryland.

DR. HORI: Yes, that is a good question, and thank you for the good point.

We haven't looked at the other organ ischemia, but as I have shown in the previous slide, there is an association between the incidence of AKI and the blood pressure management. In our insititution, majority of the perfusionists change the pump flow first to control the blood pressure. Then, they willuse phenylephrine to control the blood pressure.

Our previous studies have shown that the blood pressures below the optimal mean arterial pressure or that below the low limit of autoregulation were associated with AKI, which means that if the blood pressure is too low, the incidence of AKI would go up. But we didn't look at the dosage of phenylephrine in association with AKI. That is something that we need to look at.

And the studies show that the blood pressures below the optimal mean arterial pressure or below the low limit of autoregulation were associated with AKI, which means that if the blood pressure is too low, the incidence of AKI would go up. But we didn't look at the dosage of phenylephrine in association with an AKI, so that's something that we need to look at.

MR. SHANN: Thank you.

To follow with that question, in 1995 the Cornell group randomized 248 patients undergoing cardiopulmonary bypass to either a blood pressure of 50 to 60 or 80 to 100. They reported improved outcomes in the high pressure group; however, this work received scrutiny in part because of the high stroke rate in the low pressure group of 7.2%.

Other work your group has done, which was referenced your manuscript, to study the association between autoregulation range and outcome has been observational without measurement of interventions. And I just ask you is it time to perform a randomized trial, kind of like the Cornell group did to answer the question do interventions to maintain a patient's pressure

within their autoregulation range during cardiopulmonary bypass improve outcome?

In other words, do we need to do that randomized control trial now using your work as the basis?

DR. HORI: This is another good point, and we are actually doing a randomized trial at Hopkins right now. If the patient is randomized to treatment, we will tell the perfusionist and the anesthesiologist the optimal MAP. They will try to control the pressure at that optimal MAP, and we're going to look at the results

MR. SHANN: Do you have an algorithm for the interventions?

DR. HORI: No. That's one of the limitiations that we have.

MR. SHANN: And then, lastly, the optimal mean arterial pressure targets you have identified will keep approximately 75 to 80% of patients within their autoregulation range which leaves 20 to 25% of patients out of their autoregulation range.

In the current study, you utilized transcranial Doppler combined with mean arterial

pressure put into a data housing unit that calculates a mean velocity index and determines the upper and lower limits of autoregulation. For the majority of us in the room, that's not practical in routine clinical practice.

Your group has also published work using an investigational prototype device that you refer to as the near-infrared spectroscopy cerebral autoregulation monitor, which I don't believe has ever come to market.

You more recently published on the use of an ultrasound tag near-infrared spectroscopy autoregulation monitor that I believe is FDA approved.

So my question is how close are we to having a user friendly and clinically practical technology to monitor cerebral autoregulation during cardiopulmonary bypass?

DR. HORI: Well, I think cerebral oximetry is very easy to use. We just have to put the sensor stickers on your forehead.

If you use the ICM software, all we need to do is just plug in the NIRS signlas into the ICM computer, and it will calculate the cerebral

oximetry index for you. So it's a very easy system to use.

It's not that complicated as I wrote in the manuscript. It's just one laptop and one INVOS, and you will have the data there.

MR. SHANN: So there is an application that --

DR. HORI: So the ICM software just calculates everything for you, right. The software is the most important thing.

MR. SHANN: Thank you very much. Excellent presentation.

35. OPTIMAL BLOOD PRESSURE DURING CARDIOPULMONARY BYPASS DEFINED BY CEREBRAL AUTOREGULATION MONITORING AND ITS ASSOCIATION WITH SEVERE CORONARY ARTERY DISEASE. Paper presented by Daijiro Hori, M.D., Baltimore, Maryland.

E-mail: dougskgh05@gmail.com

Discussion by Gosta B. Pettersson, M.D., Ph.D., Cleveland, Ohio.

E-mail: petterg@ccf.org

Dr. G. Pettersson (Cleveland, Ohio):

This is, of course, a very important topic. How do you distinguish between the global and local cerebral perfusion issues? Do we have any other ways of monitoring whether the brain is adequately perfused and at risk?

What is the “reasonably safe under-perfusion limit”?

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DR. HORI: You mean for the monitoring?

DR. PETTERSSON: How far below the autoregulation limit can you go before you get damage to the brain?

DR. HORI: Well, I'm not really sure about that.We are not sure if there is a cut-off value. But our studies have shown that the magnitude of blood pressure management outside the autoregulation range is positively correlated with incidence of AKI and neurological complications.

DR. PETTERSSON: Is there any way of studying it in advance so we could know?

DR. HORI: Know the limit you mean?

DR. PETTERSSON: So we could know the autoregulation in the individual patient before he goes to the OR.

DR. HORI: Well, it is difficult to predict autoregulation range without monitoring.

To measure cerebral autoregulation using this system, You need data from wide range of blood pressure to draw the cerebral autoregulation curve.

But now, the ICM software can predict the optimal MAP by algorithm. So even if you only have few data, it will be able to draw that cerebral autoregulation curve by algorithm.