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An Illustrated Explanation of the Lower Limit of Cerebral Autoregulation and the Clinical Significance of Its Monitoring during Cardiac Surgery

Benjamin Gavish, PhD [a]; Jochen Steppan [b]

[a] School of Medical Engineering, Afeka Tel-Aviv Academic College of Engineering in Tel Aviv, Israel
[b] Johns Hopkins University, Department of Anesthesiology and Critical Care Medicine, Baltimore, MD, USA

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ABSTRACT

Autoregulation of cerebral blood flow is a vital function that guarantees that cerebral blood flow is being maintained over a wide range of blood pressure values. The matching between cerebral blood flow and the cerebral metabolic requirements involves vasodilation/constriction of the cerebral arterioles in response to decrease/increase of the cerebral perfusion pressure, respectively. The lower limit of cerebral autoregulation is defined as the mean arterial pressure below which cerebral blood flow becomes pressure passive. Keeping blood pressure within the cerebral autoregulatory range for patients undergoing cardiac surgery has been shown to improve postoperative outcomes. The objective of this article is to summarize the results of recent studies that may enable us to estimate the lower limit of cerebral autoregulation to reduce the risk of cerebral hypoperfusion.

Introduction

The brain is the most energy-demanding organ in the body accounting for 20% of the body's resting energy consumption but weighing only 2% of the total body mass.[1] Its function requires high stability under fluctuations in the internal and external environment. More specifically, the insensitivity of cerebral blood flow (CBF) to naturally occurring arterial pressure changes, called 'CBF autoregulation', is a vital function expressed by the observed relationship between CBF and the mean arterial pressure (MAP) depicted in the upper panel of FIGURE 1[2,3]. This relationship includes the desired cerebral autoregulation range, in which CBF is actively controlled and remains relatively stable in a limited range of mean arterial pressure values; a lower-pressure range, in which CBF is reduced passively with further reductions in blood pressure, displaying the so-called 'pressure passivity' and similarly, a higher-pressure range, at which CBF increases passively upon further blood pressure elevation. The matching between CBF and the cerebral metabolic requirements involves vasodilation/constriction of the cerebral arterioles in response to decrease/increase of the cerebral perfusion pressure, respectively. This process, which is mediated by changes in the tone of the arteriolar smooth muscles, is referred to as cerebral pressure autoregulation.[4-9]

The 'lower limit of cerebral autoregulation' marks the mean arterial pressure value at the borderline between the lower-pressure passive and autoregulated ranges, as depicted in the lower panel of FIGURE 1. Quantitatively, starting with mean arterial pressure at the lower-pressure passive range, lower limit of cerebral autoregulation is defined as the mean arterial pressure value above which the Pearson correlation coefficient between CBF and mean arterial pressure change drops below a pre-selected value. It is important to mention that cerebral autoregulation is effective for slow enough variations in mean arterial pressure, typically over the frequency range 0.05 Hz to 0.003 Hz,[9,10] which leads to the 'static view' of cerebral autoregulation presented in FIGURE 1.

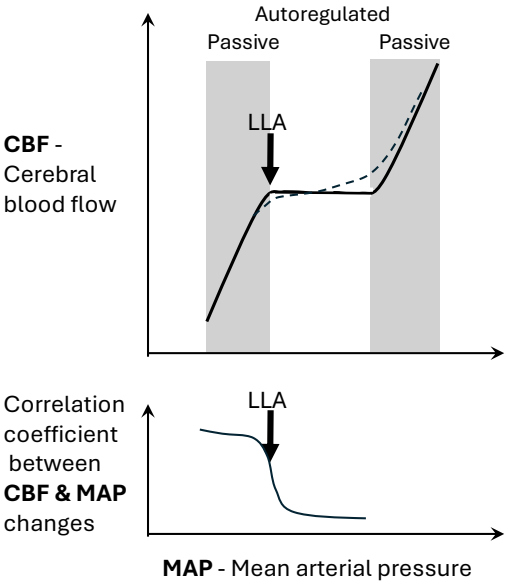

FIGURE 1. The upper panel depicts schematically the 'static autoregulation' of the relationship between slow variations in cerebral blood flow (CBF), and mean arterial pressure (MAP), as proposed (thick line),[2] and as observed (dashed line).[9] The lower panel shows the corresponding correlation between changes in the CBF and MAP, which is high in the Passive range, but low in the Autoregulated range, where the border between these regions is the lower limit of cerebral autoregulation (LLA).

Keeping mean arterial pressure within the cerebral autoregulatory range for patients undergoing cardiac surgery is most important in the perioperative setting. It appears that during cardiopulmonary bypass the duration and magnitude of mean arterial pressure values below the cerebral autoregulatory range are associated with major morbidity and operative mortality.[11] The problem of high blood pressures that may result in cerebral edema[12] is beyond the scope of this paper.

What is the clinical problem?

We traditionally have assumed a lower limit of cerebral autoregulation of 50mmHg and an upper limit of 150 mmHg for mean arterial pressure. However, more recent studies have questioned this traditional view of the autoregulatory range.[13] Since CBF autoregulation is functional during cardiopulmonary bypass, mean arterial pressure targets of 50 to 60 mmHg have been empirically chosen and are modified depending on patient age, preoperative blood pressure, or medical history.[13,14,15] One out of many reasons for the variability in the limits of the normal CBF autoregulation range is surgical patients having cerebral vascular disease that may, predispose them to cerebral ischemic injury.[12,16,17]

The lower limit of cerebral autoregulation of individual patients measured during surgery and anesthesia varies over the range of 40 to 90 mmHg.[18] These findings

question the validity of the said assumed mean arterial pressure target, and strongly suggest measuring or estimating the lower limit of cerebral autoregulation during cardiopulmonary bypass. Thus, success in selecting mean arterial pressure targets, to be within a patient's individual autoregulatory range, might prevent cerebral hypoperfusion.[12] However, measuring the lower limit of cerebral autoregulation requires special equipment, which is likely to decrease the applicability of such measurement, despite its clinical significance.[19,20]

The objective of this article is to summarize the results of recent studies that may enable us to estimate the lower limit of cerebral autoregulation and use indications for when the mean arterial blood pressure is below the lower limit of cerebral autoregulation and when it is above it during cardiac surgery for reducing the risk of cerebral hypoperfusion.

How to determine the lower limit of cerebral autoregulation?

The lower limit of cerebral autoregulation was determined by Bradly et al,[12] and by Joshi et al,[18] using CBF velocity measured by transcranial Doppler monitoring of the right and left middle cerebral artery simultaneously with direct continuous radial artery monitoring of arterial pressure, and near-infrared spectroscopy (NIRS) via self-adhesive sensors placed on the right and left forehead. Analysis included the following steps: 1) filtering out frequencies greater than 0.04-0.05 Hz and below 0.003 Hz that are used to improve the signal-to-noise ratio and are believed to represent autoregulatory compensations to slow hemodynamic oscillations.[21-23] 2) calculating consecutive and paired 10-second averaged values of filtered arterial pressure to obtain the mean arterial pressure, CBF velocity and NIRS values at 30 time points over a moving time window of 300 sec. 3) calculating the Pearson correlation coefficient (R) between mean arterial pressure and CBF velocity or NIRS at those time points. 4) Attributing $R \geq R_0$ to pressure passivity and $R < R_0$ to autoregulation and defining lower limit of cerebral autoregulation as the mean arterial pressure value, at which R changes from $R < R_0$ to $R \geq R_0$ at the next time point (FIGURE 1, lower panel). Brady et al selected $R_0=0.45$,[12] while Joshi et al selected $R_0 = 0.40$,[18] and obtained comparable results using CBF or NIRS supporting the similarity between CBF and blood oxygenation regarding cerebral autoregulation.

How to estimate the lower limit of cerebral autoregulation?

The simplest association between the lower limit of cerebral autoregulation (LLA) and a Predictor can be expressed by the regression model $LLA = \alpha+\beta\cdot[Predictor]$ where α & β are adjustable parameters determined from the measured lower limit of cerebral autoregulation and the Predictor values for the patients' population by univariate regression analysis. Given a Predictor value the estimated lower limit of cerebral autoregulation ('est_LLA') is given by $est\_LLA = \alpha+\beta\cdot[Predictor]$, which is the so-called 'regression line'. This estimation is meaningful if the Pearson correlation coefficient R between the lower limit of cerebral autoregulation and the Predictor is statistically significant (FIGURE 2A).

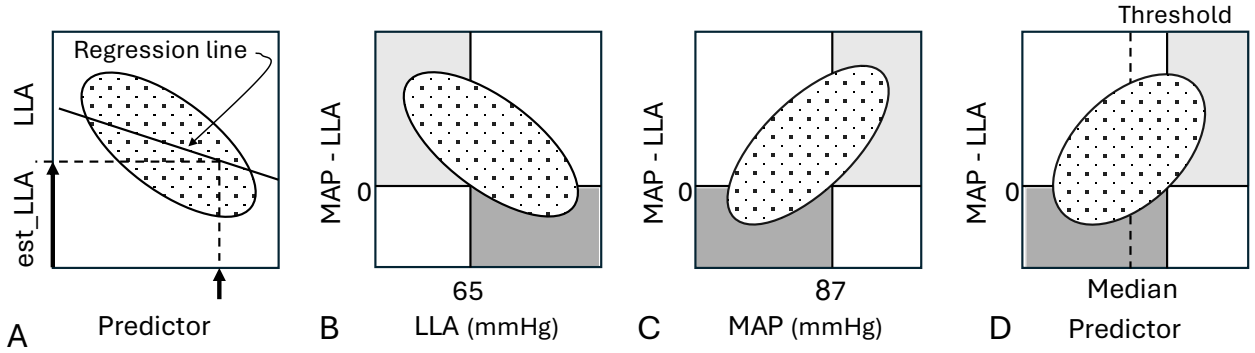

FIGURE 2. Estimation of the lower limit of cerebral autoregulation (LLA) and Threshold-based indications: The ellipses represent regions containing patients' data. A) Shows the estimated LLA (est_LLA) by a Predictor using univariate analysis, with a regression line of $LLA = \alpha+\beta\cdot[Predictor]$. Using published data,[24,25] no cases of MAP<LLA were found for LLA<65 mmHg in (B), MAP>87 mmHg in (C), and Predictor > Threshold in (D). A Predictors' Median (marked) is used for calculating the odds ratio (OR) of getting MAP<LLA. See TABLE 1 for R, α & β, Threshold, Median and OR per Predictor.

Obata et al,[24] investigated the lower limit of cerebral autoregulation association with a Predictor called 'ambulatory arterial stiffness index' (AASI). AASI was originally calculated from 24-hour ambulatory systolic blood pressure and diastolic blood pressure measurements,[26] and was demonstrated to be a predictor of cardiovascular mortality.[27] The AASI is defined as 1 minus the regression slope of diastolic over systolic blood pressure readings (FIGURE 3). Analytic derivation of the Regression Slope shows that it equals

Rds·[Symmetric Slope], where Rds is the Pearson correlation coefficient between diastolic blood pressure (DBP) and systolic blood pressure (SBP) readings, and the 'Symmetric Slope' is the Slope of the dashed line given by SD(DBP)/SD(SBP).[29,30] The Symmetric Slope best fits the slope of a linear relationship between diastolic and systolic blood pressure,[30] and was shown to be an arterial property, as its reciprocal value expresses the pressure dependence of the arterial stiffness ('stiffening'). [31,32] Obata et al determined AASI from intraoperative continuous blood pressure readings measured directly from the radial artery before the initiation of cardiopulmonary bypass,[24] while Zhang et al used it during non-cardiac surgery. [28] Hereafter, we will replace AASI with 1-AASI to achieve a negative correlation with the lower limit of cerebral autoregulation.

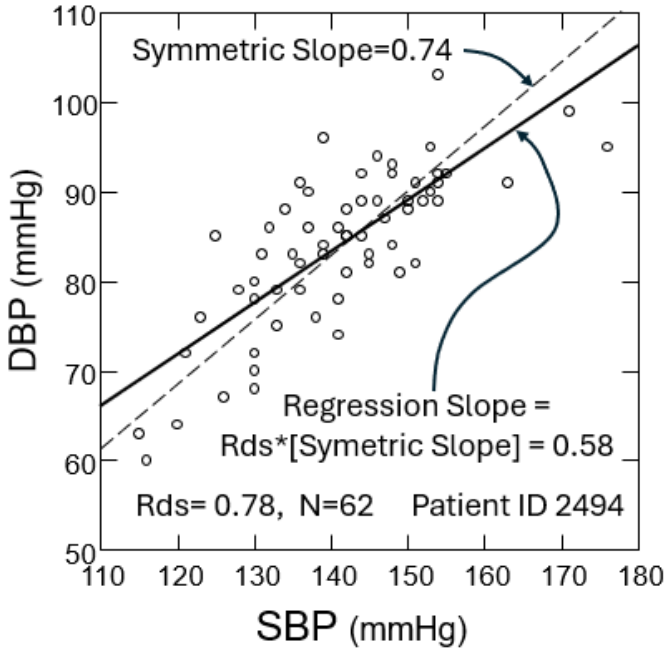

FIGURE 3. An example of determining the ambulatory arterial stiffness index (AASI) from 24-hour ambulatory blood pressure readings.[29] The slope of the full line is determined by a regression analysis of diastolic (DBP) versus systolic blood (SBP) pressure readings ('Regression Slope'). AASI is defined as 1 minus the Regression Slope.[26] The dashed line best fits the SBP-DBP linear relationship. An expression for its slope ('Symmetric Slope') is given in the text.

In addition to AASI, independent Predictors associated with the lower limit of cerebral autoregulation in a statistically significant way were recently found by Gavish et al,[25] using the data of 181 patients, who received routine intraoperative care, reported by Obata et al .[24] These Predictors included the systolic blood pressure (SBP) coefficient of variation (SBP_cv) defined as SD(SBP)/(average SBP), where SD(SBP) is the systolic blood pressure variability (SD stands for standard deviation); body mass index (BMI), and the composite multiplicative Predictor MULT=BMI·(1-AASI) ·SBP_cv was investigated, as well. Results showed that *all* Predictors were *negatively* correlated with the measured lower limit of cerebral autoregulation (FIGURE 2A). Given a Predictor value the estimated lower limit of cerebral autoregulation ('est_LLA') was expressed by the regression line est_LLA = α +β·[Predictor] where α & β were determined for each Predictor by univariate analysis and reported in TABLE 1 together with additional properties.[25] A comparison between the measured lower limit of cerebral autoregulation ('LLA') and est_LLA demonstrated that for both the single & composite LLA Predictors the est_LLA fell within ±10 mmHg of the measured lower limit of cerebral autoregulation in 50%-55% of cases,[25] while the percentage of cases, for which est_LLA deviated from lower limit of cerebral autoregulation by over 15 was smaller for the composite multiplicative Predictor (MULT) than for the single Predictors.

Predictor	R	α (mmHg)	β[a]	Median	Threshold	OR
1-AASI	-0.26	77.5	-31.2	0.42	0.59	2.14
SBP_cv	-0.26	78.4	-84.9	0.16	0.24	2.59
BMI (kg/m²)	-0.27	81.5	-0.59	28.9	37.3	3.49
MULT (kg/m²)	-0.41	76.1	-5.6	1.95	2.75	6.1

TABLE 1. Properties of the Predictors of the lower limit of cerebral autoregulation (LLA) and parameters used in the univariate regression model LLA=α + β·[Predictor] as reported by Gavish et al.[25] R is the Pearson correlation coefficient between the LLA and a Predictor. The Predictor Threshold is the highest value of a Predictor for which the mean arterial blood pressure is below the lower limit of cerebral autoregulation. OR is the odds ratio (see text). The units for β are mmHg·m²/kg for BMI and MULT, and mmHg for 1-AASI and SBP_cv. The P_value for α & β values was <0.001.

Determining if mean arterial pressure is lower or higher than the measured lower limit of cerebral autoregulation

This is the main goal of attempting to reduce the risk associated with exposing the patient to a mean arterial pressure below the lower limit of cerebral autoregulation (as measured prior to cardiopulmonary bypass). As the lower limit of cerebral autoregulation is not routinely measured during cardiac surgery, getting more indications to whether the mean arterial pressure is below the lower limit of cerebral autoregulation or above it in a subpopulation by using the lower limit of cerebral autoregulation Predictors is clinically significant.

USING A REFERENCE VALUE OF MEAN ARTERIAL PRESSURE OR LOWER LIMIT OF CEREBRAL AUTOREGULATION

The previous study demonstrated that a mean arterial pressure below the lower limit of cerebral autoregulation did not occur in 48% of patients having a lower limit of cerebral autoregulation of less than 65 mmHg but did occur in the rest of patients with a lower limit of cerebral autoregulation of 65 mmHg or above (Figure 2B).[25] However, this indication requires measuring the lower limit of cerebral autoregulation. Furthermore, a mean arterial pressure below the lower limit of cerebral autoregulation did not occur in 8.8% of patients having a mean arterial pressure of at least 87 mmHg but did occur for the rest of patients with a mean arterial blood pressure below 87 mmHg (Figure 2C).

USING ESTIMATED LOWER LIMIT OF CEREBRAL AUTOREGULATION

An indication for a mean arterial pressure lower than the lower limit of cerebral autoregulation is the sign of the difference between mean arterial pressure and estimated lower limit of cerebral autoregulation (est_LLA), where est_LLA is calculated for different Predictors, as described in the previous section. It is likely that the chance for correctly identifying the occurrence of a mean arterial blood pressure below the lower limit of cerebral autoregulation is greater if the difference between the mean arterial blood pressure and the estimated lower limit of cerebral autoregulation (est_LLA) is negative for a larger number of Predictors.

USING THE PREDICTOR THRESHOLD

Figure 2D depicts schematically the finding that each of the lower limit of cerebral autoregulation Predictors had a threshold level ('Threshold') above which a mean arterial blood pressures below the lower limit of cerebral autoregulation did not occur, but it did occur in the rest of patients with Predictor<Threshold. [25] It is noteworthy that the patients for whom this did not occur may be different when using different Predictors. In fact, in 26.5% of patients at least one Predictor exceeded its Threshold level, indicating that these patients were in the "safer" region, where the mean arterial pressure was equal or larger than the lower limit of cerebral autoregulation.

USING PREDICTOR-BASED ODDS RATIO (OR)

Using the Median of a Predictor (Figure 2D) we define a dichotomized outcome equals 1 for when the mean arterial pressure is below the lower limit of cerebral autoregulation (undesired) and 0 for if is equal or larger than the lower limit of cerebral autoregulation (desired, if the mean arterial pressure is not too high). Furthermore, we define a dichotomized Predictor equals 1 for Predictor<Median ('exposed'), i.e. subject to risk, and 0 for Predictor≥Median ('unexposed'), i.e. not at risk. The OR expresses the ratio between the number of patients with a mean arterial pressure below the lower limit of cerebral autoregulation, for whom Predictor<Median, and those with a mean arterial pressure below the lower limit of cerebral autoregulation for whom Predictor≥Median calculated using logistic regression. The OR of the present predictors (TABLE 1) suggests that the last Predictor is about twice more sensitive than the other ones in evaluating the occurrence of a mean arterial pressure below the lower limit of cerebral autoregulation. Adjusting the OR to baseline characteristics provided comparable results.[25]

Conclusions

The estimation of the lower limit of cerebral autoregulation from routine perioperative data in cardiac surgery of an individual prior to the cardiopulmonary bypass, and the use of the suggested indications for increasing the chance of finding when mean arterial pressure is below or above the lower limit of cerebral autoregulation may be helpful in selecting perioperative management strategies that may keep blood pressure in the cerebral autoregulation range during cardiopulmonary bypass without directly measuring the lower limit of cerebral autoregulation. However, it is not unlikely that the numerical values given here for the Predictors (Median, Threshold, etc.) and their association with the lower limit of cerebral autoregulation may vary with the population characteristics and the perioperative management. This suggests that routine accumulation of said Predictors and the occurrence of undesired outcomes that could be attributed to a mean arterial pressure below the lower limit of cerebral autoregulation might be clinically valuable.

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