Development of Dynamic Real-Time Robust Multivariable Monitoring Tool for Neonatology Data

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Abstract

As real-time monitoring of salient variables has become increasingly important in many realms of statistics, use has not reached its full implementation in neonatal data. Premature infants constitute a population in which monitoring particular associations between certain variables serves a preventative need. Using R, we have developed a demonstration of how three crucial variables may be modeled through a real-time monitoring algorithm to produce the autoregulation index, a statistic which displays a vital physiologic status. Not only may the successful implementation of this tool save costs in the medical and health arenas, but it has potential for great flexibility. Any relationship in life that requires instantaneous measurement of association between two continuous variables at given levels of a third categorical variable can be computed through this model. Due to its utilization through R's open-source nature, the tool may pervade areas where real-time monitoring using more expensive and established software deems implementation uneconomical.

Key Words: Loess Regression, Dynamic Graphics, Real-Time Analysis, R, Multivariable Analysis, Autoregulation Index

1. INTRODUCTION

Humans possess intrinsic physiologic mechanisms to help curtail overreactions to external stimuli, such as cerebral autoregulation, where perfusion to the brain remains constant despite changes in blood pressure. Since constant flow to the brain is critical for health and survival, intact cerebral autoregulation is necessary. [2]

Cerebral blood flow (CBF) is maintained within narrow limits in healthy humans. Both decreased and increased CBF can be injurious to the brain.

With impaired autoregulation, CBF does not stay constant during blood pressure fluctuations; with intact autoregulation, the body maintains constant CBF despite large changes in blood pressure. [2,6,12]

Very low birth weight (VLBW, birth weight less than or equal to 1500 grams) infants often require mechanical ventilation for treatment of respiratory distress syndrome. Since fluctuations of blood pressure are common in ventilated VLBW infants, those with impaired autoregulation may experience large variations in CBF that may be associated with brain injury and subsequent neurodevelopmental disability. [3,4,5]

Disturbances of CBF coupled with impaired cerebral autoregulation are undesirable in VLBW infants due to their association with the development of IVH. [8] This is because premature infants are more vulnerable to hemorrhagic and ischemic brain injury due to fragile immature blood vessels. [2,12] This is a very important problem for VLBW infants and may result in long-term neurodevelopmental disabilities including mental retardation, seizures, periventricular leukomalacia (PVL), and cerebral palsy. [4,8] Altered autonomic function has

been shown by heart rate variability analysis, the beat-to-beat fluctuation of heart rate, and reveals the balance between parasympathetic and sympathetic impulses to the heart that is under central nervous system control. It is believed that this dysfunction occurs before the development of IVH in VLBW infants. [8]

This neonatal predicament has served as a costly one in the administration of healthcare as well as in indirect costs of infants growing into adulthood with neurodevelopmental disorders. This poses a significant public health problem since there has been a lag in improvement of accurate prediction methodologies of impending IVH. [2,8] A demand exists in this field for technology that may allow clinicians to identify VLBW infants at highest risk before they actually develop it. [8] Therefore, clinicians could initiate the necessary prophylactic measures to high-risk infants, reduce the prevalence of IVH, and allow many of these infants to grow into mentally healthy adults.

2. BACKGROUND

It has been hypothesized that controlling perfusion pressure per se may result in a healthy maintenance of CBF, such as preventing hypotension or hypertension. In fact, hypotension and its treatment are common among premature infants. [7] However, hypotensive VLBW infants have been observed to have similar baseline mCBFv to normotensive infants. [7] Other studies, however, have reported lower CBF in hypotensive vs. normotensive VLBW infants. In addition, treatment of hypotension has been associated with IVH, neurodevelopmental disorders, deafness, and death. [7] Therefore, contrary to the perceived benefit of intervention, these procedures may actually increase risks for developing IVH and associated disorders.

Those who have postulated cerebral autoregulatory status in VLBW infants by the relationship between CBF and MABP alone have failed to account for a very important modifier, $PaCO_2$. [4] Hypercapnia (extremely high $PaCO_2$) causes increased vasodilation of the cerebral resistance arterioles, increases CBF in premature infants, may contribute to the development of IVH, and has been associated with impaired cerebral autoregulation in animals. [4] As carbon dioxide is a potent mediator of cerebral vascular tone, increasing levels of $PaCO_2$ are associated with progressive impairment of cerebral autoregulation in premature infants. [4]

Studies have actually shown CBF to be independent of MABP, while $PaCO_2$ was shown to be a statistically significant predictor of CBF. [12] For example, Kaiser et al. [5] were able to demonstrate with a regression model that mCBFv increased by 2.9 cm/s for every 10 mm Hg increase in $PaCO_2$, representing a 15-25% increase in mCBFv.PaCO2 had the only statistically significant coefficient in the logistic regression equation (Table 1). Figure 1 supports this by showing how $PaCO_2$ has a similar pattern to mCBFv following tracheal suctioning.

Table 1. Predictors of mCBFv following tracheal suctioning.

Variables	Coefficients	s.e.	95% CI	*p*-value
Intercept	-10.3	6.88	(-24.1, 3.38)	0.137
$PaCO_2$	0.290	0.050	(0.191, 0.389)	***<0.001***
PaO_2	0.034	0.023	(-0.012, 0.080)	0.148
MABP	0.056	0.071	(-0.085, 0.196)	.434
Estimated gestational age	0.377	0.230	(-0.082, 0.837)	0.106
Day of life	0.258	0.221	(-0.180, 0.696)	0.246

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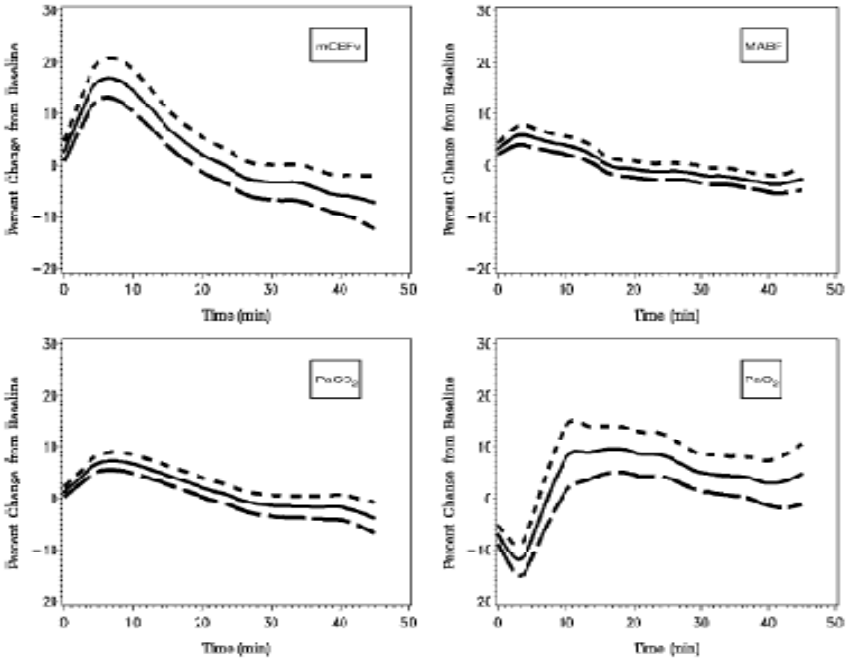
Figure 1. Relative changes of mCBFv, $PaCO_2$, MABP, and PaO_2 following tracheal suctioning.



Reproduced with permission from Kaiser et al. [5]

In another logistic regression model, Kaiser et al. [3] were again able to show a strong relationship between $PaCO_2$ and mCBFv ($OR = 107.3$, $p<.0001$), while a less significant one was found between MABP and mCBFv ($OR = 6.7$, $p = .047$). In addition, the same study revealed the relationship between mCBFv and all the directional combinations of $PaCO_2$ and MABP (Table 2).

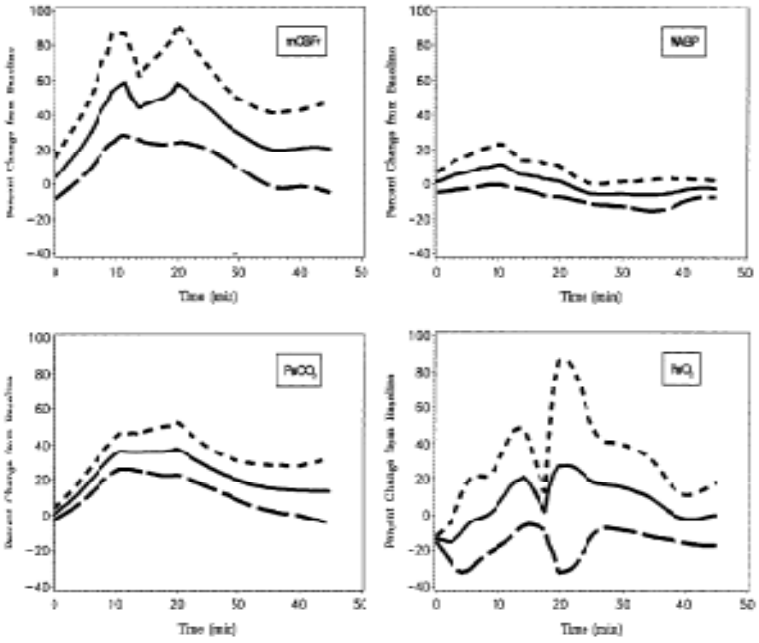
Table 2. Point estimates and 95% confidence intervals for probability of an increase in the mean of mCBFv for given changes in the means of $PaCO_2$ and MABP

Change in the mean of $PaCO_2$	Change in the mean of MABP	Point estimate	95% CI
Decrease	Decrease	0.03	(0.01, 0.12)
Decrease	Increase	0.17	(0.07, 0.34)
Increase	Decrease	0.76	(0.50, 0.91)
Increase	Increase	0.96	(0.82, 0.99)

Reproduced with permission from Kaiser et al. [3]

The important take-home message from Table 2 is the "increase, decrease" combination between $PaCO_2$ and MABP, respectively, and the "decrease, increase" combination. In regards to the former, the point estimate for the probability of an increase in mCBFv is more than four times that for the latter. It is quite intuitive that if both variables increase then mCBFv will increase with certainty, whereas the situation is confidently null when both variables decrease. This data serves as supplemental evidence that MABP alone is not an adequate surrogate for mCBFv. As well, this study produced similar graphic trends to those from Kaiser et al. [5] that support $PaCO_2$ was closely associated with mCBFv (Figure 2).

Figure 2. Relative changes of mCBFv, $PaCO_2$, MABP, and after surfactant administration.



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Therefore, it is very important to take into account other variables when measuring mCBFv as a risk factor for brain damage in VLBW infants. The important variable for this concern is $PaCO_2$. The relationship between mCBFv and MABP is dependent upon $PaCO_2$ level, which may exacerbate the problem of autoregulation impairment. Hypercapnia ($PaCO_2$> 55 mm Hg) in VLBW infants has been associated with impaired cerebral autoregulation, while hypocapnia(< 35 mm Hg) and normocapnia (35-45 mm Hg) have been associated with intact autoregulation. As well, another study found infants with the highest $PaCO_2$ to have the highest incidence of IVH. [4]

Kaiser et al. [4] revealed that the slope of the autoregulatory plateau increased as $PaCO_2$ increased ($p = 0.004$). Means were estimated for the slope with $PaCO_2$ fixed at 30, 35, 40, 45, 50, 55, and 60 mm Hg. A slope at or close to zero indicated intact autoregulation, while a slope increasing greater than zero implied progressively impaired autoregulation (Figure 3).Estimated mean slopes at $PaCO_2$ values of 30, 35, and 40 mm Hg were not significantly greater than zero, while those for values ≥ 45 mm Hg revealed a progressive loss of autoregulatory function (Figure 4). Thus, cerebral circulation becomes progressively pressure passive with hypercapnia, and increasing autoregulatory slopes may be associated with impaired autoregulation. [4]

Figure 3. Slope of autoregulatory plateau at different $PaCO_2$ partial pressures (mm Hg)

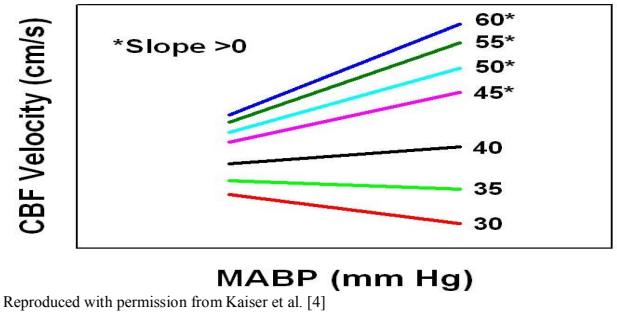

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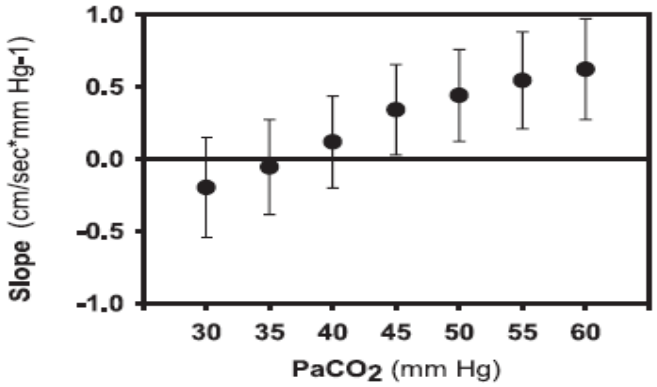
Figure 4. Estimated means with 95% CI of autoregulatory plateau slopes at different $PaCO_2$ values.



Reproduced with permission from Kaiser et al. [4]

This poses a quandary because aggravations of $PaCO_2$and other modifying or confounding variables are very often unavoidable during necessary routine procedures performed as needed on ventilated infants. In particular, three crucial procedures include permissive hypercapnia, surfactant administration, and tracheal suctioning.

Permissive hypercapnia is a widely used ventilator strategy where neonatologists allow $PaCO_2$ (45-55 mm Hg) to increase in order to minimize ventilator-induced lung damage in ventilated VLBW infants. [4] This has elicited concern in many neonatologists as the risk of impaired autoregulation and vulnerability to brain injury will consequently be escalated during the first week of life.

Exogenous surfactant is administered to VLBW infants to treat respiratory distress syndrome. [3] Unfortunately, surfactant administration is associated with transient disturbances of systemic hemodynamics and gas exchange that result in hypotension, oxygen desaturation, hypoxia, and hypercapnia. The ensuing increases in mCBFv are primarily caused by increases in $PaCO_2$, with MABP fluctuations having a lesser impact. This reiterates that MABP alone should not be used as a proxy for mCBFv. Thus, surfactant administration poses another threat of impaired regulatory function and resultant brain damage. [3]

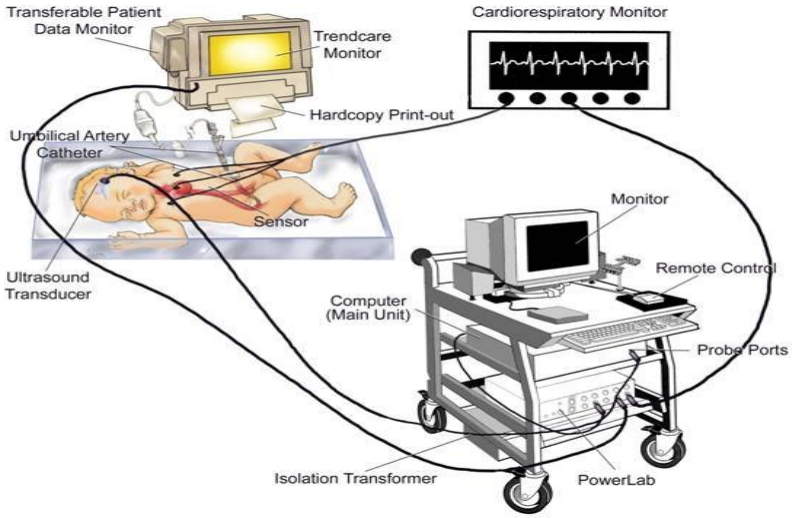
Tracheal suctioning is routinely used to clear tracheobronchial airways of secretions. [5] It is associated with elevated BP, bradycardia, hypoxemia, arterial desaturation, hypercapnia, and increased ICP. Hence, this routine acts very similar to surfactant therapy in threatening hemodynamics with $PaCO_2$being the main culprit.

While these procedures involve undesirable side effects, there is some upside to their use. They serve as good provocative tests of autoregulatory function because they disturb gas exchange and CBF. [3,4] Typical drug injections used to induce hypercapnia in adults can be extremely detrimental in premature infants. Therefore, these bedside procedures are one of the only chances neonatologists have to monitor the effects of hypercapnia on autoregulatory capacity and were essential in producing the relationships seen in Figures 1, 2, 3, and 4.

However informative these procedures may be, due to their deleterious side effects they are standardized, performed only when clinically indicated, and never routinely scheduled. [4] As well, crucial as it is to avoid hypercapnia in preventing adverse brain damage, clinicians also want to avoid the lower danger zone, hypocapnia. In fact, low ABP has been associated with impaired autoregulation. [2] This may cause PVL, IVH, cerebral palsy, decreased CBF, and decreased oxygen delivery. Therefore, the desire of neonatal clinicians to control $PaCO_2$ during the first week of life may best be fulfilled by preventing hypercapnia and hypocapnia simultaneously. An identified goal has been to use a real-time monitoring system to restore intact autoregulation and prevent initiation or extension of IVH and PVL. [4]

A proposed bedside system, the Real-Time Autoregulation Diagnostic (RAD), would work by feeding clinical variables into a bedside monitor that sends the data through a statistical modeling algorithm. It then "spits out" a graphic depicting an infant's autoregulation status (Figure 5). Hence, clinicians can be supplied with immediate information to determine whether to initiate or terminate routine interventions to prevent imminent risk factors for brain damage.

Figure 5. RAD system schematic.



Reproduced with permission from Williams & Kaiser [11]

Therefore, variables such as mCBFv, MABP, and $PaCO_2$ can be collected and fed straight into the trendcare monitor that bypasses a data storage system. Statistical models can be immediately fit to the data and displayed instantaneously on the screen with the only lag being the computer's speed at processing the data. [11]

3. METHODS

Input, analysis, and manipulation of data were performed using **R** Commander® V2.11.0. [1,9,10] Development of the ARI code (Appendix) involved several key steps.

The **R** program imports the dataset containing the key variables: mCBFv, MABP, PaCO2, and Session number.

Now that only key variables were included, it was desirable to create a new variable, PaCO2 Level, from the variable PaCO2. This was done by cutting PaCO2 values into four levels (<35, 35-44, 45-55, and >55 mm Hg) and converting these four zones, respectively, into the categorical variables "hypocapnic", "normal", "moderately hypercapnic", and "extremely hypercapnic".

Then, variables needed to be created for ΔmCBFv and ΔMABP. This was done using a lag function in **R** with an arbitrary increment value of 10. Therefore, in order for the whole code to work, the first 10 observations of the dataset had to be removed prior to creation of the Δ variables. The next step was the arbitrary selection of session 29 alone from the dataset to demonstrate the ARI for one kid session. The upper and lower autoregulation bounds for ΔmCBFv were arbitrarily set at 2 and -2. Functions to calculate current ARI for $PaCO_2$ levelsof "hypocapnic", "normal", "moderately hypercapnic", and "extremely hypercapnic", were set up, respectively, using the following code. The actual moving ARI could then be produced by running a loop including these functions.

4. RESULTS

The ARI serves as a real-time diagnostic tool that can be utilized by neonatologists and other bedside practitioners to ascertain autoregulation status of an infant instantaneously. The ARI finds its "niche" in the RAD system as the trendcare monitor (Figure 8). The glory of the ARI is its ability to incorporate three variables at once in calculating autoregulation status.

The main relationship that was modeled in this project was the dependent variable ΔmCBFv modeled against the independent variable ΔMABP, taking into account the effect modifier, $PaCO_2$ level. The clinician can take advantage of the great flexibility of the ARI by setting arbitrary lag values for ΔmCBFv and ΔMABP, bounds for ΔmCBFv in calculating the ARI, and a window value for the real-time moving index. In this demonstration, lag was set as the difference between every 10^{th} observation of both ΔmCBFv and ΔMABP, ARI bounds were defined as ΔmCBFv of 2 and -2, and the window was set as the current instantaneous 100 observations.

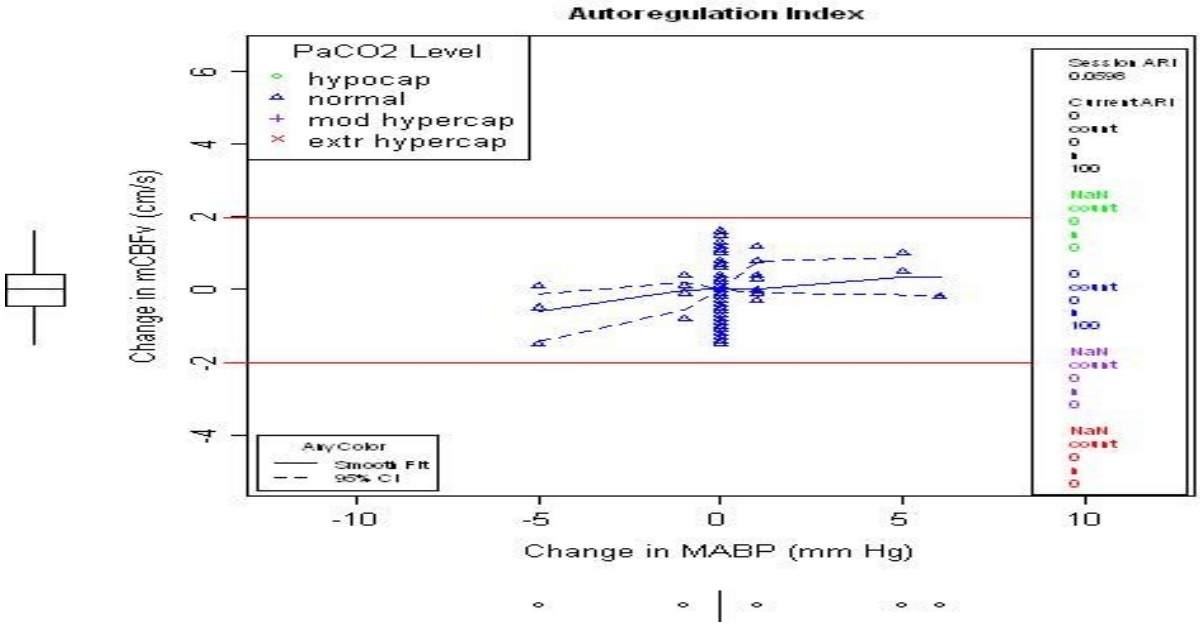
The crude ARI is the proportion of total observations falling above the upper bound or below the lower bound and can be defined by

$$\frac{n < l \mid n > u}{n}$$

where n is the total number of observations, l is the lower bound, u is the upper bound, and | stands for "or". The crude current ARI is the crude ARI of only the observations in the streaming window. Therefore, the denominator in the equation will always be the same, and the numerator will depend on the proportion falling out-of-bounds at any given moment.

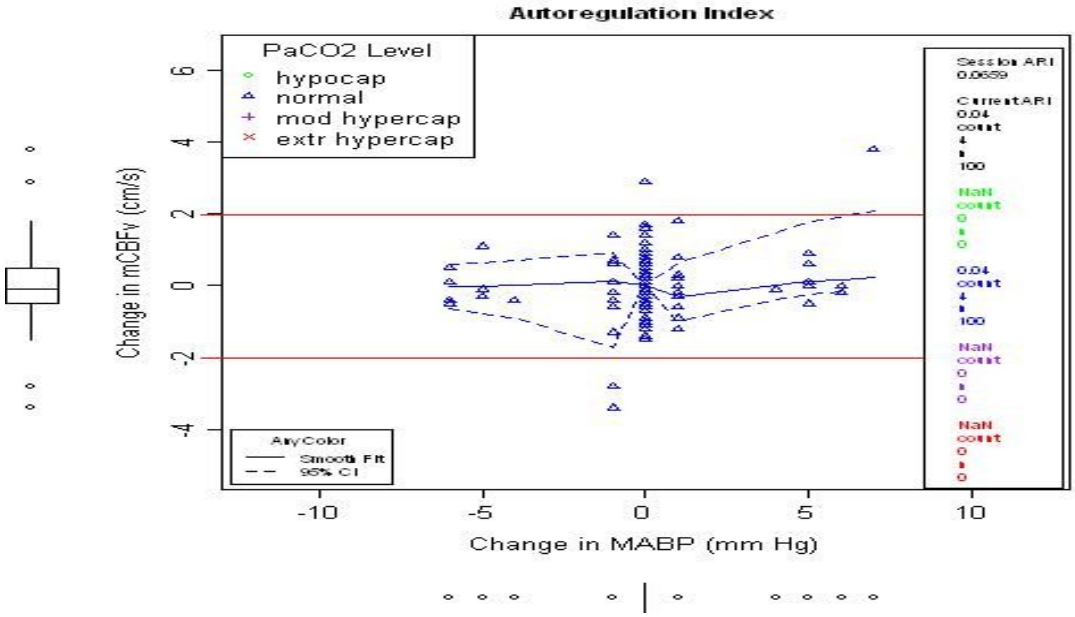
Also included is a current ARI calculation for every level of the modifier. Therefore, this will be the same as the crude current ARI only for observations meeting the given modifier level. Hence, the denominator of this statistic can take on values anywhere between zero and the window value, inclusive. Following this logic, the denominators of the current ARIs for every given modifier level will add up to the denominator of the crude current ARI; this may take on several different scenarios. For example, at any given moment the infant may be autoregulating (no values out-of-bounds) with all observations occurring at one $PaCO_2$ Level such as "normal" (Figure 6).

Figure 6. ARI with all observations "in bounds" and "normal".



Note the denominator for crude current ARI equals the denominator for normal current ARI, and the numerators are both zero since the infants is perfectly autoregulating. Figure 7 shows the same scenario with slight deviation from autoregulation with two points falling above the upper bound and two falling below the lower bound (numerator for normal current ARI equals four with denominator still equal to that of crude current ARI).

Figure 7. ARI with 4 out-of-bounds observations and normal $PaCO_2$ level.



Another scenario may have two current $PaCO_2$ levels of observations with several points falling out-of-bounds (Figure 8). Note that the normal current ARI is approximately 12%, while the moderately hypercapnic current ARI is approximately 11%. There are many other scenarios that can occur such as those involving "extremely hypercapnic" values (Figure 9), but they will not be taken into account here for the sake of brevity.

Figure 8.ARI showing mixture of normal and moderately hypercapnic observations.

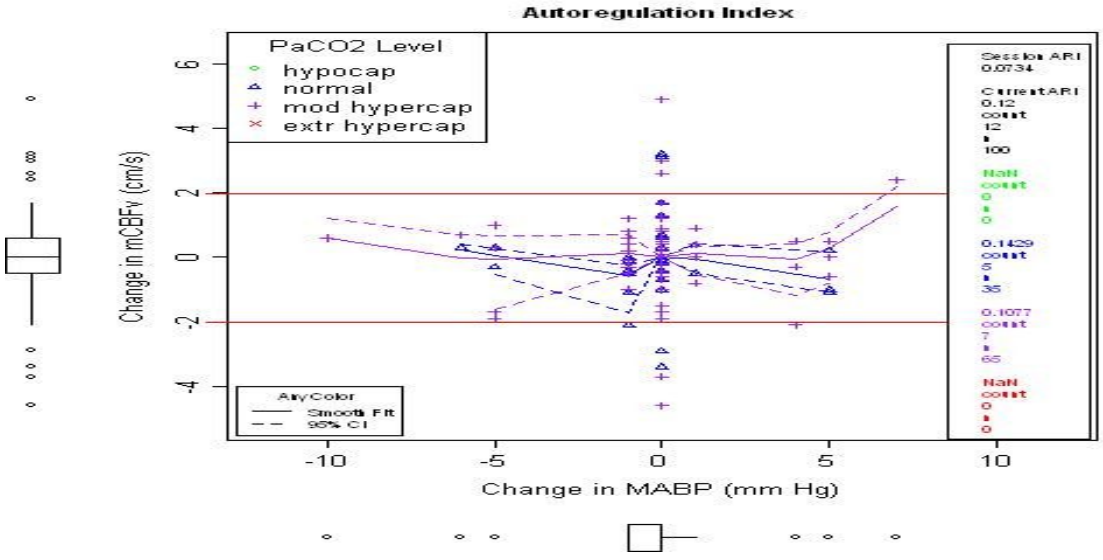
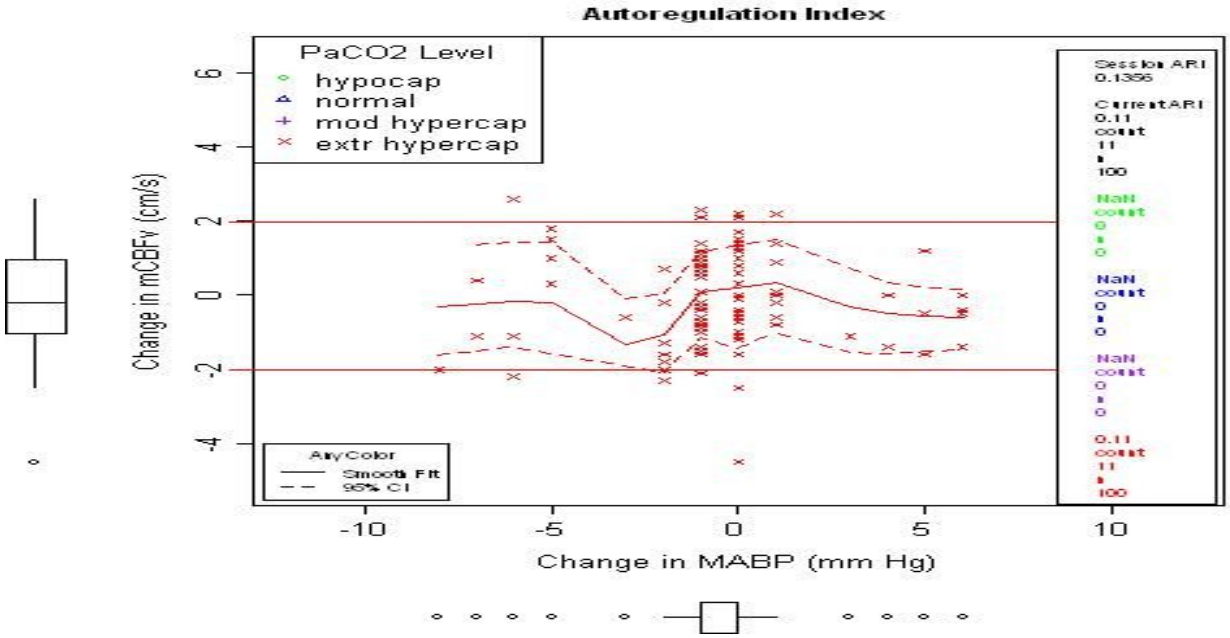


Figure 9.ARI with extremely hypercapnic values.



Hence, at any given point in time, the bedside clinician can determine a running proportion on all observations (crude ARI), a proportion for all current observations (crude current ARI), and a proportion for current observations at any given modifier level (hypocapnic current ARI, normal current ARI, moderately hypercapnic current ARI, and extremely hypercapnic current ARI). Theoretically, the higher the value of any ARI, the more impaired the infant's autoregulation, and the more dangerous the situation.

5. CONCLUSIONS

The prevalence of IVH in VLBW infants has not decreased despite advances in obstetrical and neonatal care. [8] The ARI is very promising because it perhaps solves the problem of unavailable tools necessary to accurately predict which VLBW infants are at the greatest risk of developing IVH. By monitoring autoregulation in real-time, bedside clinicians can quickly ascertain impaired function and take necessary measures to avoid IVH and prevent associated neurodevelopmental disabilities.

Other methods have been used to determine autoregulation status, such as the cerebral oximetry index. [2] This provides a running correlation between low change in ABP and cerebral oximetry as measured from induced autoregulation by near-infrared spectroscopy. However, this method does not share the ARI's ability to consider the effects of a third modifier variable.

The greatest value of the ARI is its immense flexibility. Several statistical measuring discrepancies in the past have included inconsistency in observations due to use of different suctioning and ventilation techniques (open vs. closed; use of pre-oxygenation, various ventilator manipulations and/or saline vs. non-application of these procedures), use of different CBF measurement methods, indirect and intermittent physiological monitoring systems, inclusion of heterogeneous populations (wide range of gestational and postnatal ages, different behavioral states, different respiratory diseases, and infants with and without hypotension or brain injury), differences in sedation and paralysis protocols, and measurements either during clinically indicated suctioning procedures or convenient periods. [5]

All of these problems are essentially avoided by the use of a high-quality ARI, or one that has the important arbitrary ARI values set by the attending physician in accordance with characteristics of the infant and the bedside atmosphere. Depending on previous data of a particular infant, the lag values can be set high or low for ΔmCBFv and ΔMABP, autoregulatory bounds can be tight or wide, and the running window can be set for a small or large amount of observations. Therefore, it may not matter whether the baby is large or small, has respiratory distress syndrome or not, is or is not hypotensive, whether a procedure is being performed, or what procedure is being performed (permissive hypercapnia, tracheal suctioning, surfactant administration, etc.). For example, if surfactant is currently being administrated on an infant, and the trendcare monitor begins to show a high "extremely hypercapnic" current ARI, then the clinician will know that the procedure may need to be curtailed for the moment. At this point, the clinician can more easily determine the use of slow infusion versus bolus administration, whether to reduce the number of fractionated doses, or deciding whether to nebulizer surfactant. Essentially, the ARI serves as a one-size-fits-all tool that transparently displays autoregulatory functioning regardless of activities occurring in the bedside environment. In addition, it may act as a translational research tool by which clinicians may determine which bedside procedures are ultimately essential. This has implications for beneficial future changes in clinical practice.

Therefore, if clinicians can adequately implement the ARI at many different premature infant locales, there is a great possibility of preventing a myriad of IVH cases. Not only will this save thousands of dollars in NICU healthcare, but it may provide many of these infants to grow up as normally functioning adults able to seek an independent happy life. Hence, money is saved and diverted to other needs in the healthcare industry, more humans have a chance to grow up and have real jobs, and society is that much better off.

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