

Literature Review

Cerebral Autoregulation-Directed Therapy in Adults with Non-Traumatic Brain Injury in Neuro-Critical Care: A Scoping Review

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Abstract

Cerebral Autoregulation (CA)-directed therapy, or optimal cerebral perfusion pressure (CPPopt)-targeted therapy, is a tailored bedside method of resuscitation used in critical care that aims to achieve and maintain the CPPopt, to fit the precise cerebral hemodynamics and metabolic demand. Different processes and multiple tools are available to conduct a CA-directed therapy in acute brain-damaged adult admitted into critical care settings, but literature is limited and primarily focused on traumatic brain injury; however, for other brain conditions. By this scope review, we aim to describe the main procedures used by authors to achieve a CA-directed therapy, as well as its acquisition methods and its usefulness in acute non-traumatic brain-damaged adult in neurocritical care.

More Information

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Abbreviations

ARI: Autoregulation Index; CA: Cerebral Autoregulation; CBF: Cerebral Blood Flow; CPP: Cerebral Perfusion Pressure; CPPopt: Optimal Cerebral Perfusion Pressure; DATACAR: Dynamic Adaptive Target Of Active Cerebral Autoregulation; GOS: Glasgow Outcome Scale; GOSe: Extended Glasgow Outcome Scale; ICH: Intracranial Hemorrhage; ICP: Intracranial Pressure; ICU: Intensive Care Unit; L-PRx: Low-Frequency Sample Pressure Reactivity Index; MAP: Mean Arterial Pressure; MMM: Multimodal Monitoring; mRS: Modified Rankin Score; MV: Mean Velocity; Mx: Mean Flow Velocity Index (Based On CPP); Mxa: Mean Flow Velocity Index (Based On MAP); NIHSS: National Institute Of Health Stroke Scale; NIRS: Near Infrared Spectroscopy; ORx: Oxygen Reactivity Index; Pax: Cerebrovascular Reactivity Index; PIC: Pressure(Blood)-Amplitude Index; PRx: Pressure Reactivity Index; PtiO₂: Tissue Oxygen Partial Pressure; rSO₂: Regional Oxygen Saturation; SAH: Subarachnoid Hemorrhage; SV: Systolic Velocity; Sx: Systolic Flow Velocity Index; TBI: Traumatic Brain Injury; TCD: Transcranial Doppler; TFA: Transfer Function Analysis; THx: Tissue Oxygen Index; TOx: Tissue Hemoglobin Index

Introduction

Cerebral Autoregulation (CA) can be monitored at the

bedside by assessing Cerebral Blood Flow (CBF) and its surrogates, by measuring Cerebral Perfusion Pressure (CPP) and intracranial flow, and by studying cerebral metabolism [1-3]. This monitoring is part of Multimodal Monitoring (MMM) in neurocritical care [4]. One of the most recent and elegant applications of this monitoring is the identification of the optimal CPP and Mean Arterial Pressure (MAP), looking for the pressure intervals where the monitored cerebral perfusion parameters vary the least [5]. Even though low CPP is an important secondary insult to the brain [6], most current guidelines do not endorse CA-guided therapy, and persist in recommending “target” or “threshold” numbers to be met in the management of blood pressure in acute brain-damaged patients, regardless of their usual blood pressure numbers or CA status, including in the 4th edition of the Brain Trauma Foundation guidelines for the management of traumatic brain injury [7-10]. The importance of CA monitoring and its correlation with prognosis in this population has recently been recognized by a consensus of clinicians, although no method has been validated to do so [11].

The issues raised by this review are: (1) How should CA-directed therapy be conducted, and (2) What is its place in non-traumatic brain-damaged patients admitted into critical care? (3) Given the variability of the optimal CPP interval,

should CA be monitored continuously? (4) And finally, is it essential to monitor CA in neuro-critical care?

Method

Our work was conducted according to a protocol in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [12].

We conducted a literature search using the following scientific databases PubMed (from January 2000 to October 2020), EMBASE (from January 2000 to October 2020), and Cochrane Library (from January 2000 to October 2020). The keywords used included “Cerebral Autoregulation” in combination with one of the words “Monitoring,” “Index,” or “ICU,” as well as the words “Optimal PPC,” “Optimal MAP,” and “Acute Brain Injury”. Only articles written in English or French were considered.

The inclusion criteria for the articles searched were: (1) adult population, (2) brain-damaged patients, and (3) assessment of CA in the intensive care setting. Studies involving healthy subjects, pediatric populations, or animals, as well as studies conducted in the operating room, were excluded. Selected articles were classified into two categories: (1) systematic reviews and meta-analyses, and (2) randomized clinical trials and cohort studies. For the latter category, the articles selected were sorted according to their primary objective, the nature of the brain injury in the study population, and the monitoring technique used.

The data extracted were the authors and year of publication, the number of patients studied, the variables compared (CPP, MAP, intracranial pressure (ICP), systolic (SV) and mean (MV) velocities, CBF, PtiO₂, and rSO₂) and their collection mode (intermittent or continuous), the duration of monitoring, the correlation coefficients, and the p values of the proposed thresholds.

The results and analyses of the selected studies were used comparatively to address the issues raised in the introduction.

The heterogeneity in study designs, patient populations, monitoring techniques, and outcome measures across the included studies precluded the conduct of a meta-analysis. No formal quality assessment (e.g., PRISMA scoring or risk-of-bias tools such as ROBINS-I or Cochrane tools) was conducted, which is a limitation in the interpretation of findings. Therefore, this review is presented as a scoping synthesis to map the available literature rather than quantify pooled effect sizes.

Results

A total of 393 articles, including 46 literature reviews and meta-analyses, and 347 randomized clinical trials and observational studies, were identified in the search. Of these

articles, only 329 addressed CA monitoring in the adult population and 126 in the intensive care setting. Ultimately, a total of 65 articles addressed the questions raised by our review. A flowchart of the article selection process is presented in Figure 1.

Studies were categorized by type of brain injury, monitoring method, and objective to draw clearer links between how cerebral autoregulation was assessed and the outcomes reported. This approach highlights how different monitoring strategies relate to patient prognosis and the effectiveness of CA-directed therapy.

Nature of brain injury

We included 65 articles in our review of the literature, including 59 cohort studies and clinical trials, as well as 6 systematic reviews and guidelines. From this database, we identified four main brain injuries: (1) severe traumatic brain injury (TBI) in 46 articles [13-57] and in a total population of 6176 patients; (2) spontaneous intra-parenchymal hematoma (ICH) in 4 articles [58-61] and a total population of 111 patients; (3) subarachnoid hemorrhage (SAH) in 7 articles [62-68] and a total population of 388 patients; and (4) ischemic stroke in 2 articles [69,70] and a total population of 60 patients. CA was studied in cardiac arrest in 2 studies [71,72] in a total patient population of 33.

Methods of monitoring

ICP monitoring to assess CA at the bedside was used in 44 studies [13,33,40,45, 48-57,58-60,62,71,] with a total enrollment of 5248 brain-damaged patients, and in combination with one or more other tools (invasive or noninvasive) for monitoring CA in 9 of these studies [18-20,24,32,45,68,69,71]. This monitoring was most often continuous, whereas it was ad hoc or intermittent in only 4 studies [15,33,52,54]. The main Brain Autoregulation Index (ARI) used in this group was the Pressure Reactivity index (PRx) (39 articles [13-15,17,19-28,30-33,40,45,48-57-60,62,68,71],

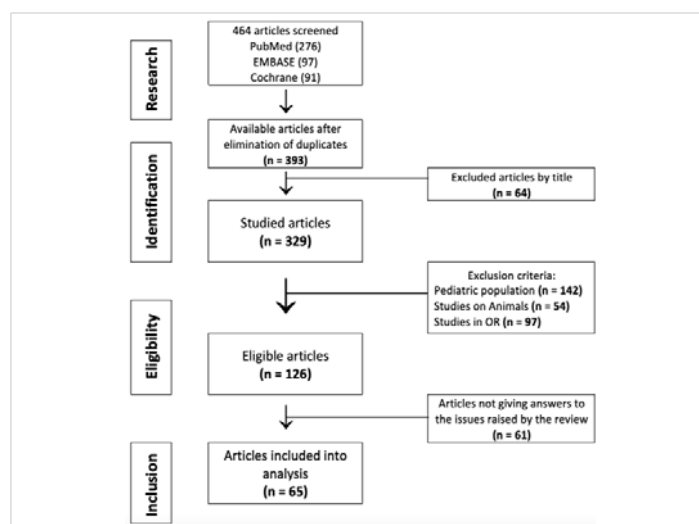


Figure 1: Flow diagram of the inclusion process for articles screened and selected.

whereas the Low frequency sample Pressure Reactivity index (L-PRx) was used in only 5 studies [29,30,33,50,54], and the Pressure(blood)-Amplitude(PIC) index of Cerebrovascular Reactivity (PAr) was used in only 3 studies [16,17,52].

Transcranial Doppler (TCD) was used in 18 studies [34-39,41-45,47,61,64-66,69,71] with a total enrollment of 1901 cerebral patients. TCD was used in combination with other CA monitoring tools in 6 studies [19,20,36,45,66,69]. Measurement of velocities was continuous in 9 articles [19,20,34-36,39,45,61,65,66,69-71] and intermittent in 9 articles [35,37,38,41-44,47,64]. The main ARIs exploited were the Mean Flow Velocity index (Mx based on CPP, Mxa based on MAP) [19,20,35,37-39,41-45,47,61,64,70]. The Dynamic Autoregulatory index (ARI) was used in 4 studies [34,44,47,65], whereas the Systolic Flow Velocity index (Sx) was used in only 2 studies [64,66].

Only 4 studies used invasive monitoring of cerebral regional oxygenation, or tissue oxygen pressure (PtiO₂), to monitor CRA [46,67,68,71], with a total population of 138 cerebral patients. PtiO₂ monitoring was used in combination with ICP monitoring in 3 studies [46,68,71], always continuously. The ARI used in these studies was the Oxygen Reactivity Index (ORx).

Finally, only 4 studies used continuous, noninvasive monitoring of regional cerebral oxygenation (rSO₂) by Near Infrared Spectroscopy (NIRS) [32,45,66,72], on a total population of 188 patients. In these studies, the ARIs exploited were Tissue Oxygen index (TOx) [45,66,72] and Tissue Hemoglobin index (THx) [32,45].

Purposes of the studies

In terms of goals of the included studies, 28 studies investigated the correlation of calculated ARIs with patient prognosis (Glasgow Outcome Scale (GOS) from 3 to 6 months [13,20-23,34,35,38,46,59,61,69], extended GOS (GOSe) [26,50-54,65], modified Rankin score (mRS) at discharge [20,61,69], NIHSS [59]), whereas 16 studies evaluated the correlation of calculated ARIs with mortality of brain-damaged patients [13-20,34-36,48,49,71,72]. Together, these studies find a good correlation between ARI values and morbidity-mortality of brain-injured patients admitted into critical care. However, the cut-offs of the same ARI differ from one study to another, which does not allow us yet to validate or retain one as the ARI of choice.

The identification of an optimal CPP and/or MAP was undertaken in 9 studies [25,27-31,40,48,49,54-57,60, 62,63] in a total population of 1547 patients, and in which only ICP-derived ARIs were used (PRx and L-PRx). The most commonly used method was the second order polynomial formula, resulting in a U-shaped curve, and varying the calculated ARI as a function of MAP or CPP [25,28,30,31,48,54-57,60,62]. The Dynamic Adaptive Target of Active Cerebral Autoregulation (DATACAR) method was used in only 2 studies [29,40].

Finally, the optimal CPP was sought in 2 studies via the lowest ARI [27,63]. The DATACAR method found optimal CPP more often than the second order polynomial formula, with better accuracy as well as better correlation with morbi-mortality when there was a discrepancy between actual CPP and optimal CPP identified by these methods (CPPopt) [48,49]. The larger and/or more prolonged the gap is, the worse survival and the worse neurological prognosis are. This is particularly true when the CPP is lower than the Optimal CPP [30,56,57,62].

Validation of the ARIs was performed by 12 studies among those included in our analysis [19,32,33,35,42-45,47,59,64,68]. All of these studies used Pearson's index to establish a correlation between the ARIs in order to validate them in brain-damaged patients admitted to critical care.

The statistical data (*r* value, *p* value) have been grouped in Table 1 (see Appendix).

Discussion

CA protects the brain from inappropriate variations in CBF and maintains it constant despite large variations in MAP [73,74]. The loss of the CA submits the variation of the CBF to those of the MAP following the loss of cerebrovascular reactivity, which in turn involves several mechanisms (myogenic [75], chemical by variation of capnia and pH [76], flow-metabolism coupling [77], endothelial [78] and neuroendocrine [79]). Therefore, any decrease in MAP or increase in ICP exposes the risk of hypoperfusion and cerebral ischemia by decreasing CPP [80]. Similarly, any increase in MAP is at risk of hyperemia and intracranial hypertension [80]. Thus, loss of CA is associated with poor prognosis in multiple acute neurological conditions [81].

The ability of the cerebral vasculature to maintain constant CBF can be assessed by two modalities: static and dynamic assessment [82]. The static assessment corresponds to the assessment of the capacity of the cerebral vascular bed to contract or dilate when the CPP varies [83]. Dynamic assessment also incorporates the notion of the rate at which these adaptive vascular changes can occur, a quality unique to continuous monitoring tools. Only dynamic assessment allows real-time evaluation of cerebral vascular reactivity of CA and thus determination of optimal MAP and CPP, and thus rapid evaluation of the impact of therapies undertaken [84]. This is the principle of CA-directed therapy at the bedside in critical care.

How to conduct CA-directed therapy in the ICU?

CA-directed therapy at the bedside employs one or more correlation coefficients between cerebral blood flow variables (e.g., ICP, TCD velocities...) and MAP or CPP. These coefficients are called cerebral autoregulation indices (ARI) and are obtained by simultaneous collection and analysis of continuous measurements, using the Intensive Care Monitor + (ICM+, University of Cambridge) [85] software, or by Transfer

Table 1(Appendix): Summary of data extracted and studies included.

Pathologie	Outil	Auteur (Année)	Objectif	Population (n)	Méthode	Modalité de Recueil	Durée de Recueil	Indice d'ARC	Ref
								(r ; p)	
Traumatic Brain Injury	ICP	Steiner et al. (2002)	Mortalité	114	Calcul ARI	Continu	118 h	PRx (p = 0.003)	13
		Ang et al. (2007)	Mortalité	40	Calcul ARI	Continu	3 j	PRx (p = 0.002)	14
		Zweifel et al. (2008)	Mortalité	193	Calcul ARI	Continu	-	PRx (p < 0.0002)	15
		Radolovich et al. (2011)	Mortalité	243	Calcul ARI	Continu	96 min	PAx (p < 0.0003)	16
		Aries et al. (2012)	Mortalité	327	Calcul ARI	Continu	-	PRx (p = 0.001)	17
								PAx (p < 0.001)	
		Lewis et al. (2012)	Mortalité	187	Calcul ARI	Continu	30 min	Flx (p = 0.005)	18
		Budohoski et al. (2012)	Mortalité	486	Calcul ARI	Continu	96 min	PRx (p = 0.018)	19
		Schmidt et al. (2016)	Mortalité	36	Calcul ARI	Continu	3 h	PRx (p < 0.0001)	20
		Liu et al. (2017)	Mortalité	526	Delta PPC Optimal	Continu	2 – 8 h	Courbe de PRx	80
								(p < 0.001)	
		Petkus et al. (2020)	Pronostic	81	Calcul ARI	Continu	4 h	PRx (p < 0.001) chez les jeunes	81
					Delta PPC Optimal			PRx (p = 0.018)	
								Chez le sujet âgé	
		Kirkness et al. (2001)	Pronostic	52	Calcul ARI	Continu	50 min	PRx (p = 0.67)	21
		Steiner et al. (2003)	Pronostic	22	Calcul ARI	Continu	2 h	PRx (p = 0.13)	22
		Hiler et al. (2006)	Pronostic	107	Calcul ARI	Continu	24 h	PRx (p < 0.0002)	23
		Jaeger et al. (2006)	Pronostic	27	Calcul ARI	Continu	156 h	PRx (p = 0.005)	24
		Johnson et al. (2011)	Pronostic	54	Delta PPC Optimale	Continu	24 h	Courbe de PRx	25
								(p < 0.05)	
		Budohoski et al. (2012)	Pronostic	486	Calcul ARI	Continu	96 min	PRx (p = 0.024)	19
		Howells et al. (2015)	Pronostic	100	Calcul ARI	Continu	67 h	PRx (p < 0.0001)	26
		Petkus et al. (2017)	Pronostic	52	Delta PPC Optimale	Continu	4h	PRx (p < 0.001)	82
		Wettervik et al. (2019)	Pronostic	362	Calcul ARI	Continu	4 h	PRx	83
					Delta PPC Optimale			PRx55-15	
								(p < 0.00001)	
		Zeiler et al (2019)	Pronostic	204	Calcul ARI	Continu	4 h	PRx, PAx	84
		Wettervik et al. (2020)	Pronostic	362	Calcul ARI	Continu	4 h	PRx	85
					Variabilité PA				
		Riemann et al. (2020)	Pronostic	224	Calcul ARI	Continu	2 – 8 h	PRx	86
								L-PRx	
		Jaeger et al. (2010)	PPC Optimale	38	ARI le plus bas	Continu	48 h	PRx	27
								(valeur absolue)	
		Johnson et al. (2011)	PPC Optimale	54	Courbe en U	Continu	24 h	PRx (p < 0.05)	25
		Aries et al. (2012)	PPC Optimale	307	Courbe en U	Continu	4 h	PRx (mauvais pronostic en dehors de la PPC optimale)	28
		Depreitere et al. (2014)	PPC Optimale	55	DATA CAR	Continu	1 – 24 h	L-PRx (mauvais pronostic en dehors de la PPC optimale)	29
		Dias et al. (2015)	PPC Optimale	18	Courbe en U	Continu	4 h	PRx (mauvais pronostic en dessous de la PPC optimale)	30
		Weersink et al. (2015)	PPC Optimale	48	Courbe en U	Continu	4 h	PRx	31
								(Valeur absolue)	
		Howells et al. (2018)	PPC Optimale	104	Courbe en U	Continu	68 à 93 h	PRx	87
								(valeur absolue)	
		Donnelly et al. (2018)	PPC Optimale	231	Courbe en U	Continu	4 h	PRx (mauvais pronostic en dessous de la PPC Optimale)	88
		Kramer et al. (2019)	PPC Optimale	71	Courbe en U	Continu	6 h	PRx (mauvais pronostic en dessous de la PPC Optimale)	89
		Cahya et al. (2019)	PPC Optimale	14	DATA CAR	Continu	12.7 h	PRx vs L-PRx	40
								(p = 0.463)	
		Zweifel et al. (2010)	Validation ARI	40	Comparaison	Continu	5 min	PRx vs THx	32
					(PIC vs NIRS)			(r = 0.56; p = 0.0002)	
		Lang et al. (2015)	Validation ARI	307	Comparaison	Instantané	60 sec	PRx vs L-PRx	33
								(r = 0.7; p < 0.00001)	

	TCD	Panerai et al. (2004)	Mortalité	32	Calcul ARI	Continu	45 min	ARI (p = 0.011)	34
		Sorrentino et al. (2011)	Mortalité	248	Calcul ARI	Continu	96 min	Mx (p < 0.05)	35
								Mxa (p < 0.05)	
		Lewis et al. (2012)	Mortalité	187	Calcul ARI	Continu	30 min	Flx (p = 0.005)	36
		Schmidt et al. (2016)	Mortalité	36	Calcul ARI	Continu	3 h	Mx (p < 0.005)	20
		Lang et al. (2003)	Pronostic	37	Calcul ARI	Instantané	-	Mx (p < 0.01)	37
								Mxa (p < 0.05)	
		Lang et al. (2003)	Pronostic	40	Calcul ARI	Instantané	-	Mx	38
		Lewis et al. (2007)	Pronostic	151	Calcul ARI	Continu	30 min	Mx (p = 0.007)	39
								Mxa (p = 0.05)	
		Liu et al. (2015)	Pronostic	288	Calcul ARI	Instantané	-	Mx (p < 0.0001)	43
								Mxa (p = 0.0002)	
		Lang et al. (2003)	Validation ARI	37	Comparaison	Instantané	-	Mx vs Mxa	44
								(r = 0.566; p < 0.01)	
		Lavinio et al. (2007)	Validation ARI	10	Comparaison	Instantané	-	Mx vs Mxa	45
								(r = 0.755; p < 0.001)	
		Czosnyka et al. (2008)	Validation ARI	50	Comparaison	Instantané	-	Mx vs ARI	46
								(r = 0.62; p = 0.0001)	
		Sorrentino et al. (2011)	Validation ARI	248	Comparaison	Continu	96 min	Mx vs Mxa	35
								(r = 0.789; p < 0.001)	
		Budohoski et al. (2012)	Validation ARI	486	Comparaison	Continu	96 min	PRx vs Mx	19
					(PIC vs DTC)			(0.58; p < 0.001)	
		Highton et al. (2015)	Validation ARI	27	Comparaison	Continu	30 – 60 min	PRx vs TOx	47
					(PIC vs DTC			(r = 0.4; p = 0.04)	
					vs NIRS)			PRx vs THx	
								(r = 0.63; p < 0.001)	
								Mxa vs TOx	
								(r = 0.61; p = 0.004)	
								Mxa vs THx	
								(r = 0.26; p = 0.28)	
		Liu et al. (2020)	Validation ARI	34	Comparaison	instantané	-	Mx vs ARI (r = -0.95 ; p < 0.001)	79
	PtIO ₂	Jaeger et al. (2006)	Pronostic	27	Calcul ARI	Continu	156	ORx (p < 0.01)	48
Intracranial hemorrhage	ICP	Eide et al. (2007)	Pronostic	18	Calcul ARI	Continu	2 j	PRx (p < 0.001)	49
		Santos et al. (2011)	Pronostic	18	Calcul ARI	Continu	2 j	L-PRx (p < 0.001)	50
		Santos et al. (2011)	Validation ARI	18	Comparaison	Continu	2 j	PRx vs L-PRx	50
								(r = 0.846; p < 0.001)	
		Diedler et al. (2014)	PPC Optimale	38	Courbe en U	Continu	-	PRx	51
	TCD	Reinhard et al. (2010)	Pronostic	28	Calcul ARI	Continu	10 min	Mx (p = 0.013)	52
Sub-arachnoid hemorrhage	ICP	Bijlenga et al. (2010)	PPC Optimale	25	ARI le plus bas	Continu	-	PRx	53
		Johnson et al. (2017)	PPC Optimale	82	Courbe en U	Continu	4 h	PRx (Bas DSC en dessous de la PPC Optimale)	41
	TCD	Soehle et al. (2004)	Pronostic	30	Calcul ARI	Intermittent	-	Mx (p = 0.021)	54
		Barth et al. (2012)	Pronostic	22	Calcul ARI	Continu	-	ARI (p = 0.0173)	55
		Budohoski et al. (2012)	Pronostic	98	Calcul ARI	Continu	5h 40min	Sx (p < 0.0001)	56
		Soehle et al. (2004)	Validation ARI	30	Comparaison	Intermittent	-	Mxa vs Sx	54
								(r = 0.89; p < 0.001)	
	PtIO ₂	Jaeger et al. (2012)	Pronostic	80	Calcul ARI	Continu	8 j	ORx (p = 0.001)	57
		Barth et al. (2010)	Validation ARI	21	Comparaison (PIC vs PtIO ₂)	Continu	1 h	PRx vs ORx	58
								(r = 0.851; p < 0.043)	
	NIRS	Budohoski et al. (2012)	Pronostic	98	Calcul ARI	Continu	5h 40min	TOxa (p < 0.0001)	56
Ischemic stroke	ICP	Dohmen et al. (2007)	Pronostic	15	Calcul ARI	Continu	30 min	COR ; R	59
	TCD	Dohmen et al. (2007)	Pronostic	15	Calcul ARI	Continu	30 min	COR ; R	59
		Reinhard et al. (2012)	Pronostic	45	Calcul ARI	Continu	10 min	Mx (p < 0.01)	60
Cardiac arrest	ICP	Mypinder et al. (2019)	Mortalité	10	Calcul ARI	Continu	47 h	PRx (p < 0.001)	42
	NIRS	Pham et al. (2015)	Mortalité	23	Calcul ARI	Continu	-	TOxa (p < 0.001)	61



Function Analysis (TFA) [86]. They reflect the degree to which the cerebral circulation is submitted to variations in the systemic circulation. The weaker the correlation (closer to 0) or negative the ARIs, the more operational is the CA. Conversely, the more oscillations in the systemic hemodynamic state are transferred to the cerebral circulation, and thus the closer calculated ARIs are to 1, the less functional the CA is [19,35,37,46,87-90].

The search for the optimal CPP is done by looking for the lowest value of the chosen ARI. To do this, three methods are possible: (1) the second order polynomial formula, (2) DATACAR, and (3) finding the nadir ARI.

The first method (1) allows the graphical study of the variation of the ARI according to the variation (spontaneous or pharmaco-induced) of MAP or CPP within a 4-hour window. The curve thus obtained is most often an upwardly concave parabola (or 'U-shaped curve'), with an apex having as its abscissa the value of MAP or CPP corresponding to the lowest value of ARI, and thus to the cerebral hemodynamic conditions in which CA is most effective. The optimal MAP or CPP value is calculated by deriving the second-degree polynomial formula (ax^2+bx+c) relative to the obtained plot [5,31]. It is important to remember that this technique does not always result in a 'U-shaped' curve. It is indeed possible that the curve described is ascending, descending or anarchic, in which case it remains difficult to draw a conclusion. A recent study showed that the absence of slow blood pressure changes, a high PRx value, poor sedation-analgesia, high doses of catecholamines, and the presence of a decompressive craniectomy were independently related to the absence of a 'U-shaped' curve.

DATACAR is a method that also uses of the second order polynomial formula, but over variable time windows (e.g., 2h, then 4h, then 8h ...), making it possible to obtain several U-shaped curves. This method gives the PPCopt a major credibility, especially when the vertices of the parabolas (lowest ARI) coincide. Nevertheless, this protocol was found in only 2 studies out of a total of 69 patients. In these studies, DATACAR allows to find the optimal CPP more often than in a single window using the polynomial formula, and also has a better correlation with the neurological prognosis of the patients [29].

The unsystematic search of the lowest ARI (Nadir) was performed in 2 studies, involving a total population of 63 brain-damaged patients [27,63]. It does not take into account the monitoring time interval, nor the CPP variation interval. As a result, this method remains less accurate than previous methods in identifying the optimal CPP, however no studies have compared these methods with each other.

CA-guided therapy via the identification of optimal CPP is being evaluated with the aim of making it a standard of care, the field of research currently being reserved exclusively

for severe TBI. This is the case of the randomized clinical trial COGiTATE, currently in phase II of its development (NCT02982122).

What is the place of CA-directed therapy in non-traumatized brain-damaged patients admitted to critical care?

CA monitoring was conducted in non-traumatized brain-damaged patients admitted into critical care in 15 studies, with a total of 592 patients [58-72]. The pathologies found were mainly SAH, ICH, Acute ischemic stroke, and cardiac arrest. No CA monitoring has been studied in adult patients with metabolic, toxic, or septic encephalopathy, neuromeningeal infection, or autoimmune encephalitis in critical care.

When it could be done, the identification of an optimal CPP was done using ICP monitoring and the resulting ARIs (PRx and L-PRx), only in the context where patients were at risk or in clinical intracranial hypertension (SAH, ICH). This is in line with the recommendations from the international multidisciplinary consensus conference on MMM in neurocritical care, regarding the use of ICP outside the context of TBI [4]. No study has been done to identify the optimal CPP using TCD or a cerebral oxygenation monitor in this population, even in the setting of severe TBI, and despite a good correlation between the ARIs from these methods and those from ICP monitoring [19,32,45,68]. Because ICP monitoring has not yet had the primary purpose of identifying optimal CPP, independently of the risk of intracranial hypertension, it remains reasonable to use noninvasive tools in non-traumatized brain-damaged patients in critical care to conduct CA-directed therapy, and thus more studies and clinical trials are needed to validate their use.

In many series, the identification of an optimal MAP or CPP has been shown to predict the prognosis of patients resuscitated via PPCopt-targeted therapy [48,49]. Thus, the greater was the discrepancy between optimal and actual CPP in brain-damaged patients, the higher were the mortality and the worse the neurological prognosis, as early as a threshold of 5 mmHg in the context of impaired CA [49]. Also, the more deviation events from CA operative ranges occur and the longer they last, the worse the outcome of the patients tends to be. Therefore, CA-directed therapy could improve the prognosis of severe neurological patients, and particularly in those with preserved CA. This has been proven in trauma patients, but has yet to be proven in the rest of the resuscitated brain-damaged patients.

Should CA be monitored continuously?

All studies conducted in critical care use continuous monitoring of CA. Only noninvasive methods requiring operator intervention, including TCD, have been used on an ad hoc and repeated basis to monitor CA [37,38,41-44].

In a meta-analysis evaluating the correlation between

ARIs and morbidity and mortality in brain-injured patients admitted to the ICU, continuous monitoring was superior to intermittent monitoring in its ability to predict mortality [3]. 3 Recommendations for CA monitoring also emphasize the need for continuous assessment. However, when it comes to determining optimal CPP, the time windows used to do so vary from a study to another. There is no consensus on the duration of these windows. However, it is reasonable that data acquisition should be equitable for each blood pressure level as it increases, and that this pressure change should be consistent throughout the measurement window. The risk of error increases when acquisition is prolonged for a given MAP or CPP level, compared with other pressure levels where the monitoring time was less than 3% of the overall monitoring time [5].

Is CA-guided therapy essential?

Loss of CA is a multifactorial and unpredictable event in cerebral patients. Its occurrence in the context of intracranial hypertension can go unnoticed and lead to irreversible ischemic damage within minutes [80]. CA monitoring-guided therapy can detect such an abnormality, for which a “tailored” management of cerebral perfusion adapted to cerebral metabolic needs can be proposed. Also, a maintained CA allows to tolerate high blood pressure figures and to avoid cerebral edema that can be induced by hyperemia.

There is currently no strong recommendation for the use of an ARI to guide the choice of optimal CPP or MAP, as no ARI has yet been validated by a randomized clinical trial. Only PRx has been proposed by the Neurocritical Care Society and the European Society of Intensive Care Medicine (Low Recommendation, Low Level of Evidence), as part of MMM [4]. CA-directed therapy represents a promising resuscitation strategy in patients at risk of brain damage, regardless of the type of brain injury, and especially in those at risk of intracranial hypertension or with neurovascular damage. However, there is a lack of evidence to make it an indispensable method.

Conclusion

The identification and maintenance of optimal CPP in the brain-damaged subject using CA-directed therapy is an attractive strategy that can improve the neurological prognosis and survival of these patients. However, as the current level of evidence is insufficient, this method remains under investigation, with objectives including the modalities of application, in particular the technique of choice and its indications according to the nature of the cerebral aggression, the optimal duration of monitoring, and the frequency of measurements. To date, no randomized clinical trial has been conducted on this approach, both diagnostic and therapeutic, in non-traumatized brain-damaged patients in critical care settings, hence the urgent need for work in this area.

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Author contributions

YH contributed to the acquisition and analysis of data, and to drafting the text.

MD contributed to acquisition and analysis of data, and approving the text.

MA contributed to editing and approving the text.

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