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LETTER TO THE DIRECTOR

Immunomodulation using CONVEHY® for COVID-19: from the storm to the cytokine anticyclone*

Inmunomodulación mediante CONVEHY® para COVID-19: de la tormenta al anticiclón de citoquinas

To the Editor,

The cause of the COVID-19 pandemic is severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Severe forms of the disease occur predominantly in older adults or in individuals with underlying medical comorbidities, such as cardiovascular disease, hypertension, diabetes mellitus, chronic lung disease, and chronic kidney disease. The reason for the fatality of COVID-19 is viral sepsis. This host organ dysfunction is caused by a life-threatening, dysregulated inflammatory response (DIR) that initially has severe pulmonary complications.[1,2] Therefore, there is generalized endothelial dysfunction leading to multiple organ dysfunction syndrome.

Emerging evidence suggests that some patients may respond to COVID-19 with a disproportionate ''cytokine storm,'' called secondary hemophagocytic lymphohistiocytosis (HLH).[3,4] This, however, is not merely a quantitative problem, and dysregulated inflammatory response, which is a functional problem not just a particular cytokine threshold is a better term to describe this phenomenon. This response must be associated with an organ dysfunction to be considered pathological.[5] Currently, although there are some promising data, there is insufficient evidence to support the recommendation for a specific, effective treatment for patients with COVID-19.[6] While numerous antiviral treatments are under investigation, their exclusive use may not be sufficient to control the aforementioned dysregulated inflammatory response. Therefore, there is growing interest in identifying alternatives with immunomodulatory action that can eliminate or reduce the formation of cytokines, thereby reducing both inflammatory tissue damage, particularly lung damage,[7] and mortality. An optimal blood purification technique could play a key role in this context.[8]

The CONVEHY® protocol (online supplements 1, 2, 3) was developed by the Hyperfiltration Research Group to control DIR and the cytokine storm through immunomodulation in patients with septic shock.[9] The DIR can be triggered by various events, including viral infections such as COVID-19, and can have different systemic effects on endothelial glycocalyx, such as vasodilation, fluid extravasation, and platelet micro-aggregation, in addition to kidney injury. Immunomodulation strategies that involve the elimination of inflammatory mediators should be considered in patients with poor response to treatments.[10]

The oXiris® membrane[5] (BaxterTM, Illinois, USA) is hollow fibre acrylonitrile and methanesulfonate (AN69ST) membrane with a surface treated with polyethyleneimine (PEI) and anchored heparin (AN69-ST-anchored heparin). It is a haemofilter that can eliminate interleukins (IL), tumour necrosis factor alpha (TNF-α), migration inhibitory factor (MIF), interleukin-1 receptor antagonist (IL1-ra), high mobility group box 1 protein (HMGB-1), lipopolysaccharides (LPS), fibroblast growth factors (FGF21, FGF23), complement factors (C3a, C5a), and plasminogen activator inhibitor 1 (PAI-1), in addition to endotoxins. Its ability to remove molecules is related to its electrical charge, and therefore its isoelectric point. Although clinical experience in COVID-19 is limited,[11–13] in a single-centre, randomized, double-blind clinical trial, oXiris® proved effective in purifying blood and reducing the need for vasoactive agents in bacterial sepsis.[14] The Prismaflex system™ (BaxterTM, Illinois, USA) is used in conjunction with oXiris®. CONVEHY® uses a dose of citrate in a specific stage of the process, in this case specifically adapted to COVID-19. Adsorption capacity decreases over time due to membrane saturation, and membrane replacements are scheduled every six hours, at the discretion of the physician. The membrane can also be used solely for hemofiltration if only renal support is required at that time. The preliminary results of the use of the CONVEHY® protocol comparing outcomes before and after the inclusion of citrate have recently been published.[9]

The SARS-CoV-2 receptor binding domain spike (S) binds to the ACE2 receptor through a remarkable network of hydrophilic interactions. Multiple bonds and two salt bridges can be found at the interface of this complex, with multiple tyrosine residues forming hydrogen-bonding interactions with the polar hydroxyl group.[15,16] The aforementioned hydrophilic and hydrophobic characteristics of the SARS-CoV-2 virus allows it to adhere to the oXiris® membrane.[17,18] Similar adsorption-based removal by lectin affinity plasmapheresis has been studied in other RNA viruses such as hepatitis C and Ebola virus.[19]

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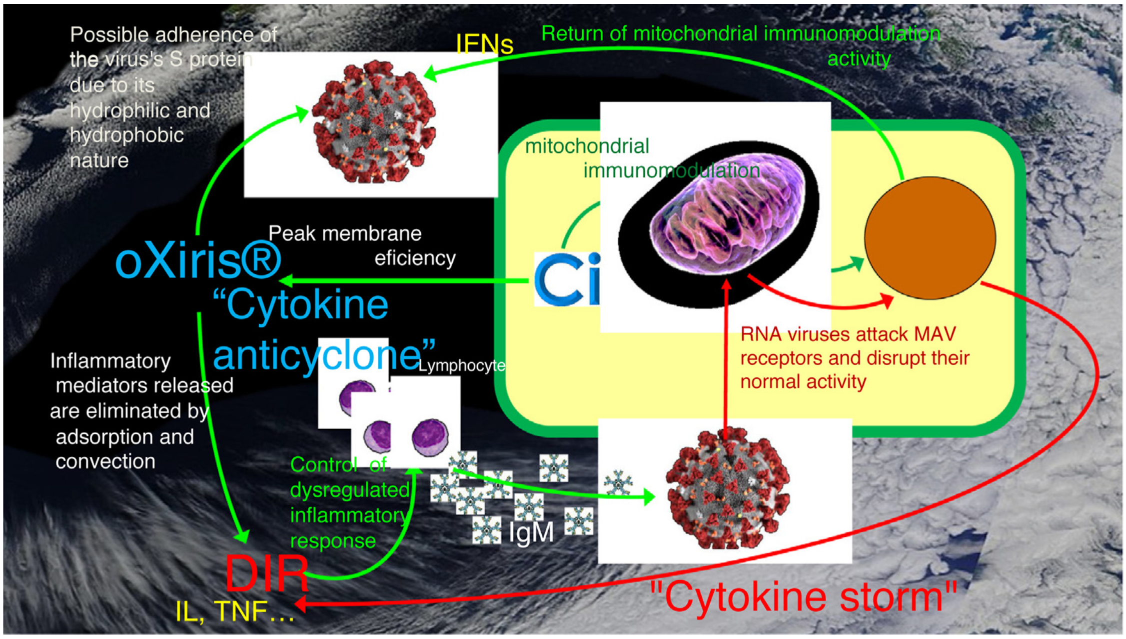

Figure 1 Combined immunomodulation strategy of the CONVEHY® protocol. oXiris®: trademark of the acrylonitrile 69-surface-treated heparin-anchored membrane; Ci: citrate; RNA: ribonucleic acid; DIR: dysregulated inflammatory response; IFNs: interferon; IL: interleukin; TNF: tissue necrotic factor; IgM: immunoglobulin M; curved red arrow: reduction or deterioration; curved green arrow: activation or enhancement.

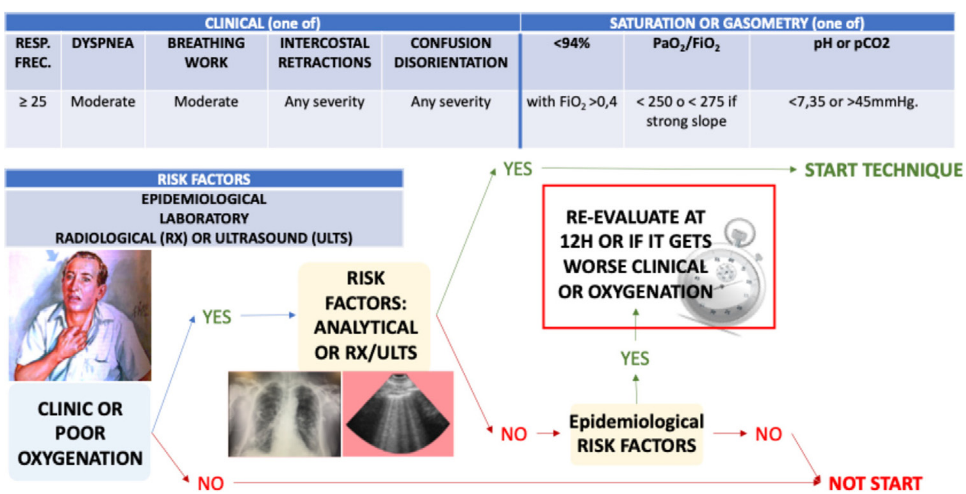

Figure 2 Indication for the early immunomodulation technique for COVID-19 (EIT-C19): patients with manifest symptoms or poor oxygenation who have signs of COVID-19 either on X-ray, pulmonary ultrasound and/or laboratory tests. Particular focus on the subgroup with epidemiological risk factors. See decision tree.

The oXiris® membrane was given an emergency use authorization (EUA) by the United States Food and Drug Administration (FDA) to treat patients with confirmed COVID-19. This technique can be used to reduce pro-inflammatory cytokine levels in adult patients presenting any of the following conditions:

- Early acute lung injury/early ARDS.
- Serious disease
- Life-threatening disease, defined as:
  - Respiratory insufficiency
  - Septic shock and/or
  - Multiple organ dysfunction or failure.

Being an RNA (ribonucleic acid) virus, SARS-CoV-2 directly affects the immunomodulatory function of the mitochondria by modifying the mitochondrial antiviral signalling (MAV) receptors, thereby preventing interferon synthesis by the innate immune response. Other interleukins can also be modulated in the same way.[20]

If the inflammatory response can be controlled in time, the immune system may be able to produce antibodies and overcome the infection.[21] The same strategy is used by our group in bacterial shock, although in this case we facilitate

Table 1 Risk factors for severe disease.

Symptoms (1 parameter)						O_2 saturation or blood gas (1 parameter)			
Resp. rate	Heart rate	Dyspnoea	Work of breathing	Respiratory distress	Confusion disorientation	$SatO_2$% baseline	<94%	PaO_2/FiO_2 $SpFiO_2$	pH or $PaCO_2$
≥25 rpm	>125 bpm	Moderate	Moderate	Any severity	Any severity	<91%	With FiO_2 >0.4	<300 or $SpFiO_2$ < 315 or if abrupt descent	<7.35 or >45 mmHg

Epidemiological	Laboratory	Radiological or ultrasound
>65 years	D-dimer > 1000 ng/mL	Multilobular infiltrates.
History of lung disease	CPK > twice baseline	Completely diffuses, widely spaced B lines (''Berticals'') (moving with pleura) Waterfall sign.
		''White'' lung.
		Pleura thickened, irregular.
		Healthy and diseased lung patches.
		Subpleural consolidation.
Mod-sev CKD	CRP > 100 mg/L	
DM HbA1c > 7.6% poorly controlled	LDH > 500 U/L	
Uncontrolled HT	Elevated troponin	
Cardiovascular disease	Ferritin > 1000 μg/L	
Transplantation or other immunosuppression	Lymphopenia < 500/mm³	
HIV with CD4 < 500/mm³		

Resp. rate: respiratory rate; rpm: respirations per minute; Heart rate: heart rate; bpm: beats per minute; FiO_2: fraction of inspired O_2; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; SpO_2/FiO_2: ratio of peripheral oxygen saturation to percentage of inspired oxygen; $PaCO_2$: partial pressure of carbon dioxide in arterial blood.
CPK: creatine phosphokinase; mod-sev CKD: moderate–severe chronic kidney disease; CRP: C-reactive protein; DM HbA1c: glycated haemoglobin in patients with diabetes mellitus; LDH: lactate dehydrogenase; HT: arterial hypertension; HIV: human immunodeficiency virus; CD4: CD4 lymphocytes or T4 lymphocytes.

and allow time for antibiotics to act, and also determine whether the root cause can be controlled or an invasive treatment is needed. The use of high doses of citrate may be more beneficial that heparin with the oXiris® membrane due to:

1. Greater membrane efficiency – there is less activation of leukocytes and platelets and therefore less saturation[22] and greater durability at peak performance.
2. The PEI surface treatment is not completely saturated with the initial sodium heparin flushing solution – more PEI is available for adsorption;
3. The unpredictable negative effect of heparin in patients with septic shock and ischaemia–reperfusion injury, which could cause inflammation and microthrombi in the microcirculation[23] and have disastrous effects on COVID-19 patients. Microthrombus involvement in the microcirculation has been described in autopsies of these patients[24];
4. Citrate, being a substrate of the respiratory cycle, can act at the mitochondrial level to improve metabolic alterations and keep respiratory complexes active, thus avoiding apoptosis[25];
5. Citrate can revive mitochondria and their respiratory and immunomodulatory function.[20]

We believe that combining an effective adsorptive cleaning strategy with oXiris®, with controlled convection that helps eliminate inflammatory molecules, together with the effect of citrate on the mitochondria can result in faster and better recovery. This opinion contrasts with other solely renal support approaches (Fig. 1). In patients with COVID-19 timing the start of the technique can be decisive, and for now we have to rely on epidemiological and clinical risk factors for this purpose (Fig. 2 and Table 1).

CONVEHY® COVID-19 is intended as an early use protocol or rescue technique. It is designed to act as an anticyclone for the cytokine storm, thus restoring proper immune function. Its effectiveness could make it suitable for use in dialysis centres and critical care units, where it can treat as many patients as possible.

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Conflict of interests

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Co-authors of the CONVEHY GROUP® RESEARCH:

1. Rafael García-Hernández. Specialist in Anaesthesiology and Resuscitation. Head of the Post-surgical Resuscitation Unit. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
2. María Isabel Espigares-López. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
3. Reyes Gámiz-Sánchez. Specialist in Anaesthesiology and Resuscitation. Internal Medicine specialist. Head of the Post-surgical Resuscitation Unit. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
4. Francisco Miralles-Aguiar. Specialist in Anaesthesiology and Resuscitation. Internal Medicine specialist. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
5. Francisco Javier Arroyo Fernández. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
6. Miguel Ángel Moguel-González. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz. Spain
7. Gonzalo García-Benito. Specialist in Anaesthesiology and Resuscitation. Internal Medicine specialist. Anaesthesiology and Resuscitation Service. Hospital Universitario de Salamanca. Spain
8. María Victoria García-Palacios. Specialist in Preventive Medicine. Preventive Medicine Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
9. Manuel Samper. Specialist in clinical analysis. Clinical Analysis Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
10. Beatriz Gómez Tapia. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
11. Patricia Martín Falcón. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
12. Pablo Jorge-Monjas. Specialist in Anaesthesiology and Resuscitation. Hospital Clínico Universitario de Valladolid. Spain
13. Carlos Márquez Rodríguez. M.D., Ph.D. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
14. Encarnación Meléndez Leal. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
15. Anabel Carnota Martín. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
16. Aurora Piña Gómez. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
17. Iván Ramírez Ogalla. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
18. Estefanía Cabezuelo Galache. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
19. Carmen Fernández Mangas. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
20. Carmen Fernández Riobó. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
21. Manuel Muñoz Alcántara. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
22. Manuel Mato Ponce. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
23. Francisco J Pérez Bustamante. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
24. Antonio Pérez Pérez. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
25. José Ramón Ferri Ferri. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
26. Ángela Gonzálvez Galinier. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
27. Pedro De Antonio del Barrio. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
28. María Borrego Costillo. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
29. Elena Borreiros Rodríguez. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
30. Irene Delgado Olmos. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
31. Ana Martínez-Almendro Fernández. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
32. Paula Lozano Hierro. Anaesthesiology resident Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain

33. Isidoro Jiménez Pérez. Haemofiltration nurse. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
34. Carlos García Camacho. Perfusionist nurse. Cardiovascular Surgery Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
35. Antonio Pernia Romero. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
36. María Jesús Sánchez del Pino. Department of Biomedicine, Biotechnology and Public Health. Biochemist. University of Cádiz – Spain
37. Manuel Antonio Rodríguez Iglesias. Department of Biomedicine, Biotechnology and Public Health. Biochemist. University of Cádiz.
38. Eduardo Tamayo Gómez. Specialist in Anaesthesiology and Resuscitation. Hospital Clínico Universitario de Valladolid. Spain
39. Gerardo Aguilar. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology Service. Consorcio Hospital General Universitario de Valencia. Spain
40. Manuel E. Herrera Gutiérrez. Internal Medicine specialist. Intensive care unit. Hospital Regional Universitario Carlos Haya. Spain
41. Luis Miguel Torres Morera. Specialist in Anaesthesiology and Resuscitation. Head of the Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain
42. Enrique Calderón Seoane. M.D., Ph.D. Specialist in Anaesthesiology and Resuscitation. Anaesthesiology and Resuscitation Service. Hospital Universitario Puerta del Mar, Cadiz – Spain

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.redar.2020.08.001.

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R. García-Hernández[a,*,1], M.I. Espigares-López[b,1], F. Miralles-Aguiar[c,1], R. Gámiz-Sánchez[d,1], F.J. Arroyo Fernández[b,1], A. Pernia Romero[e,1], L.M. Torres[f,1], E. Calderón Seoane[b,1], on behalf of the CONVEHY® Research Group[1]

[a] *Especialista en Anestesiología y Reanimación, Coordinador de la Unidad de Reanimación Postquirúrgica, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*
[b] *Especialista en Anestesiología y Reanimación, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*
[c] *Especialista en Anestesiología y Reanimación, Especialista en Medicina Intensiva, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*
[d] *Especialista en Anestesiología y Reanimación, Especialista en Medicina Interna, Coordinadora de la Unidad de Reanimación Postquirúrgica, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*
[e] *Especialista en Anestesiología y Reanimación, Jefe de Sección, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*
[f] *Especialista en Anestesiología y Reanimación, Jefe de servicio, Servicio de Anestesiología y Reanimación, Hospital Universitario Puerta del Mar, Spain*

[*] Corresponding author.
E-mail address: rafaghernandez@yahoo.es
(R. García-Hernández).
[1] All the authors have made substantial contributions in each of the following aspects: the conception and design of the study, or the acquisition of data, or the analysis and interpretation of the data, the draft of the article or the critical review of the intellectual content and the final approval of the version presented.

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The «new cerebral autoregulation curve», let's take a step further to keep learning☆

La «nueva curva de autorregulación cerebral», demos un paso más para seguir aprendiendo

Dear Editor,

The editorial by García-Orellana et al.[1] brings to mind Claude Bernard words: ''It is what we think we know already that often prevents us from learning''. The classic cerebral autoregulation curve described in the 1950s by Lassen is physiologically inaccurate and prevents us from correctly interpreting what happens in clinical practice. Perhaps the time has come to go beyond this model and deal more effectively with changes in cerebral blood flow.

Although the incidence of perioperative adverse cardiac events has decreased in recent years, there is evidence of an increase in the incidence of stroke. This is why maintaining cerebral perfusion is a problem that transcends neurosurgery or cardiac surgery. The ageing of the surgical population in the western world has raised awareness of the need to prevent perioperative neurocognitive disorders, which are related to other complications, prolong hospital length of stay, consume resources, and affect the quality of life of patients and their families.

Cerebral perfusion is a more complex process than that shown in the classic curve. In 2012, Tan[2] developed a new brain autoregulation curve. This author's investigations showed major intra- and interindividual variability in the shape of the curve, and revealed three things: first, that the autoregulation plateau is not always horizontal and is usually shorter than represented in the classic model – in some cases it may be reduced to a range of only 10 mmHg. Second, cerebral blood flow (CBF) adapts better to an increase in mean arterial pressure (MAP) than to a decrease in this pressure. And finally, the faster the MAP

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