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EDITORIAL (BY INVITATION) - BRAIN TRAUMA

Univariate comparison of PRx, PAx, and RAC—much ado about what?

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Traumatic brain injury (TBI) includes a variety of pathoanatomical and pathophysiological conditions with very different clinical course and outcome. Following the primary injury, a complex cascade of events determines the eventual clinical outcome. Measures to secure cerebral energy metabolism is initially in focus during neurocritical care. For this purpose, various bedside techniques have been developed to monitor cerebral biochemical and physiological variables. However, cerebral energy metabolism is not the only factor determining outcome. More complex cascade reactions—e.g., inflammation, neuroimmunological reactions—will contribute to tissue damage and clinical outcome. These complex reactions are less well known but increased knowledge and new monitoring techniques may in the future lead to new therapies.

Contrasting to the view that outcome after brain trauma is determined by complex cascade reactions, several reports have claimed that measurements of hydrostatic pressure alone—i.e., arterial blood pressure (AP) and intracranial pressure (ICP)—may be used to predict clinical outcome. From continuous measurements of these variables, a moving correlation coefficient between 30 consecutive 10-s mean windows (expected to reflect spontaneous slow-wave fluctuations in ICP) is derived. In this issue of *Acta Neurochirurgica*, Zeiler et al. [7] compare the outcome association for three related reactivity indices: PRx, PAx, and RAC. All three indices are expected to reflect cerebrovascular reactivity caused by variations in AP—cerebral pressure autoregulation.

Cerebral pressure autoregulation was first described in 1934 by the Danish neurologist Mogens Fog in his doctoral dissertation "*Om Piaarteriernes vasomotoriske Reaktioner*" later in part extended and published in English [2]. In the latter publication, the author summarized his view regarding the clinical importance of autoregulation: "The sensitiveness of the pial arteries to variations of the intravascular pressure is in the first place significant as an "emergency reaction," which comes into play when the auto-regulation of the systemic blood pressure fails, or, rather, is insufficient. It prevents, within certain limits, a rise of the capillary pressure during a rise in systemic blood pressure and thus protects the brain against injurious œdema. When the systemic blood pressure falls following hemorrhage or shock this vascular reaction conduces to the maintenance of the cerebral blood flow by a reduction of the local peripheral vascular resistance."

In his experimental studies, Mogens Fog used a cranial window technique for measuring and recording of pial arterial diameters at variations of the arterial blood pressure. With the development of various techniques for measuring cerebral blood flow (CBF) in man, autoregulation could also be studied in volunteers and under clinical conditions [3]. For obvious reasons, a correct evaluation of cerebral vascular resistance can only be obtained by simultaneous quantitative measurements of CBF and cerebral perfusion pressure. The three methods mentioned above (PRx, PAx, RAC) were developed to circumvent this problem by introducing a surrogate technique that could be used for continuous bedside evaluation of cerebral vasoreactivity. By comparison with other techniques, it has been shown that PRx gives information regarding cerebral autoregulation during standardized control conditions [6]. However, when used in neurocritical care for several days, simultaneous changes in AP and ICP will occur that are not related to autoregulation (e.g., due to variations in energy metabolism by variation in sedation level, stress reactions etc.). In clinical routine, these episodes will intermingle with the data reflecting pressure autoregulation which will interfere with the interpretation.

In defense of the PRx technique, it is often stressed that the data obtained have repeatedly been shown to correlate with

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clinical outcome and that the technique may be used for outcome prediction [1, 5]. In view of the fact that secondary brain injuries are caused by complex cascade reactions, it might seem unexpected that information obtained from measurements of hydrostatic pressure alone would predict clinical outcome. As we have no reason to believe that impaired cerebral vasoreactivity per se may cause tissue damage, its influence on outcome should be expected to be mediated via known physiological and biochemical mechanisms.

According to the three methods studied (PRx, PAx, RAC), periods of impaired cerebral vasoreactivity alternated with periods of normal reactivity in the studied patients. The prediction of clinical outcome is in the study shown to be related to the duration of impaired vasoreactivity compared to the total duration of intensive care. In the Tables, this relation is given as percent. For PRx, the following data are presented:

	Alive	Dead	*p* value
% time PRx > 0	50	67	< 0.0001
	Favorable	Unfavorable	*p* value
% time PRx > 0	49	59	0.002

Although the time periods with impaired vasoreactivity constitute a high percentage of the total time irrespective of clinical outcome, the statistical comparison reveals a remarkably high significance. For the two other studied methods (PAx, RAC) and for other cutoff levels for evaluation of impaired vasoreactivity, the results were similar. The clinical relevance of the presented data needs a critical discussion.

Obviously, the time period with impaired vasoreactivity constituted a large part of the intensive care period irrespective of clinical outcome. Although a highly significant statistical difference was obtained when a large group of patients was studied, it seems unlikely that the presented limited differences in duration of impaired autoregulation could be used in clinical practice or for choice of therapy in the individual patient. Further, calculation of the percentage of time with impaired vasoreactivity cannot be performed until intensive care is terminated. What is the clinical relevance of predicting mortality and unfavorable outcome when the period of critical care has already passed?

This large multicenter study has shown that mortality and unfavorable outcome is related to the length of time of impaired vasoreactivity during neurocritical care and independent of the initial trauma as admittance GCS score was not related to outcome. As there is no reason to believe that vasoreactivity per se is related to tissue damage, other explanations should be considered. Impaired pressure autoregulation may—as already suggested by Mogens Fog in 1938—increase cerebral vulnerability to a pronounced increase as well as decrease in systemic AP. The obvious and expected result of the present multicenter study is accordingly that the risk of such secondary adverse events is increased when the time period of impaired vasoreactivity is increased. However, the limited clinical relevance remains: the period of time with impaired vasoreactivity cannot be assessed until the intensive care is terminated.

In neurocritical care, several techniques are available for bedside evaluation of cerebral biochemical and physiological variables that are directly related to secondary brain damage and tissue outcome [4]. When these techniques are used and interpreted correctly, the information obtained bedside can be used to direct appropriate therapy, decrease tissue damage, and improve clinical outcome. Contrasting to these quantitative techniques, various surrogate markers for cerebral vasoreactivity have been presented and extensively studied. A number of parallel and almost identical reports have lately been published including multicenter studies with large number of patients. These studies may generate statistically highly significant results for groups of patients that appear to be of little clinical relevance for the individual patient.

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