Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data

Clinical article

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Object. In severe traumatic brain injury, a universal target for cerebral perfusion pressure (CPP) has been abandoned. Attempts to identify a dynamic CPP target based on the patient’s cerebrovascular autoregulatory capacity have been promising so far. Bedside monitoring of pressure autoregulatory capacity has become possible by a number of methods, Czosnyka’s pressure reactivity index (PRx) being the most frequently used. The PRx is calculated as the moving correlation coefficient between 40 consecutive 5-second averages of intracranial pressure (ICP) and mean arterial blood pressure (MABP) values. Plotting PRx against CPP produces a U-shaped curve in roughly two-thirds of monitoring time, with the bottom of this curve representing a CPP range corresponding with optimal autoregulatory capacity (CPPopt). In retrospective series, keeping CPP close to CPPopt corresponded with better outcomes. Monitoring of PRx requires high-frequency signal processing. The aim of the present study is to investigate how the processing of the information on cerebrovascular pressure reactivity that can be obtained from routine minute-by-minute ICP and MABP data can be enhanced to enable CPPopt recommendations that do not differ from those obtained by the PRx method, show the same associations with outcome, and can be generated in more than two-thirds of monitoring time.

Methods. The low-frequency autoregulation index (LAx) was defined as the moving minute-by-minute ICP/MABP correlation coefficient calculated over time intervals varying from 3 to 120 minutes. The CPPopt calculation was based on LAx-CPP plots and done for time windows between 1 and 24 hours and for each LAx type. The resulting matrix of CPPopts were then averaged in a weighted manner, with the weight based on the goodness of fit of a U-shape and the lower value of the LAx corresponding to the U-bottom, to result in a final CPPopt recommendation. The association between actual CPP/CPPopt and outcome was assessed in the multicenter Brain Monitoring with Information Technology Research Group (BrainIT) database (n = 180). In the Leuven-Tübingen database (60-Hz waveform data, n = 21), LAx- and PRx-based CPPopts were compared.

Results. In the BrainIT database, CPPopt recommendations were generated in 95% of monitoring time. Actual CPP being close to LAx-based CPPopt was associated with increased survival. In a multivariate model using the Corticosteroid Randomization After Significant Head Injury (CRASH) model as covariates, the average absolute difference between actual CPP and CPPopt was independently associated with increased mortality. In the high-frequency data set no significant difference was observed between PRx-based and LAx-based CPPopts. The new method issued a CPPopt recommendation in 97% of monitoring time, as opposed to 44% for PRx-based CPPopt.

Conclusions. Minute-by-minute ICP/MABP data contain relevant information for autoregulation monitoring. In this study, the authors’ new method based on minute-by-minute data resolution allowed for CPPopt calculation in nearly the entire monitoring time. This will facilitate the use of pressure reactivity monitoring in all ICUs.

* Abbreviations used in this paper: BrainIT = Brain Monitoring with Information Technology Research Group; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CPPopt = optimal CPP; CRASH = Corticosteroid Randomization After Significant Head Injury; DATACAR = Dynamic Adaptive Target of Active Cerebral Autoregulation; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; IQR = interquartile range; LAx = low-resolution autoregulation index; MABP = mean arterial blood pressure; Mx = mean arterial Doppler flow velocity based autoregulation index; PRx = pressure reactivity index; RMSE = root mean squared error; TBI = traumatic brain injury.

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pressure (CPP) is the pressure gradient for cerebral blood flow to the brain, expressed as the difference between the mean arterial blood pressure (MABP) and the ICP. Based on experimental and clinical work by Rosner and Daugh- ton, the original recommendation was to target CPP at 70 mm Hg or higher. A randomized trial comparing CPP-targeted therapy with ICP-targeted therapy only could not demonstrate a benefit for this strategy. Moreover, low CPP protocols, first introduced in Lund, Sweden, did not seem to negatively affect outcome. As a consequence, the CPP target guideline of 70 mm Hg and later 60 mm Hg in TBI was abandoned in the 2007 revision of the Brain Trauma Foundation guidelines for the management of severe TBI.

In recent years, a more dynamic patient-tailored CPP target, based on the autoregulation capacity of the patient’s cerebral vasculature, has been proposed. Cerebrovascular pressure autoregulation is the capacity of the cerebrum to maintain a constant cerebral blood flow (CBF) through varying CPP by adapting the basal tone of the arteriolar smooth muscles. It is well known that autoregulation is often deficient in severe TBI, albeit that the degree and range of this dysfunction can vary among patients, and in time within the same patient. Howells et al. were the first to successfully provide proof of concept for the idea of autoregulation-based management by demonstrating a relation between the ICP/MABP correlation coefficient and outcome in 2 distinct retrospective patient cohorts in 2 centers with different treatment protocols. However, an adaptive CPP target based on the autoregulatory status of the patient has not been tested prospectively. To investigate this as a strategy, a continuous measure for autoregulation is needed. Czosnyka et al. have pioneered such a tool by developing the pressure reactivity index (PRx) as a continuous measure for cerebrovascular autoregulation, by calculating ICP changes in reaction to slow wave variability (30–200 seconds) of the blood pressure. The PRx is calculated as the moving correlation coefficient between 40 consecutive 5-second averages of ICP and MABP based on signal capture at a frequency of at least 60 Hz. PRx was shown to correlate with outcome. Moreover, PRx appeared to be affected by CPP in such a way that plotting PRx against CPP produced a U-shaped curve in about 60% of patients, enabling to define the CPP range correlating with optimal autoregulatory capacity as the CPP range corresponding to the bottom of the U-shaped curve (that is, CPPopt). It was demonstrated in retrospective studies that outcome was better in patients with a mean actual CPP close to the mean CPPopt.

Because PRx calculation requires additional software solutions to extract continuous waveform data from the bedside monitor, thus far PRx monitoring has been limited to research-minded academic centers. Other measures of autoregulation, based on transcranial Doppler flow velocity measurement, laser Doppler flowmetry, or brain tissue oxygenation (PbtO2) monitoring require additional expertise and/or the placement of additional expensive probes. Moreover, none of the methods proposed so far is able to issue CPP recommendations during the entire critical phase after TBI.

The present study investigates how the processing of the information on cerebrovascular pressure reactivity that can be obtained from routine minute-by-minute ICP and MABP data can be enhanced to enable CPPopt recommendations in as much monitoring time as possible and to validate such method against the PRx method. The eventual goal is to provide neurosurgeons and neurointensivists with a practical software tool that should allow them to calculate pressure reactivity and optimal CPP at the bedside based on routine data capture, and, hence, enable autoregulation-steered CPP management without investment in additional equipment.

Methods

Data

The Brain Monitoring with Information Technology Research Group (BrainIT) database collected information from 264 consecutive TBI patients with ICP monitoring admitted to 22 neuro-ICUs in 11 European countries between March 2003 and July 2005. Among others, baseline risk factors, minute-by-minute ICP and MABP monitoring data, and Glasgow Outcome Scale (GOS) score at 6 months were registered. Complete data on ICP and MABP measurements for the first 48 hours of the ICU stay and GOS score at 6 months were available in 180 patients. The Multi-Centre Research Ethics Committee for Scotland approved the use of these data for scientific purposes on February 14, 2002. All BrainIT centers obtained local ethics committee approval, and the need for informed consent was waived. Artifacts in the data were removed during the validation phase of this database. Moreover, signals were independently and manually checked again by 2 clinicians in Leuven (first and last authors), and artifacts and questionable data were removed. The second data set comprised 21 patients who were admitted to the ICUs of the University Hospitals Leuven, Belgium, between September 2010 and March 2012 and Universitätsklinikum Tübingen, Germany, between February and December 2009. Both centers routinely monitor and collect data from their TBI patients, including 60-Hz waveform ICP and MABP data (for calculation of PRx and PRx-based CPPopt via ICM+ software, Cambridge Enterprises). Data collection also includes demographic and injury data, including baseline risk factors, and 6-month GOS scores. All data referring to the identity of the patients were removed, and ethics committee approval was obtained in Leuven as well as in Tübingen to use these data for retrospective data analysis. Artifacts were removed by 2 Leuven clinicians (first and last authors) who independently and manually checked all signals. Both data sets are described in detail in Table 1.

LAx and DATACAR

The low-resolution autoregulation index (LAx) for time interval t at a given time t(0) was calculated as the correlation coefficient between minute-by-minute measurements of ICP and MABP for the time interval [t(i−x+1), t(i)]. For the present study, LAx values were calculated for the time intervals 3, 5, 10, 20, 30, 60, 90, and 120 minutes.
CPP target recommendation in severe traumatic brain injury

**TABLE 1: Patient demographic information**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BrainIT (n = 180)</th>
<th>Leuven-Tübingen (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>median age in yrs (IQR)</td>
<td>33 (21–51)</td>
<td>49 (31–66)</td>
</tr>
<tr>
<td>% male sex</td>
<td>80.0</td>
<td>61.9</td>
</tr>
<tr>
<td>mechanism of trauma: %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>road traffic accident</td>
<td>37.8</td>
<td>23.8</td>
</tr>
<tr>
<td>pedestrian</td>
<td>8.9</td>
<td>0.0</td>
</tr>
<tr>
<td>assault</td>
<td>8.9</td>
<td>0.0</td>
</tr>
<tr>
<td>work</td>
<td>2.8</td>
<td>0.0</td>
</tr>
<tr>
<td>sport</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>fall</td>
<td>31.7</td>
<td>66.7</td>
</tr>
<tr>
<td>unknown/missing</td>
<td>6.6</td>
<td>9.5</td>
</tr>
<tr>
<td>GCS (total/15) on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>7 (5–10)</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td>% missing</td>
<td>6.7</td>
<td>9.5</td>
</tr>
<tr>
<td>pupil reactivity at the accident: %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>both reacting</td>
<td>71.1</td>
<td>85.7</td>
</tr>
<tr>
<td>1 reacting</td>
<td>7.8</td>
<td>4.8</td>
</tr>
<tr>
<td>neither reacting</td>
<td>12.2</td>
<td>4.8</td>
</tr>
<tr>
<td>untestable/missing</td>
<td>8.9</td>
<td>4.8</td>
</tr>
<tr>
<td>presence of extracranial injury: %</td>
<td>58.3</td>
<td>33.3</td>
</tr>
<tr>
<td>median GOS (IQR)</td>
<td>4 (3–5)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>% mortality</td>
<td>17.0</td>
<td>19.0</td>
</tr>
<tr>
<td>median LOS in days (IQR)</td>
<td>13 (7–23)</td>
<td>23 (12–27)</td>
</tr>
</tbody>
</table>

* GCS = Glasgow Coma Scale; LOS = length of stay.

For continuous CPPopt calculation we applied Steiner’s	extsuperscript{3} and Aries’	extsuperscript{2} method of plotting CPP and PRx, and fitting a U-shaped curve, with the most negative value of the autoregulation index indicating a 5–mm Hg range of optimal CPP. However, instead of limiting this to the previous 4 hours of data as in the method of Aries, we applied this method on time windows of 1, 2, 4, 6, 8, 12, and 24 hours and did this for each LAx defined above. Hence, for each t(0), 45 plots were generated. These plots were given a weight based on 2 criteria: the better a U-shaped curve could be fitted and the lower the LAX-value corresponding to the plot-specific CPPopt, the higher the weight. The final resulting CPPopt of our method was computed as the weighted average of the plot-specific CPPopts (Fig. 1). This final CPPopt was then rounded and presented as the middle of a 5–mm Hg recommended CPP range. The rationale of this more elaborate method of CPPopt calculation was to optimize the capacity of detection of glimpses of active autoregulation in the registered monitoring data over the past period (with a maximum retrospective scope of 24 hours). We named this method the “dynamic adaptive target of active cerebral autoregulation” (DATACAR), in which the term “dynamic” refers to the use of time windows of varying lengths to determine the CPP zone where the most active autoregulation is present.

**Analyses Based on the BrainIT Database**

Based on the DATACAR method, a recommended CPPopt range was calculated for each minute of the first 48 hours of monitoring. We concentrated on the first 48 hours after admission to the ICU for 2 reasons. First, the largest differences in outcome in relationship with the autoregulatory status of the patients can be observed in the first 2 days of monitoring.	extsuperscript{2,4} Second, we wanted to avoid bias introduced by differences in monitoring time duration. We calculated the percentage of time during which a CPPopt recommendation could be given and studied the contribution of the different time windows in the CPPopt calculation. The accordance between CPPopt and actual CPP and its association with survival was calculated in 6 ways: 1) the percentage of time for which the actual CPP was within the recommended CPPopt range; 2) the average absolute difference between actual CPP and CPPopt; 3) the average absolute difference when actual CPP was outside the CPPopt range; 4) the average difference where actual CPP was below CPPopt; 5) the average difference where actual CPP was above CPPopt; and 6) the average absolute difference between actual CPP and CPPopt was used in a multivariate logistic regression model together with the CRASH basic model risk factors age, GCS, pupillary reaction, and presence of extracranial injury.

**Analyses Based on the Leuven-Tübingen Database**

The multicenter Leuven-Tübingen data set was used to compare the DATACAR-based CPPopt recommendations with the high-resolution PRx-derived CPPopt recommendations. First, the absolute values of DATACAR- and PRx-based CPPopt recommendations were compared. Second, the proportion of time a CPPopt recommendation could be calculated was evaluated for both methods. Third, the association of the accordance between actual CPP and CPPopt and mortality was assessed (univariately). Analyses were performed for the first 48 hours of monitoring.

**Data Analysis and Statistics**

The building of the indices (LAx variants and PRx), calculation of CPPopt for both methods, and the univariate and multivariate statistics were done using Matlab (version B2011b, MathWorks). Student t-tests were used to compare recommended calculated CPPopt values calculated by both the DATACAR and the PRx method. Wilcoxon ranking tests were used to assess the associations between actual CPP/CPPopt relations and survival. As for assessing the multivariate relation between survival on the one hand and the actual CPP/CPPopt relations and CRASH variables on the other hand, multivariate logistic regression was used.

**Results**

**BrainIT Database Analyses**

The DATACAR method was able to produce a CPPopt recommendation in 95% (90%–97%) of monitoring time (median and IQR) in the first 48 hours. The 1-hour time window contributed to 18.7% of CPPopt recommendations and the 2-, 4-, 6-, 8-, 12-, and 24-hour windows to 20.4%, 19.1%, 14.7%, 11.9%, 9.7%, and 5.5%, respectively.
The percentage of monitoring time during which actual CPP was within the CPPopt range was significantly higher in survivors than in nonsurvivors (25.6% vs 19.7%, p = 0.01), and actual CPP was significantly closer to CPPopt in survivors (average absolute difference was 5.2 mm Hg for survivors and 6.9 mm Hg for nonsurvivors, p = 0.01). The average absolute differences outside the CPPopt range were significantly larger for nonsurvivors (8.5 mm Hg vs 7 mm Hg, p = 0.01). Deviations in the positive sense were higher in nonsurvivors (8.0 vs 6.8 mm Hg, p = 0.05), and the same was true for deviations in the negative sense (−8.4 vs −6.7 mm Hg, p = 0.01). In a multivariate logistic regression model using the CRASH outcome prediction model variables age, Glasgow Coma Scale (GCS) score, pupillary reactivity, and presence of extracranial injury as covariates, the average absolute difference between actual CPP and CPPopt in the first 48 hours after ICU admission remained an independent and negative predictor of survival (Table 2).

**Leuven-Tübingen Database Analyses**

Evaluating the difference per patient between CPPopts obtained by both methods resulted in a root mean squared error (RMSE) of 7.35 ± 1.72 mm Hg (±SD), a mean absolute error of 5.60 ± 1.83 mm Hg, and a mean error of −0.25 ± 3.89 mm Hg. Furthermore, 71.4% of all the differences between CPPopts for each minute that both methods produced a CPPopt over the first 48 hours for all patients were within −5 mm Hg and 5 mm Hg (Fig. 2). There was no statistically significant difference between the per-patient medians of CPPopt for DATACAR and PRx (p = 0.802), which had medians of 72.5 mm Hg (IQR 62.5–77.5 mm Hg) and 72.5 mm Hg (IQR 67.5–77.5 mmHg), respectively.

The DATACAR method was able to produce a CPPopt recommendation in a median 97% (IQR 94%–98%) of monitoring time, whereas the PRx-based method could issue a recommendation in a median 44% (IQR 31%–55%) and could only issue a recommendation for more than 5% of the duration for 1 nonsurviving patient. Differences between nonsurvivors and survivors were only statistically significant for the DATACAR method regarding deviations in the negative sense (−10.0 mm Hg vs −6.1 mm Hg, p = 0.04); likewise, average absolute values outside the CPPopt range were significantly larger for nonsurvivors (9.6 mm Hg vs 5.8 mm Hg, p = 0.01).

**Discussion**

Building on the method developed by Steiner and Aries for CPPopt determination, the novelty of the current method lies in both the use of minute-by-minute ICP
and MABP data and in the combination of correlation coefficients (LAx values) over different time intervals with CPPopt calculation over different time windows. The multiple resulting CPPopts were then combined in a weighted manner into a final CPPopt recommendation. Hence, autoregulation was investigated in a dynamic way by scanning different time scales to maximally exploit and optimize the potential information on cerebrovascular pressure reactivity capacity within routinely obtained monitoring data. This method is compatible with fully automated processing and, hence, can easily be programmed in common software, as in common patient data management systems.

In the retrospective study based on the BrainIT database, the actual CPP being closer to the CPPopt recommendation was independently associated with increased survival. Moreover, no significant difference in the recommended CPPopt could be found when both the PRx method and the DATACAR method were compared in the Leuven-Tübingen database. Importantly, DATACAR was able to issue a recommendation almost all the time in the first 48 hours of ICU stay, which means a significant improvement of the performance of the CPPopt concept.

In the landmark paper by Howells et al., pressure reactivity was determined as a single coefficient for the entire monitoring period of the patient. Such a long time interval allows for retrospective determination of pressure reactivity but does not have the temporal resolution required for clinical decision making. In the PRx methodology, slow variations in MABP are used to calculate MABP/ICP correlations. As a consequence, the PRx method requires high-resolution data (at least 60 Hz). It was demonstrated that PRx becomes clearly positive in episodes of ICP plateau waves, refractory intracranial hypertension, and arterial hypotension and hypertension, that episodes of positive PRx correlate with a disturbed transcranial Doppler–derived index of autoregulation, and that averaged PRx negatively correlates with outcome, all suggesting a strong effective relationship between PRx and actual autoregulation capacity. More recently, in a small study of 18 patients with intracerebral hemorrhage, a moving correlation coefficient of minute-by-minute MABP and ICP over a 20-minute time window, called L-PRx, has been shown to correlate well with the original PRx and was able to generate CPPopt recommendations in the same range. We have been able to demonstrate in a previous study on the BrainIT database that the ICP/MABP correlation, calculated on minute-by-minute data, was a significant predictor of future critical elevations of ICP as well as of unfavorable outcome. These data support the results of the present study, that is, that the minute-by-minute resolution is sufficiently accurate to monitor pressure autoregulation in TBI patients.

The results of the present study also add to the body of evidence for the hypothesis that a universal CPP threshold or even a fixed CPP target valid for all patients cannot be recommended and that a dynamic CPP target based on pressure autoregulatory capacity likely represents a more promising concept. Interestingly, it was shown that not only negative deviations from CPPopt resulted in poorer outcomes, but also positive deviations did. In other words, too high CPP, at the right side of autoregulatory capacity in the CBF-CPP plot, also resulted in a detrimental effect.

The current study has a number of limitations. First, LAx and DATACAR have been developed by retrospective data analysis and have not yet been validated in a pro-

![Figure 2](image-url)
spective clinical setting. Second, the presented method is computational. Studying the effect of arteriolar vasoconstriction and vasodilation through its effect on ICP will inevitably include a dampening effect. This is also true for other proposed indices of cerebrovascular reactivity, such as the Ursino model, based on the mathematical modeling of different vascular pressures and ICP including interactions based on CO₂ reactivity and CSF flow,¹⁴,²⁶ or the Ragauskas noninvasive method based on the assessment of the phase shift between MABP variation secondary to the respiratory cycle and ultrasound-based capture of intracranial blood volume waves.²⁶ Other models describe the transfer function analysis between arterial blood pressure and flow velocity in the middle cerebral artery, measured by transcranial Doppler.¹²,²⁵ Mx describes variations in flow velocity, measured at the middle cerebral artery vessels secondary to variations in CPP, and has been shown to correlate with PRx.³ We do have to keep in mind that all methods described represent attempts to indirectly assess the physiological phenomenon of changes in cerebrovascular smooth muscle tone secondary to altered intravascular pressure. None of the methods was validated directly by juxtaposing it to the actual smooth muscle cell phenomenon in an in vivo animal experiment. Nevertheless, all models do describe direct consequences of pressure reactivity and intact or deficient pressure autoregulation and, hence, can be considered to be reflections of the actual phenomenon, as shadows in Plato’s cave. The association of the indices and derived CPPopt recommendations and outcome, albeit retrospectively, provides additional evidence for the hypothesis that the indices do describe an actual physiological phenomenon.

The results of the current study demonstrate that continuous monitoring of pressure autoregulatory capacity based on standard resolution physiological monitoring data are equivalent to pressure autoregulation monitoring based on capturing waveform quality physiological data. Moreover, the tools presented here enable to significantly increase the percentage of monitoring time for which a CPPopt recommendation could be given. Consequently, DATACAR-based CPPopt recommendation enables for pressure autoregulation steered CPP management without investment in waveform data capture equipment, making the technique widely applicable in most ICUs.

A recent randomized controlled trial in TBI patients in low-income countries could not demonstrate a difference in outcome of an ICP-lowering strategy based on invasive ICP monitoring versus management based on imaging and clinical examination.⁴ These findings suggest that the measurement of a certain clinical parameter per se is not likely to change outcome, but rather the reaction and therapeutic strategy upon changes in this clinical parameter. A clinical trial on autoregulation monitoring–based CPP management in TBI patients is thus likely to have a complex design. The developed indices in the present study contribute to the feasibility of such trial, and to the rationale for autoregulation-driven CPP management. Meanwhile, prospective validation of the tool developed in the current study is adamant, and initiatives for such studies are being developed.

Conclusions

The present study presents a computational method based on which it is demonstrated that minute-by-minute ICP/MABP data contain relevant information for autoregulation monitoring in TBI patients. Moreover, the new method allowed for CPPopt calculation in nearly the entire monitoring time. The method, which can easily be programmed in an automated tool at the bedside, has the potential to make the technique of pressure autoregulation steered management widely applicable in most ICUs.

Acknowledgments

We wish to acknowledge the BrainIT steering members: Iain Chambers, Giuseppe Citerio, Bart Depreitere, Per Enblad, Barbara Gregson, Tim Howells, Julia Mattern, Pelle Nilsson, Ian Piper, Arminas Ragauskas, and Juan Sahuquillo.

Disclosure

The present study was supported by the Foundation for Scientific Research Flanders (Fonds voor Wetenschappelijk Onderzoek Vlaanderen, FWO) (Research project G. 0904.11). Geert Meyfroidt receives funding from FWO as senior clinical investigator (1846113N). Geert Van den Berghé receives long-term structural research financing via the Flemish Government (METH/08/07). BrainIT data collection was supported by The European Framework Programme (FP5-QLRI-2000-00454, QLG-2002-00160, and FP7-IST-2007-217049). The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Depreitere, Güiza, Meyfroidt. Acquisition of data: Depreitere, Schuhmann, Maier, Piper, Meyfroidt. Analysis and interpretation of data: Depreitere, Güiza. Drafting the article: Depreitere. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Depreitere. Statistical analysis: Güiza. Administrative/technical/material support: Van den Berghé, Maier, Piper.

References

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