

## VIEWPOINT

# How much oxygen in adult cardiac arrest?

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See related commentary by Gershengorn, <http://ccforum.com/content/18/5/556>

### Abstract

Although experimental studies have suggested that a high arterial oxygen pressure (PaO<sub>2</sub>) might aggravate post-anoxic brain injury, clinical studies in patients resuscitated from cardiac arrest (CA) have given conflicting results. Some studies found that a PaO<sub>2</sub> of more than 300 mm Hg (hyperoxemia) was an independent predictor of poor outcome, but others reported no association between blood oxygenation and neurological recovery in this setting. In this article, we review the potential mechanisms of oxygen toxicity after CA, animal data available in this field, and key human studies dealing with the impact of oxygen management in CA patients, highlighting some potential confounders and limitations and indicating future areas of research in this field. From the currently available literature, high oxygen concentrations during cardiopulmonary resuscitation seem preferable, whereas hyperoxemia should be avoided in the post-CA care. A specific threshold for oxygen toxicity has not yet been identified. The mechanisms of oxygen toxicity after CA, such as seizure development, reactive oxygen species production, and the development of organ dysfunction, need to be further evaluated in prospective studies.

### Introduction

Sudden cardiac arrest (CA) is the leading cause of death among adults worldwide [1,2]. In most patients, attempts at cardiopulmonary resuscitation (CPR) remain ineffective and spontaneous cardiac activity cannot be restored [3]. Among those patients who do achieve return of spontaneous circulation (ROSC), there are two key periods when death may occur: early (during the first three days), usually because of recurrent CA or severe cardiovascular failure resulting in multiple organ failure (MOF), and late (beyond day 3), usually secondary to withdrawal of life-sustaining therapies in the absence of neurological recovery [4]. Although several interventions, including target temperature management (TTM), have been introduced into the post-CA care of these patients [5,6], conflicting results have been obtained [7], and these approaches are not sufficient to prevent the deleterious consequences of brain ischemia in all patients. During the post-CA care, secondary brain insult must be avoided [8] and optimization of brain oxygenation is likely to be an important component of brain recovery. The restoration of adequate systemic hemodynamics is a prerequisite to provide adequate cerebral blood flow in CA patients [9,10], but brain oxygenation is also determined by

the arterial oxygen content. Arterial oxygen pressure (PaO<sub>2</sub>) itself may influence brain cellular oxygen supply; if hypoxemia (that is, PaO<sub>2</sub> of less than 60 mm Hg) is associated with poor outcomes after CA [11], a high PaO<sub>2</sub> may also be detrimental in a vulnerable brain, as suggested in patients with traumatic brain injury or stroke [12,13]. The aims of this article are to review the potential mechanisms of oxygen toxicity after CA and to discuss the clinical impact of oxygen management on post-CA care.

### Post-cardiac arrest syndrome: the role of oxygen

Post-cardiac arrest syndrome (PCAS) is a complex phenomenon, which shares several features with septic shock [7,14]. In particular, PCAS includes a systemic inflammatory response that can be triggered by the ischemia-reperfusion injury and also specific precipitating events, such as concomitant infections or heart disease. Moreover, PCAS can contribute to brain injury and myocardial dysfunction and can rapidly lead to MOF. The primary ischemia-reperfusion injury [15] activates various intracellular pathways, promoting ion concentration disequilibrium with increased intracellular levels of inorganic phosphate, lactate, and H<sup>+</sup>, and resulting in an influx of calcium into the cell [16], which aggravates mitochondrial dysfunction and eventually leads to programmed cellular death (apoptosis). After reperfusion has

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occurred, other mediators, including superoxide ( $O_2^-$ ), peroxynitrite ( $ONOO^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radicals ( $OH^\cdot$ ), contribute to worsen cellular function by oxidizing and damaging numerous cellular components [17] (Figure 1). These reactive oxygen species (ROS) then have a central role in initiating and enhancing the post-ischemic damage [15]. Indeed, supra-normal oxygen concentrations in this context may further stimulate ROS production and contribute to worsen cellular function in a setting of impaired mitochondrial function and impaired oxygen utilization. Moreover, some other systemic detrimental effects of hyperoxemia have been known for many years [18-20]. Hyperoxemia causes systemic and coronary vasoconstriction, which can decrease cardiac output and induce myocardial ischemia. In some experimental models of global cerebral ischemia, hyperoxemia has been shown to be detrimental to the brain, probably also because of its vasoconstrictor effects [21,22]. Hyperoxemia may also provoke or exacerbate seizures, which could aggravate brain injury [23,24].

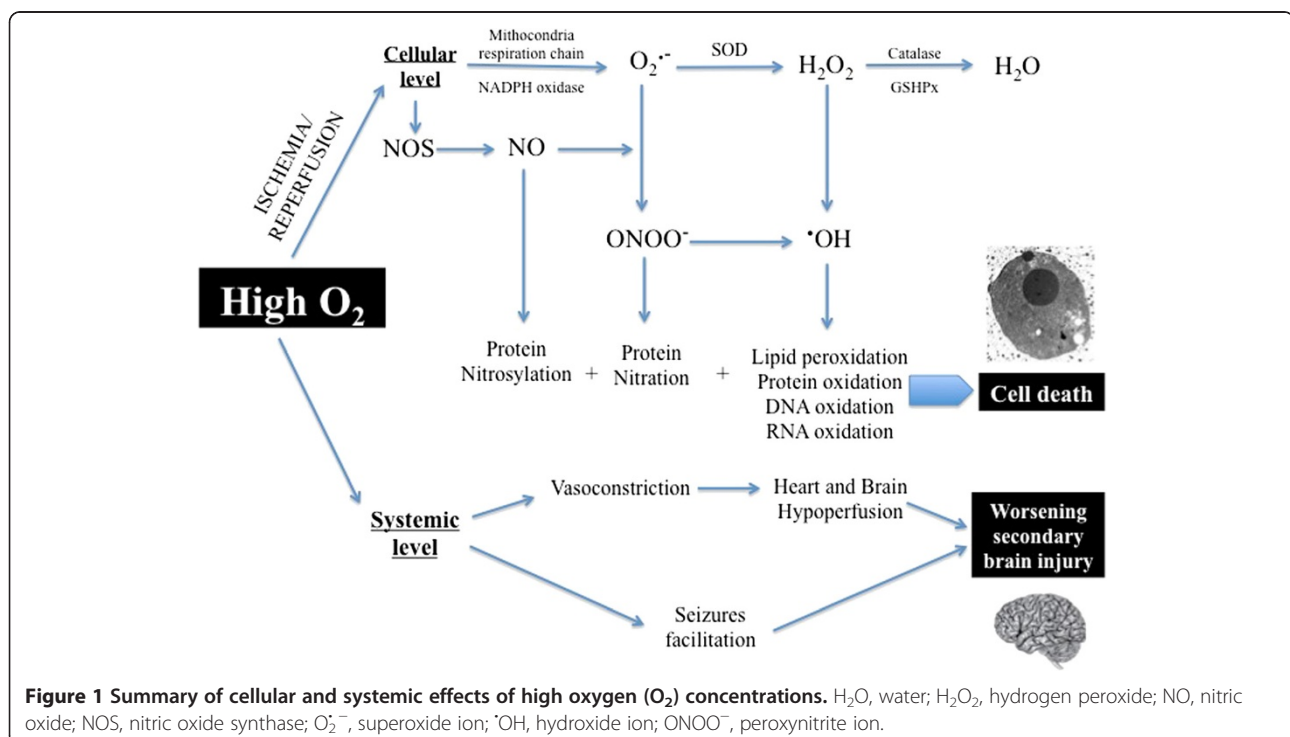
### Oxygen therapy after cardiac arrest: animal studies

Several studies have assessed the effects of administering high oxygen concentrations in experimental models of CA. Pilcher and colleagues [25] recently reviewed studies that evaluated the role of different oxygenation strategies - that is, one with 100% inspired oxygen fraction ( $FiO_2$ ) and the other with lower  $FiO_2$  as a control - after ROSC. Six studies including 95 animals of different species were included in their final meta-analysis; in general, administration

of high  $FiO_2$  (100%) for 1 hour after ROSC resulted in a worse neurological outcome, as assessed by a neurological deficit score, than other  $FiO_2$  values. Four of the five studies that assessed histological damage reported a significantly higher neuronal injury with high  $FiO_2$ ; cerebral metabolic function was also more altered in the high  $FiO_2$  group. The extrapolation of such findings to humans, however, may be misleading. First, in all of these experimental studies, the animals were already mechanically ventilated before CA, and this is not usually the case in humans; also, control animals did not all receive the same  $FiO_2$  (ranging from 21% to higher levels based on  $PaO_2$  values), and the intervention period was rather short (that is, 1 hour). Moreover, different models of CA were employed (that is, asphyxia versus electrical-induced ventricular fibrillation), with shorter durations of CPR than in humans, and in some articles clear  $PaO_2$  targets were aimed at, whereas in others only  $FiO_2$  was modified without looking at  $PaO_2$  values. In addition, no potential neuroprotective therapy, such as TTM, was provided, so that its influence cannot be ascertained. In summary, animal data have highlighted a clear correlation between the application of high  $FiO_2$  after CA and poor neurological recovery. Nevertheless, experimental models are quite remote from the human setting, so that the observations cannot be readily translated to humans in the post-CA management.

### Oxygen after cardiac arrest: human studies

Two studies reported conflicting results regarding oxygen management during the early phase of CA (Table 1).



**Table 1 Summary of clinical studies evaluating the role of oxygen concentrations on outcome after cardiac arrest**

Reference	Type	Patients (period)	% of HO	OHCA	Definition HO	Evaluation	TH (% treated)	Cutoff <sup>a</sup>	Outcome	Main results
During CPR										
Spindelboeck <i>et al.</i> [26]	R	145 (8 years)	14%	100%	>300 mm Hg	During CPR	NA	NR	In-hospital CPC	Higher rate of hospital admission in hyperoxemic patients
After ROSC										
Kuisma <i>et al.</i> [27]	RCT	28 (NA)	50%	100%	1 hour of ventilation at FiO <sub>2</sub> 100%	24- and 48-hour	No (50%)	No	NSE and S100B	No difference in biomarkers of brain injury
Post-CA care (ICU stay)										
Kilgannon <i>et al.</i> [28]	R/D	6,326 (5 years)	18%	43%	First ABG >300 mm Hg	24-hour	NR ≈ 6%	No	In-hospital death Neurological function	Increased hospital mortality in hyperoxemic patients
Kilgannon <i>et al.</i> [29]	R/D	4,459 (5 years)	18%	45%	First ABG	24-hour	NR ≈ 6%	No	In-hospital death Neurological function	Increased hospital mortality for every 100 mm Hg increase in PaO <sub>2</sub>
Bellomo <i>et al.</i> [31]	R/D	12,108 (10 years)	11%	68%	Worst (A-a) ΔO <sub>2</sub> > 300 mm Hg	24-hour	NR ≈ 33%	No	In-hospital death <sup>b</sup>	Hyperoxemia did not affect outcome when adjusted for several confounders.
Janz <i>et al.</i> [32]	R	170 (5 years)	≈ 25%	80%	Highest PaO <sub>2</sub>	24-hour	Yes	No	In-hospital death In-hospital CPC	Increased hospital mortality for every 100 mm Hg increase in PaO <sub>2</sub>
Ihle <i>et al.</i> [33]	R	584 (5 years)	≈ 6%	100%	Worst (A-a) ΔO <sub>2</sub> > 300 mm Hg	24-hour	NR	No	In-hospital death	Hyperoxemia did not affect outcome.
Lee <i>et al.</i> [34]	R	213 (4 years)	<3%	83%	Mean PaO <sub>2</sub> value	24-hour	Yes	No	In-hospital death	V-shaped association between the mean PaO <sub>2</sub> and poor neurologic outcome at hospital discharge
Vaahersalo <i>et al.</i> [35]	P	409 (1 year)		100%	Mean PaO <sub>2</sub> value >300 mm Hg	24-hour	Yes (71%)	No	1-year CPC	PaO <sub>2</sub> was not correlated to outcome

<sup>a</sup>Identification of an arterial oxygen pressure (PaO<sub>2</sub>) threshold to accurately separate patients with good and poor outcome. <sup>b</sup>After adjustment on Acute Physiology and Chronic Health Evaluation III (APACHE III) score. (A-a)ΔO<sub>2</sub>, alveolo-arterial oxygen difference; ABG, arterial blood gas (analysis); CA, cardiac arrest; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; FiO<sub>2</sub>, inspired oxygen fraction; HO, hyperoxemia; NA, not available; NR, not reported; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest; P, prospective; R, retrospective; RCT, randomized clinical trial; R/D, retrospective analysis of database; ROSC, return of spontaneous circulation; S100B, protein S100B; TH, therapeutic hypothermia.

In 145 out-of-hospital CA patients, Spindelboeck and colleagues [26] observed that high PaO<sub>2</sub> (more than 300 mm Hg) levels during CPR were associated with higher rates of ROSC and intact neurological survival when compared with low (PaO<sub>2</sub> of less than 60 mm Hg) and normal PaO<sub>2</sub>. In contrast, Kuisma and colleagues [27] randomly assigned 28 patients to receive either 30% or 100% FiO<sub>2</sub> for 1 hour after ROSC; five patients (36%) in the group with lower FiO<sub>2</sub> required an increase in FiO<sub>2</sub> to 40% because oxygen saturation fell below 95%, according to a standardized protocol. The primary endpoints were biomarker levels of brain injury - that is, neuron-specific enolase (NSE) and S100B - at 24 and 48 hours after ROSC, with no differences in absolute values between the two groups overall. However, in the subgroup of patients who did not undergo TTM, those receiving lower FiO<sub>2</sub> had lower NSE levels at 24 hours than the other patients (7.6 ± 4.2 versus 13.5 ± 9.6 µg/mL, *P* = 0.049). Thus, one may argue that high PaO<sub>2</sub> during CPR reflects better lung function or better quality CPR or both, with higher blood flow and better tissue oxygenation (indeed all patients received FiO<sub>2</sub> of 100%), whereas administration of high FiO<sub>2</sub> immediately after ROSC could enhance brain injury. Importantly, the retrospective nature of the study by Spindelboeck and colleagues [26] may have limited the analysis of all factors possibly affecting outcome (that is, quality of CPR, comorbidities, and so on). Also, blood gas analysis samples were drawn within 60 minutes from CPR initiation, and it is difficult to compare patients analyzed in the early CPR with those included in the later phase, who may have developed pulmonary injury with reduced PaO<sub>2</sub> due to prolonged resuscitation itself. It is difficult to determine the role of oxygen levels during CPR *per se* on neurological outcome of CA patients because they may be a surrogate marker of resuscitation performance or better cardiorespiratory status or both. Moreover, brain injury is a continuous process, and the time course of PaO<sub>2</sub> may more significantly influence neurological outcome in these patients.

Few clinical studies have evaluated the role of hyperoxemia during the ICU stay on outcome of CA patients. Kilgannon and colleagues published two different analyses on the same large database from a cohort of patients from 131 US hospitals (Increase Minority Participation and Awareness of Clinical Trials (IMPACT) Database). In the first study [28], including 6,326 patients, hospital mortality was higher in patients with hypoxemia (defined as a PaO<sub>2</sub> of less than 60 mm Hg or altered gas exchange with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of less than 300) or hyperoxemia (PaO<sub>2</sub> of more than 300 mm Hg) detected in the first arterial blood gas (ABG) available within 24 hours after admission, compared with patients with normal oxygen levels (hypoxemia 53% versus hyperoxemia 67% versus normoxemia 45%, *P* < 0.001). In a multivariable logistic regression analysis, hyperoxemia was independently associated with

in-hospital mortality: odds ratio (OR) 1.8, 95% confidence interval (CI) 1.5 to 2.2. In the second study, after exclusion of patients with hypoxemia, the investigators wanted to evaluate the association between PaO<sub>2</sub>, considered as a continuous variable, and in-hospital mortality [29]. In the 4,459 patients studied, the median PaO<sub>2</sub> was 231 (interquartile range 149 to 349) mm Hg and in-hospital mortality was 54%. Multivariable analysis yielded a significant 6% increase in mortality for any PaO<sub>2</sub> increase by 25 mm Hg (OR 1.06, 95% CI 1.05 to 1.07). Although these two studies support the hypothesis that hyperoxemia is associated with worse outcome after CA, some limitations must be acknowledged. First, only a small proportion of patients were treated with hypothermia. Second, the use of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio does not really reflect hypoxemia, because it is a surrogate of lung failure rather than of low arterial oxygen content. Third, data were not collected following the Utstein style [30] or corrected for severity of disease (for example, Acute Physiology and Chronic Health Evaluation III, or APACHE III). Finally, and even more importantly, only the first ABG was taken into account in the final analysis instead of a mean value over the first 24 hours, which might be more representative of real oxygen exposure during this crucial period.

In a large Australian database (Australian and New Zealand Intensive Care Society-Adult Patient Database, or ANZICS-APD), Bellomo and colleagues [31] evaluated the correlation between different PaO<sub>2</sub> levels and hospital mortality in 12,108 patients. Although these authors used the same definitions of hypoxemia and hyperoxemia used in previous studies [28,29], they reported a lower percentage of patients with hyperoxemia (11% [31] versus 18% [28]) but still a higher mortality rate for patients with hyperoxemia (59%) and hypoxemia (60%) when compared with normoxic patients (47%). In a multivariable model including some major confounding factors, hyperoxemia was significantly associated with mortality (OR 1.2, 95% CI 1.1 to 1.6); however, in a Cox proportional hazards regression model, after adjustment for other relevant covariates (year of admission, treatment limitations, patient's lowest glucose level in the first 24 hours, patient's indigenous status, and hospital source from home), PaO<sub>2</sub> was no longer statistically associated with poor outcome (hazard ratio 1.1, 95% CI 1.0 to 1.2; *P* = 0.20). Despite the limitation of a retrospective analysis, this study highlights that some confounders not taken into account in previous studies may have influenced the statistical association between high PaO<sub>2</sub> and poor outcome. Importantly, other issues may further limit the power of these findings. The PaO<sub>2</sub> from the ABG analysis associated with the worst alveolo-arterial oxygen difference was used, and this PaO<sub>2</sub> correlated only fairly with the mean PaO<sub>2</sub> (as shown in the analysis of a subgroup of patients) and may not have adequately reflected the exposure of patients to high



oxygen concentrations. This observation was also suggested by the lower PaO<sub>2</sub> values recorded in this study when compared with previous publications (112 versus 231 mm Hg) [29]. Also, no data on neurological outcomes were reported. Finally, as in previous studies, only a minority of patients underwent hypothermia, but cooling is considered to mitigate ROS production and possibly influence hyperoxemia-mediated brain injury [8].

The first article to include patients treated with hypothermia [32] showed that those with a poor outcome had higher PaO<sub>2</sub> values than others (254 versus 198 mm Hg;  $P = 0.022$ ). A multivariable regression model, including factors known to be associated with poor outcome after CA, confirmed an independent correlation of PaO<sub>2</sub> with mortality (OR for a PaO<sub>2</sub> increment of every 100 mm Hg above 54 mm Hg 1.48, 95% CI 1.03 to 2.01) and worse neurological outcome (OR 1.48, 95% CI 1.03 to 2.14) at hospital discharge; however, neither FiO<sub>2</sub> nor APACHE III score was included in the final analysis. Unfortunately, no specific cutoff of PaO<sub>2</sub> was identified to predict poor outcome, although a PaO<sub>2</sub> of more than 228 mm Hg was associated with a lower likelihood of neurological recovery. More recently, Ihle and colleagues [33] reviewed 584 patients selected from the ANZICS-APD database, for whom variables could be found following the Utstein model [30]. Unadjusted in-hospital mortality did not differ across different PaO<sub>2</sub> ranges (51% hypoxia, 41% normoxia, and 47% hyperoxia;  $P = 0.28$ ). In a multivariable model including CA characteristics, neither hypoxemia nor hyperoxemia was an independent predictor of in-hospital mortality. In a retrospective cohort of 213 adult patients with CA, Lee and colleagues [34] reported that PaO<sub>2</sub> obtained during the first 24 hours was not related to hospital mortality or neurological outcome. In a multivariable model adjusted for established confounding factors after CA, the authors showed a V-shaped relationship between PaO<sub>2</sub> and neurological outcome, with the highest probability of good neurologic outcome at PaO<sub>2</sub> around 130 mm Hg. Finally, in a prospective observational study ( $n = 409$ ), Vaahersalo and colleagues [35] calculated the proportion of time spent in different oxygen categories (less than 75 mm Hg, 75 to 150 mm Hg, 150 to 225 mm Hg, and more than 225 mm Hg) during the first 24 hours after CA. The proportion of time spent with a PaO<sub>2</sub> of more than 225 mm Hg was similar between groups, as was the association of time within different PaO<sub>2</sub> categories and outcome. Mean and highest PaO<sub>2</sub> values were higher in patients with good neurological outcome (120 versus 113 mm Hg and 173 versus 150 mm Hg, respectively). Interestingly, the proportion of patients with good neurological outcome was higher in patients with the combination of high mean PaO<sub>2</sub> and PaCO<sub>2</sub> values.

## Perspectives and conclusions

The International Liaison Committee on Resuscitation states that oxygen administration should be titrated to obtain an oxygen saturation of 94% to 96% after ROSC [36]. Thus, routine administration of an FiO<sub>2</sub> of 100% is no longer recommended after CPR [36,37]; however, it still seems prudent to use 100% oxygen during CPR, although the impact of high PaO<sub>2</sub> on survival needs to be further evaluated. Although some studies have suggested that hyperoxemia after CA should be considered a cost-free, potentially modifiable risk factor for poor outcome, many potential confounders have been identified and strongly challenge this concept. Moreover, it is very difficult to identify a specific threshold of toxicity, as most of the studies used a PaO<sub>2</sub> of more than 300 mm Hg to define hyperoxemia, while some brain injury may also potentially occur at lower values. Also, when a single ABG value was used, the proportion of patients with hyperoxemia ranged from 3% to 25% in the different studies [27-29,31-34]. Nevertheless, when all ABG values are considered, the incidence of hyperoxemia may exceed 40% [38], so that the real impact of exposure to high oxygen concentrations has probably been underestimated. Other parameters obtained from the ABG, such as acidemia or hypocapnia, may also be important determinants of poor outcome after CA [39,40]; however, these variables were not considered in these studies. Importantly, it is worthwhile to prospectively evaluate the mechanisms of oxygen toxicity after CA, such as seizure development, ROS production, impaired microcirculation, or the development of organ dysfunction. Finally, further studies are needed to help understand whether an absolute PaO<sub>2</sub> value (that is, 'peak') could be more detrimental than a continuous exposure above a specific threshold and to assess the impact of the timing of hyperoxemia occurrence (early versus late phase after arrest) or of variability in oxygen levels (that is, from hypoxemia to hyperoxemia) in this setting.

## Key messages

- Hyperoxemia may potentially exacerbate or aggravate brain injury after experimental cardiac arrest.
- Hyperoxemia has been associated with controversial results in humans.
- Administering high FiO<sub>2</sub> (100%) during CPR still seems to be advisable because it may facilitate ROSC.
- Because of the limited benefit of maintaining potentially harmful supra-normal oxygen levels in such patients, mechanical ventilation should be titrated to maintain an oxygen saturation between 94% and 96% in most patients after ROSC.

## Abbreviations

ABG: Arterial blood gas; ANZICS-APD: Australian and New Zealand Intensive Care Society-Adult Patient Database; APACHE III: Acute Physiology and Chronic Health Evaluation III; CA: Cardiac arrest; CI: Confidence interval; CPR: Cardiopulmonary resuscitation; FIO<sub>2</sub>: Inspired oxygen fraction; MOF: Multiple organ failure; NSE: Neuron-specific enolase; OR: Odds ratio; PaO<sub>2</sub>: Arterial oxygen pressure; PCAS: Post-cardiac arrest syndrome; ROS: Reactive oxygen species; ROSC: Return of spontaneous circulation; TTM: Target temperature management.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

FST and AMDA helped to conceive the manuscript, participated in the data collection, and helped to draft the manuscript. IL participated in the data collection and helped to critically revise the manuscript. JLV helped to critically revise the manuscript. All authors read and approved the final version of the manuscript.

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