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Postcardiac Arrest Neuroprognostication Practices: A Survey of Brazilian Physicians

OBJECTIVES: End-of-life care and decisions on withdrawal of life-sustaining therapies vary across countries, which may affect the feasibility of future multicenter cardiac arrest trials. In Brazil, withdrawal of life-sustaining therapy is reportedly uncommon, allowing the natural history of postcardiac arrest hypoxic-ischemic brain injury to present itself. We aimed to characterize approaches to neuroprognostication of cardiac arrest survivors among physicians in Brazil.

DESIGN: Cross-sectional study.

SETTING: Between August 2, 2019, and July 31, 2020, we distributed a web-based survey to physicians practicing in Brazil.

SUBJECTS: Physicians practicing in Brazil and members of the Brazilian Association of Neurointensive Care, who care for patients resuscitated following cardiac arrest.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: Responses from 185 physicians were obtained. Pupillary reflexes, corneal reflexes, and motor responses were considered critical to prognostication, whereas neuroimaging and electroencephalography were also regarded as important. For patients without targeted temperature management, absent pupillary and corneal reflexes at 24 hours postarrest were considered strongly predictive of poor neurologic outcome by 31.8% and 33.0%, respectively. For targeted temperature management-treated patients, absent pupillary and corneal reflexes at 24-hour postrewarming were considered prognostic by 22.9% and 20.0%, respectively. Physicians felt comfortable making definitive prognostic recommendations at day 6 postarrest or later (34.2%) for nontargeted temperature management-treated patients, and at day 6 postrewarming (20.4%) for targeted temperature management-treated patients. Over 90% believed that improving neuroprognostic accuracy would affect end-of-life decision-making.

CONCLUSIONS: There is significant variability in neuroprognostic approaches to postcardiac arrest patients and timing of prognostic studies among Brazilian physicians, with practices frequently deviating from current guidelines, underscoring a need for greater neuroprognostic accuracy. Nearly all physicians believed that improving neuroprognostication will impact end-of-life decision-making. Given the tendency to delay prognostic recommendations while using similar neuroprognostic tools, Brazil offers a unique cohort in which to examine the natural history of hypoxicischemic brain injury in future studies.

KEY WORDS: cardiac arrest; heart arrest; neurologic examination; neuroprognostication; outcomes assessment; postcardiac arrest syndrome

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lthough the success rate of resuscitation from cardiac arrest (CA) has improved, the majority of CA survivors remain unconscious in the immediate aftermath (1). In these situations, the likelihood of recovery is frequently variable, and decisions on prolonged care versus withdrawal of life-sustaining therapies (WLSTs) frequently hinge on the perceived prognosis. The European Resuscitation Council (ERC)/ European Society of Intensive Care Medicine (ESICM) and the American Heart Association (AHA) both recommend that, whenever possible, the approach to prognostication should be multimodal (2, 3). Available neuroprognostic tools include features of the clinical examination, neuroimaging, electrophysiologic studies (e.g., electroencephalography [EEG] and somatosensory evoked potentials [SSEP]), and chemical biomarkers (e.g., serum neuron specific enolase [NSE]). Although the specificity of these tests likely increases with time, providers and families must balance the allowance of adequate recovery time with prolongation of care only when an acceptable level of recovery is potentially achievable. However, most studies examining neuroprognostic practices inevitably suffer from the bias of a self-fulfilling prophecy, in which premature WLST masks delayed recovery and thus perpetuate perceptions on poor prognostic findings. Thus, the most reliable combination of assessments and their appropriate timing remain to be determined.

Given the challenges to prognostication, we previously conducted an international, web-based survey study of 762 physicians to characterize approaches to prognostication after CA (4). The findings demonstrated substantial variation in individual beliefs and practices; however, most responses came from the United States. Meanwhile, previous studies have found cross-national differences in WLST and prognostic practice patterns (5–7). In Brazil, WLST is reportedly less common than that in areas like the United States or Europe, though its prevalence has increased with changes in legislative and ethical codes (8, 9), including the 2006 resolution by the Federal Council of Medicine that allowed physicians to limit life-sustaining therapies in terminally ill patients. A 2011 survey found that most physicians favored limiting such therapies in terminally ill patients but were more likely to sustain therapies for an unconscious patient (10).

Differences in goals of care and end-of-life decision-making approaches present an opportunity to elucidate the natural history of hypoxic-ischemic brain injury-as well as the true impact of WLST-by comparing the cohorts of CA survivors; thus, Brazil, with its low prevalence of WLST, has emerged as a region of interest for studies on post-CA neuroprognostication and outcomes. Such studies, however, necessitate an understanding of current neuroprognostic practices and their impact on decision-making. In this study, we aim to characterize approaches to post-CA neuroprognostication among Brazilian physicians. We hypothesize that, despite WLST being uncommon in Brazil, there is significant heterogeneity in individual perceptions on optimal neuroprognostic decision-making and that, similar to the United States, practices frequently deviate from recommendations in evidence-based guidelines.

MATERIALS AND METHODS

Study Design

This is a cross-sectional, survey-based study assessing individual beliefs and practices of physicians in Brazil involved in the care of patients resuscitated after CA. The open and voluntary survey link was disseminated to approximately 500 members of the Brazilian Association of Neurointensive Care beginning on August 2, 2019, and closing on July 31, 2020. No incentives were offered for participation, and no personal information was collected. Of 196 total responses received, responses from nonphysicians (n = 11) and from physicians not caring for CA patients (n = 5) were excluded, for a total of 180 physicians included in subsequent analyses (Fig. S1, http://links.lww.com/CCX/ A488—legend, http://links.lww.com/CCX/A492). The study was granted exemption from review by the Yale University (Human Investigation Committee, number 2000026209), and informed consent was waived.

Survey Instrument

The development of the web-based survey tool (Qualtrics, Provo, Utah) has been previously described; in short, the survey was tested in a group of neurointensivists at Yale New Haven Hospital and used in an international, cross-sectional study of 762 physicians (4). For this study, the survey was modified and translated into Portuguese. The instrument (available in English and Portuguese as **supplemental materials**, http://links.lww.com/CCX/A487) is comprised of 33

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questions pertaining to individual practices and beliefs on post-CA neuroprognostication. Not all questions were mandatory, and some questions were conditionally displayed based on responses to previous questions (Figure S1, http://links.lww.com/CCX/A488—legend, http://links.lww.com/CCX/A492).

Statistical Analysis

Categorical variables are presented as counts and percentages or frequency distributions. Denominators vary based on the number of responses to a given question, as not all questions were mandatory, and incomplete survey responses were included in analyses. Continuous variables are presented as median and interquartile range (IQR).

Differences in neuroprognostic practices were analyzed in prospectively defined subgroups of neurologists versus nonneurologists and intensivists versus nonintensivists. Additional post hoc analyses were performed to compare findings between physicians who employ targeted temperature management (TTM) versus those who do not. Depending on response totals, Pearson chi-square test or Fisher exact test was used to compare response frequencies between the subgroups, with post hoc rowwise testing performed on significant results. An alpha level of 0.05 was used. Analyses were performed using R Version 4.0.2 (R Core Team, Vienna, Austria, 2020) and the "rstatix" package Version 0.6.0 (Kassambara, 2020).

RESULTS

Characteristics of Respondents

Among survey respondents, the most highly represented specialties were neurology (47.5%; n = 75/158), general intensive care (32.9%; n = 52/158), and neurointensive care (24.1%; n = 38/158), with respondents allowed to select more than one specialty; furthermore, the majority (60.5%; n = 95/157) had completed dedicated intensive care training. The median time since graduation from medical school was 12.5 years (IQR, 7–20). Responses stemmed from 17 states and the Federal District, with most practicing in São Paulo (46.8%; n = 74/158) or Rio de Janeiro (25.9%; n = 41/158) (**Fig. S2**, http://links.lww.com/CCX/A489—legend, http://links.lww.com/CCX/A492). Fifty-seven percent (n = 90/158) practiced in a public hospital, whereas 74.1%

(n = 117/158) practiced in a private hospital and 46.2% (n = 73/158) in a university-affiliated hospital. Most respondents (76.4%) treated between 1 and 25 successfully resuscitated CA patients annually at their primary facility (**Table S1**, http://links.lww.com/CCX/A493).

Characteristics of TTM Use

Approximately half (51.3%; n = 80/156) of respondents endorsed use of TTM at their primary facility of practice. Among 74 respondents, temperatures of 32–34°C were targeted by 35.1% (n = 26), whereas 21.6% (n = 16) targeted 36°C and 43.2% (n = 32) reported a range of 32– 36°C. The target temperature was generally maintained for 24 hours (51.4%; n = 38/74) or 24–48 hours (39.2%; n = 29/74). The most common TTM methods were cooling blankets (59.5%; n = 44/74), cold saline infusions (51.4%; n = 38/74), ice packs (45.9%; n = 34/74), and surface cooling adhesive pads (24.3%; n = 18/74), with 60.8% employing more than one method (**Table S2**, http://links.lww.com/CCX/A493).

Availability and Use of Prognostic Tools

Of 140 respondents, head CT and brain MRI were available to 97.1% (n = 136) and 78.6% (n = 110), respectively. To assess prognosis, CT was "very often" or "almost always" used by 86.9% (n = 119/137), compared with 59.7% (n = 80/134) for use of MRI. EEG was available to 80.7% (n = 113/140), and 64.0% (n = 87/136) reported "very often" or "almost always" obtaining this study. SSEP were available to 27.9% (n = 39/140) and "almost always" obtained by 5.2% (n = 7/134) (**Fig. 1***A*). Only 9.3% (n = 13/140) had access to serum NSE testing. Compared with neurologists, more nonneurologists reported never obtaining MRI (15.7% vs 2.4%; p = 0.033) (**Table S3**, http://links.lww.com/CCX/A493; **Fig. S3**, http://links.lww.com/CCX/A492).

To assess pupillary light reflexes, 83.6% (n = 92/110) of respondents used light with the naked eye. Ten percent (n = 11/110) used a magnifying glass, and 6.4% (n = 7/110) used a pupillometer. There were no differences between neurologists and nonneurologists (p = 0.299) (**Table 1**), nor between intensivists and nonintensivists (p = 0.361) (**Table S4**, http://links.lww.com/CCX/A493).

To assess corneal reflexes, 67.3% (n = 68/101) used a light cotton touch as the most definitive technique, whereas 24.8% (n = 25/101) used saline or water,



	Important	Important	Important	Important
NSE	9 (6.6%)	66 (48.5%)	49 (36.0%)	12 (8.8%)
EEG	2 (1.5%)	14 (10.2%)	64 (46.7%)	57 (41.6%)
SSEP	4 (3.0%)	47 (35.3%)	57 (42.9%)	25 (18.8%)
CT head	4 (3.0%)	27 (20.3%)	46 (34.6%)	56 (42.1%)
MRI brain	4 (2.9%)	21 (15.1%)	57 (41.0%)	57 (41.0%)
Pupillary light reflex	1 (0.7%)	6 (4.3%)	23 (16.5%)	109 (78.4%)
Corneal reflex	0 (0.0%)	5 (3.6%)	29 (20.7%)	106 (75.7%)
GCS motor response	2 (1.4%)	18 (12.9%)	31 (22.1%)	89 (63.6%)
Observed myoclonus	5 (3.6%)	28 (20.1%)	43 (30.9%)	63 (45.3%)

Figure 1. Use and perceived importance of prognostic tools **A**, Frequency of use of various prognostic assessments. **B**, Perceived importance of various prognostic assessments. Tables for each rating are included below each panel, with cells displaying counts and percentages as n (%). EEG = electroencephalography, GCS = Glasgow Coma Scale, NSE = neuron specific enolase, SSEP = somatosensory evoked potentials.

and 7.9% (n = 8/101)endorsed use of a cottontipped applicator with pressure. Stimulation was most commonly applied to the temporal conjunctiva rather than the cornea (Fig. 2). Although both neurologists and nonneurologists most frequently employed a light cotton touch, use of a saline/ water squirt was more prevalent among neurologists (33.3% vs 10.5%; p = 0.048) (Table 1). There was no difference between the intensivists and nonintensivists (p = 0.152) (Table S4, http://links.lww.com/ CCX/A493).

Motor response was most frequently assessed using nail bed pressure (78.1%; n = 75/96) and supraorbital pressure (57.3%; n = 55/96), followed by temporomandibular joint pressure (49.0%; n = 47/96), sternal rub (42.7%; n = 41/96), and trapezius squeeze (31.2%; n = 30/96) (Table 1).

Perceived Importance of Prognostic Information

Using a 4-point Likert scale, EEG, head CT, and brain MRI were deemed either "very" or "critically" important by 88.3% (n = 121/137), 76.7% (n = 102/133), and 82.0% (n = 114/139) of respondents, respectively, whereas SSEP were considered very or critically important by

TABLE 1.

Neurologic Examination: Perceived Relevance and Technique

Neurologic Examination Component/ Technique	Total, <i>n</i> (%)	Neurologists, n (%)	Nonneurologists, n (%)	p
Finding considered relevant ($n = 134$)				
Eye opening	95 (70.9)	59 (71.1)	36 (70.6)	1.000
Pupillary light reflex	120 (89.6)	77 (92.8)	43 (84.3)	0.207
Corneal reflex	111 (82.8)	68 (81.9)	43 (84.3)	0.905
Cough reflex	93 (69.4)	54 (65.1)	39 (76.5)	0.231
Gag reflex	54 (40.3)	35 (42.2)	19 (37.3)	0.703
Motor response	105 (78.4)	64 (77.1)	41 (80.4)	0.816
Oculocephalic reflex ("doll's eyes")	92 (68.7)	60 (72.3)	32 (62.7)	0.335
Vestibulocular reflex ("cold calorics")	82 (61.2)	50 (60.2)	32 (62.7)	0.915
Pupillary reflex technique ($n = 110$)				0.299
Light with magnifying glass	11 (10.0)	5 (6.9)	6 (15.8)	
Light with naked eye	92 (83.6)	63 (87.5)	29 (76.3)	
Pupillometer	7 (6.4)	4 (5.6)	3 (7.9)	
Corneal reflex technique ($n = 101$)				0.005ª
Saline/water squirt	25 (24.8)	21 (33.3)	4 (10.5)	0.048ª
Light cotton touch	68 (67.3)	40 (63.5)	28 (73.7)	0.382
Puff of air	0 (0)	0 (0)	0 (0)	-
Cotton-tip applicator with pressure	8 (7.9)	2 (3.2)	6 (15.8)	0.100
Motor response stimulus ($n = 96$)				
Trapezius squeeze	30 (31.2)	21 (35.6)	9 (24.3)	0.351
Proximal limb noxious stimulation	24 (25.0)	15 (25.4)	9 (24.3)	1.000
Sternal rub	41 (42.7)	24 (40.7)	17 (45.9)	0.767
Nipple pinch	12 (12.5)	3 (5.1)	9 (24.3)	0.009ª
Temporomandibular joint pressure	47 (49.0)	35 (59.3)	12 (32.4)	0.019 ^a
Nail bed pressure	75 (78.1)	49 (83.1)	26 (70.3)	0.222
Supraorbital pressure	55 (57.3)	39 (66.1)	16 (43.2)	0.046ª

^aSignificant p values of less than 0.05.

For significant χ^2 or Fisher test results from contingency tables with greater than two rows, post hoc rowwise testing was performed, and subsequent p values adjusted using Holm method are listed.

61.7% (n = 82/133) (**Fig. 1***B*). Serum NSE was perceived as "somewhat" or "not at all" important (55.1%; n = 75/136). There were no differences between neurologists and nonneurologists (**Table S5**, http://links.lww.com/CCX/A493; **Fig. S4**, http://links.lww.

com/CCX/A491—legend, http://links.lww.com/CCX/A492). Compared with intensivists, more nonintensivists regarded MRI as only somewhat important (26.9% vs 8.0%; p = 0.024) (**Table S6**, http://links.lww.com/CCX/A493).



Figure 2. Corneal reflex assessment: heat maps of areas for stimulus application in assessing the corneal reflex. **A**, Question displayed to respondents. Heat map of (**B**) total responses, (**C**) responses from neurologists, defined as those specializing in neurology and/or neurointensive care, and (**D**) responses from nonneurologists quantified as clicks per region of interest (ROI). Of 95 total responses, 14 were located outside of the ocular globe, concentrated over the "Temporal" and "Nasal" labels; these responses were excluded from the analysis.

Each element of the neurologic examination, with the exception of the gag reflex, was considered relevant to neuroprognostication by the majority of physicians (Table 1). Approximately 20% of physicians considered all examination findings to be relevant, whereas a minority believed that none were relevant (**Fig. 3**). Pupillary reflexes, corneal reflexes, and motor response were considered "critically important" by 78.4% (n = 109/139), 75.7% (n = 106/140), and 63.6% (n = 89/140) of respondents, respectively. Postarrest myoclonus was perceived as less important, though 45.3% (n = 63/139) still regarded this finding as critical (Fig. 1*B*).

Timing

For non-TTM-treated patients, 31.8% (n = 34/107) and 33.0% (n = 32/97) considered absent pupillary and corneal reflexes, respectively, to be predictive of a poor outcome at 24-hour postarrest (**Fig. 4A**). Poor EEG findings were considered prognostic at 24 hours by 35.6% (n = 37/104), though no particular patterns were specified. In contrast, respondents were frequently unsure of the optimal timing of SSEP (27.2%; n = 28/103) and NSE (29.8%; n = 31/104). For all neurologic examination findings as well as SSEP, NSE, and EEG testings, there were no differences in timing between the physicians employing TTM and those who do not (data not shown).

In TTM-treated patients (**Fig.** 4*B*), absent pupillary reflexes were most commonly considered prognostic at 24-hour postrewarming, as selected by 22.9% (n = 11/48) of respondents, whereas 20% (n = 9/45) considered absent corneal reflexes to be predictive at 24-hour postarrest and 17.8% (n = 8/45) at 24-hour postrewarming. Many respondents were again unsure about the timing of SSEP (21.2%; n = 11/52) and NSE (23.1%; n = 12/52).

In a multiselect question, 45 of 112 respondents (40.2%) considered 24-hour postarrest to be an appropriate time to obtain a head CT, whereas 33 (29.5%) considered 48-hour postarrest to be suitable. Neurologists had greater odds of favoring a head CT immediately postarrest compared with nonneurologists (25.0% vs 7.5%; p = 0.024) (Table S7A, http:// links.lww.com/CCX/A493). In a single-select question, 48 of 112 respondents (42.9%) considered days 3–5 to be the most appropriate timing for a brain MRI, whereas 35 (31.3%) preferred days 1–2, and 22 (19.6%) felt days 6-14 were ideal (Table S7B, http://links.lww. com/CCX/A493). Compared with physicians who regularly use TTM, physicians not employing TTM were more likely to consider a brain MRI at day 0 (12.1% vs 0%; p = 0.013) and a head CT at 24-hour postarrest (53.4% vs 25.9%; p = 0.004) (Table S7C, http://links. lww.com/CCX/A493).

Clinical Decision-Making

Sixty-nine of 113 respondents (61.1%) defined a poor neurologic outcome as a Cerebral Performance Category (CPC) score of 3 or greater—comprising states ranging from consciousness with lack of independence to

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Figure 3. Perceived relevance of examination findings to prognostication Alluvial plot displaying the concordance of perceptions on relevant examination findings, stratified by neurologists and nonneurologists. Each column reflects physicians' opinions for the specified tool. From *left* to *right*: the proportion of physicians who perceived a tool as relevant decreases. No clear discordance between neurologists and nonneurologists can be tracked.



Figure 4. Timing of prognostic assessments earliest time points at which various findings were considered strongly predictive of a poor neurologic outcome in patients resuscitated from cardiac arrest (CA). **A**, Patients not treated with targeted temperature management (TTM). **B**, Patients treated with targeted temperature management. EEG = electroencephalography, NSE = neuron specific enolase, SSEP = somatosensory evoked potentials.



Figure 5. Timing of prognostic decision-making earliest time points at which physicians would feel comfortable making definitive prognostic recommendations for patients resuscitated from cardiac arrest. **A**, Patients not treated with targeted temperature management (TTM). **B**, Patients treated with TTM.

death—whereas 74 (34.5%) considered the threshold to be CPC 4—persistent vegetative state (**Table S8**, http:// links.lww.com/CCX/A493).

For non-TTM-treated patients, 34.2% of respondents (n = 38/111) considered the earliest time point for definitive prognostic recommendations to be day 6 postarrest or later (**Fig. 5A**). Neurologists did not differ from non-neurologists in their preferred timing (**Table S9A**, http://links.lww.com/CCX/A493), nor did physicians employing TTM differ from those not using TTM (**Table S9C**, http://links.lww.com/CCX/A493). There was a significant difference between intensivists and nonintensivists (p = 0.016), though post hoc rowwise comparisons were observed to be nonsignificant (**Table S9B**, http://links.lww.com/CCX/A493).

For TTM-treated patients, 20.4% of respondents (n = 11/54) endorsed day 6 postrewarming as the earliest acceptable time for prognostic recommendations

(Fig. 5*B*). There were no differences in timing among subgroups (Table S10, http://links.lww.com/CCX/A493).

The vast majority (91.2%; n = 104/114) of respondents believed that improving the accuracy of neuroprognostication would affect end-of-life decision-making and practices in Brazil. Only three respondents disagreed with this statement, all citing the belief that, regardless of accuracy and prognosis, families would not allow for WLST; additionally, one respondent endorsed discomfort from providers as a barrier to WLST.

DISCUSSION

Our findings demonstrate substantial heterogeneity in neuroprognostic practices among Brazilian physicians—not dissimilar to findings in the United States, despite differences in the prevalence of WLST. As in the

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United States, the valuation of prognostic tools and their timing are frequently discrepant from those of current evidence-based guidelines, threatening the accuracy of neuroprognostication and clinical decision-making.

The neurologic examination remains the cornerstone of assessing prognosis in patients resuscitated from CA. Specifically, pupillary light reflexes, corneal reflexes, and motor response were widely considered to be "critically important," whereas clinical myoclonus was also perceived as important. However, high falsepositive rates have been demonstrated using motor response as a prognostic indicator (11–15). Similarly, myoclonus has been observed in patients who achieve a good recovery (14, 15) and is not recommended as a sole predictor of poor outcome (16). The presence of status myoclonus may be more specific (2), but the associated electrophysiology is critical, as patients with persistent myoclonus but distinct EEG patterns have achieved a good outcome (17, 18). In contrast, pupillary and corneal reflexes boast strong evidence in support of their utility, as their false-positive rates are reportedly low though nonzero at 72-hour postarrest or postrewarming (2, 3, 19). In our cohort, pupillary reflexes were most commonly assessed using light with the naked eye; however, studies have demonstrated greater specificity and interrater reliability through use of automated pupillometry (20, 21). In assessing the corneal reflex, the area of stimulus application tended to concentrate not on the cornea, but rather on the temporal bulbar conjunctiva (Fig. 2), which generates a reduced irritative response (22). Few respondents used a cotton-tipped applicator to apply corneal pressure, despite this technique introducing the greatest noxious stimulation to corneal nerve endings (23).

The lack of consensus on optimal prognostic timing highlights an area of uncertainty that may facilitate improvements in accuracy. Both the ERC/ESICM (2) and the AHA (3) recommend waiting at least 72-hour postarrest or postrewarming before considering absent pupillary and corneal reflexes to be predictors of futility. In our cohort, these findings were prematurely considered prognostic at 24-hour postarrest or postrewarming. All other examination findings were also considered strongly predictive within the first few days after arrest or rewarming, despite a lack of robust evidence in the literature (14, 15, 24).

Among ancillary testing, neuroimaging and EEG remain commonplace and valued, yet there was substantial variability in the timing of these studies. Current guidelines recommend obtaining a head CT within 2-24 hours of arrest and brain MRI between day 2 and day 6 (2, 3). In our cohort, over 30% preferred obtaining an MRI at a premature time point of days 1-2, when sensitivity for hypoxic-ischemic changes is poor (25), whereas nearly 20% favored days 6-14, despite a risk of subacute pseudonormalization during this period (26, 27). In non-TTM-treated patients, poor EEG findings were prematurely considered prognostic at 24-hour postarrest, despite recommendations to delay prognostication based on EEG until 72 hours after arrest (2, 3). No definition for "poor" EEG findings was specified in the survey, and thus, the perceived importance of specific EEG patterns, such as burst suppression or unreactive background, was not explored.

In contrast, SSEP and NSE testings were less accessible and less frequently used. SSEP was still considered highly important, mirroring its high reliability in the literature (14, 15, 19); however, the majority reported never using this modality, likely due to its unavailability. NSE testing was regarded as less important—perhaps a reflection of its unavailability as well as its more tenuous evidence base, particularly as optimal cutoff levels remain controversial and are assay-dependent (28). Additionally, NSE may offer more insight when observed serially (29–31), a factor not explored in our survey.

Despite a perception of early, premature findings strongly indicating a poor prognosis, the earliest time at which physicians felt comfortable making prognostic recommendations, were commonly day 6 postarrest or later in patients without TTM and day 6 postrewarming in TTM-treated patients. In contrast, in our recent survey of over 700 physicians internationally, definitive prognostic recommendations were most frequently considered at day 3 postarrest or postrewarming (4). The heterogeneity within and between these cohorts, particularly with regard to timing, underscores gaps in knowledge on robust neuroprognostic practices after CA; ultimately, both cohorts endorsed practices that were misaligned with the current literature.

Our findings suggest that Brazilian physicians may favor prolonging care and delaying prognostic decision-making compared with physicians in other countries, which perhaps reflects underlying sociopolitical and cultural differences (32). In Brazil, endof-life decisions are reported in up to 36% of adult deaths—a prevalence much lower than that of the

United States or European countries-and the decision to withhold treatment is more common than the decision to withdraw actively life support (10, 33-35). Alternatively, delays in decision-making may reflect prognostic uncertainty, particularly in the setting of a multimodal approach; though guidelines recommend delaying prognostication until 72-hour postarrest or postrewarming, further postponement is warranted in the setting of uncertainty or confounders (e.g., sedation or neuromuscular blockade) to allow for further data collection and monitoring of changes (2, 36). Regardless of the rationale for delayed decision-making, such an approach counteracts the self-fulfilling prophecy of WLST by granting more time for the extent of hypoxicischemic brain injury to declare itself. As postarrest recovery is highly variable, improving our understanding of hypoxic-ischemic injury and trajectories of neurologic recovery will almost certainly benefit prognostic accuracy and decision-making.

Our study has important limitations, including its descriptive nature, limited sample size, and univariate analyses. Because the survey was administered in an anonymous and open manner via membership in a professional organization, the number of eligible recipients and the participation rate cannot be measured. Not all respondents answered all questions, and not all questions may have been interpreted in the same manner. Reported answers may not be consistent with true practices, and heterogeneous clinical practices-such as protocols for sedation and neuromuscular blockade-are not captured in our survey but may influence the timing of clinical assessments and decisions. Furthermore, these findings may be urban-centric or biased by society membership status and may not be representative of the entirety of practice in Brazil. Details on the structure of care organization and delivery were at respondents' sites were not explored. Most respondents cared for a low volume of patients resuscitated from CA, and nearly half practiced at facilities that did not use TTM. Despite these limitations, the study captures a diverse physician population with respect to specialty areas as well as years of clinical experience. These findings identify important gaps in knowledge that must be addressed to improve clinical decision-making.

CONCLUSIONS

Among physicians in Brazil, approaches to neuroprognostication after CA are not only heterogeneous but also frequently divergent from current evidence-based guidelines, underscoring critical gaps in knowledge and areas for improvement. Unlike in the United States and Europe, many physicians favored delaying definitive prognostic recommendations until day 6 postarrest or postrewarming, or beyond. Such a distinct cohort lends itself to the examination of post-CA trajectories and prognostic indicators under less influence of the self-fulfilling prophecy, given Brazil's reportedly low prevalence of WLST and the trend toward prolongation of care. Understanding these trajectories and the natural history of hypoxic-ischemic brain injury will facilitate improvements in prognostic accuracy and decision-making.

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REFERENCES

- Deakin CD, Fothergill R, Moore F, et al: Level of consciousness on admission to a Heart Attack Centre is a predictor of survival from out-of-hospital cardiac arrest. *Resuscitation* 2014; 85:905–909
- Nolan JP, Soar J, Cariou A, et al: European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med* 2015; 41:2039–2056
- Callaway CW, Donnino MW, Fink EL, et al: Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; 132(18 Suppl 2):S465–S482
- Maciel CB, Barden MM, Youn TS, et al: Neuroprognostication practices in postcardiac arrest patients: An international survey of critical care providers. *Crit Care Med* 2020; 48:e107–e114
- 5. Azoulay E, Metnitz B, Sprung CL, et al; SAPS 3 Investigators: End-of-life practices in 282 intensive care units: Data from the SAPS 3 database. *Intensive Care Med* 2009; 35:623–630
- Sprung CL, Cohen SL, Sjokvist P, et al; Ethicus Study Group: End-of-life practices in European intensive care units: The Ethicus Study. JAMA 2003; 290:790–797
- Mark NM, Rayner SG, Lee NJ, et al: Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: A systematic review. *Intensive Care Med* 2015; 41:1572–1585
- 8. Mazutti SR, Nascimento AF, Fumis RR: Limitation to advanced life support in patients admitted to intensive care unit with integrated palliative care. *Rev Bras Ter Intensiva* 2016; 28:294–300
- Moritz RD, Machado FO, Heerdt M, et al: Evaluation of medical decisions at the end-of-life process. *Rev Bras Ter Intensiva* 2009; 21:141–147
- Fumis RR, Deheinzelin D: Respiratory support withdrawal in intensive care units: Families, physicians and nurses views on two hypothetical clinical scenarios. *Crit Care* 2010; 14:R235
- Rossetti AO, Oddo M, Logroscino G, et al: Prognostication after cardiac arrest and hypothermia: A prospective study. *Ann Neurol* 2010; 67:301–307
- Al Thenayan E, Savard M, Sharpe M, et al: Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology* 2008; 71:1535–1537

- Dragancea I, Horn J, Kuiper M, et al; TTM Trial Investigators: Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: Results from a randomised controlled clinical trial. *Resuscitation* 2015; 93:164–170
- Sandroni C, Cavallaro F, Callaway CW, et al: Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 1: Patients not treated with therapeutic hypothermia. *Resuscitation* 2013; 84:1310–1323
- Sandroni C, Cavallaro F, Callaway CW, et al: Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. *Resuscitation* 2013; 84:1324–1338
- Neumar RW, Shuster M, Callaway CW, et al: Part 1: Executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; 132(18 Suppl 2):S315–S367
- Elmer J, Rittenberger JC, Faro J, et al; Pittsburgh Post-Cardiac Arrest Service: Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann Neurol* 2016; 80:175–184
- Dhakar MB, Sivaraju A, Maciel CB, et al: Electro-clinical characteristics and prognostic significance of post anoxic myoclonus. *Resuscitation* 2018; 131:114–120
- Sandroni C, D'Arrigo S, Cacciola S, et al: Prediction of poor neurological outcome in comatose survivors of cardiac arrest: A systematic review. *Intensive Care Med* 2020; 46:1803–1851
- Oddo M, Sandroni C, Citerio G, et al: Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: An international prospective multicenter double-blinded study. *Intensive Care Med* 2018; 44:2102–2111
- 21. Olson DM, Stutzman S, Saju C, et al: Interrater reliability of pupillary assessments. *Neurocrit Care.* 2016; 24:251–257
- 22. Acosta MC, Tan ME, Belmonte C, et al: Sensations evoked by selective mechanical, chemical, and thermal stimulation of the conjunctiva and cornea. *Invest Ophthalmol Vis Sci* 2001; 42:2063–2067
- 23. Maciel CB, Youn TS, Barden MM, et al: Corneal reflex testing in the evaluation of a comatose patient: An ode to precise semiology and examination skills. *Neurocrit Care* 2020; 33:399-404
- Young GB, Doig G, Ragazzoni A: Anoxic-ischemic encephalopathy: Clinical and electrophysiological associations with outcome. *Neurocrit Care* 2005; 2:159–164
- Youn CS, Park KN, Kim JY, et al: Repeated diffusion weighted imaging in comatose cardiac arrest patients with therapeutic hypothermia. *Resuscitation* 2015; 96:1–8
- Wu O, Sorensen AG, Benner T, et al: Comatose patients with cardiac arrest: Predicting clinical outcome with diffusionweighted MR imaging. *Radiology* 2009; 252:173–181
- 27. Kawahara H, Takeda Y, Tanaka A, et al: Does diffusionweighted magnetic resonance imaging enable detection of

early ischemic change following transient cerebral ischemia? *J Neurol Sci* 2000; 181:73–81

- Zellner T, Gärtner R, Schopohl J, et al: NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest. *Resuscitation* 2013; 84:1382–1386
- 29. Wiberg S, Hassager C, Stammet P, et al: Single versus serial measurements of neuron-specific enolase and prediction of poor neurological outcome in persistently unconscious patients after out-of-hospital cardiac arrest - a TTM-trial substudy. *PLoS One* 2017; 12:e0168894
- Tiainen M, Roine RO, Pettilä V, et al: Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. *Stroke* 2003; 34:2881–2886
- 31. Stammet P, Collignon O, Hassager C, et al; TTM-Trial Investigators: Neuron-specific enolase as a predictor of death

or poor neurological outcome after out-of-hospital cardiac arrest and targeted temperature management at 33°C and 36°C. *J Am Coll Cardiol* 2015; 65:2104–2114

- 32. Forte DN, Vincent JL, Velasco IT, et al: Association between education in EOL care and variability in EOL practice: A survey of ICU physicians. *Intensive Care Med* 2012; 38:404–412
- 33. Soares M, Terzi RG, Piva JP: End-of-life care in Brazil. *Intensive Care Med* 2007; 33:1014–1017
- Yaguchi A, Truog RD, Curtis JR, et al: International differences in end-of-life attitudes in the intensive care unit: Results of a survey. *Arch Intern Med* 2005; 165:1970–1975
- 35. Soares M: End of life care in Brazil: The long and winding road. *Crit Care* 2011; 15:110
- Cronberg T, Brizzi M, Liedholm LJ, et al: Neurological prognostication after cardiac arrest---Recommendations from the Swedish Resuscitation Council. *Resuscitation* 2013; 84:867–872