Feasibility of Cognitive Functional Assessment in Cardiac Arrest Survivors Using an Abbreviated Laptop-Based Neurocognitive Battery

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Cardiac arrest survivors exhibit varying degrees of neurological recovery even in the setting of targeted temperature management (TTM) use, ranging from severe impairments to making a seemingly full return to neurologic baseline function. We sought to explore the feasibility of utilizing a laptop-based neurocognitive battery to identify more subtle cognitive deficits in this population. In a convenience sample of cardiac arrest survivors discharged with a cerebral performance category (CPC) of 1, we evaluated the use of a computerized neurocognitive battery (CNB) in this group compared to a healthy control normative population. The CNB was designed to test 11 specific neurocognitive domains, including such areas as working memory and spatial processing. Testing was scored for both accuracy and speed. In a feasibility convenience sample of 29 cardiac arrest survivors, the mean age was 52.9 ± 16.7 years; 12 patients received postarrest TTM and 17 did not receive TTM. Patients tolerated the battery well and performed at normative levels for both accuracy and speed on most of the 11 domains, but showed reduced accuracy of working memory and speed of spatial memory with large magnitudes (>1 SD), even among those receiving TTM. Across all domains, including those using speed and accuracy, 7 of the 29 subjects (24%) achieved statistically significant scores lower from the normative population in two or more domains. In this population of CPC 1 cardiac arrest survivors, a sensitive neurocognitive battery was feasible and suggests that specific cognitive deficits can be detected compared to a normative population, despite CPC 1 designation. Such testing might allow improved measurement of outcomes following TTM interventions in future trials.

Introduction

CARDIAC ARREST SURVIVORS OFTEN exhibit varying degrees of neurological recovery despite the use of postarrest care modalities, such as targeted temperature management (TTM), from experiencing persistent and severe impairments to making a seemingly full return to neurologic baseline function. In recent practice, the two most common measures of cognitive function for resuscitated cardiac arrest patients have been the cerebral performance category (CPC) score and the mini-mental state examination (MMSE) (Moulaert *et al.*, 2009; Alexander *et al.*, 2011). Both tests provide healthcare providers with rapid yet nongranular diagnostic tools for potentially differentiating a spectrum of cognitive impairments. However, neither test is sensitive enough to detect subtle cognitive deficits, specifically at the higher end of neurological function (Cummins, 1996; Cummins *et al.*, 1997; Lim *et al.*, 2004; Torgersen *et al.*, 2010).

The limitations of these tests and the need for more detailed alternatives were highlighted by a recent American Heart Association scientific statement on cardiac arrest outcomes, in which the authors stated that "...the lack of an easy-to-administer, validated neurological functional outcome is a major limitation to the (cardiac arrest resuscitation) field" (Becker *et al.*, 2011).

Several investigations of resuscitated arrest patients have utilized formal neurocognitive testing, finding that roughly half of the survivors suffer from measurable cognitive impairments (Roine *et al.*, 1993; Sauve *et al.*, 1996; van Alem *et al.*, 2004). These studies utilized different batteries of clinically based neurological tests and compared findings to different normative data sets, making comparisons between the studies difficult. Common limitations of the tests utilized in these studies include the requirement for highly trained personnel to administer the batteries, the associated costs

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from this requirement, and the time necessary to perform traditional paper-and-pencil neurocognitive testing (Gur *et al.*, 2010).

The lack of a single, easy to administer, highly sensitive neurocognitive test makes it difficult to use cognitive impairment as an outcome measure when assessing the effectiveness of cardiac arrest and postarrest treatment approaches, such as trials of TTM, in which granular neurocognitive outcomes are important measures. In this feasibility study, we sought to test the utility of a validated computerized neurocognitive battery (CNB) to assess similar cognitive domains, while limiting the testing to less than 90 minutes and allowing for testing in the convenience of the patients' homes or other nonclinic locations. In addition, the battery can be administered by research assistants, thus providing a potentially scalable infrastructure for broader use in clinical practice or as an outcome measure for clinical trials of TTM and other postarrest care approaches.

Materials and Methods

The current investigation received approval from the University of Pennsylvania Institutional Review Board. We enrolled a convenience sample of resuscitated adult (age >18 years) cardiac arrest subjects who were discharged with a CPC score of 1 and a Glasgow Coma Scale (GCS) score of 14 or 15. For this initial pilot work, we allowed a minimum time from initial arrest to neurocognitive testing of 3 months and maximum time to testing of 36 months. A convenience sample of patients who underwent postarrest TTM and those who did not were both eligible for inclusion. Exclusion criteria included diagnosed anoxic brain injury, head trauma, and neurological disorders (i.e., epilepsy, stroke). Individuals with diagnosed psychological disorders (i.e., anxiety disorders, depression) before cardiac arrest were also excluded.

In addition to CNB testing, patients completed a questionnaire of self-assessed well-being before CNB administration. Patients were asked if they had noticed a change in seven different senses or abilities since their arrest and rated their answers on a Likert scale of 1 (extremely affected) to 4

(no change). The categories, based on preliminary survey data, included touch, taste, smell, sight, hearing, memory, and coordination (Abotsi *et al.*, 2009).

In collaboration with the Hospital of the University of Pennsylvania (HUP) Brain Behavior Laboratory, we customized the CNB to include tests that were previously validated for use in large-scale studies involving healthy adults (Gur *et al.*, 2001). The CNB consisted of 11 tests that assessed the following cognitive domains: executive functions—abstraction and mental flexibility, attention, working memory; episodic memory—verbal, facial, spatial memory (immediate and delayed); complex cognition—language reasoning, spatial processing; social cognition—emotion identification; and processing speed—sensorimotor speed, motor speed (Gur *et al.*, 2010). The administration time of the CNB was ~80 minutes, including brief standardized rest periods. The CNB was designed so that it can be administered using a laptop computer either at the patient's residence, place of work, or in an office room at HUP by a trained research assistant. The raw scores of the tests were uploaded to a data repository using an automated script for secure data transfer and scored upon completion of the battery using a program written in the Python programming language. Table 1 shows the two performance indices used in calculating each domain: (1) accuracy—the number of correct responses and (2) speed—the median response time for correct responses. Each domain is scored for both accuracy and speed except for two domains (sensorimotor, motor speed) where only speed is measured. The raw scores for each CNB test were transformed to standardized z-scores based on a healthy sample. The average z-score of the cardiac group provided magnitude estimates, and the difference between that average and the average of the normative sample was tested using a Student's t-test with Bonferroni correction for multiple comparisons. There were 20 comparisons in total, 11 categories for speed and 9 for accuracy; therefore, we used an adjusted *p*-value cutoff of 0.0025 (0.05/20). For a categorical appraisal of the results, a z-score of less than or equal to -2 was used as a cutoff to mark statistical significance (Lezak *et al.*, 2004).

TABLE 1. DOMAINS ASSESSED IN THE LAPTOP-BASED NEUROCOGNITIVE TEST BATTERY

Domain	Test(s)	Dependent measure(s)
Abstraction and mental flexibility	Penn Conditional Exclusion Task (PCET)	Accuracy, speed
	Penn Matrix Reasoning Test (PMAT)	Accuracy, speed
Attention	Penn Continuous Performance Task (PCPT)	Accuracy, speed
Working memory	Short Letter and Back (SLNB)	Accuracy, speed
Episodic memory (verbal)	Word Immediate (IWRD)	Accuracy, speed
	Word Delayed (DWRD)	Accuracy, speed
Episodic memory (facial)	Face Immediate (IFAC)	Accuracy, speed
	Face Delayed (DFAC)	Accuracy, speed
Episodic memory (spatial)	Spatial Immediate (SVT)	Accuracy, speed
	Spatial Delayed (SVTLD)	Accuracy, speed
Language reasoning	Penn Verbal Reasoning Test (PVRT)	Accuracy, speed
Spatial processing	Penn Line Orientation Task (PLOT)	Accuracy, speed
Emotion identification	Emotion Recognition Task (ER40)	Accuracy, speed
	Measured Emotion Differentiation Test (MED)	Accuracy, speed
Sensorimotor	Motor Praxis Task (MP) ^a	Speed
Motor speed	Computerized Finger Tapping Task (CTAP) ^a	Speed

^aTests without healthy, age-matched normative sample.

Because we did not collect normative data concomitant with patient data, we used the normative database of the Brain Behavior Laboratory to find matched controls. Control subjects were selected from a normative pool using a variable optimal matching algorithm to maximize the demographic similarity between the case and control subjects (Reference: SAS Macros, 2012. <http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm>). The algorithm determines the demographic distance of each candidate normative subject from each case subject on a set of defined demographic dimensions. It then finds the set of normative-to-case pairs (or set of multiple normative-to-case pairs) that minimizes the sum of these distances. We used this algorithm to find a set of three normative-to-case matches using age, sex, and race as the demographic dimensions. The tests measuring motor speed and sensorimotor domains were updated versions of previously validated tests and did not have data available to provide an appropriate match. Unmatched norms were used for these two domains. All analyses were done using a standard statistical package (SAS version 9.3; SAS Institute, Inc., Cary, NC).

Results

Thirty-one subjects were enrolled and 29 were included in this pilot feasibility study comprising a convenience sample of patients who experienced cardiac arrest between January 2009 and October 2011. Two individuals were initially considered; however, after completing the battery, it was discovered that they had both sustained a traumatic cardiac arrest with associated brain injury and thus were excluded. Demographic characteristics are summarized in Table 2. All patients were discharged with favorable outcome, defined as having a CPC score of 1 and a GCS score of 14 or 15 as per our *a priori* enrollment criteria. Sixteen (55%) patients experienced out-of-hospital arrest, and 20 (69%) patients had a shockable initial arrest rhythm. Patients who underwent TTM ($n=12$) and those who did not ($n=17$) were included in the cohort. The mean age was 52.9 ± 16.7 years (range 20–86 years). The average time between cardiac arrest and date of testing was 15.2 ± 7.4 months (range 4–27 months). The average duration of the CNB was 81 ± 20 minutes for each subject (range 55–133 minutes). All 29 patients were determined to be CPC 1 at discharge.

Performance measures (accuracy and speed) for each domain are provided in Figure 1. As can be seen, patients tolerated the testing well and performed at normative levels on most. Notably, however, they showed a deficit in working memory accuracy, $t=8.59$, $df=108.57$, $p<0.0001$. The deficit was of a large magnitude (>1 SD), with patients per-

forming between -2.69 and -0.68 below average. Spatial memory speed was also impaired in the cardiac group, $t=3.50$, $df=32.23$, $p=0.001$.

An evaluation of a categorical approach indicated that performance deficits were seen in nearly one quarter of the subjects for two of the domains, where speed was used as a measurement (Table 3), including two patients who underwent postarrest TTM. Spatial episodic memory speed and spatial processing speed (21%) were the most affected domains. Domains using accuracy as a measure were not affected as much. Across all domains, including those using speed as a measurement and those using accuracy, 7 of the 29 subjects (24%) had a z-score below -2 across two or more domains (data not shown). The three oldest patients (age 79, 80, 86) had at least one task in the battery that they were unable to complete, either because they were unable to understand the instructions or could not understand how to complete the task. These incomplete tasks did not generate numerical values and thus were unable to be included in the analysis.

Performance on the CNB for all domains was compared in patients who self-identified as having residual effects from their cardiac arrest to those who did not report any difference in their abilities. Individuals who ranked any of the seven categories with a 1 (extremely affected) or 2 (moderately affected) were compared with those individuals who ranked all of their categories with either a 3 (slightly affected) or a 4 (no change). Among the 14 individuals who ranked at least one category with a 1 or 2, 72% noted residual effects in memory (10/14) followed by 29% (4/14) for coordination, touch, and sight. The least reported residual effects were in smell (3/14), hearing (2/14), and taste (1/14). The Mann–Whitney U test comparing the groups across domains was performed and differences were not statistically significant in any of the values for speed or accuracy (data not shown).

Discussion

The goal of this feasibility study was to assess the effectiveness of an abbreviated laptop-based neurocognitive battery in identifying cognitive deficits in patients resuscitated from cardiac arrest, which might be useful clinically and as outcome tool for future trials of postarrest TTM. We found that the battery was well tolerated and that patients generally performed at normative levels. However, against this background, cardiac arrest survivors showed reduced accuracy in their working memory performance and reduced speed of spatial memory. The magnitudes were large (>1 SD) and for working memory, the top performer was at -0.68 SDs below normal mean. The test used for measuring working memory activates the dorsolateral prefrontal cortex, whereas the face memory test activates frontotemporal and limbic regions (Ragland *et al.*, 2002).

A number of previous investigations in postarrest care have defined patients with “favorable outcome” as those with a CPC score of 1–2, which by definition ranges from “good cerebral performance” to “sufficient cerebral function for independent activities of daily life,” a wide and subjective range of cognitive ability (Grenvik and Safar, 1981). Although the MMSE was initially developed as a screening for dementia, studies have utilized this test as another tool for determining cognitive impairment in

TABLE 2. SUBJECT DEMOGRAPHICS AND CLINICAL DATA

Subjects	n=29
Mean age, years $\pm$ SD	52.9 ± 16.7
Female, n (%)	8 (28)
Out-of-hospital arrest, n (%)	16 (55)
Shockable rhythm, n (%)	20 (69)
Therapeutic hypothermia, n (%)	12 (41)
CPC 1, n (%)	29 (100)

CPC, cerebral performance category; SD, standard deviation.

FIG. 1. Cardiac and control performance measures (accuracy and speed) for each domain. ABF, abstraction and mental flexibility; ATT, attention; WM, working memory; VMEM, episodic memory (verbal); FMEM, episodic memory (facial); SMEM, episodic memory (spatial); LAN, language reasoning; SPA, spatial processing; EID, emotion identification; SM, sensorimotor; and MOT, motor speed.

postcardiac arrest patients. It offers greater sensitivity and objectivity than the CPC; however, the MMSE has been shown to be ineffective in detecting more subtle cognitive impairment, particularly those in abstract reasoning, executive functioning, and visual perception/construction, some of the specific areas for which the neuropsychological battery is used to assess (Nys *et al.*, 2005).

Several studies have explored the utility of more in-depth neurocognitive testing in assessing cognitive deficits among cardiac arrest survivors. One study found that 50% of survivors had neurocognitive deficits at 1 year following arrest, with the most common impairment seen in delayed memory (Roine *et al.*, 1993). A second study showed a similar incidence of cognitive impairment, with 48% of patients studied being impaired in at least one domain (van Alem *et al.*, 2004). A third study illustrated cognitive differences between a control subject group and a patient group following out-of-hospital arrest. Two-thirds of the patients showed mild

deficits in memory and one-third showed more severe impairments in memory, psychomotor function, and other cognitive domains (Alexander *et al.*, 2011). Newer studies have also explored novel tests that are not as specific and time-consuming as a complete neurocognitive battery; these have been shown to be more sensitive than the MMSE or the CPC. One such study showed that a Frontal Lobe Assessment Battery, administered at the bedside by an occupational therapist, was appropriate in identifying cognitive impairment (Cronberg *et al.*, 2009). These studies all found significant deficits in cardiac arrest patients and indicate that further exploration of novel testing methods on this patient population is warranted.

In addition to being relatively brief, easy to administer, and portable, our laptop-based battery measures both speed and accuracy for every relevant test so that the results can be analyzed independently of one another. It is important to assess both these factors when analyzing cognitive deficits,

TABLE 3. SPEED AND ACCURACY MEAN Z-SCORES AND PERCENT OF IMPAIRED PATIENTS FOR 11 COGNITIVE DOMAINS

Domain	Mean z-scores for speed (SD)	% Impaired ^a	Mean z-scores for accuracy (SD)	% Impaired ^a
Abstraction and mental flexibility	-0.40 (1.50)	7	-0.16 (0.79)	0
Attention	0.08 (1.32)	7	-0.65 (1.91)	10
Working memory	-0.08 (1.12)	7	-1.12 (0.40)	3
Episodic memory: verbal	-0.29 (0.93)	3	-0.21 (0.95)	3
Episodic memory: facial	-0.30 (1.11)	7	-0.11 (1.07)	7
Episodic memory: spatial	-1.26 (1.82)	21	0.02 (0.80)	0
Language reasoning	0.04 (0.54)	0	0.24 (0.71)	0
Spatial processing	-0.99 (1.97)	21	-0.29 (0.87)	3
Emotion identification	-0.51 (1.20)	14	0.58 (0.93)	3
Sensorimotor	-0.25 (1.31)	3	n/a	n/a
Motor speed	-0.01 (1.21)	7	n/a	n/a

^aCognitive impairment defined as having z-score of ≤ -2 .

n/a, not applicable. Sensorimotor and motor speed are only scored for speed.

since accuracy might be within the normal range of performance, while the length of time to identify the appropriate response may be abnormally long. Moreover, the battery includes a unique domain for emotion identification, which identifies social cognition, a domain if affected could have quality of life ramifications for the cardiac arrest survivors and is often neglected (Gur *et al.*, 2010).

This laptop-based neurological testing approach could offer healthcare providers a cognitive baseline score at the time of discharge following resuscitation from cardiac arrest. The score could also serve as a useful measure when following the patient's cognitive function over time, allowing for a more complete understanding of neurological recovery in the outpatient setting whether or not patients received TTM and other modalities of postarrest care. It is possible that a more subtle cognitive improvement or decline not seen with an MMSE or CPC scoring system could be observed. As more targeted therapies are developed to improve mortality and cognitive outcomes for postcardiac arrest patients, there will be a need for more sensitive tests to determine the effectiveness of such treatments. In addition, the relatively short testing time of 80 minutes on average was well tolerated in our pilot feasibility study, a finding supported by previous literature using this tool in healthy cohorts (Gur *et al.*, 2010).

Limitations

There are several limitations to this feasibility study with the lack of healthy, age-matched normative data for our complete battery being the most significant. Two of the tests did not have relevant matched normative data sets available. Our small sample size, combined with our broad inclusion criteria, also makes determining statistical significance against healthy controls difficult; our goal with this work was oriented toward proof-of-concept and was therefore not designed for specific comparisons. The neurological state of our patients after the return of spontaneous circulation was also highly variable. Some individuals were awake and oriented immediately after being resuscitated, whereas some, specifically those who underwent TTM, were unconscious for much longer periods of time and this might be an important factor to adjust future enrollment and testing. We did not standardize the time to testing, however, after stratifying our patients into individuals tested less than 6 months following cardiac arrest and those tested over 6 months following cardiac arrest, no significant differences were observed (data not shown). In addition, only cardiac arrest survivors discharged with a CPC 1 were analyzed. The two individuals excluded from our analysis due to traumatic brain injury were discharged with CPC 2 and able to complete the battery without complications. However, the ability of more impaired patients to complete the battery has yet to be determined and should be explored in future studies.

Finally, there are broader limitations to utilizing neurocognitive testing in the context of resuscitated cardiac arrest victims. Lengthy hospitalization as well as underlying medical conditions (coronary artery disease, history of myocardial infarction) could result in different test scores regardless of cardiac arrest and, therefore, should be controlled in future work. These effects can be limited in future studies by only including tests most likely affected by relevant neuropathological mechanisms, obtaining new normative data sets, and

further customizing the neurocognitive battery to fit the needs of cognitive assessment for cardiac arrest patients. It will be important to compare the results from the CNB to other easy to administer tests, as well as a standardized quality of life measure, to more accurately determine the effectiveness of this test in the context of postcardiac arrest care. Future work with larger sample sizes will also allow a meaningful comparison of neurocognitive outcomes in patients receiving TTM against those who did not.

Conclusions

In this feasibility study, we found that a CNB was well tolerated by cardiac arrest survivors with favorable neurological outcomes and could successfully be administered to postcardiac arrest patients in 80 minutes by a trained research assistant. Performance was in the normative range for both accuracy and speed on most domains, but showed significantly reduced accuracy of working memory and speed of spatial memory. Further work will focus on developing a shorter battery with a carefully matched and concurrent control data set, controlled for both age and comorbidities. In addition, we would like to explore possible cognitive differences between those patients who undergo TTM and those who do not.

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