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Detecting Cognitive Impairment in Individuals at Risk for Cardiovascular Disease: The ‘Clock-in-the-Box’ Screening Test

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Abstract

Objective—The purpose of this study was to evaluate the performance on the Clock-in-the-Box (CIB), a screening measure for cognitive function, relative to neuropsychological testing in an older population with cardiovascular risk.

Methods—A prospective cohort of older patients (>50 years) with cardiovascular risk were recruited to perform the CIB and complete a brief neuropsychological battery consisting of Trailmaking tests, the Hopkins Verbal Learning Test (HVLT), and fluency tasks. Performance on the CIB was scored according to standard criteria (range 0–8, 0–worst). The performance on the total CIB, working memory subscale (CIB-WM), and planning/ organization (COB-PO) were compared to neuropsychological measures.

Results—The cohort (n=127) was older (age 67±7 years) and diverse with 33% female (n=42) and 42% non-white race (n=53). Cardiac risk factors were prevalent: hypertension (83%), hyperlipidemia (74%), overweight (84%), diabetes (48%), prior cardiac disease (39%), and smoking (11%). The CIB (mean 6.5±1.3) took 84±21 seconds on average to complete and had good inter-rater reliability ($\kappa=.809$, $p<.01$). The CIB-WM subscale was significantly correlated with performance on Trailmaking B and HVLT learning, recall, and recognition. The CIB-PO subscale was significantly associated with semantic and phonemic fluency, Trailmaking B, and HVLT learning and recall. In regression modeling, CIB-WM significantly predicted performance on HVLT learning, recall, and retention. CIB-PO subscale predicted performance on Trailmaking B, HVLT learning, and HVLT recall.

Conclusions—The CIB is a brief cognitive screening instrument with good reliability and predictive validity in a CV risk population. The CIB-WM and CIB-PO subscales could provide utility for clinicians.

Keywords

clock drawing; cognitive screening; cardiovascular; executive function; memory

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Introduction

With a prevalence of 34%, cardiovascular disease is the most common pathology in older adults and is the leading cause of death (Lloyd-Jones, et al. 2010). While cardiovascular disease may present as a number of specific illnesses including hypertension, coronary artery disease, or congestive heart failure, the underlying pathology is similar – atherosclerosis. Atherosclerosis is not confined to arteries of the heart and may symptomatically occur in the kidneys, eyes, extremities, and brain. Specifically, there is increasing evidence that cardiovascular disease, and the risk factors associated with the development of cardiovascular disease, is accompanied by cognitive deficits that may compromise a patient's level of functioning, as well as his/her ability to comply with medical recommendations aimed at controlling the cardiovascular disease itself (Brady, et al. 1999; Izquierdo-Porrera and Waldstein 2002; Pugh, et al. 2003).

The cognitive changes observed in patients with cardiovascular risk factors have been linked with silent infarcts in the deep subcortical white matter, subcortical gray nuclei, and the brainstem (Cohen, et al. 2002; Schmidt, et al. 1995; Strassburger, et al. 1997). These white matter pathways provide a number of specific and reciprocal connections between the prefrontal cortex and the deep subcortical nuclei (Brown dyke, et al. 2002). Silent infarcts affecting these pathways may disrupt the connectivity between these brain regions, resulting in altered functioning of the frontal lobe (Bogousslavsky, et al. 1988; O'Sullivan, et al. 2004; Van Petten, et al. 2004). In fact, specific deficits in executive functions, which are thought to be mediated by the frontal lobe, have been noted in patients with cardiovascular risk factors (Brady et al. 1999; Izquierdo-Porrera and Waldstein 2002; Pugh et al. 2003).

A number of existing well-validated and reliable neuropsychological measures have demonstrated excellent sensitivity and specificity in detecting subtle impairment (e.g., Wisconsin Card Sorting Test, Wechsler Memory Scale; (Heaton, et al. 1993; Wechsler 1997); however, such measures are time consuming and require training and experience to administer, thereby making them unsuitable as screening measures. Thus, there is a need for a clinically useful screening instrument that can detect memory and executive function deficits, is rapidly administered with good inter-rater and test re-test reliability, and has high levels of sensitivity and specificity, concurrent validity, and predictive validity (Shulman 2000). Ultimately, the Clock Draw Test (Goodglass and Kaplan 1983) may possess many of the necessary properties for a screening test for cognitive function: brief administration time; correlation with executive abilities (Cahn-Weiner, et al. 1999; Libon, et al. 1996; Shulman 2000; Tuokko, et al. 1992); potential usefulness in assessment of memory functions (Seigerschmidt, et al. 2002; Shulman 2000); and strong psychometric properties (Rouleau, et al. 1996; Shulman 2000; Stubner, et al. 1999).

We developed a modification of the CDT, called the Clock-in-the-Box (CIB), which contains both working memory and planning/organization (executive function) components. The working memory and planning/organization subscores were designed to provide specificity in the identification of cognitive impairment. The aim of this study was to investigate the utility of an experimental screening measure (Clock-in-the Box) in the identification of early cognitive problems in individuals with cardiovascular risk factors. We predicted that performance on the CIB would be associated with performance on validated and reliable existing measures of memory and executive function. Additionally, we predicted that performance on the CIB subscores would be associated with performance on standardized measures assessing executive function.

Methods

Participants

Community-dwelling older patients (n=127) over age 50 years were recruited for participation. Most patients were recruited from cardiology and diabetes clinics, and we developed an oversampling protocol to increase minority and female participation. All patients provided written informed consent and the study was approved by the human subjects committees of the VA Boston Healthcare System. Cardiovascular risk patients (CV) were recruited based on the self reported diagnosis of one or more of the following: coronary artery disease, hypertension, diabetes, hyperlipidemia, body mass index ≥ 25 kg/m², current tobacco use. Participants with a prior stroke were included provided that they otherwise met the inclusion criteria. Participants with no current or previous diagnosis of cardiovascular disease were considered healthy controls. All patients spoke English as a first language. Exclusionary criteria included: (1) history of neurological disorder or loss of consciousness due to head injury (either formally documented or self-reported); (2) a self-reported history of major psychiatric illness that would interfere with testing; (3) acute intoxication or withdrawal from drugs or alcohol; (4) significant visual or hearing impairment that would impair the ability to complete cognitive measures.

Clock-in-the Box (CIB)

The CIB measure consisted of a modified version of the CDT in which participants completed the task with written instructions and a response sheet. The written instructions were: "In the blue box on the next page, draw a picture of a clock, put in all the numbers, and set the time to ten past eleven." Once the participant read the instructions and indicated his/her understanding, the instruction sheet was removed and the participant completed the task. The response sheet consists of four colored boxes (yellow, red, green and blue), each in a quadrant. The response sheet was presented to the participant with the blue colored box located in the lower right quadrant. The examiner did not provide any cues or reminders regarding the instructions while the participant was engaged in the drawing.

Participants were allowed sufficient time to complete the task. A subset of cardiovascular risk participants was timed (n=25) with an average administration time of 84 ± 21 seconds (range 55-158). Each CIB was scored using an eight point total scale (Figure 1), consisting of a four-point working memory subscore (CIB-WM) and a four-point planning/organization subscore (CIB-PO). The CIB-WM subscore items are directly related to the specific details provided in the written instructions, whereas the CIB-PO items are associated with organizational and abstract features of the clock and are not linked to the specific written instructions. Additionally, a subsample of 20 participants was randomly selected, and CIB performance for this sample was rated by a naïve research assistant, blinded to the study hypotheses, performance on the standardized measures, and participant demographics. Comparison of scores revealed significant agreement between raters for CIB total score and CIB subscores: CIB total score ($\kappa = .809$, $p < .01$), CIB-WM ($\kappa = .914$, $p < .01$), and CIB-PO ($\kappa = .705$, $p < .01$).

Standardized Neuropsychological Measures

Performance on the CIB measure was compared to common, validated, and reliable neuropsychological measures of working memory and executive function. All clinical measures were administered using their standardized procedures and were conducted in a quiet space allocated for testing. The executive function tests administered were Trailmaking B and semantic and phonemic fluency. Semantic fluency was assessed by asking patients to name as many animals as possible in a 60-second period, and the score was the number of correct responses. The phonemic fluency task (Benton and Hamsher

1976) asked participants to name words beginning with a specific letter (F, A, and S) in 60 seconds, and the total score is the sum of correct responses for each trial. After administering Trailmaking A as a primer, participants completed the Trailmaking B task, which is a measure of alternating or shifting attention and requires individuals to connect encircled numbers and letters in an alternating manner. Performance is based on the amount of time required to complete the task (Spreeen and Strauss 1998). The memory test administered was the Hopkins Verbal Learning Test-Revised (HVLT). The HVLT-Revised (Benedict, et al. 1998) is a 12-item list learning test in which individuals are presented three learning and recall trials followed by a delayed recall and 24 item recognition test. The HVLT-Revised produces four outcome variables including: learning across trials (HVLT learning), the number of items recalled after the delay (HVLT delayed recall); the percentage of delayed recall items relative to the maximum items learned (HVLT retention percent), and the number of recognition items correctly identified (HVLT Recognition).

Statistics

Comparison of CIB and neuropsychological test performances—Partial correlations were calculated with CIB scores (total and subscores) and the neuropsychological test t-scores.

Predictive Validity—To determine the predictive validity of the CIB total score for performance on standardized measures, a series of stepwise linear regressions was conducted where the CIB subscale, as well as age and education, were entered into a linear regression model predicting the raw score for each standardized cognitive measure. For each regression, we report the number of participants included, the R^2 for the overall regression, the F-value for the regression, the p-value for the regression, and whether the CIB subscore significantly contributed to the regression.

Defining Decline—To develop cutoffs for the experimental measure, a cohort of patients (n=42) was recruited from primary care clinics with similar inclusion and exclusion criteria, although cardiovascular risk factors were *not* present in this control group. This control cohort provided informed consent and underwent an identical protocol. The control cohort had similar age, education, and sex. Scores that were one standard deviation below the mean were considered to indicate “suspected” impairment, and scores that were 1.5 standard deviations below the mean were considered to indicate “probable” impairment (Heaton, et al. 2004). The CIB cutoff for suspected impairment was 6 and the CIB cutoff for probable impairment was 5.

Results

The control cohort was primarily older (mean age 67.0 ± 7 years), male (67%), well-educated (mean 13 ± 2 years), and diverse (non-white 42%). Mean scores and standard deviations for each of the standardized measures are presented in Table 1. Four participants did not complete the semantic fluency task; all patients completed the CIB, Trailmaking tests, HVLT, and phonemic fluency.

Table 2 reports the partial correlations between the CIB and the standardized measures. Bivariate correlations relating performance on the CIB to the standardized measures revealed significant associations between the CIB total and CIB subscores with a number of the standardized cognitive measures. The CIB-WM subscale was significantly correlated with performance on Trailmaking B, HVLT learning, HVLT delayed recall, and HVLT recognition. The CIB-PO subscale was significantly associated with semantic and phonemic fluency, Trailmaking B, HVLT learning, and HVLT delayed recall. Overall, the findings

from these correlational analyses indicate that the CIB possesses good concurrent validity with standardized cognitive measures.

Table 3 describes the predictive validity of the CIB subscores in regression modeling. In linear regression models controlling for age and education, the CIB-PO score was a significant independent predictor of Trailmaking B, HVLT Learning, and HVLT delayed recall. The CIB-WM score was a significant predictor of HVLT learning, HVLT delayed recall, and HVLT retention after adjustment for age and education. Thus, the CIB-PO may possess good predictive validity for measures of set-shifting and verbal learning, and the CIB-WM may possess good predictive validity for measures of verbal learning and recall.

Employing the cutoff for suspected impairment (i.e., CIB total of 6 or less) resulted in 45% of the participants being classified with suspected impairment. Employing the cutoff for probable impairment (i.e., CIB total of 5 or less) resulted in 20% percent of the participants being classified as impaired. Interestingly, these rates of impairment on the CIB are similar to that of the neuropsychological measures. On neuropsychological tests, 32% (range 15-47%) of the participants were classified as impaired.

Discussion

Cognitive screening in the primary care setting presents some specific challenges, the most obvious of which relates to time and efficiency. This study examined the performance and reliability of a brief cognitive screening measure, the CIB, relative to standard neuropsychological measures in a control population and a population with high cardiovascular risk. Performance on the CIB is predictive of performance on standardized, well-validated cognitive measures. Additionally, the CIB is simple and quick to administer and score, and it has high inter-rater reliability. Further, impaired performance on the CIB was found to be consistent with impaired performance on standardized measures of executive functioning and verbal recognition. These findings indicate that the CIB may be a valid cognitive screening measure with clinical populations in which executive dysfunction is expected, such as patients with cardiovascular disease.

A number of published studies have investigated the use of the clock drawing test in the clinical setting. This study utilizing the CIB has face validity because it is consistent with other studies utilizing clock draw tasks that have found high levels of inter-rater reliability, positive predictive value across the varied versions, and a high correlation between clock drawing tasks with other neuropsychological tests (Shulman 2000). Additionally, our study expands the clock literature with the development of the working memory and planning/organization subscales, as well as with its inclusion of patients at high risk for cognitive deficits due to cardiovascular disease. Finally, an important advance was the administration and scoring of the CIB by a trained, non-clinician. The administration of the CIB by trained clerical staff could provide rapid, reliable screening of cognitive function in a clinical setting, preserving the clinicians' time for interpretation of the CIB and secondary assessment.

The utility of the CIB in identifying patients with cognitive impairment, particularly those with cardiovascular disease is an important development of the CIB. Although 20 percent of participants performed at 1.5 standard deviations below the control group, none of these clinical participants were referred for formal cognitive testing. This finding underscores the need for a measure such as the CIB to be administered routinely to older adults in the cardiovascular clinical setting because of serious ramifications that may be associated with cognitive decline.

There are several important strengths to this study. First, our study recruited a diverse older patient population, which improves external validity (generalizability) to older patients with cardiovascular risk factors. Second, the inclusion of a control group allowed for the creation of impairment cutoffs, which provided an element of predictive validity. Next, the performance reference standard was neuropsychological tests, which are lengthy, but have high sensitivity, specificity, and predictive value. Thus, the correlation of the CIB and neuropsychological tests provides a face validity that the CIB is capturing cognitive performance. Finally, the development of the CIB-WM and CIB-PO subscores could guide clinicians to the type of cognitive deficits, the need for additional cognitive testing, and potentially, the associated functional deficit.

This study also has noteworthy limitations. First, this study did not compare to the commonly-used Mini Mental State Examination or other clinical rating scale (e.g., dementia rating scale). However, this independent, community-dwelling population was unlikely to have dementia. Second, this study would have benefitted from a detailed measure of working memory to capture that component of the CIB-WM scale. Third, due to study design, we were unable to address cultural/language independence and test re-test reliability. Along the same lines, this study is further limited by the low presence of women since there is a lower prevalence of cardiovascular disease in this population. Although our population was diverse, all participants were native English speakers, thereby limiting our generalizability to non-English speaking populations. Additionally, test-retest reliability and longitudinal assessment of function with the CIB would be a valuable addition to future studies. Finally, this study does not validate the CIB for use in populations other than CV risk populations. Ultimately, the true test of the CIB's utility would be to determine whether participants who at one point in time are "suspected" to be cognitively impaired, or are "probable" with regard to cognitive impairment based on the CIB, perform within the impaired range on the standardized measures during subsequent assessments.

Conclusion

This study found that the CIB, a 90-second screening instrument, shows promise as a cognitive screening measure in the medical setting. The CIB is designed to provide a brief overview of cognitive function, including assessment of working memory and planning/organization, in an effort to assist the clinician in determining which patients may require further evaluation. The CIB was found to be strongly correlated with neuropsychological testing, particularly in patients with cardiovascular disease. Thus, the brief time required to administer and complete the CIB, along with its administration and scoring ease, makes it ideal for the primary care setting where clinical time is limited.

Key Points

- The Clock-in-the-Box is a cognitive screening measure that can be completed in about 90 seconds and correlates with standard neuropsychological tests.
- Patients with cardiovascular risk may have cognitive deficits and the Clock-in-the-Box was able to detect these deficits.
- The Working Memory and Planning/Organization subscales of the Clock-in-the-Box may guide clinicians to investigate cognitive function with additional testing.

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Working Memory Subscore (4 possible points)	
1.	Drawing completed in correct (blue) square.
2.	Drawing resembles a clock or an attempt was made to draw a clock.
3.	Drawing includes all numbers (in any order and any location).
4.	Correct time is indicated in any manner (correct number may circled, or time may be written).
Planning/Organization Subscore (4 possible points)	
5.	Drawing of clock is of appropriate size (small enough to fit in blue square and large enough to accommodate numbers)
6.	Numbers are in correct order
7.	Numbers are evenly spaced (opposing anchors of 3 and 9, and 6 and 12 are well aligned, each quadrant of the clock should include non-anchor digits)
8.	Hands are of differing length and hand origin must be located within 50% of center of clock (hour hand must be 80% or less of the minute hand)
Total CIB Score = Working Memory Subscore + Planning/Organizational Subscore	

Figure 1.
Scoring Criteria for the Clock-in-the-Box Measure

Table 1

Characteristics of the Cardiovascular Risk Population (n=127)

Characteristic	Mean (SD) n (%)
Age (years)	67.0 (7.4)
Female	42 (33%)
Non-white	53 (42%)
Education (years)	13.4 (2.6)
Framingham Risk Score	12.9 (7.7)
Cardiac Risk Factors	
Prior Coronary Event	49 (39%)
Hypertension	105 (83%)
Diabetes	61 (48%)
Overweight (BMI>25 kg/m ²)	107 (84%)
Active Smoker	14 (11%)
Hyperlipidemia	94 (74%)
Clock-in-the-Box	
Total Score	6.5 (1.3)
Working Memory Subscore	3.5 (0.7)
Planning/Organization Subscore	3.0 (0.8)
Neuropsychological Test Results	
Phonemic Fluency (number of words)	36 (12)
Semantic Fluency (number of words)	17 (4)
Trailmaking A (sec)	46 (19)
Trailmaking B (sec)	126 (69)
HVLT Learning (number learned)	21 (5)
HVLT Delayed Recall (number recalled)	7 (3)
HVLT Retention Percent (recalled/learned)	76% (26)
HVLT Recognition (multiple choice)	10 (2)

[†]Mean t-scores and standard deviations (SD) for the CIB and standardized cognitive measures.

CIB = Clock-in-the-Box

HVLT = Hopkins Verbal Learning Test - Revised

Table 2

Bivariate correlations comparing the Clock-in-the-Box and neuropsychological measures.

	CIB Total	CIB Working Memory	CIB Planning / Organization
CIB – Total		0.81 ^{**}	0.86 ^{**}
CIB – Working Memory			0.40 ^{**}
Phonemic Fluency	0.22 [*]	0.07	0.27 [*]
Semantic Fluency	0.16	0.09	0.18 [*]
Trailmaking B	−0.34 ^{**}	−0.22 [*]	−0.35 ^{**}
HVLT Learning	0.37 ^{**}	0.24 [*]	0.38 ^{**}
HVLT Delayed Recall	0.32 ^{**}	0.26 [*]	0.28 [*]
HVLT Retention Percent	0.17 [*]	0.21 [*]	0.09
HVLT Recognition	0.07	0.09	0.04
Discrimination			

^{**}
p<.001

^{*}
p<.05

CIB = Clock-in-the-Box

HVLT = Hopkins Verbal Learning Test - Revised

Table 3

Linear regression predicting neuropsychological test score with adjustment for age, education and Clock-in-the-Box subscore

Test	CIB-Working Memory				CIB-Planning / Organization			
	n	Regression R ²	Regression F-value (p-value)	Significant CIB-WM contribution	n	Regression R ²	Regression F-value (p-value)	Significant CIB-PO contribution
Phonemic Fluency	127	0.26	14.4 (<.001)	No	127	0.27	15.0 (<.001)	No
Semantic Fluency	122	0.14	6.6 (<.001)	No	122	0.15	6.7 (<.001)	No
Trail Making B	127	0.23	12.3 (<.001)	No	127	0.25	13.4 (<.001)	Yes
HVLT Learning	127	0.19	9.4 (<.001)	Yes	127	0.23	11.8 (<.001)	Yes
HVLT Delayed Recall	127	0.16	7.7 (<.001)	Yes	127	0.14	6.7 (<.001)	Yes
HVLT Retention Percent	127	0.07	3.2 (.03)	Yes	127	0.04	1.5 (.22)	No
HVLT Recognition Discrimination	127	0.06	2.4 (0.7)	No	127	0.06	2.5 (.07)	No

CIB = Clock-in-the-Box; HVLT = Hopkins Verbal Learning Test – Revised; PO – planning / organization subscale; WM – working memory subscale