

# Relation of Brain Natriuretic Peptide Levels to Cognitive Dysfunction in Adults >55 Years of Age With Cardiovascular Disease

John Gunstad, PhD<sup>a,\*</sup>, Athena Poppas, MD<sup>b</sup>, Steven Smeal, PhD<sup>c</sup>, Robert H. Paul, PhD<sup>d</sup>, David F. Tate, PhD<sup>d</sup>, Angela L. Jefferson, PhD<sup>e</sup>, Daniel E. Forman, MD<sup>f,g,h</sup>, and Ronald A. Cohen, PhD<sup>d</sup>

Cardiovascular disease (CVD) is associated with cognitive deficits long before the onset of stroke or dementia. Recent work has extended these findings and shown that patients with congestive heart failure also exhibit reduced cognitive performance. Brain natriuretic peptide (BNP) is used to help diagnose heart failure, but no study has examined whether BNP predicts cognitive dysfunction in older patients with CVD. BNP values and performance on the Dementia Rating Scale were assessed in 56 older adults with documented CVD. Forty-eight percent of the participants were women, and their average age was  $70 \pm 8$  years. All participants had Mini-Mental State Examination scores greater than the cutoff for dementia and no histories of neurologic or severe psychiatric disorders. The average BNP level was  $122 \pm 202$  pg/ml. Hierarchical regression analyses showed that log-transformed BNP levels predicted Dementia Rating Scale total score after adjusting for possible demographic and medical confounders ( $\Delta R^2 = 0.09$ ,  $F[1, 44] = 6.14$ ,  $p = 0.017$ ). Partial correlation analysis adjusting for these possible confounders showed a particularly strong relation to the conceptualization subtest ( $r = -0.44$ ,  $p = 0.002$ ), a measure of verbal and nonverbal abstraction abilities. In conclusion, the results of the present study provide the first evidence for an independent relation between BNP and cognitive dysfunction in older adults with CVD. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:538–540)

We hypothesized that brain natriuretic peptide (BNP) levels might predict cognitive dysfunction and assessed BNP levels and cognitive performance in a sample of older adults with documented stable cardiovascular disease (CVD).

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The following methods were approved by the local institutional review board, and all participants provided written informed consent.

Fifty-six participants enrolled in a larger, prospective study of the neurocognitive consequences of CVD were included in the present study. For inclusion into the parent study, all participants had to have documented histories of CVD, be between the ages of 55 and 85 years, have Mini-Mental State Examination total scores greater than the cut-

off for dementia,<sup>1</sup> and have no histories of neurologic or severe psychiatric disorders (e.g., stroke, bipolar disorder). The demographic and medical characteristics of the sample are presented in Table 1.

BNP levels were obtained on the same day as the neuropsychologic battery was conducted and <3 weeks after cardiac evaluation. BNP levels were quantified using the Bayer Advia Centaur (Bayer HealthCare, Tarrytown, New York). Blood samples were sent to the local laboratory for analysis. To promote comparison with past studies, BNP levels were log transformed before statistical analysis to adjust for the skewed distribution.<sup>2</sup>

The Dementia Rating Scale (DRS) is a commonly used neuropsychologic measure that is sensitive to dementia and cognitive decrease in older adults.<sup>3–5</sup> In addition to the DRS total score, 5 subtests assess function in different cognitive domains, namely, attention, initiation and perseveration, construction, conceptualization, and memory. The DRS was administered and scored according to established protocols by a trained research assistant.

A complete transthoracic echocardiogram was obtained with 2-dimensional apical views from each participant according to the standards of the American Society of Echocardiography. From these data, 2 indexes were derived: the left ventricular ejection fraction and cardiac output (CO). Left ventricular stroke volume was calculated on the basis of biplane volumes (i.e., stroke volume = [end-diastolic volume – end-systolic volume]/end-diastolic volume). The biplane method of discs uses 2 orthogonal views from the

<sup>a</sup>Department of Psychology, Kent State University, Kent, Ohio; <sup>b</sup>Department of Cardiology, Rhode Island Hospital, Brown Medical School; <sup>c</sup>Department of Pathology, The Miriam Hospital; and <sup>d</sup>Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island; <sup>e</sup>Alzheimer's Disease Center, Department of Neurology, Boston University School of Medicine; <sup>f</sup>Department of Cardiology and Aging, Brigham and Women's Hospital; <sup>g</sup>VA Medical Center; and <sup>h</sup>Harvard Medical School, Boston, Massachusetts. Manuscript received November 2, 2005; revised manuscript received and accepted February 16, 2006.

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\*Corresponding author: Tel: 330-672-2589; fax 330-672-3786.

E-mail address: jgunstad@kent.edu (J. Gunstad).

Table 1  
Demographic and medical characteristics of older patients with cardiovascular disease (n = 56)

Characteristic	Observed Values	Clinical Cutoff
Age (yrs)	70 ± 8	
Women	27 (48%)	
White	43 (77%)	
Education (yrs)	14 ± 3	
BNP (pg/ml)	122 ± 202	>100
Ejection fraction (%)	58 ± 13	<50
Cardiac output (L/min)	4.4 ± 1.4	<4
DRS total score	136.4 ± 5.5	<122 total points
Heart failure	15 (27%)	
Myocardial infarction	19 (34%)	
Coronary artery bypass graft	14 (25%)	
Valve repair/replacement	4 (7%)	
Atrial fibrillation	7 (13%)	
Hypertension	40 (71%)	
Type 2 diabetes mellitus	13 (23%)	

apex. This directly assessed area is independent of pre-conceived ventricular shape and is less sensitive to geometric distortions; it is therefore recommended in patients with coronary artery disease and regional wall motion abnormalities. The biplane method of discs (or Simpson's rule) calculates volumes from the summation of areas from diameters of 20 cylinders, discs of equal height; these are apportioned by dividing the chamber's longest length into 20 equal sections. The left ventricular ejection fraction was calculated on the basis of biplane volumes (i.e., ejection fraction =  $[(\text{end-diastolic volume} - \text{end-systolic volume}) / \text{end-diastolic volume}] \times \text{heart rate}$ ).

CO is the amount of blood in liters per minute that is pumped from the heart to perfuse the systemic circulation. Because the flow is pulsatile, CO is a function of stroke volume and heart rate. Stroke volume can be calculated as the mean velocity of blood flow leaving the left ventricle, as recorded with Doppler echocardiography, times the area of the left ventricular outflow tract measured from the 2-dimensional echocardiographic image ( $\text{CO} = [\text{time velocity integral} \times \text{cross-sectional area}] \times \text{heart rate}$ ). Although this method reflects a noninvasive procedure for obtaining CO, previous research has shown that data generated from such noninvasive procedures strongly correlate with Doppler-based CO.<sup>6</sup>

Hierarchical regression analysis was conducted to examine the relation between BNP levels and DRS total score. In this analysis, possible demographic (age, gender, education) and medical confounding variables (CO, history of hypertension, type 2 diabetes, coronary artery bypass graft, or valve-related surgery) were entered in the first step. Log-transformed BNP levels were entered in the second step. Log transformation was used to reduce positive skew, consistent with other studies examining BNP.<sup>7</sup>

Two-tailed partial Pearson's correlation analyses were then conducted to further clarify the relation between BNP and cognitive dysfunction. Log-transformed BNP levels

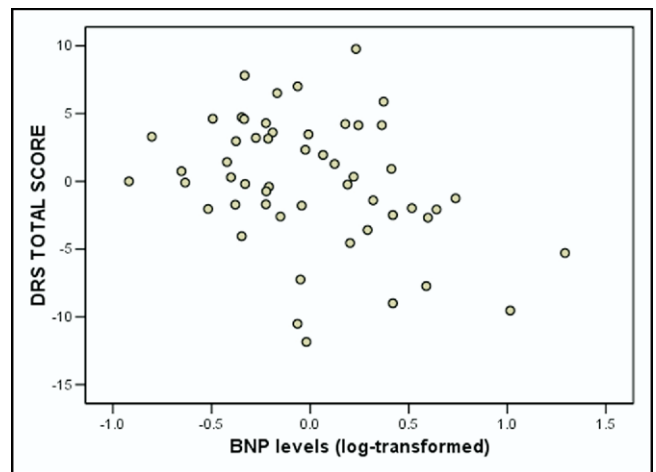


Figure 1. Regression scatterplot for the relation between BNP levels and DRS total score after adjusting for demographic and medical confounders.

were correlated with each DRS index after adjusting for the effects of the aforementioned demographic and medical confounders.

Hierarchical regression showed that BNP levels predicted DRS total score after correcting for possible demographic and medical confounders. Specifically, log-transformed BNP levels accounted for an additional 9% of the variance in DRS total score after adjusting for the demographic and medical variables ( $F[1, 44] = 6.14, p = 0.017$ ). Figure 1 illustrates the relation between DRS total score and BNP levels after adjusting for demographic and medical confounders.

After adjusting for the aforementioned demographic and medical variables, log-transformed BNP levels were significantly related to DRS total score ( $r = -0.34, p = 0.02$ ) and DRS conceptualization ( $r = -0.44, p = 0.002$ ). No such relations emerged for other DRS subtests.

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The results of the present study indicate an inverse relation between BNP levels and cognitive function in older adults with CVD. This relation emerged even after adjusting for the effects of relevant demographic and medical variables. A particularly strong relation was found between BNP and DRS conceptualization, a subtest composed of items tapping verbal and nonverbal abstraction abilities. This finding is consistent with past studies showing a relation between CVD and reduced executive function.<sup>8-10</sup> Of note, BNP levels were not significantly associated with DRS initiation and perseveration ( $r = -0.20$ ), a subtest composed of tasks involving semantic verbal fluency, reciprocal coordination, and pattern generation. Performance on similar tasks is often impaired in older adults with CVD, and the reason for the absence of an effect in the current sample is unknown.<sup>8,9</sup>

Also unclear is the mechanism by which BNP is related to cognitive dysfunction. Elevated BNP levels can be found in patients with ischemic stroke and with adverse blood-brain barrier changes, and our sample generated an average

greater than the cutoff suggested for use in acute care settings.<sup>11–14</sup> It is possible that patients with CVD with greater cerebrovascular disease or blood-brain barrier disturbance have higher BNP levels and poorer cognitive function. Another possible explanation involves endothelial function. High levels of BNP are associated with reduced endothelial function, particularly in patients with heart failure.<sup>15</sup> In turn, endothelial abnormalities have recently been linked to cerebrovascular disease and reduced cognitive function.<sup>9,16,17</sup> Further research is needed to clarify the relation between BNP and these possible mechanisms.

There are several limitations of the present study. Although BNP levels were significantly related to cognitive performance in the current sample, further examination in larger and more diverse samples would strengthen the generalizability of the findings. Similarly, determining the relation between BNP and cognition in more specific cardiac disorders may also provide important insight into possible mechanisms. Few studies have directly compared cognitive performance between specific CVD patient groups, such as those with diastolic versus systolic heart failure and those with and without atrial fibrillation. Such studies may provide key insights into the mechanisms underlying CVD-related cognitive dysfunction. Finally, the present study was not adequately powered to determine possible interactions between medications and BNP levels. Recent work indicates a growing number of medications that may influence BNP levels, and the possible cognitive benefits of those interventions are unknown.<sup>18</sup>

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