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# The independent association of hypertension with cognitive function among older adults with heart failure ☆

Michael L. Alosco [a,*], Adam M. Brickman [b], Mary Beth Spitznagel [a,c], Manfred van Dulmen [a], Naftali Raz [d], Ronald Cohen [e], Lawrence H. Sweet [f], Lisa H. Colbert [g], Richard Josephson [h,i,j], Joel Hughes [a,c], Jim Rosneck [c], John Gunstad [a,c]

[a] Department of Psychology, Kent State University, Kent, OH, USA
[b] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA
[c] Department of Psychiatry, Summa Health System, Akron City Hospital, Akron, OH, USA
[d] Institute of Gerontology, Wayne State University, Detroit, MI, USA
[e] Department of Cardiology, Rhode Island Medical Center, Providence, RI, USA
[f] Department of Psychiatry and Human Behavior, Brown Medical School, Providence, RI, USA
[g] Department of Kinesiology, University of Wisconsin, Madison, WI, USA
[h] University Hospitals Case Medical Center and Department of Medicine, Cleveland, OH, USA
[i] Harrington Heart & Vascular Institute, Cleveland, OH, USA
[j] Case Western Reserve University School of Medicine, Cleveland, OH, USA

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ABSTRACT

*Objective:* Hypertension is the most common comorbidity among heart failure (HF) patients and has been independently linked with cognitive impairment. Cognitive impairment is prevalent among HF patients, though the extent to which hypertension contributes to cognitive function in this population is unclear.
*Methods:* 116 HF patients (31.0% women, 67.68 ± 11.16 years) completed neuropsychological testing and impedance cardiography. History of physician diagnosed hypertension, along with other medical characteristics, was ascertained through a review of participants' medical charts.
*Results:* 69.8% of the HF patients had a diagnostic history of hypertension. After adjustment for demographic and medical characteristics (i.e., cardiac index, medication status, and resting blood pressure), hypertension was independently associated with attention/executive function/psychomotor speed ($\Delta F(1,103) = 10.85$, $\Delta R^2 = .07$, $p < .01$) and motor functioning ($\Delta F(1,103) = 4.46$, $\Delta R^2 = .04$, $p < .05$). HF patients with a diagnosed history of hypertension performed worse in these domains than those without such history.
*Conclusion:* The current findings indicate that diagnostic history of hypertension is an important contributor to cognitive impairment in HF. Hypertension frequently precedes HF and future studies should examine whether sustained hypertension compromises cerebral autoregulatory mechanisms to produce brain damage and exacerbate cognitive impairment in this population.



## 1. Introduction

Heart failure (HF) is a chronic disease that affects nearly 6 million people in the United States [1] and the prevalence rate of HF is projected to increase 25% by the year 2030 [2]. Heart failure is a major source of burden to the health care system, as it has become the most common reason for rehospitalization [3] and is associated with elevated rates of mortality with nearly 50% of patients predicted to die within 5 years of diagnosis [4,5]. Heart failure is associated with a vast array of other adverse outcomes, including decreased functional independence [6] and reduced quality of life [7].

There is extant evidence linking HF to cognitive impairment with up to as many as 75% of HF patients demonstrating impaired performance on neuropsychological testing [8]. Heart failure is also associated with elevated risk for Alzheimer's disease and vascular dementia [9,10]. The exact etiology of cognitive impairment in HF is unclear, though medical comorbidity appears to play an important role. Medical conditions such as stroke history, metabolic abnormalities, high plasma brain natriuretic peptide, and hyperglycemia are common in persons with HF and linked with elevated risk for cognitive impairment [11,12].

Hypertension is the most common medical comorbidity among HF patients and is likely an important contributor to cognitive impairment in HF. Nearly 75% of HF patients have hypertension prior to a HF diagnosis [1] and prospective studies have shown that hypertension is

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* Corresponding author at: Department of Psychology, Kent State University, Kent, OH 44242, USA. Tel.: +1 330 672 2589; fax: +1 330 672 3786.
*E-mail address:* Malosco@kent.edu (M.L. Alosco).

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significantly associated with incident risk of Alzheimer's disease and cognitive decline independent of HF [13–17]. Indeed, HF (i.e., reduced cardiac functioning) has been linked with increased white matter hyperintensities [18]. However, hypertension may produce additive vascular pathology in this population through disruptions of cerebral perfusion homeostasis and blood–brain barrier function, reduced functional neuroconnectivity, vascular remodeling, systemic inflammation, endothelial dysfunction, and/or artherosclerosis in the large cerebral and cervicocerebral arteries, among many other conditions that promote cerebrovascular disease [19–21].

In turn, the unique pathological effects of hypertension on the vascular system likely produce extended deficits in cognitive function beyond those associated with HF. In fact, Trojano and colleagues [22] demonstrated hypertension to be a significant risk factor for cognitive impairment among a sample of HF patients. However, the authors of this study failed to account for key variables including cardiac functioning and medication status and also did not provide insight of specific cognitive deficits produced by hypertension above and beyond those of HF. For instance, deficits in frontal systems functioning (i.e., attention and executive function) are common in HF patients [23,24] and hypertension may progress these deficits due to the frontal lobes vulnerability to disruptions in cerebral perfusion [25]. Despite these findings, the extent to which a diagnostic history of hypertension independently affects cognitive function in HF remains unclear.

We examined whether diagnostic history of hypertension was associated with reduced cognitive functioning relative to those without such history after controlling for cardiac functioning, resting blood pressure, and current hypertensive medication status among a sample of older adults with HF. We expected that HF patients with a history of physician-diagnosed hypertension would demonstrate significantly reduced cognitive function relative to their non-hypertensive counterparts.

## 2. Methods

### 2.1. Participants

A total of 116 consecutive persons with HF were selected from an ongoing NIH-funded study on cognitive function in HF. Participants were recruited from Summa Health System in Akron, Ohio, and reflect the HF population receiving treatment at that facility. The inclusion criteria were age of 50–85 years, English as a primary language, and a diagnosis of New York Heart Association (NYHA) class II or III at the time of enrollment. Potential participants were excluded for history of significant neurological disorder (e.g., dementia), history of head injury with >10 min loss of consciousness, severe Axis I psychiatric disorders (e.g. schizophrenia, bipolar disorder), substance use, and renal failure. Participants averaged $67.68 \pm 11.16$ years of age, were 31.0% female, and 84.5% Caucasian. See Table 1 for demographic and medical information.

### 2.2. Measures

#### 2.2.1. Neuropsychological measures

All neuropsychological tests used in the current study demonstrate strong psychometric properties, including excellent reliability and validity. The domains and neuropsychological tests administered are as follows:

- Attention/executive function/psychomotor speed: Trail Making Test A [26], Trail Making Test B [27], Digit Symbol Coding [28], and Letter Number Sequencing [29].
- Memory: the California Verbal Learning Test-II (CVLT-II) short delay free recall, long delay free recall, and total hits [30].
- Language: Boston Naming Test (BNT) [31], and Animal Fluency [32].
- Motor: Grooved Pegboard dominant and non-dominant hand [27,33,34].

**Table 1**
Demographic and clinical characteristics of 116 Older Adults with Heart Failure.

| | |
|---|---|
| *Demographic characteristics* | |
| Age, mean (SD) | 67.68 (11.16) |
| Female, *N*(%) | 36(31.0) |
| Race, *N*(% Caucasian) | 98(84.5) |
| Years of education, mean (SD) | 13.34 (2.63) |
| *Clinical characteristics* | |
| Hypertension *N*(% positive history) | 81(69.8) |
| Diabetes *N*(% positive history) | 41(35.3) |
| Systolic blood pressure, mean (SD) | 116.21 (16.35) |
| Diastolic blood pressure, mean (SD) | 65.12 (9.54) |
| Cardiac index males (L/min), mean (SD) | 2.67 (1.08) |
| Cardiac index females (L/min), mean (SD) | 2.72 (0.78) |
| Cardiac index total sample (L/min), mean (SD) | 2.68 (0.99) |
| *Medications, N(% yes)* | |
| Diuretics | 44(37.9) |
| Beta-blockers | 91(78.4) |
| ACE Inhibitors | 53(45.7) |
| Angiotensin II receptor blockers | 5(4.3) |

*Note*: ACE = angiotensin converting enzyme.

#### 2.2.2. HF severity

Cardiac output (CO) from a seated resting baseline was calculated for each patient to estimate preservation of cardiac function. Impedance cardiography signals were recorded via a Hutcheson Impedance Cardiograph (Model HIC-3000, Bio-Impedance Technology, Chapel Hill, NC) using a tetrapolar band-electrode configuration. The electrocardiogram (ECG) was recorded from the Hutcheson Impedance Cardiograph using disposable ECG electrodes. The basal thoracic impedance (Zo), the first derivative of the pulsatile impedance (dZ/dt) and the ECG waveforms were processed using specialized ensemble-averaging software (COP, BIT Inc., Chapel Hill, NC), which was used to derive stroke volume using the Kubicek equation. Following instrumentation, impedance cardiographic signals were recorded for seven 40-second periods during a 10-minute resting baseline. Finally, all CO measurements were divided by body surface area (BSA), yielding cardiac index. See Table 1.

Blood pressure was measured seven times during the 10 minute resting baseline using an automated oscillometric BP device (Accutor Plus Oscillometric BP Monitor, Datascope Corp, Mahwah, NH) providing systolic, diastolic, and mean arterial pressures. Initiating the blood pressure reading triggered a concurrent 40-second impedance cardiography measure.

#### 2.2.3. Demographic and medical history

History of hypertension, along with other demographic and medical characteristics, was collected through a review of participants' medical charts. Specifically, participants were classified as having a positive history of hypertension based on physician diagnosis as indicated in medical records. History of other medical comorbidities (i.e., diabetes) was also ascertained using this method. Current prescribed hypertensive medications were also ascertained through medical record review and served as covariates to control for possible confounding effects on cognitive function. Antihypertensive medications were categorized into four categories as according to the American Heart Association, namely: diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers [35]. Refer to Table 1.

### 2.3. Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. In addition to medical record review, participants completed demographic and medical history self-report measures. Individuals then completed impedance cardiography conducted by a trained research assistant. Finally, a brief neuropsychological test battery was administered to assess attention, executive function, psychomotor speed, memory, language, and motor functioning.

### 2.4. Statistical analyses

To facilitate clinical interpretation and to avoid undue influence of discrepancy in scales, all raw scores of the neuropsychological measures assessing cognitive function were transformed to *t*-scores (a distribution with a mean of 50, and a standard deviation of 10) using normative data correcting for age. Memory measures were also corrected for gender. Composite scores for attention/executive function/psychomotor speed, memory, language, and motor functions were means of the *t*-scores within each cognitive domain. Consistent with convention in many clinical settings, impairment in these domains for the current study was defined as a *t*-score $\leq 35$.

To examine the independent association of hypertension on cognitive function a series of multivariable hierarchical regression analyses was performed with composite scores for the attention/executive function/psychomotor speed, memory, language, and motor functions as the dependent variables. For each model, age, sex (0 = female; 1 = male), years of education, diagnostic history of diabetes as ascertained through medical record review (1 = positive history; 0 = negative history), current use of diuretics, beta-blockers, ACE inhibitors, and/or angiotensin receptor blockers (1 = yes; 0 = no), average resting systolic and diastolic blood pressure, and cardiac index were all entered into the first block. Finally, diagnostic history of hypertension (1 = positive history; 0 = negative history) was entered into the second block of each model to determine its independent association with cognitive function.

## 3. Results

### 3.1. Heart failure severity

The current sample of older adults with HF demonstrated average rates of resting cardiac index (M = 2.68, SD = 0.99). However, many HF patients of the current sample demonstrated reduced resting cardiac index, as 15.5% of the sample had a resting cardiac output less than 2.00 L/min.

### 3.2. Prevalence of hypertension and anti-hypertensive medication

Hypertension was common in the current sample of HF patients with 69.8% (81 of 116) of the sample having a positive diagnostic history of hypertension. Nearly the entire sample had controlled hypertension, as 94% (109 of 116) were prescribed medication with known hypertensive effects. Specifically, 37.9% of the sample had prescription for a diuretic medication, 78.4% beta-blockers, 45.7% ACE inhibitors, and 4.3% had a prescribed antiogensin II receptor blocker. Many of the participants were on a combination of these medications. Not surprisingly given that a majority of the sample had prescribed anti-hypertensive medication, the sample exhibited average levels of resting blood pressure (mean systolic = 116.22 ± 16.35; mean diastolic = 65.12 ± 9.54).

Heart failure patients with a diagnostic history of hypertension were not significantly different from those without such history in terms of age ($t(114) = 1.18, p = .24$), sex ($\chi^2$ (1, $N = 116$) = .14, $p = .71$), education ($t(114) = -1.68, p = .10$), or cardiac index ($t(114) = .20, p = .85$), Conversely, HF patients with a history of hypertension trended toward a greater likelihood of having a history of diabetes ($\chi^2$ (1, $N = 116$) = 3.42, $p = .06$; 40.7% vs. 22.9%).

### 3.3. Prevalence of cognitive impairment

When using a *t*-score cutoff of 35, examination of the composite scores for each cognitive domain revealed 9.5% of the sample exhibited impairments in attention/executive function/psychomotor speed, 10.3% in memory, and 34.5% demonstrated impairments in motor functioning. Impairments in language were less common (6.9%). See Table 2 for raw and *t*-score mean and standard deviations of neuropsychological test performance.

**Table 2**
Neuropsychological test performance in older adults with HF ($N = 116$).

| | Raw test performance, mean (SD) | *t*-score, mean (SD) |
|---|---|---|
| *Attention/executive* | | |
| Function/psychomotor speed | | |
| TMTA (seconds) | 41.65 (18.34) | 49.71 (12.03) |
| TMTB (seconds) | 130.85 (81.23) | 43.41 (18.22) |
| Digit symbol | 50.22 (15.55) | 47.66 (9.20) |
| LNS | 8.91 (2.72) | 51.07 (9.56) |
| Memory | | |
| CVLT SDFR | 7.30 (3.50) | 46.93 (10.69) |
| CVLT LDFR | 7.78 (3.71) | 46.68 (10.91) |
| CVLT total hits | 13.42 (2.43) | 44.48 (12.43) |
| Language | | |
| Boston naming test | 54.20 (5.71) | 51.18 (13.92) |
| Animals | 19.37 (5.28) | 54.47 (11.89) |
| Motor function | | |
| Grooved Pegboard dominant (seconds) | 105.98 (33.15) | 34.40 (21.50) |
| Grooved Pegboard non-dominant (seconds) | 111.91 (31.96) | 38.07 (15.80) |

TMTA = Trail Making Test A; TMTB = Trail Making Test B; LNS = Letter Number Sequencing; CVLT = California Verbal Learning Test; SDFR = Short Delay Free Recall; LDFR = Long Delay Free Recall.

### 3.4. Diagnostic history of hypertension is independently associated with cognitive function

Demographic and medical factors were associated with test performance. Greater years of education were significantly associated with better functioning in attention/executive function/psychomotor speed and language. Additionally, a positive history of ACE inhibitors was associated with better performance in attention/executive function/psychomotor speed and there was a trend for worse performance in

**Table 3**
Hypertension independently predicts cognitive function in older adults with heart failure ($N = 116$).

| Variable | Attention/executive/ psychomotor *b*(*SE b*) | Memory *b*(*SE b*) | Language *b*(*SE b*) | Motor *b*(*SE b*) |
|---|---|---|---|---|
| *Block 1* | | | | |
| Age | −.04(.08) | −.09(.09) | .00(.09) | −.29(.15) |
| Sex | 1.80(1.88) | −1.91(2.03) | 2.52(2.17) | −2.75(3.74) |
| Education | 1.12(.34)** | .70(.37) | 1.04(.39)** | 1.04(.67) |
| Diabetes | −.92(1.92) | 1.70(2.05) | −2.03(2.18) | −4.79(3.76) |
| Diuretics | −.92(1.92) | −2.42(2.07) | −.36(2.21) | −1.79(3.82) |
| Beta-blockers | .11(2.18) | −.54(2.35) | 1.11(2.51) | −2.93(4.33) |
| ACE inhibitors | 5.47(1.79)** | 1.09(1.93) | 3.20(2.06) | 2.25(3.55) |
| Angiotensin | 6.33(4.35) | −1.60(4.70) | 3.20(5.01) | 11.31(8.64) |
| Systolic BP | .04(.08) | −.01(.09) | .11(.10) | −.05(.17) |
| Diastolic BP | −.08(.15) | −.01(.16) | −.25(.17) | .04(.29) |
| CI | −.82(.91) | −1.01(.98) | .77(1.05) | −1.18(1.80) |
| $R^2$ | .24 | .08 | .14 | .11 |
| *F* | 3.02* | .83 | 1.49 | 1.11 |
| *Block 2* | | | | |
| Hypertension | −6.56(1.99) | 1.22(2.26) | −3.60(2.39) | −8.60 |
| $R^2$ | .31 | .08 | .16 | .14 |
| *F* for $\Delta R^2$ | 10.85** | .29 | 2.28 | 4.46* |

*Note*: *denotes p<0.05; **denotes p<.01.
Abbreviations: b — unstandardized regression coefficients, SE — standard error; ACE = angiotensin converting enzyme; Angiotensin = angiotensin II receptor blockers; BP = blood pressure; CI = cardiac index.

this domain for those with a positive diagnostic history of diabetes. Cardiac index and average resting systolic or diastolic blood pressure were not associated with cognitive function across any of the domains ($p > .05$).

Finally, after controlling for age, sex, education, history of diabetes, medications, resting systolic and diastolic blood pressure and cardiac index hypertension were independently associated with attention/executive function/psychomotor speed and motor functioning domains. In each case, diagnostic history of hypertension was associated with worse performance in these domains ($p < .05$). See Table 3 for a full summary of hierarchical regression analyses.

## 4. Discussion

Consistent with past work, cognitive impairment was common in the current sample of older adults with HF. Previous work suggests reduced cardiac pumping efficiency and its resulting inadequate cerebral perfusion to be an important mechanism for cognitive impairment in HF [36–38], although some studies question the shape or even the existence of the relationship between cardiac and cognitive functioning [12,39]. The present study extends such work and identifies hypertension as an important contributor to cognitive dysfunction in this population.

The current study suggests that HF patients with hypertension have greater reductions in cognitive function (i.e., attention/executive function/psychomotor speed and motor function) than those patients without hypertension independent of cardiac functioning, medication status, and resting blood pressure. There are several possible mechanisms by which hypertension could exacerbate cognitive impairment in HF. One explanation involves the effects of hypertension on cerebral autoregulation. In normotensive persons, autoregulatory mechanisms ensure stability in cerebral perfusion [40,41]. However, among chronic hypertensive patients, the autoregulatory curve is shifted to the right and higher perfusion pressure is required to maintain cerebral blood flow levels [40,42–44]. Elevated blood pressures alter the structure of cerebral blood vessels and may result in ischemic injury and hypoperfusion due to formation of atherosclerotic plaques and vascular narrowing [44–47]. Even further, due to the right-shift in the lower boundary of the autoregulatory curve, chronic hypertensive patients are more vulnerable to cerebral ischemia during brief drops in arterial pressure, which has important implications for administration of blood pressure lowering medication [43,48,49]. For example, recent work found that high blood pressure levels and blood pressure fluctuations among older adults are associated with greater cerebrovascular disease (i.e., white matter hyperintensities) [42]. Future studies should further elucidate the mechanisms by which hypertension leads to cognitive impairment among older adults with HF, particularly studies involving direct and simultaneous examination of both cardiac and cerebral perfusion.

HF patients are at elevated risk for Alzheimer's disease [9] and hypertension may contribute to the development of dementia related pathology in this population. Indeed, recent work demonstrates that hypertension increases risk for Alzheimer's disease pathology (i.e., beta-amyloid) and subsequent cognitive decline through activation of glycand end product of the cerebral vascular system [50]. Such findings are consistent with the wide array of evidence that supports vascular origins of Alzheimer's disease that may be attributable to cerebral hypoperfusion [51–53]. This is noteworthy, as cognitive impairment in HF is believed to stem from reduced cerebral blood flow, possibly due in part to the effects of medical comorbidities (i.e., hypertension). Our findings raise the possibility that anti-hypertensive agents may play a key role in preventing or slowing cognitive decline in persons with HF. Interestingly, extant experimental evidence shows that anti-hypertensive drugs attenuate beta-amyloid accumulation and subsequent cognitive decline associated with Alzheimer's disease [54,55]. Future empirical studies examining the role of anti-hypertensive treatment in preventing cognitive deterioration in HF is strongly encouraged.

The current study also revealed that resting blood pressure was not associated with cognitive functioning in the current sample of HF patients. Such findings are perhaps not surprising, given that a majority of the sample was on antihypertensive medication (i.e., 94%) and demonstrated average systolic and diastolic blood pressure readings. However, we found that a diagnostic history of hypertension is associated with cognitive dysfunction. Thus, while antihypertensive medication is known to slow cognitive decline in other samples, a diagnostic history of hypertension may serve as a proxy for the sustained effects of hypertension on cognitive function in HF. However, to accurately assess hypertension duration is difficult, as many patients are unaware of the length of time they have had elevated blood pressure prior to diagnosis (i.e., as many as 34% of hypertensive patients have been shown to be unaware of their diagnosis) [56]. Similarly, many persons that report being "normotensive" actually have sustained elevated blood pressure [56]. Based on these findings, it is likely that patients with sustained controlled hypertension, similar to the current sample, have at some time experienced periods of uncontrolled blood pressure due to unawareness of their condition. Interestingly, previous work has demonstrated that the combination of diagnostic history of hypertension and uncontrolled blood pressure is significantly associated with reduced performance on neuropsychological testing relative to those with only elevated blood pressure [56]. Hypertension is one of the most common risk factor for HF [1] and given poor medication adherence in this population [57] patients are likely to have experienced past and current periods of uncontrolled blood pressure. Thus, the sustained effects of hypertension combined with periods of uncontrolled blood pressure may be interacting to produce irreversible brain damage in this population [42,56]. Further work is strongly encouraged to identify mechanisms by which sustained hypertension may impair cognitive function in older adults with HF.

Several limitations of the current study merit brief mention. First, the current study consisted of cross sectional data and prospective studies are needed to clarify the mechanisms and extent to which hypertension produces additive cognitive impairment above and beyond HF over time. In addition to further investigation of hypertension, future work should specifically examine the prevalence and adverse effects of blood pressure fluctuations in HF patients, as fluctuating blood pressure has been linked with increased risk for white matter hyperintensities in an elderly population [42]. Similarly, in addition to its effects on autoregulation, future studies are needed to identify other potential mechanisms of the adverse effects of hypertension on cognitive function among HF patients, such as cerebral perfusion, atrophy and white matter hyperintensities [42,58]. As previously mentioned, the current study also demonstrated that HF patients whom were prescribed ACE inhibitors had better performance on tests of attention/executive function/psychomotor speed. Past work has shown that medicated hypertension is associated with less Alzheimer disease-related neuropathology than non-medicated persons with hypertension [59]. Such findings highlight the need for future research to clarify the role of antihypertensive medication in attenuating the adverse effects of hypertension on cognitive function. Finally, our findings also suggested a possible role for a positive history of diabetes with reduced cognitive function in HF. It would be worthwhile for future studies to investigate whether treatment of diabetes may also slow cognitive decline in HF, as recent work suggests insulin resistance in the brain may increase risk for Alzheimer's disease and cognitive decline [60].

In summary, the current study suggests that hypertensive older adults with HF perform more poorly on tests of attention, executive function, psychomotor speed and motor dexterity than non-hypertensive HF patients. These findings emerged despite controlling for current levels of cardiac functioning. Future work is strongly needed to elucidate the mechanisms of the additive effects of hypertension on cognitive function among patients with HF.

## Conflict of interest

There are no conflicts of interest.

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