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Review Article

# Cardiogenic Dementia: The Role of Chronic Cerebral Hypoperfusion in Cardiogenic Dementia and Cognitive Impairment in Patients with Cardiovascular Diseases

**Nicholas A Kerna[1,2]*, Kevin D Pruitt[3], Kyle Kadivi[4], Uzoamaka Nwokorie[5], Olufemi Odugbemi[6], Oluwatosin A Atolagbe[7], Shain Waugh[8] and Emmanuella Solomon[9]**

[1]*SMC–Medical Research, Thailand*

[2]*First InterHealth Group, Thailand*

[3]*Kemet Medical Consultants, USA*

[4]*Global Health Group LLC, USA*

[5]*University of Washington, USA*

[6]*Olabisi Onabanjo University, Nigeria*

[7]*Zorvis Inc., USA*

[8]*Fettle Path, USA*

[9]*Obafemi Awolowo University, Nigeria*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com

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## Abstract

The relationship between the brain and heart has been suspected and alluded to for several millennia. More recently, studies have associated low cardiac functioning with a decline in cognitive ability and established a link between vascular risk determinants and dementia. Cognitive function is dependent on several factors, which affect hemodynamic function and cardiac disease progression, contributing to cognitive decline (termed, cardiogenic dementia). Poor perfusion of cerebral tissues (termed, cerebral hypoperfusion) can adversely affect cognitive function, resulting in reduced attention span and memory. A dysfunction in cerebral autoregulation and neurometabolic inadequacy have been implicated in cognitive decline. Recently, specific treatment, namely cardiac resynchronization, is advancing enhancements in cardiac functioning in patients with symptomatic heart failure by improving cardiac hemodynamics and ejection fractions, resulting in improved executive functioning, global cognition, and visuospatial performance. However, at this time, studies on the efficacy of cardiac resynchronization and lessening the effects of cardiogenic dementia are limited.

***Keywords:*** *Alzheimer's Disease; Cerebral hyperperfusion; Cognitive Decline; Dementia; Proteinopathy; Revascularization*

## Abbreviations

AD: Alzheimer's Disease; CAS: Carotid Artery Stent; CATCH: Critically Attained Threshold of Cerebral Hypoperfusion; CRT: Cardiac Resynchronization Therapy

## Introduction

The intimate association between the brain and heart was mentioned for the first time in the *Ebers Papyrus*, a medical scroll written in 1552 BCE or earlier. Since then, this view has been well recognized [1]. The earlier concept, especially among the Greeks, including

Aristotle, was that the brain "cools" the blood while the heart functions as a site of memory retention. This notion was strengthened by religious and scientific communities of that era. However, during the 16th and 17th centuries, the Belgian anatomist, Andreas Vesalius, and English physician, William Harvey, opposed that assumption and provided a nearly accurate anatomical account of the functions of the brain and heart [2].

In the 1970s, specific studies associated low cardiac functioning with worsening cognitive ability, resulting in vascular dementia [3]. This phenomenon, known as cardiogenic dementia, was discounted mainly as a casual finding. However, over time, impaired cardiac function has been recognized to trigger cognitive impairment [3,4].

In the 1990s, specific studies identified that cardiac diseases could trigger Alzheimer's disease (AD). This discovery was significant as it not only underlined a possible etiology of AD but also highlighted a possible causal link between vascular risk determinants, both cardiac and extra-cardiac, and dementia [5,6].

## Discussion

Cardiac conditions are of different types. The disease's ultimate impact on cognitive functioning depends on several factors, such as age, clinical history, lifestyle, and underlying genetic and pathological conditions—all of which affect hemodynamic functions and disease progression. Based on the heart's affected structure, cardiac conditions are classified as coronary heart disease: cardiomyopathy (a disease of the cardiac muscle), arrhythmia (abnormality in cardiac rhythm generation or conduction), heart failure, and congenital cardiac abnormalities [7].

### Impairment of cognitive function and cardiac diseases

The initial accounts of cardiac dementia were described based on the increased cardiac arrhythmia incidence in patients with vascular dementia [6,7]. Long-standing cardiac block and dysrhythmias were speculated to reduce the cardiac output, causing persistent impairment of cognitive functions and finally dementia [7,8]. Cardiac pacing has been reported to improve or even reverse cognitive function decline in patients with arrhythmia (as the possible cause of impaired brain function) [8,9]**.** This treatment helps restore the brain's reduced blood supply by maintaining an optimum heart rate [7,8].

Inadequate cerebral tissue perfusion (e.g., cerebral hypoperfusion) due to low cardiac output or low blood pressure can diminish cognitive functioning, leading to insufficient attention span and poor memory [10]. Long-standing perfusion deficits in the cerebral tissue have been postulated to result in AD [11,12]. However, the association between hypotension and cognitive impairment has been overlooked. This disconnect could be due to the current hypothesis, suggesting that low systemic blood pressure does not cause the brain function to decline, as cerebral autoregulation prevents hypoperfusion of the cerebral tissue through compensatory activities [13].

On the contrary, certain studies have confirmed the cerebral autoregulatory system's failure in protecting the brain from hypoperfusion, resulting from low blood pressure and reduced cardiac output in elderly individuals. This chain of events can lead to low brain tissue perfusion with adverse consequences, such as cognitive impairment [10,13].

Evidence linking cerebral perfusion with cognitive function indicates that blood flow to the brain increases in healthy individuals following moderate exercise. However, the opposite occurs in patients with limited cardiac output due to an underlying cardiac pathology, such as arrhythmia [7,14]. Thus, it is evident that cerebral autoregulation may be unable to protect or reverse brain hypoperfusion in patients with compromised cardiac function.

### Mechanism of autoregulation

Under normal physiological conditions, cerebral autoregulation maintains an uninterrupted blood supply to the brain at a mean arterial pressure of 50–150 mmHg. This autoregulation maintains cerebral perfusion by directing the brain arterioles to dilate or constrict following a decrease or increase in blood pressure [15]. Cerebral autoregulation may be impaired in elderly patients, although the exact underlying cause remains unclear [7]. This patient population may take years, even decades, for the underlying pathological conditions, such as atherosclerosis, artery stiffness, and cardiovascular diseases, to result in cognitive impairment [16].

Typically, low perfusion of the cerebral tissue causes a decline in brain functioning in elderly patients. This decline could be exacerbated by neurometabolic dysfunction due to age-related low supply of energy substrates to the cerebral tissue [17,18]. Published literature indicates that the normal aging process can reduce the cerebral blood flow by approximately 20% in patients aged about 60 years compared to those aged about 20 years [7,19,20]**.** Thus, any additional blood flow decrease, due to underlying cardiac diseases, can further diminish the already compromised cardiac perfusion, leading to irreversible damage and even death of susceptible neurons [7,18].

Glucose is the primary energy substrate for the brain. An uninterrupted, adequate blood supply to the brain, which ensures optimal glucose level, is vital for the proper and healthy functioning, and structural integrity of this organ [7,21].

### Compromised autoregulation and cognitive impairment

Impaired cerebral autoregulation is a contributory factor for cognitive failure, especially in the elderly population due to persistent vascular compromise. Also, various cerebral vasoactive molecules, such as endothelial nitric oxide, adenosine, and prostacyclin, can act as a precipitating factor for cardiac dementia [7,21].

Cerebral hypoperfusion is also known to impair cerebrovascular activity, possibly due to decreased nitric oxide production by pathological endothelial cells [22]. Moreover, other factors shift autoregulation to elevated blood pressure, including chronic hypertension [7,23].

### Co-factors and their mitigation in hypoperfusion

In some cases, the protective mechanisms that safeguard the brain against hypoperfusion can cause it to be susceptible to cerebral hypoperfusion, especially in elderly individuals exhibiting chronic hypotension following aggressive long-term treatment with antihypertensive drugs [24,25]. Thus, to avoid unregulated hypotension and increased risk of dementia, a careful prescription of antihypertensive drugs, especially in the elderly with mild to moderate hypertension, is advocated [22]. Carotid endarterectomy or stent placement can mitigate brain hypoperfusion caused by impaired cerebral autoregulation due to unilateral cerebral artery stenosis [26].

Raabe., *et al.* (2010) assessed 12-month neurocognitive outcomes associated with carotid artery stent (CAS) placement. A battery of standardized tests to evaluate cognitive function was performed at 3, 6, and 12 months after CAS placement in 62 patients. The researchers noted that cognitive functioning did not deteriorate; instead, it improved in many patients following revascularization of CAS placement [27]. Another study revealed that vertebral artery disease could impair cerebral autoregulation [28].

However, cognitive impairment, due to cardiac diseases, is not well explored in the literature. A few studies have investigated the relationship between cardiac diseases and cerebral hypoperfusion, even though cerebral hypoperfusion can occur indirectly due to left ventricular dysfunction from reduced cardiac output [7,29]. Moreover, persistent cerebral hypoperfusion, especially in elderly individuals, can significantly lower the adequate substrate supply required for normal brain functioning [7,28,29].

### Proposed mechanism of decline in cognitive function in cardiovascular disease

Evidence suggests that cerebral hypoperfusion's underlying mechanism is due to disturbances in the hemodynamic flow-pattern observed in patients with cardiovascular diseases. Continuous inadequate blood supply to the cerebral tissues might result in a critically attained threshold of cerebral hypoperfusion (CATCH) [18,23]**.** Once CATCH is reached, there is a significant decrease in glucose delivery to the brain, leading to neuron-glial cells facing an energy crisis, which typically occurs in the initial phase in brain components associated with memory and learning. Subsequently, the energy crisis precipitates proteinopathy, characterized by misfolding and impaired clearance of proteins, such as A-beta peptide, from the cerebral tissues [7,18,30]. This process is followed by microcirculation impairment, which further precipitates the ineffective wash-out of toxic waste molecules [18,30]. This series of events leads to a decline in cognitive functioning. Non-memory-related executive functions, such as verbal, mental, and psychomotor functioning, are affected, followed by more severe cognitive impairment [31].

### Is cardiogenic dementia reversible?

Recently, cardiac resynchronization has been shown to be effective in improving cardiac functioning in patients with symptomatic heart failure. The treatment acts by improving cardiac hemodynamics, enhancing ventricular contractility and stroke volume at the same time. However, the process is associated with a decrease in myocardial energy consumption [32].

Hoth., *et al.* (2010) explored the association between the change in cognitive performance and left ventricular functioning following cardiac resynchronization therapy (CRT). A total of 27 patients with moderate to severe heart failure were assessed by neuropsychological assessment, echocardiogram, and 6-minute walk test before and after (3 months) CRT. The researchers found that improvement in ejection fraction following CRT was associated with better cognitive functioning, observed in improved executive functioning, global cognition, and visuospatial performance [33].

In a similar study, Dixit., *et al.* (2010) examined the cognitive changes in 20 patients with congestive heart failure before and after (3 months) using standard neurocognitive and psychosocial testing tools [34]. They found a significant improvement in clinical parameters and cognitive functioning (both qualitative and quantitative). The neurological benefits covered both cognitive and psychosocial aspects [34].

Also, age and underlying pathological conditions should be considered as independent risk factors for cognitive decline. A decrease in ejection fraction to < 30% in patients aged > 63 years leads to a significant decline in memory, especially verbal delayed recall and recognition, compared to patients aged < 63 years with similar ejection fraction [35].

CRT, which restores cardiac functioning and maintains adequate cerebral perfusion, can help reduce cognitive compromise in individual patients with cardiovascular impairment, although the contribution of independent risk factors, including age, cannot be overlooked [36].

## Conclusion

Growing evidence indicates a connection between cognitive decline in patients and cardiovascular diseases; however, only a few studies have investigated this association. Low cardiac output leading to persistent cerebral hypoperfusion triggers a cascade of events that eventually affect cognitive functioning. Studies have demonstrated that techniques, such as cardiac resynchronization therapy, can restore cardiac functioning (stroke volume), cerebral perfusion, and, to a certain degree, cognitive function. However, clinical trials with larger sample sizes are required to establish this fact equivocally.

## Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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