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Cardiac Output as a Potential Risk Factor for Abnormal Brain Aging

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Abstract

Heart failure has served as a clinically useful model for understanding how cardiac dysfunction is associated with neuroanatomic and neuropsychological changes in aging adults, theoretically because systemic hypoperfusion disrupts cerebral perfusion, contributing to clinical brain injury. This review summarizes more recent data suggesting that subtle cardiac dysfunction or low normal levels of cardiac function, as quantified by cardiac output, are related to cognitive and neuroimaging markers of abnormal brain aging in the absence of heart failure or severe cardiomyopathy. Additional work is required, but such associations suggest that reduced cardiac output may be a risk factor for Alzheimer's disease (AD) and abnormal brain aging through the propagation or exacerbation of neurovascular processes, microembolism due to thrombosis, and AD neuropathological processes. Such mechanistic pathways are discussed in the context of a theoretical model that posits a direct pathway of injury between cardiac output and abnormal brain aging (i.e., reduced systemic blood flow disrupts cerebral blood flow homeostasis), contributing to clinical brain injury, independent of shared risk factors for both cardiac dysfunction and abnormal brain aging.

Keywords

Alzheimer's disease; cardiac output; cardiovascular disease; cognition

INTRODUCTION

As the population continues to age, cognitive decline and dementia are becoming increasingly important public health issues with Alzheimer's disease (AD) prevalence expected to triple between now and 2050 [1]. Vascular factors, such as hypertension, diabetes mellitus, and atherosclerosis, are associated with increased risk for unhealthy cognitive aging in older adults, including abnormal neuroanatomical alterations [2,3], cognitive changes [4], and clinical AD [5,6]. Vascular risk factors can also result in myocardial damage, often without overt myocardial infarction, thereby altering cardiac function [7,8]. Resultant alterations in systemic blood flow (even if subtle or subclinical) may pose an *additional risk* for accelerating age-related brain injury by affecting cerebral blood flow homeostasis [9–11]. However, the association between cardiac function and central nervous system (CNS) injury, including risk for AD, remains a poorly understood aspect of vascular cognitive aging.

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Clinical trials targeted at reducing AD progression have demonstrated that patients continue to decline despite therapeutic intervention [12–14]. Thus, there is an urgent need to concurrently identify risk factors for abnormal cognitive aging, such as lower levels of cardiac output, because interventions initiated prior to the onset of clinical AD may be more effective than current treatment strategies for delaying progression [15,16]. In fact, estimates suggest that delaying onset of AD by a mere year would yield nine million fewer cases of AD by the year 2050 [17].

This paper reviews current data that relates cardiac function, and *cardiac output* in particular, to cognitive and neuroimaging markers of abnormal brain aging and considers cardiac output as a possible risk factor for AD.

HEART FAILURE AS A CLINICAL MODEL FOR UNDERSTANDING CARDIAC FUNCTION AND BRAIN AGING

Though heart failure has been associated with reduced cerebral blood flow for more than five decades [18,19], it was not until 1977 when the term “cardiogenic dementia” was introduced that clinical features (i.e., a mild dementing state) were associated with heart failure [20]. The theory behind “cardiogenic dementia,” which was considered controversial at the time [21,22], proposed that cerebral blood flow changes resulted in a fluctuating cognitive state that could be progressive in nature. Such cerebral blood flow changes were purportedly due to life-long episodes of subnormal cardiac output.

While the term “cardiogenic dementia” is no longer used, there has been considerable research since 1977 relating cardiac function to clinical CNS abnormalities, emphasizing patients with end-stage heart failure or severe cardiomyopathy [23–33]. Based on this vast literature, it is now well known that heart failure is associated with abnormal brain changes, including cognitive impairment [34,35], structural changes [36], and dementia [29,30]. Specifically, among patients with heart failure, reduced cardiac function is related to impaired global cognition [34] and executive dysfunction [35]. Such associations between heart failure and abnormal cognitive aging do not appear to be wholly attributable to vascular load or shared vascular risk factors, as heart failure patients, when compared to cardiovascular patients without heart failure, perform worse on neuropsychological measures assessing global cognition, attention, verbal fluency, and memory [27]. Similarly, neuroimaging markers of abnormal brain aging, including white matter hyperintensities (WMHs), infarcts, global atrophy, and medial temporal lobe atrophy, are increased in heart failure patients with cardiovascular disease (CVD) compared to patients without CVD [36]. With enhancements in the medical management of heart failure symptoms and progression, patients are living longer, which has allowed for the observation that, among older adults, heart failure also poses a risk for the development of dementia [29], including AD [30]. Therefore, heart failure and end-stage cardiac dysfunction serve as excellent clinical models for testing relations between cardiac dysfunction and CNS injury, including cognitive impairment, structural brain changes, and incident dementia.

FOCUSING ON CARDIAC OUTPUT AS A MEASURE OF CARDIAC FUNCTION

The hypothesized relation between cardiac function and brain aging is that reduced cardiac function alters systemic perfusion values, which then affects cerebral perfusion homeostasis. Therefore, blood flow leaving the heart and perfusing the system is a critical variable of interest when studying relations between cardiac function and brain aging. However, most prior work relating cardiac function to brain aging has emphasized ejection fraction [24,34,36], as it is a common measure for staging heart failure disease severity, it is

relatively easily assessed, and it is generally stable across repeated measurements. Ejection fraction reflects the proportion of blood ejected with each heartbeat relative to total ventricular volume (measured in percent). Though ejection fraction represents the global integrity of the heart's pumping efficiency during systolic contraction, it does not take into account diastolic relaxation, and it is frequently discordant from overall pumping capacity and subsequent systemic blood flow. Thus, it may be a limited parameter of cardiac function in the absence of end-stage heart disease.

Alternatively, cardiac output is another measure of cardiac function, which quantifies the amount of blood exiting the heart (in liters per minute, L/min). It is calculated as stroke volume (the amount of blood ejected with each cardiac cycle) multiplied by heart rate. Though cardiac output fluctuates secondary to homeostatic variables, it may serve as a better metric for assessing the relation between clinical or subclinical cardiac dysfunction and brain aging because it is a more precise measure of overall cardiac function in the absence of end-stage disease.

In fact, unpublished data from the author's laboratory indicates that when ejection fraction and cardiac output values are compared within the same patient sample, these variables are not always consonant measures of cardiac function. That is, among a small cohort of adults (n = 68) over age 55 years with prevalent CVD who were free of end-stage heart disease, 43% of participants with normal ejection fraction had low cardiac output values. In this clinical referral sample, less than half the time (i.e., 47%) the two measurements were in agreement regarding normal versus low cardiac function status based on clinical cut-offs (see Table 1). These data support the hypothesis that ejection fraction and cardiac output can be discordant measurements, each representing something unique with regard to cardiac function with cardiac output being more reflective of systemic blood flow. Therefore, when studying cardiac function and systemic blood flow in relation to brain health, cardiac output may be the preferred variable of choice. In light of the hypothesis that systemic blood flow a ffects cerebral blood flow homeostasis and contributes to clinical or subclinical brain aging, the ensuing discussion emphasizes cardiac output as a metric of interest for studying cardiac function and systemic blood flow as they relate to CNS integrity.

CARDIAC OUTPUT AS A POTENTIAL RISK FACTOR FOR ABNORMAL BRAIN AGING

In the absence of end-stage heart failure, very little is known about how clinical or subclinical reductions in cardiac output relate to abnormal brain aging; however, it is plausible that lower cardiac output could be a risk factor for abnormal brain aging and dementia. Recent cross-sectional work from the author's laboratory has emphasized referral-based samples of older non-demented CVD patients who are free of end-stage heart disease. These studies have detected associations between low cardiac output and cognitive and neuroimaging abnormalities. Specifically, CVD patients with low cardiac output (i.e., values less than 4.0 L/min) performed significantly worse on neuropsychological measures of executive functioning, including sequencing and planning tasks, than CVD patients with clinically normal cardiac output (i.e., values equal to or greater than 4.0 L/min) [37]. However, these two patient groups had comparable global cognitive scores (i.e., as assessed by the Mini-Mental State Exam [38]), suggesting that the between-group cognitive differences were subtle and specific to executive dysfunction. A follow-up study on a subset of these CVD patients found that cardiac output was inversely associated with WMHs, a purported neuroimaging marker of microvascular disease, such that lower cardiac output values were related to higher volumes of WMHs [39]. The result was not attenuated when adjusting for covariates, such as age, history of hypertension, or current systolic blood pressure [39]. These two clinical studies indicate that reduced cardiac output is associated

with cognitive [37] and neuroimaging [39] markers of abnormal brain changes, suggesting that even subtle cardiac dysfunction (as quantified by cardiac output) is related to CNS injury.

Epidemiological work relating cardiac output to abnormal brain aging is limited despite the fact that pathological cardiac dysfunction (i.e., heart failure) is a known risk factor for dementia [29,30]. One exception is a study from the author in collaboration with the Framingham Heart Study in which among a large cohort of adults 34–84 years of age, cardiac index, i.e., cardiac output indexed for body surface area reflected as liters/minute/square meter (L/min/m^2), was associated with total brain volume in multivariable models adjusting for several covariates, including age, sex, systolic blood pressure, smoking status, diabetes, atrial fibrillation, and prevalent CVD [40,41]. Results were not attenuated when participants with prevalent CVD were excluded, suggesting that the findings were independent of vascular comorbidities. Descriptive results from the study indicated that 30% of the community-based sample had low cardiac index or values less than or equal to 2.5 L/min/m^2 [40,41]. When individuals with prevalent CVD were excluded, the frequency of low cardiac index remained in 30% of the sample [40,41]. In this same study, cardiac index tertiles were compared to assess differences in brain volume across participants. Results indicated that individuals not only in the bottom tertile (i.e., < 2.5 L/min/m^2 or values considered as low cardiac index) but also individuals in the middle tertile (i.e., normal cardiac index values ranging 2.5 L/min/m^2 to 2.9 L/min/m^2) had significantly lower total brain volumes as compared to participants in the top tertile (i.e., high normal cardiac index values > 2.9 L/min/m^2) [40,41]. The cross-sectional difference between the top tertile and the two lower tertiles was equivalent to nearly two years in accelerated brain aging [40,41].

Collectively, these epidemiological results [40,41] suggest that cardiac output indexed for body surface area is associated with brain aging, as measured by total brain volume, even in the absence of prevalent CVD. Plus, the threshold at which cardiac output is associated with abnormal brain aging may be higher (i.e., in the low end of the normal cardiac index range) than the clinical threshold for defining normal cardiac output (i.e., < 2.5 L/min/m^2). This latter observation could have major implications for the early identification of individuals with low or low normal cardiac index values for prevention purposes, as one third of the sample had low cardiac index, and cardiac index appears to be related to lower brain volumes even among individuals with low normal cardiac index values.

Additional studies comparing cardiac output to markers of brain aging are needed for replication of prior findings [37,39–41] and to determine the longitudinal impact of cardiac output on abnormal brain aging, including whether lower values of cardiac output act as a risk factor for AD. Once the clinical and epidemiological evidence are better integrated, future work can focus on early detection and prevention studies.

THEORETICAL MODEL ACCOUNTING FOR RELATIONS BETWEEN CARDIAC OUTPUT AND ABNORMAL BRAIN AGING

It is not yet known what mechanism(s) account for the previously reported associations between lower levels of cardiac output and abnormal brain aging [37,39–41], defined as cognitive impairment, neuroanatomical changes, and increased risk for dementia. In an effort to illustrate the proposed theoretical model accounting for possible pathways between cardiac output and abnormal brain aging, the Figure outlines a multidirectional (and working) vascular cognitive aging model that integrates complex relations between reduced cardiac output and abnormal brain aging. Some features of the model are supported by existing clinical [37,39,42] and epidemiological evidence [41] while other features are purely hypothetical and not yet empirically supported. There are three essential elements of

the model. First, genetic and environmental risk factors contribute to changes in both cardiac and brain function. Second, the model emphasizes a primary or direct pathway of injury between cardiac output and abnormal brain aging independent of shared risk factors. Third, because previously reported relations between cardiac output and brain aging may be due to an epiphenomenon, the model considers the possibility that there are indirect, intermediate pathways that account for the association between lower cardiac output and abnormal brain changes. Each of these elements is discussed below.

First, the model acknowledges that shared environmental and genetic risk factors exist between reduced cardiac output and abnormal brain aging (i.e., element “A” in the Figure). For instance, vascular risk factors are associated with abnormal brain aging, including neuroanatomical [2,3] and cognitive changes [4] as well as dementia [5,6]. Similarly, vascular risk factors can result in myocardial damage, often without overt myocardial infarction, thereby altering cardiac function [7,8].

Second, independent of these shared risk factors, the model emphasizes a *direct pathway* of injury in which lower levels of cardiac output affect cerebral blood flow homeostasis and contribute directly to unhealthy brain aging (i.e., element “B” in the figure). The direct pathway of injury between cardiac function and brain aging relies on the assumption that cerebral blood flow homeostasis is affected by fluctuations in systemic blood flow. This hypothesis is modestly supported by animal [9,11] studies documenting that cerebral blood flow changes can occur secondary to manipulation in cardiac function, despite auto-regulatory mechanisms to preserve blood flow to the brain [43]. Specifically, lowering cardiac output directly reduces cerebral blood flow in ischemic brain regions in macaque monkeys [9] and chronic reductions in cardiac output are associated with a reduction in cerebral blood flow among New Zealand White rabbits [11].

The human evidence linking systemic blood flow to cerebral blood flow is limited to patients with end-stage heart failure [10,44,45]. In particular, cerebral blood flow is significantly reduced among patients with severe cardiomyopathies, but values rise when cardiac output is increased via pacing [44], and low cerebral perfusion values are restored to healthy levels following heart transplantation [10,45]. Such cerebral perfusion increases correspond to the finding that cognitive impairments improve following heart transplantation, purportedly because increases in cardiac function improve cerebral blood flow [46,47]. Collectively, these studies support the notion that auto-regulatory mechanisms for maintaining cerebral perfusion are disrupted under conditions of reduced cardiac output.

However, to date, there has been limited direct comparison between cardiac output and cerebral blood flow measurements to determine if very subtle reductions in systemic perfusion or cardiac output directly affect cerebral perfusion alterations in humans. Work from the author’s laboratory has examined healthy normative cerebral perfusion in relation to areas of WMHs among CVD patients as a function of cardiac output. Though preliminary, cross-sectional findings suggest that despite having comparable WMHs burden, patients with low cardiac output had WMHs in areas of relatively reduced cerebral perfusion while patients with normal cardiac output had WMHs in regions of relatively higher perfusion [42]. Additional studies within this research line are needed.

The last major element of the working theoretical model presented in the Figure (i.e., element “C”) takes into account the possibility that previously reported relations between cardiac output and abnormal brain aging may be due to an epiphenomenon or shared phenomenon that is not necessarily causal [37]. That is, the model takes into account additional possible intermediate pathways between lower levels of cardiac output and abnormal brain aging, such as neurohumoral factors [48], oxidative stress [49], and

enhanced inflammatory markers [50,51], that may be related to both reduced cardiac function and abnormal brain changes. However, there is no empirical evidence to date to support an epiphenomenon, so future studies are required to explore possible intermediate pathways to better understand the underlying mechanism accounting for previously reported associations between cardiac output and brain aging [37,39,41,42].

NEUROBIOLOGICAL MECHANISMS ACCOUNTING FOR RELATIONS BETWEEN CARDIAC OUTPUT AND ABNORMAL BRAIN AGING

If the hypothesis that lower values of systemic blood flow directly alter cerebral blood flow homeostasis is true (as supported by the corresponding data reviewed above [9–11,44,45]), then reductions in cardiac output may contribute to clinical or subclinical brain injury via numerous mechanisms related to reduced cerebral blood flow. The discussion below reviews three possible mechanistic pathways, including (1) propagating or exacerbating neurovascular pathological processes, (2) microembolism due to thrombosis, and (3) propagating or exacerbating AD neuropathological processes. The possibility of a mixed vascular and AD mechanism is also considered.

First, the cerebral microvasculature plays an essential role in maintaining cerebral blood flow to brain tissue, and generally speaking, acute alterations in cerebral perfusion lead to changes in microvessel structure, expression of vascular cell receptors, alterations in microvessel permeability, and vascular remodeling [52,53]. Chronic cerebral hypoperfusion contributes to the development [54,55] and progression [55] of white matter lesions in animals. In humans, structural [56] and perfusion-weighted [57] magnetic resonance imaging (MRI) reveal that WMHs (as compared to normal appearing white matter) are associated with reduced cerebral blood flow. These findings are supported by past research suggesting WMHs represent areas of ischemic tissue damage [58].

A second mechanistic pathway is microembolism due to thrombosis. Complications associated with cardiac dysfunction predispose to thrombus formation and subsequent microemboli [59]. As illustrated by animal models, thrombosis and embolism are known to affect capillary perfusion pressure, obstruct or impair cerebral blood flow, and degrade the blood-brain barrier [60,61]. Longitudinal research shows that the presence of cerebral emboli correlate with cognitive decline over time [62]. Therefore, reductions in cardiac output may also affect CNS integrity through the propagation of thrombosis and subsequent microemboli.

A third potential pathway is based on the observation that reductions in cerebral blood flow are associated with AD neuropathology. In transgenic mouse models of AD, chronic cerebral hypoperfusion places the brain at risk for amyloid deposition, resulting in neuronal death [63]. In clinical studies, patients with AD have reduced cerebral blood flow relative to cognitively normal controls [64], and cerebral blood flow is inversely associated with dementia severity, such that as blood flow decreases, dementia severity increases [65]. Furthermore, reduced cerebral perfusion is related to conversion from prodromal AD (i.e., mild cognitive impairment) to clinical dementia [66]. These associations may be due to the evolving burden of AD neuropathology, as atrophied brain tissue has less metabolic demand than healthy tissue [67]. Alternatively, these associations may be causal in nature, such that decreases in cerebral perfusion, including oxygen and glucose delivery, contribute to the pathophysiological changes associated with AD progression [68], as supported by prior animal studies [63,69].

It is highly plausible that these vascular and AD pathological pathways co-occur, such that reduced systemic blood flow affects cerebral perfusion and contributes to the common

phenomenon of mixed pathology. Mixed dementia, which includes clinical or neuropathological features of both AD and vascular dementia, is more common than originally thought. For instance, clinical data suggests mixed dementia accounts for nearly one third of all dementia cases [70]. Neuropathological data suggests that the density of vascular changes in the brain correlate with the presence of AD neuropathology, including neurofibrillary tangles [71] and amyloid-β deposition [72], suggesting microvascular damage and the pathogenesis of AD are related. Furthermore, it is well known that mixed pathology may affect the clinical expression of dementia symptoms. In a classic study by Snowdon and colleagues [73], neuropathological data revealed that the clinical expression of AD neuropathology is worse when there is concomitant vascular pathology. Specifically, those participants with neuropathologically confirmed AD *plus infarcts* had worse cognitive profiles than those participants with neuropathologically confirmed AD alone. More recently, clinical evidence has suggested that concomitant cerebrovascular disease in patients with prodromal AD (i.e., mild cognitive impairment) accelerates conversion to dementia [74,75]. Therefore, it is plausible that reduced systemic blood flow may affect cerebral blood flow homeostasis and contribute to mixed pathological features.

CONCLUSION

Though vascular risk factors are known to increase the risk of abnormal brain aging, the examination of cardiac function as a risk factor for AD remains a poorly understood aspect of vascular cognitive aging. The research literature examining cardiac output and brain aging in the absence of heart failure remains in its infancy, but existing clinical studies have shown that reduced cardiac output is related to executive dysfunction [37] and increased evidence of microvascular disease on MRI [39]. Recent epidemiological work suggests that lower levels of cardiac output are related to MRI markers of reduced brain volume, even when cardiac output is in the low normal range [40,41]. The purported underlying mechanism for these associations is that systemic perfusion impacts cerebral blood flow homeostasis, leading to subclinical and clinical brain injury. However, the possibility that these associations are due to some epiphenomenon cannot be ruled out.

Additional research is needed to better understand how lower levels of cardiac output are associated with abnormal brain aging. In particular, human studies using complex neuroimaging techniques, such as perfusion arterial spin labeling, are needed to assess the direct relation between systemic and cerebral blood flow patterns. Finally, it is not yet known if cardiac output poses a risk factor for AD, so transgenic animal studies are needed to better understand if reduced cardiac output contributes to the pathogenesis of AD pathology. Longitudinal epidemiological work is also needed to determine if reductions in cardiac output are predictive of cognitive decline, structural brain changes, and incident dementia over time. Once additional supporting evidence is in place, this evolving line of research can focus on early identification for prevention purposes and randomized clinical trials for treatment purposes. For instance, routine echocardiogram or more innovative cardiac MRI methods could be used to identify patients with lower levels of cardiac output who might be at risk for cognitive decline and dementia.

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Fig. 1.

Working theoretical model accounting for complex relations between reduced cardiac output and abnormal brain aging. A) There are established shared environmental and genetic risk factors that contribute to reduced cardiac output and abnormal brain aging. B) The model, as identified by the grey shadowed components, posits that reduced cardiac output creates a direct pathway of injury for the brain, *independent of shared risk factors*, in which reduced systemic blood flow alters cerebral blood flow homeostasis. This pathway accounts, in part, for previously reported relations between cardiac function and abnormal cognitive aging (e.g., executive dysfunction [37], WMHs [39], reduced brain volume [41]). C) However, a second plausible mechanism exists in which some epiphenomenon may account for previously reported associations between lower levels of cardiac output and abnormal brain aging. That is, that there may be intermediate pathways, such as vascular stiffness or neurohumoral factors, which contribute to both reduced cardiac output and abnormal brain aging.

Table 1

Comparison of ejection fraction and cardiac output

	Normal ejection fraction	Low ejection fraction‡
Normal cardiac output	*n* = 24	*n* = 18
Low cardiac output†	*n* = 18	*n* = 8

Note: this table illustrates that ejection fraction and cardiac output are not concordant measures of cardiac function, as all patients with low cardiac output do not always have low ejection fraction;

† normal cardiac output defined as ≥ 4.0 L/min [37,42];

‡ normal ejection fraction defined as ≥ 55% [76]; participants include 68 men and women over age 55 years with prevalent CVD; participants exclude individuals with end-stage heart failure.