



Heart and Brain: Complex Relationships for Left Ventricular Dysfunction

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Abstract

Purpose of Review This review summarizes the evidence for the established vascular/hypoperfusion model and explores the new hypothesis that configures the heart/brain axis as an organ system where similar pathogenic mechanisms exploit physiological and pathological changes.

Recent Findings Although associated by common risk factors, similar epidemiological stratification and common triggers (including inflammation, oxidative stress, and hypoxia), heart failure and Alzheimer's disease have been, for long time, viewed as pathogenically separate illnesses. The silos began to be broken down with the awareness that vascular dysfunction, and loss of cardiac perfusion pump power, trigger biochemical changes, contributing to the typical hallmark of Alzheimer's disease (AD)—the accumulation of A β plaques and hyperphosphorylated Tau tangles. Compromised blood flow to the brain becomes the paradigm for the “heart-to-head” connection. Compelling evidence of common genetic variants, biochemical characteristics, and the accumulation of A β outside the brain suggests a common pathogenesis for heart failure (HF) and AD. These new findings represent just the beginning of the understanding the complex connection between AD and HF requiring further studies and interdisciplinary approaches.

Summary Altogether, the current evidence briefly summarized in this review, highlight a closer and complex relationship between heart failure and Alzheimer's that goes beyond the vascular/perfusion hypothesis. Genetic and biochemical evidence begin to suggest common pathogenic mechanisms between the two diseases involving a systemic defect in the folding of protein or a seeding at distance of the misfolded proteins from one organ to the other.

Keywords Heart failure · Cardiomyopathy · Alzheimer's disease · A β · Vascular dementia · Protein folding

Introduction

Heart failure (HF) and Alzheimer's disease (AD) are growing age-dependent diseases worldwide and major health threats in

terms of morbidity, mortality, quality of life and health care costs. There are more than 5 million individuals suffering from HF in the USA and 60 million worldwide [1] with an aging prevalence growth of 4 to 9% from age 60 to 80. The

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Table 1 Summary of the key findings reported in this review

Disease determinant	Notable feature	Key findings	Ref
Reduced cerebral perfusion	Oxidative stress	<ul style="list-style-type: none"> • Hypoxia-induced cellular respiration exhaustion and increased ROS production, promoting cell, and BBB injury • Worsened by Aβ build-up and consequent mitochondrial dysfunction 	[21–23] [24–26]
	A β accumulation	<ul style="list-style-type: none"> • Reduced Aβ clearance via BBB, interstitial bulk flow, and/or meningeal lymphatic impairment • Reduced Aβ clearance via BBB, interstitial bulk flow, and/or meningeal lymphatic impairment 	[27, 28] [29–33]
	Inflammation	<ul style="list-style-type: none"> • Reduced microglial presence and functioning around Aβ plaques, impairing Aβ internalization and clearance 	[34]
Cardiovascular changes	Diastolic dysfunction	<ul style="list-style-type: none"> • Preserved EF accompanied by high filling pressures, weakened myocardial contractility, reduced peripheral vasodilation, diminished HR response, and less organ perfusion • Retrospectively, HFpEF and LV hypertrophy were more likely to be seen in AD patients 	[35–48] [6]
	Arterial stiffness, increased central pulsatility	<ul style="list-style-type: none"> • Associated with decreased peripheral BF, central Aβ accumulation, BBB injury, cerebrovascular compromise, and brain hypoperfusion 	[49–51]
Genetic variants	Presenilin (PSEN) -1 and -2	<ul style="list-style-type: none"> • Same variants associated with both early-onset AD and sporadic iDCM • Promoter-specific variants have been observed in iDCM but not yet AD 	[4] [4]
	Protein aggregation	<ul style="list-style-type: none"> • AD aggregates composed of Aβ, tau, metal ions, and chaperones • Cofilin rods implicated in AD neuritis 	[52] [53]
Systemic alterations	Heart deposition	<ul style="list-style-type: none"> • Aggregates have been identified in atrial fibrillation, cardiac amyloidosis, and cardiomyopathies—notably, cofilin was isolated from iDCM aggregates • Aβ and PAO deposits seen in AD patients 	[4, 6, 54] [7•]
	Peripheral A β accumulation	<ul style="list-style-type: none"> • Aβ peripheral clearance impaired by decreased scavenger receptors, less proteolytic enzymes, and liver/kidney malfunctioning • BBB damage promotes Aβ release into the periphery and potential seeding to other organs 	[55–58] [27, 59]
	Peripheral A β Production Exosome trafficking	<ul style="list-style-type: none"> • Promotes central Aβ deposition and associated inflammation • Help carry Aβ locally and systemically following Aβ endocytosis or APP cleavage • Bring MiR-1 from ischemic myocardium to hippocampus, inducing microtubule damage 	[60–64] [65–67] [68•]

prevalence of symptomatic HF in individuals over 65 years of age is estimated to be 6–10%. Likewise, according to the World and Alzheimer's Association's Alzheimer's Reports, there are over 5 million cases of dementia in the USA, and 35 million worldwide [2]. One in nine people older than 65 years has AD [3]. By 2050, the number of cases of AD in age > 65 may nearly triple, reaching as high as 16 million. Thus, if individually alone, HF and AD are modern plagues, recognizing their coexistence in the same patient [4–6, 7•] is an alarming prospective as people are living longer.

Epidemiological evidence indicates that HF also shares similar profiles in term of prevalence, age distribution, and high mortality [8, 9] with neurodegenerative processes including AD. Notably, HF represents, per se, a risk factor for developing dementia and AD [10].

In addition to these independent associative observations, over the past years it became increasingly evident that AD pathogenesis involves tissues and organs beyond the brain. Thus, in addition to the traditional view linking CVD and AD via vascular, microvascular, and perfusion defects,

clinical and experimental evidence join HF and AD though analogous biochemical characteristics and genetic profiles inferring the new hypothesis of a systemic (or metastatic) entanglement of the disease [4–6, 7•, 11–15].

While current estimates of the prevalence of dementia in HF are computed between 30 and 80% of patients [16–19], since its first discovery [4–6, 7•] initial reports provide a frightful estimate that HF occurs in a third of cases of AD accounting for over 20 million people affected worldwide [20].

Here, we will review the established knowledge and the latest insights on the link between heart and brain dysfunction through the lens of a systemic disorder or a communication between two of the body vital organs (summarized in Table 1).

The Traditional View of “Cardiogenic Dementia”

Since over four decades ago, cognitive dysfunction has been known to occur in patients with CVD, from which the term

“cardiogenic dementia” was coined [69]. Yet, to the recent days, besides some neurological diseases such as the frontotemporal dementia with Parkinsonism adjoining two neurodegenerative phenotypes, AD is typically viewed, and addressed, as unique disease limited to the target organ or, at early stages, even restricted to specific brain regions.

Instead, there is a significant evidence, built over many years, indicating that more complex mechanisms are involved in AD and CVD altogether. Those, however, have mostly been considered as revolving around vascular dysfunction and brain hypoperfusion. Clinical studies have linked CVD, dementing processes, and AD through common triggers, including inflammation, oxidative stress, and hypoxia [70, 71], which are also common features in both neurodegenerative diseases and HF separately (Fig. 1).

The Vascular Hypothesis

A growing body of evidence has supported the role of blood perfusion in the pathogenesis of AD [72–74]. The current paradigm is that compromised blood flow to the brain is a major determinant for the “heart-to-head” connection [75–77]. Cognitive decline from impaired blood flow to the brain is shown early in pre-symptomatic AD, while increasing blood flow to the brain improves AD symptoms [75]. Therefore, the vascular hypothesis had prevailed [78, 79] and, at times, risen over the original amyloid hypothesis [34, 80, 81].

Because the brain is a highly metabolically active organ that receives about 20% of cardiac output, it is subject to hypoxia induced by reduced blood flow [20, 15]. Tight regulations exist in order to maintain adequate blood flow and, consequently, oxygen delivery. Any insult to these

mechanisms, therefore, confers a unique susceptibility to impaired perfusion [82]. Conditions that disrupt blood flow include structural changes as induced by atherosclerosis, or functional changes due to hypertension or cardiovascular dysfunction and HF. These have been shown to be significant risk factors for the development of dementia, independent of amyloid deposition and aging (Rev in [83]) [74].

To be noted, although vascular dementia is linked to reduced brain perfusion and often coexists with other dementia such as AD, the vascular hypoperfusion hypothesis of AD is different from vascular dementia. Vascular dementia (not discussed here) is a condition due to any disorder that causes damages to the vessels (documented at imaging), such as stroke that can also lead to mild cognitive impairment and dementia [72].

The Vascular Hypothesis—Structural Damage, Oxidative Stress, and Inflammation

The cornerstone of the AD vascular hypothesis centers on the hypoxia, oxidative stress, and neurovascular unit (NVU) injury induced by reduced blood flow. Notably, the mixture of neural, glial, and other non-neuronal cells comprising the NVU helps regulating blood flow and maintain the integrity of the vasculature surrounding the brain [84, 85].

In response to this damage and disrupted perfusion, cellular respiration capabilities are quickly exhausted, and ATP is consumed without compensatory regeneration [22]. Reactive oxygen species (ROS) are produced [23], ion gradients become disrupted, and the resulting increase in intracellular calcium triggers cellular catabolism [21]. Damage to the endothelial cells, the main sentry of the blood brain barrier (BBB), will increase its permeability. Under normal physiologic conditions,

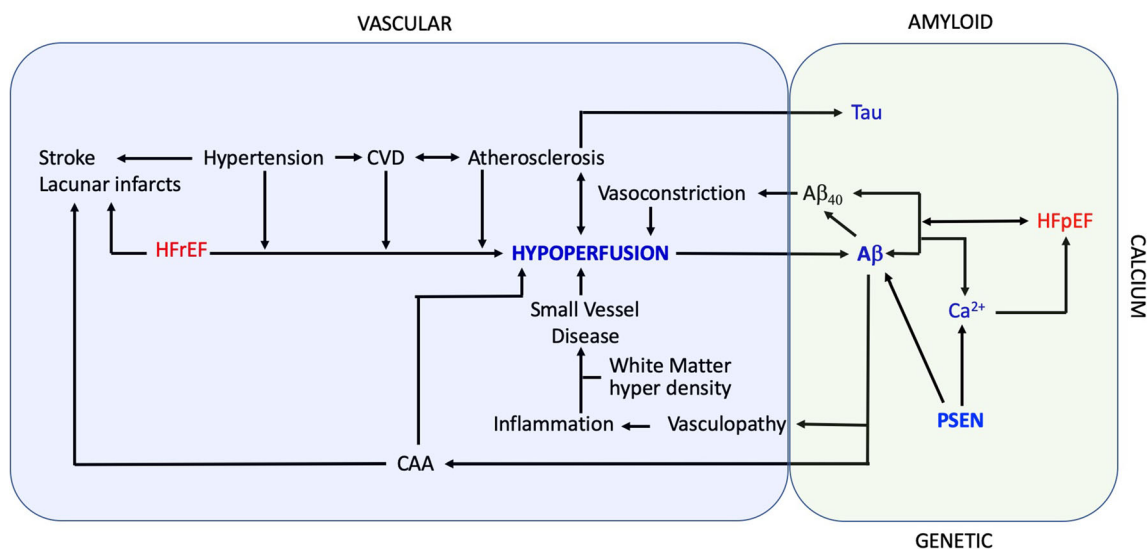


Fig. 1 Graphic abstract summarizing the currently known pathways for the vascular hypothesis (shaded in blue) on the left and the novel hypothesis for the common proteinopathy hypothesis of HF and AD

(shaded in green) on the right. The two pathways are coexisting in the complex relationship between HF and AD

A β is removed from the brain through the BBB, the interstitial bulk flow clearance (glymphatic) system, or meningeal lymphatics [27, 28]. Substantial evidence exists highlighting the impairment of these drainage systems—in addition to the up-regulation of β secretase, BACE1 [29], and the action microRNA-124 [30–33]—in chronic cerebral hypoperfusion and AD with the subsequent accumulation of A β within the perivascular space [28, 59, 85].

Amyloid- β would in turn evoke oxidative imbalance with the accumulation of A β in the mitochondria worsening mitochondrial dysfunction, ROS production, and overall oxidative imbalance as shown in mice models and human subjects with AD [24–26]. Worsening this vicious circle, the accumulation of A β in the brain also exerts profound vascular effects due to its vasoconstrictive properties and ability to promote BBB disruption with a major impact in favoring the neurodegenerative processes. Moreover, the increased BBB permeability is also responsible for increased adherence and transmigration of monocytes from the periphery-to-CNS, which then differentiates into microglia promoting neuro-inflammation [86].

While previously thought of as a coincidental event, new evidence has emerged implicating immune mediators in disease progression [87]. Various cytokines and chemokines are released from an array of cells following an ischemic event [21]. Activation of the microglia has been regarded as particularly important, as these scavenger cells function both in the inflammatory cascade and the removal of A β from the brain [34, 87]. Under conditions of chronic low blood flow and glucose delivery, activated microglia were scarce in areas surrounding A β plaques and exhibited impaired functioning [34]. Thus, the reduced capability for these microglia to effectively clear A β confers an environment ideal for accumulation, aggregation, and further plaque formation.

Cardiovascular Hemodynamics: HFrEF and HFpEF

As an extension of the vascular hypothesis of dementia and AD, reduced perfusion to the brain [74, 84, 88, 89] was considered also the predominant contributor to the reduced cognitive function in patients with HF. However, improved cognitive function from increased blood flow to the brain would be expected in all dementia, and atherosclerosis with reduced blood flow to the brain is present also in non-demented subjects.

While clinical studies have shown an association between dementia and HF, with HF patients incurring more than four-fold increase in cognitive impairment [90], further refinement of the characteristics of the patient's populations provided clues that perfusion per se might not be the primary pathogenic initiator of the cognitive dysfunction in all HF patients. A subgroup of patients within the prospective population-based Rotterdam Study included 3291 participants age 58 to 98 years in order to determine if cardiac function is associated with the

risk of stroke and dementia. When echocardiographic signs of diastolic dysfunction (E/A ratio) were analyzed, it emerged that, in elderly people, free of clinical cardiac disease, dementia is associated with worse diastolic, but not systolic function. The latter was only related to clinical stroke [36]. Similarly, the study of the Swedish Heart Failure Registry and the Swedish Dementia Registry also failed to see a prevalent distribution of dementia and AD in subjects with HF with reduced ejection fraction (HFrEF) with striking overlapping distributions of dementia and AD within the HF with preserved ejection fraction (HFpEF) group of patients [35].

Those results seem to imply that preserved cardiac ejection fraction and, thus, preserved brain perfusion associates with the risk of dementia. Despite impaired LV diastolic function, LV end-diastolic volume (preload) is generally normal in HFpEF patients, though this comes at the expense of high filling pressure. Notwithstanding, the ability of LV to increase the stroke volume during stress or exercise is impaired owing to the inability of the myocardium to increase contractility (impaired contractile reserve) [37–44]. This phenomenon is further amplified by inadequate peripheral vasodilation and blunted heart rate response to exercise [37, 40, 43, 45–48] leading to organ hypoperfusion. Moreover, increased arterial stiffness combined with increases in LV end-systolic elastance give rise to exaggerated fluctuation in blood pressure resulting in abrupt transient decline of peripheral perfusion [49, 50] and pulsatile pressure transmitted to the brain microcirculation (“biomechanical hypothesis”). The increased central arterial stiffness and elevated central pulsatility have been associated with greater A β accumulation in the brain of older subjects [51]. Furthermore, the increased arterial stiffness and central pressure exceeding the levels expected from aging and hypertension alone [91] in HFpEF, in turn, promote cerebrovascular dysfunction, parenchymal injury of the brain, and BBB disruption.

These profound hemodynamic derangements are accompanied by anatomic (capillary rarefaction) and functional dysfunction (reduced endothelial nitric oxide bio-availability) of the microcirculation and cerebrovascular flow dysregulation which altogether concur to chronic brain hypoperfusion and hypoxia. Those changes together with key pathogenic factors in HFpEF—namely the pro-inflammatory state, coronary microcirculation dysfunction, and capillary rarefaction—complicate the link between myocardial function and risk of dementia.

A Transformative View of HF—AD Pathogenesis

The close interaction between HFpEF and AD is not simply characterized by the abovementioned commonalities in risk factors and the independent association between HF and AD

[10]. Similar genetic backgrounds and pathophysiology mechanisms have recently emerged and, in addition to the risk of AD in HF patients, known pathogenic clues of AD seem to participate in the pathogenesis of HF.

Recently described specific biological relationships between the two conditions, in fact, include (1) the presence of misfolded protein aggregates in the myocardium of patients with idiopathic dilated cardiomyopathy (iDCM) [4]; (2) common genetic variants in the same gene associated with early-onset AD (*PSEN*) being also associated with iDCM [4, 12]; and (3) common biochemical components of the aggregates in AD and non-ischemic [6] and ischemic cardiomyopathies [92, 93]. Notably, (4) the same mechanism of toxicity attributed to the soluble PAO [94] now links the amyloid and calcium hypothesis of AD to the well-known calcium abnormalities that represented the traditional central pathogenesis in HF [4, 95–98] (an aspect not discussed in this review).

HF a Novel Proteinopathy

Accumulation of aggregates of misfolded proteins in the form of extracellular plaques and intracellular tangles was the first breakthrough in the identification of a new illness by Alois Alzheimer [99] and, for a long time, it remained pathogenically restricted to the specific form of dementia of AD. The extension of the misfolding of proteins as a key pathogenic event to neurodegenerative diseases beyond dementia and AD represented the first step to the consequent discovery that misfolded protein can accumulate in any tissue/organ in degenerative diseases. Now more than 300 different illnesses are recognized as diseases of protein folding or proteinopathies [100].

Proteinopathy of the heart has been among the last to be included in the family. Protein aggregates were described in mice models of skeletal muscle diseases affecting the heart (desmin cardio/myopathy) [101], in human primary cardiomyopathies [4], and atrial fibrillation [54] raising confusion with the “classical” cardiac amyloidosis. While traditional cardiac amyloidosis presents prevalent extracellular aggregates, due to the extracardiac origin of the amyloid migrating to the heart, the discovery of intracellular amyloid aggregates due to their primary cardiac origin will present a new challenge for the definition and classification of cardiac amyloidosis, retracing the shift from the clinical (primary, secondary) to the biochemical (AAL, AAT) definition.

Common Genetics

The genetic fingerprint of AD was recently found to converge with iDCM. Mutations in the genes commonly associated with familial AD (FAD), namely presenilin-1 and -2 (*PSEN1* and *PSEN2*), have been found to be associated with familial iDCM [12]. Even though iDCM and AD share a

common genetic background, in both conditions less than 5% of the cases are inherited in a Mendelian autosomal dominant manner. The majority of cases, instead, occur sporadically in individuals without a clear Mendelian inherited profile. Our group identified genetic variants of *PSEN1* and *PSEN2* in sporadic cases of iDCM, suggesting that genetic variants in *PSEN* may not only increase the risk of developing chronic degenerative diseases in the heart and brain as for the APOE4 gene in AD, but are directly associated with the disease [4]. Interestingly, our group found that not only genetic variants of the same *PSEN* gene, but also the same type of genetic variants associated with AD are associated with sporadic cases of iDCM and new variants (affecting the promoter region) not yet described in AD cases, appear in sporadic iDCM cases [4].

Common Proteomic Profiles in AD and HF

Although commonly referred as composed of aggregated proteolytic fragments (amyloid- β) of the amyloid precursor protein (APP) and hyperphosphorylated Tau protein, aggregates in the brain of AD contain a mixture of other molecules such as metal ions [52] as well as other proteins including molecular chaperones. Among the proteins composing the aggregates in AD, the actin depolymerizing protein cofilin, known to precipitate in rod-like inclusions causing neuritis in AD, was the first protein purified from the cardiac aggregates from iDCM human samples [6] and shown to be linked to the pathogenesis of dilated cardiomyopathy in a mouse model. Cofilin pathology also plays a role in a range of other neurodegenerative diseases (including corticobasal degeneration, William’s syndrome, fragile X syndrome, spinal muscular atrophy) [53] as well as muscle diseases such as Nemaline myopathy [102] underlying the no one-to-one correspondence between aggregate’s composition and disease, but rather a promiscuous nature of proteinopathies.

Whereas the first hallmark of AD, the A β deposits, have not yet been formally documented in primary cardiomyopathy, both A β_{40} and A β_{42} are not blameless when it comes to affecting myocardial function. In an autopsic series, our group showed that AD patients, besides presenting A β plaques in the brain, showed deposits of A β and PAOs in the heart as well, and the magnitude of cardiac aggregates was 10-fold higher in comparison to non-AD age- and gender-matched subjects without brain’s A β deposits [7•]. By retrospective analysis, the clinical and transthoracic echocardiography data of AD patients and age and gender-matched non-AD subjects demonstrated higher likelihood to present with LV hypertrophy and HFpEF in AD patients than controls. The clinical results were endorsed in a subsequent study of AD and control patients supporting the significance of the study in a separate replication cohort [103]. Furthermore, the pathological findings were confirmed by another autopsic study, where cerebral

amyloid angiopathy, a condition characterized by A β deposition in media and adventitia of the cerebral vessels, was strongly associated with A β aggregates in the cardiomyocytes [104].

Whereas this evidence underlies common pathogenetic mechanisms in cardiomyopathy and AD, whether the disease originates in one of the organs first or to both at the same time, and, in this case, why the disease presents with a prevalent cardiac phenotype in some patients and a brain disease in others is unknown. Those are difficult questions to answer due to the long asymptomatic latency in the development of the disease in humans and the challenging reproducibility of the human disease in the mouse models.

AD and HF: a Systemic Disease

Growing experimental evidences support the concept that AD, may extend beyond the brain as a result of the systemic accumulation of A β and PAOs [105].

A β is produced by the β - and γ -secretases sequential processing of the APP. This process gives rise to small amyloidogenic peptides of 40 (A β_{40}) and 42 (A β_{42}) amino acids that are able to aggregate to form soluble PAOs and insoluble A β fibrils and plaques. In addition to brain cells, APP is processed by peripheral cells, including leukocytes, platelets, skeletal muscle, and cardiomyocytes; A β and PAOs deposits have been described in the skin, subcutaneous tissue, skeletal muscle, guts, eyes, and now the heart [7, 106–108] suggesting that tissues other than the brain may (even primarily) contribute to the diffuse accumulation of A β within the new systemic view of Alzheimer's.

However, the level of A β are from 5 to 15 times higher in the cerebrospinal fluid (CSF) than in plasma [109, 110] possibly reflecting the less efficient cleavage of APP isoforms, higher amount of A β -binding proteins (e.g., albumin and lipoproteins) [111] and number of cells (e.g., erythrocytes) [112] facilitating the clearance outside the brain. Failure to clear these peptides from the CNS promotes AD development or progression, and the failure to thwart the A β and PAOs accumulation in the periphery may in turn cause or contribute to the amyloid-related systemic diseases hypothesis.

Furthermore, the pool of A β has been reported to differ between the brain and the other body organs with a prevalent amyloidogenic prone and toxic A β_{42} accumulating in the brain while A β_{40} levels prevail outside the brain [113]. While there is still no clear explanation for the difference, the specific isoform distribution of APP has been documented with APP₆₉₅, expressed predominantly in the brain, and APP_{751/770}, mostly expressed by platelets and leucocytes [114], together with organ specific APP processing by the secretase enzymes [113, 115]. However, the fluctuating levels of A β_{40} and A β_{42} in normal vs. pathological conditions, but also between individuals, make it difficult to draw definitive

conclusions. The liver of normal individuals in fact present higher levels of A β , perhaps reflecting the organ's clearance function [116], with liver function showing an inverse correlation with plasmatic levels of A β [117]. Additionally, the dilution effect of the non-CNS districts and local biophysical factors contributing to A β_{42} accumulation and oligomerization (pH, ionic strength, metals distribution) may contribute to the inhomogeneous distribution of A β and, consequently, the preferred organ deposition and disease development.

AD and HF: a Metastatic Communication

Whereas A β production in the CNS and other organs suggests that A β can independently accumulate outside the brain, A β is released from the CNS for clearance and reduced clearance or increased production from other organs may seed back to the brain. The homeostasis of A β and PAOs in the CNS is, in fact, closely interwoven with that in the periphery [105] enabling the bi-directional transmission of the peptide.

In the brain, A β and PAOs are cleared via phagocytosis by various cells (microglia, perivascular macrophages, neurons, and oligodendroglia), proteolysis by A β -degrading enzymes (neprilysin, insulin-degrading enzyme, or metalloproteinases), but also efflux to peripheral circulation via transportation across BBB and blood-CSF barrier, interstitial fluid bulk flow, arachnoid villi, and glymphatic-lymphatic pathways [28]. Notably, more than 60% of A β is cleared outside the brain [118–123]. Aging, cardiovascular, and AD risk factors may result in reduced A β peripheral clearance, given decreased expression of A β scavenger receptors, A β -degrading enzymes, impaired renal and liver function [55–58], and increased BBB permeability and leakage. The increase BBB permeability favors A β efflux increasing circulating level of A β . This phenomenon may promote peripheral seeding of A β and PAOs in highly perfused organs such as the heart.

As macromolecule, A β crosses the BBB by active transport mediated by lipoprotein receptor-1 (LPR-1) and P-glycoprotein (P-gp) (from the CNS-to-periphery, A β efflux), but also by receptor for advanced glycation end-product (RAGE) (from the periphery-to-CNS, A β influx).

Recent evidences suggested that peripherally generated A β and PAOs can enter the brain and contribute to A β deposition in the case of BBB dysfunction. Peripheral inoculation of A β -containing brain extracts in fact induces cerebral A β deposition, underpinning the potential role of peripherally generated A β in the pathogenesis of AD [59–63]. Similarly, peripherally generated A β , circulating inflammatory cytokines, and immune cells can travel back to the brain and contribute to AD pathogenesis, promoting A β and PAOs aggregation and neuro-inflammation [64]. In a mouse model of AD (2xTg-AD), Grigorova et al. have shown that AD mice exhibited earlier onset of age-associated increase in aortic stiffness and LV hypertrophy as compared to age-matched non-transgenic

counterparts, and that cardiac remodeling occurs only after the onset of brain amyloid accumulation [124].

Trafficking of molecules within and between organs has been recently revived by the growing evidence of the critical role of extracellular vesicles. In the brain, exosomes maintain important physiological functions, such as facilitating communication between neurons and glial cells [125], with impact on neuronal firing rate, signal transduction, and gene expression [126] and participate in A β metabolism. Release of insulin-degrading enzymes from the exosomes would facilitate proteolysis of extracellular A β [127], and exosomes facilitate phagocytosis and degradation by microglia cells [128, 129]. Exosomes containing A β_{42} can originate directly from the cleavage of APP in lysosomes [65] or as a result of endocytosis of extracellular accumulated A β_{42} in turn facilitating the transmission of A β between cells in the same organ and between organs [66, 67].

In addition to shuttling A β per se, exosomes mediate other molecular interaction between the brain and heart. Sun et al. described a new mechanism of brain damage originating in the heart [68]. In a mouse model of myocardial infarction, high levels of MiR-1 (MicroRNA) were produced in the ischemic area and border zone. Once released in the bloodstream, MiR1 can reach the hippocampus where it would decrease TPPP/p25 protein expression and induce microtubule damage.

Altogether, those abnormalities provide yet another mechanism for the initiation or the progression of AD: the seeding of toxic PAO to and from sites outside the brain.

Conclusions

The relationship between AD and cardiovascular diseases, in particular heart failure (HF), is a new and intriguing field of research, at genetic/biomolecular and clinical levels. Statistical correlation between dementia, AD and HF is well proven and recognized. However, new emerging concepts compel the intriguing hypothesis of a common pathogenesis for HF and AD either from a systemic or metastatic origin. Notably, HFpEF could promote AD and vice versa, resulting in a reciprocal interaction amplifying their mutual pathogenic effects in two of the most vulnerable organs. The coexistence and reciprocal reinforcement of the brain and heart disease pose an alarming threat to population health with people living longer.

This picture might change in the near future. The current pandemic of coronavirus, first identified in January 2020 and almost swiftly declared Global Pandemic by March 11 by the World Health Organization, is rapidly affecting the most vulnerable population of chronically ill and senior citizens around the world with high mortality rates. Although this tragic sudden outbreak will sadly decimate the senior population (the

most affected by degenerative diseases of the heart and brain). On the other hand, cardiovascular disease (CVD) emerged as a potential complication due to the high inflammatory load to the vasculature and heart in addition to questioning potential effects on the central nervous system. This will leave unpredictable long-term consequences on the epidemiology and patient stratification for chronic cardiovascular and neurodegenerative outcomes. Overall, this new epidemic might add a new population of patients at risk, further increasing the prevalence and, importantly, shifting the burden to an overall younger patient population.

Compliance with Ethical Standards

Conflict of Interest Gianlorenzo Daniele, Stephanie DiLucia, Pier-Giorgio Masci, and Federica del Monte declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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