Acta Biochim Biophys Sin, 2020, 52(1), 1–8
doi: 10.1093/abbs/gmz115
Advance Access Publication Date: 3 January 2020
Review

Review

Interrelationship between Alzheimer's disease and cardiac dysfunction: the brain–heart continuum?

Mingjie Yang[1,†], Congye Li[2,†], Yingmei Zhang[1], and Jun Ren[1,*]

[1]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 210032, China, and [2]Department of Cardiology, Xijing Hospital, the Air Force Military Medical University, Xi'an 710032, China

[†]These authors contributed equally to this work.

*Correspondence address. Tel: +86-21-64041990; Fax: +86-21-64223006; E-mail: ren.jun@zs-hospital.sh.cn

Received 1 February 2019; Editorial Decision 31 July 2019

Abstract

Dementia, a devastating neurological disorder commonly found in the elderly, is characterized by severe cognitive and memory impairment. Ample clinical and epidemiological evidence has depicted a close association between dementia and heart failure. While cerebral blood under perfusion and neurohormonal activation due to the dampened cardiac pump function contribute to the loss of nutrient supply and neuronal injury, Alzheimer's disease (AD), the most common type of dementia, also provokes cardiovascular function impairment, in particular impairment of diastolic function. Aggregation of amyloid-β proteins and mutations of Presenilin (PSEN) genes are believed to participate in the pathological changes in the heart although it is still debatable with regards to the pathological cue of cardiac anomalies in AD process. In consequence, reduced cerebral blood flow triggered by cardiac dysfunction further deteriorates vascular dementia and AD pathology. Patients with atrial fibrillation, heart failure, and other cardiac anomalies are at a higher risk for cognitive decline and dementia. Due to the increased incidence of dementia and cardiovascular diseases, the coexistence of the two will cause more threat to public health, warranting much more attention. Here, we will update recent reports on dementia, AD, and cardiovascular diseases and discuss the causal relationship between dementia and heart dysfunction.

Key words: cardiac dysfunction, heart failure, cognitive impairment, dementia, Alzheimer's disease

Introduction

Dementia is becoming one of the biggest challenges for public health worldwide with extended human life expectancy. It was estimated that ~47 million individuals suffered from dementia in 2015, and the number is expected to triple by 2050 [1]. The most common forms of dementia encompass Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and fronto-temporal dementia, together accounting for nearly 90% of all dementia cases. Many risk factors are involved in the development of dementia including obesity, hypertension, diabetes, smoking, and depression [1]. The World Dementia Council stated in 2014 the importance of regular physical exercise and reconciliation of cardiovascular risk factors in reducing the risk of dementia [2].

As the most common type of dementia, AD is a rather important and detrimental neurodegenerative disease typically manifested by gradual loss of memory and impairment of recognition. Patients with AD gradually lose their ability of thinking, remembering, and reasoning and can no longer handle daily life over time. A significant portion of patients develop language, visual, or executive problems long before memory impairment [3]. According to the latest report from the Alzheimer's Association in 2016, ~5.4 million Americans are afflicted with AD, and the number will rise to 13.8 million by the middle of this century. AD ranks the sixth leading cause of

© The Author(s) 2020. Published by Oxford University Press on behalf of the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Table 1. Comparison between familiar early-onset and sporadic late-onset subtypes of AD

	Familial AD	Sporadic AD
Age	Early, usually between 30 and 60	Late, usually older than 60
Proportion	<5%	>90%
Progression	Fast	Slow
Genetic mutations	Pathogenic gene mutations of PSEN1, PSEN2, and APP	Mutations of APOE4 and some other unnecessarily related genes
Risk factors	Family history	Advancing age and lifestyle risk factors such as smoking, obesity, and hyperglycemia
Mechanisms	Overproduction of Aβ proteins → aggregation in the brain	Failure to eliminate Aβ and tau proteins → aggregation in the brain
Transgenic (Tg) mouse models	APP/PS1 mice, 3 × Tg AD mice	ALDH2$^{-/-}$ mice, APOE4 transgenic mice

death in the USA and the fifth among individuals aged 65 or older [4]. Epidemiological survey has shown that over 40 million people worldwide suffer from dementia, which will be doubled over the next 20 years, among which AD ranks the most common cause [5]. Undoubtedly, AD greatly jeopardizes one's mental health, increases burden to families and society for personal care, as well as imposes major financial loss to communities.

As depicted in Table 1, aging is a significant risk factor, and ~90% of AD appears sporadically after 60 years old, while only 1–5% happens at a much younger age, in which case family history is usually found. Risk factors including previous head trauma or depression, vascular diseases, diabetes, obesity, and smoking are also considered [6]. The current understanding of AD highlights aggregation of insoluble amyloid-β (Aβ) peptides such as $A\beta_{42}$ and neurofibrillary tangles of tau proteins as the most important pathological hallmarks in AD. Aβ derives from amyloid precursor protein (APP) with the assistance of the proteolytic enzymes γ- and β-secretase, which contains presenilin 1 (PSEN1) and PSEN2. Pathogenic gene mutations of APP, PSEN1, or PSEN2 result in the overproduction of Aβ proteins and ultimately contribute to the onset of familial AD (FAD) [7]. Nonetheless, late-onset sporadic AD results from the failure to eliminate Aβ deposits in the brain with advancing age. *APOE4* gene, a binding partner for Aβ, is deemed the major genetic risk factor for sporadic AD. Other hypotheses such as oxidative stress, neuroinflammation, or mitochondrial dysfunction have also been brought up for the pathogenesis of AD [6].

Efforts have been made toward improving methods of diagnosis and treatment. Apart from typical signs and symptoms gathered from patients, their family members, care givers, and neuropsychological tests, new cerebrospinal biomarkers and imaging methods were developed for early diagnosis such as amyloid positron emission tomography (PET) [3]. Since patients gradually lose ability for self-management of daily life activities, care and support are the most important components in the personal care. As for drug therapies, only four cholinesterase inhibitors donepezil, galantamine, rivastigmine, and tacrine as well as the N-methyl-D-aspartate (NMDA) receptor inhibitor memantine are approved by American Food and Drug Administration although these drugs can only deal with symptoms without retardation of pathological progression. Many studies and clinical trials are carried out to explore other possible options. Preventing the aggregation or promoting the clearance of tau and Aβ proteins is the new target treatment to alleviate AD pathology [6]. Other therapeutic strategies are designed mainly targeting on oxidative stress or neurotransmission such as NMDA receptor antagonism, GABAergic modulation, and serotonin receptor modulation.

Experimental animal models are vital in the advance of AD management. Several murine models have developed over the past decades to mimic the development of the disease. For example, a transgenic murine model overexpressing APP with Sweden mutation and ablating exon 9 of *PSEN1* gene (APPswe/PS1dE9) has been created to resemble FAD in the experimental setting, manifested by classical Aβ accumulation and cognitive impairment [8]. In addition, aldehyde dehydrogenase 2 (ALDH2) is an irreplaceable enzyme to detoxicate 4-hydroxynonenal (4-HNE) produced by oxidative stress in the late-stage AD. Therefore, genetic ablation of ALDH2 (ALDH2$^{-/-}$ mice) inevitably results in 4-HNE accumulation, neurodegeneration, and memory decline, which is considered as an ideal model for late-stage sporadic AD [9]. Tg2576, APP23, 3 × Tg AD, 5 × FAD, and APOE4 transgenic mice are also commonly employed in the scientific research [10].

As the second most prevalent dementia, vascular dementia takes up to 15% of all dementia cases. Cognitive impairment caused by cerebrovascular diseases varies from mild cognitive deficits to dementia. However, the concept still remains controversial, and there are still no well-acknowledged diagnostic criteria [11]. Vascular dementia sometimes also coexists with AD, together making it the leading cause of age-related cognitive impairment [12]. Dementia with Lewy bodies is the third common type of dementia although it is extremely difficult to reach a definite diagnosis due to overlap with other types of dementia in clinical symptoms. Three main symptoms include fluctuating cognition, visual hallucinations, and Parkinsonism, but the accurate diagnosis cannot be done until the discovery of Lewy bodies in autopsy [13].

Intriguingly, besides the well-recognized brain damage and cognitive impairment, dementia especially AD has received recent attention as a systemic disease with other organs involved in particular cardiovascular complications in many cohort studies. On the other hand, patients with cardiac abnormalities are also at a higher risk to develop cognitive decline and dementia, possibly due to reduced cardiac output and chronic cerebral hypoperfusion. To this end, this mini review will update the recent advance in the field focusing on dementia, AD, and cardiovascular diseases. We mainly used the key words including 'cardiac dysfunction', 'dementia', 'AD', and 'vascular dementia' to analyze the reports appeared during the past decade.

Cardiovascular Abnormalities in AD Patients

Unlike vascular dementia, correlation between AD and cardiac abnormalities remains unclear. Ample clinical evidence has shown

an elevated risk of cardiovascular diseases in patients with AD [14–16]. A study from Turkey including 29 patients with AD and 24 age-matched normal controls showed that patients with AD were more likely to develop diastolic dysfunction, which is manifested by lower peak velocity of E wave (peak flow velocity of the early rapid filling wave), higher velocity of A wave (peak velocity of the late filling wave caused by atrial contraction), and increased deceleration time and isovolumetric relaxation time. Prolonged duration of conduction and higher arterial stiffness were also found in AD group, with significant lower D (aortic distensibility) and higher Ep (pressure-strain elastic modulus) [17]. Similarly, pulse wave velocity, an important parameter for arterial stiffness, was found much higher in patients with AD or vascular dementia, comparing to those without any cognitive impairment [18]. Patients with AD displayed impairment of transmitral flow efficiency during diastolic filling, as indicated by vortex formation time and consolidating diastolic dysfunction [19]. These findings support the presence of well-developed diastolic dysfunction in AD patients.

Up-to-date, limited reports are available with regards to the mechanistic insights behind AD-associated cardiac anomalies. Mechanistically, aggregation of aberrant Aβ peptides and tau proteins in the brain caused complicated pathological change and neuronal cell death in AD patients. Likewise, proteotoxicity caused by accumulation of misfolded proteins in cardiomyocytes also contributes to heart diseases, including dilated or hypertrophic cardiomyopathies (DCM or HCM), heart failure, ischemic, and hereditary cardiac diseases [20]. It is intriguing to examine if a parallel mechanism of protein aggregation and proteotoxicity exists in the pathogenesis of neurodegenerative and heart diseases. There are several reports supporting such notion. For example, protein aggregation and fibrillar deposits have been reported in cardiomyocytes and two patients carrying PSEN1 genetic variants and idiopathic DCM (iDCM). The abnormal protein oligomers disturbed Ca^{2+} homeostasis and contributed to the cardiac pathology [21]. The same group reported previously the deposition of $A\beta_{40}$ and $A\beta_{42}$ in both heart and brain specimens from four patients diagnosed with AD histopathologically without any known heart diseases, such as coronary artery disease (CAD), myocardial infarction, DCM, HCM, and hypertension. Echocardiography showed compromised left ventricular diastolic function in AD patients compared with age-matched controls. In addition, left ventricular wall thickness was increased with aging in AD patients [22]. Aβ aggregation is the most prevalent hypothesis for AD pathogenesis, which triggers immune response and cell death. Intramyocardial and cardiac interstitial deposits were considered to be responsible for cardiac dysfunction [23]. Findings from other labs also revealed that protein aggregates in myocardium of iDCM patients were similar to the deposits in AD biochemically [24], and proteotoxic soluble pre-amyloid oligomers were commonly found in heart failure patients [25,26]. A case-control study including 32 AD patients and age-matched controls showed that AD patients were of 2-fold higher risk for diastolic dysfunction (70% vs 35%), with an increased maximum wall thickness (10.8 ± 1.7 vs 9.3 ± 1.1 mm) and an intraventricular septum (10.1 ± 1.3 vs 9.3 ± 1.1 mm) according to echocardiography. Furthermore, AD patients were also at a higher prevalence of low-voltage QRS complexes, denoting cardiac insufficiency, with myocardial and interstitial deposition of Aβ in the heart [27].

Aggregation of Aβ is responsible for cerebral amyloid angiopathy (CAA). In particular, $A\beta_{40}$ may worsen atherosclerotic lesions in vessels and was positively correlated with arterial stiffness. Circulating level of $A\beta_{40}$ is believed to predict the overall disease progression, cardiovascular mortality, and major adverse cardiac events in CAD patients [28]. Among various factors contributing to elevated $A\beta_{40}$, polymorphism in C allele of oxidized low-density lipoprotein (LDL) receptor 1 gene is known to impair $A\beta_{40}$ clearance and aggravate CAA in AD patients without APOE ε4 allele [29].

Besides proteotoxicity, pathogenic variants of *PSEN1* and *PSEN2* genes were associated with familial and sporadic DCM, contributing to diastolic dysfunction and heart failure in a study including 315 patients [30]. In order to find out the role of PSEN1 mutation in cardiomyopathy, different genetically modified mice were developed. PSEN1 null mutation was embryonic lethal because of retardation in cardiac growth and development. Ablation of PSEN1 in adulthood resulted in the decrease of muscle fibers and sarcomere length in cardiomyocytes. Cardiac-specific knockout of *PSEN1* gene also led to diastolic dysfunction and severe heart failure in a myocardial ischemia mouse model, with serious ultrastructural abnormalities and abnormally expressed genes regarding cell proliferation or Ca^{2+} modulation [31]. Other studies suggested that *PSEN* genes are perhaps the key regulatory factors in cardiac development and function [32,33]. For example, heart rate may be decreased with silencing of the ortholog of *PSEN* gene in *Drosophila* [34].

Ample evidence has shown diastolic cardiac dysfunction in AD patients although no consensus is reached with regards to the systolic function. A study including 34 AD patients and 34 controls showed that patients displayed lower ejection fractions and more plaques in carotid and aortic arteries [35]. Although there are no cohort studies to this point, data from our group demonstrated that cardiac contractile function was impaired in an APP/PS1 transgenic mouse model of FAD. Echocardiography revealed overtly faster heart rate, shorter R-R interval, reduced R and QRS wave amplitudes in APP/PS1 transgenic mice. Peak shortening and maximal velocity of contraction/relaxation (±dL/dt) were significantly decreased in APP/PS1 cardiomyocytes. Several possible mechanisms of action were postulated to explain the mechanical dysfunction, including the disturbance of intracellular Ca^{2+} homeostasis, impairment of contractile proteins, and damage of oxidative stress [8]. Nonetheless, clinical data are still lacking to consolidate these experimental findings. In sum, patients with AD may have a higher risk of contractile dysfunction comparing to those without memory deficits. The aberrant aggregation of Aβ proteins and PSEN gene mutations are believed to be the common changes for the pathogenesis of cerebral and cardiac abnormalities in AD patients.

Dementia Associated With Cardiovascular Diseases

On the other side of the coin, a series of cohort studies have shown that patients with cardiovascular diseases are more prone to cognitive decline and dementia, mainly due to increased incidence of stroke and cerebral hypoperfusion over time. Many shared risk factors including diabetes mellitus, hypertension, atherosclerosis, obesity, metabolic syndrome, smoking, inflammation, oxidative stress, and APOE polymorphisms are involved in the pathogenesis of dementia (as summarized in **Fig. 1**) [36,37].

Atrial fibrillation and dementia

The occurrence of atrial fibrillation (AF) and dementia increases with advancing age, and sometimes they may coexist at the presence of certain common risk factors. Ample studies have shown that AF is significantly associated with risk of cognitive impairment and

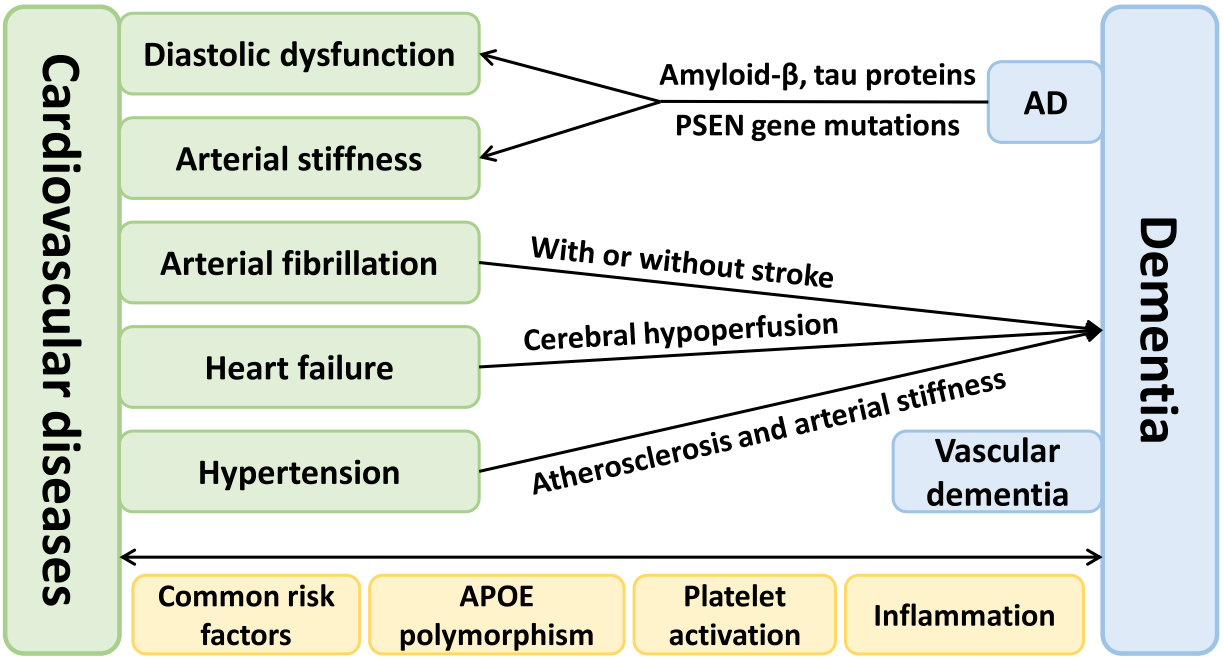

Figure 1. Interrelationship between cardiovascular diseases and dementia Patients with AD have a higher risk of cardiac diastolic dysfunction, possibly due to Aβ and tau protein aggregation and PSEN gene mutations. On the other hand, arterial fibrillation, heart failure, and hypertension may also increase the risk of vascular dementia and AD through complicated mechanisms. Meanwhile, many shared vascular risk factors, ε4 allele of APOE gene, platelet overactivation, and systemic inflammation may be the common changes between cardiovascular and neurodegenerative diseases.

dementia. In the Intermountain Heart Collaborative Study including 37,025 patients and followed up for 5 years, a total 27% participants developed AF and 4.1% developed dementia, including 0.48% vascular dementia, 0.87% senile dementia, and 0.94% AD. AF was independently associated with all forms of dementia, and the highest risk was in the group younger than 70 though the incidence of dementia is commonly thought to be positively associated with aging. In addition, coexistence of dementia and AF increased patients' mortality [38]. Another prospective study enrolled a total of 6514 participants without dementia at the beginning with a 20-year follow-up. AF increased the risk of dementia (hazard ratio [HR]: 1.33; 95% confidence interval [CI]: 1.02–1.73), especially in those aged 67 or younger (HR: 1.81; 95% CI: 1.11–2.94). The study also suggested that the risk of developing dementia was positively related to the exposure time to AF in younger patients but not in the elder group [39]. A cohort study in Taiwan also showed that AF patients had a higher risk of developing dementia (HR: 1.42) [40]. Another independent study with 2000 participants and 25-year follow-up showed that late-life AF increased the risk of dementia (HR: 2.61; 95% CI: 1.05–6.47) and AD (HR: 2.54; 95% CI: 1.04–6.16) although coronary heart disease does not have any impact on the AD prevalence [41]. A meta-analysis including eight prospective observational studies and 77,668 patients with an average follow-up of 7.7 ± 9.1 years also showed that AF was significantly associated with a higher risk of dementia (HR: 1.42; 95% CI: 1.17–1.72) [42]. Moreover, a study including 135 patients with dementia showed that patients with AF had more rapid cognitive decline according to Mini-Mental State Examination scores and clinical rating of the disease, which suggested that cardiovascular risk factors may influence the progression rate of dementia [43].

The mechanism of dementia triggered by AF remains largely unclear until now. One possible explanation is that AF increased the risk of stroke by 5 folds, which is followed by cognitive decline in many cases. However, a meta-analysis including 21 studies showed that AF increased the risk of cognitive deficits in individuals with or without notable clinical stroke (relative risk [RR]: 1.40) [44]. In those stroke-free patients, reduced cardiac output and cerebral perfusion caused by AF over time may contribute to cognitive decline. Meanwhile, AF and dementia share common vascular risk factors, such as diabetes mellitus, hypertension, hyperlipidemia, heart failure, alcohol abuse, and sleep disorders. These risk factors not only increase the occurrence of vascular dementia but also contribute to neurodegenerative disorders such as AD with unknown mechanisms [45].

Heart failure, cardiac dysfunction, and dementia

Heart failure is the end stage of many cardiovascular diseases such as myocardial infarction, hypertension, cardiomyopathies, and valve diseases. A community-based cohort study including 1301 participants showed that patients with heart failure in their late life had a higher risk for dementia (HR: 1.84; 95% CI: 1.35–2.51) and AD (HR: 1.80; 95% CI: 1.25–2.61) after 9-year follow-up. Heart failure together with low diastolic pressure (lower than 70 mmHg) had a further increased risk for dementia (HR: 3.07; 95% CI: 1.67–5.61) [46]. Another nationwide cohort study with 35-year follow-up showed that patients with heart failure had an increased risk for vascular dementia (HR: 1.49; 95% CI: 1.40–1.59) but not for AD (HR: 1.00; 95% CI: 0.96–1.04) [47]. In a case-control study including 50 patients with heart failure and 50 matched control subjects, 46% heart failure patients and 16% control participants had mild-to-severe cognitive impairment based on neuropsychological test scores. Logistic analysis further suggested that cognitive impairment was independently associated with heart failure (odds ratio: 4.47), and

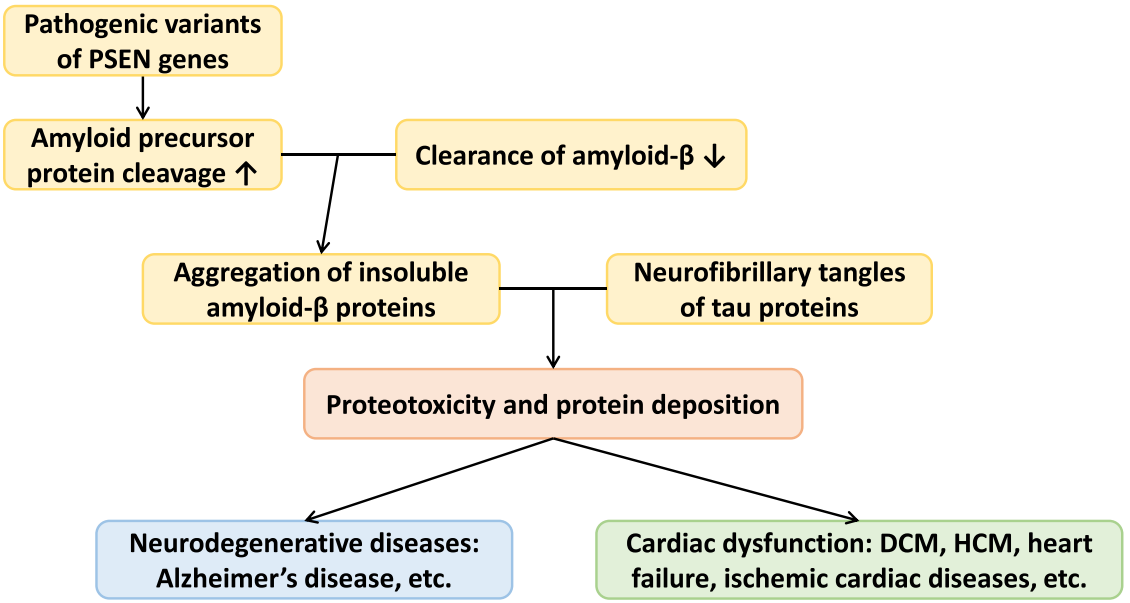

Figure 2. Deposition of Aβ and tau proteins may be the common contributing factor to trigger both neurodegenerative and cardiac diseases Protein aggregation is resulted from impaired clearance of Aβ and increased APP cleavage caused by PSEN gene mutations.

severity of cognitive decline was correlated with the severity of heart failure [48].

The mechanism of action behind heart failure-induced AD onset remains debatable. On one hand, heart failure results in decreased cardiac output and cerebral perfusion, leading to white matter injury and cognitive decline. On the other hand, activation of neurohormonal system, systemic inflammation, and microvascular dysfunction in the brain may be involved in cerebral pathogenesis as well [49]. For AD, low cardiac output in heart failure patients directly decreases cerebral blood flow, and therefore Aβ proteins cannot be cleared in time. APP cleavage caused by hypoxia and impairment in Aβ clearance may contribute to Aβ aggregation in the brain. Hypoxia is also believed to be involved in the hyperphosphorylation of tau proteins and formation of neurofibrillary tangles, along with other factors including acidosis, inflammation, oxidative stress, neurohormonal activation, and microvascular dysfunction caused by diffused amyloid angiopathy [49]. This is consistent with the evidence that increasing blood flow to the brain may alleviate AD symptoms [50].

The risk of dementia is also increased for those patients with low cardiac output and myocardial dysfunction. In a community-based cohort Framingham Heart Study including 1039 participants in the absence of clinical stroke, transient ischemic attack, or dementia, 32 subjects developed dementia and 26 of them developed AD after a 7.7-year follow-up. One standard deviation decrease in cardiac index may result in the increase of relative risk for dementia (HR: 1.66; 95% CI: 1.11–2.47) and AD (HR: 1.65; 95% CI: 1.07–2.54) after adjustment for age, sex, and education background. Even with exclusion of patients with prevalent cardiovascular diseases and AF from the analysis, cardiac index was still significantly associated with the incidence of dementia and AD [51]. However, a study including 3291 participants without stroke, dementia, coronary heart disease, heart failure, or AF showed that systolic function (indicated by fractional shortening) failed to affect the overall incidence of dementia, while patients with better diastolic function (indicated by E/A ratio) exhibited a lower risk of stroke (HR: 0.82; 95% CI: 0.69–0.98) and dementia (HR: 0.82; 95% CI: 0.70–0.96) [52]. Therefore, it still remains controversial whether cardiac systolic or diastolic dysfunction increases the risk of cognitive impairment.

Blood pressure and dementia

The relationship between blood pressure and cognitive capacity still remains controversial with disparate conclusions from different studies. While some evidence suggested that severity of cognitive decline was associated with increased blood pressure, others indicated that cognitive impairment was not correlated with blood pressure at all or a 'U-shaped curve' relationship between blood pressure and cognitive level [37]. In short, hypertension has been considered as the most predominant vascular risk factor in AD progression, since it may aggravate atherosclerosis and arterial stiffness in the long term, while extreme low blood pressure may also be responsible for the onset and development of dementia due to cerebral hypoperfusion [53]. Meanwhile, diastolic blood pressure (DBP) seems to have bigger influence on small arteries, and therefore high DBP may lead to ischemic lesions in white matter and deteriorated age-related cognitive decline [54].

Cardiovascular risk factors and dementia

Beside the risk factors covered above, a number of cardiovascular cues have also been indicated in the onset and progression of AD. For example, a study including 1138 participants free from any form of dementia at the beginning showed that vascular risk factors including diabetes, hypertension, heart disease, and current smoking were related to the increased prevalence of AD after follow-up for 5.5 years in average, among which diabetes and smoking were the strongest risk factors. The risk was sharply increased with the presence of three or four risk factors combined (HR: 3.4; 95% CI: 1.8–6.3; $P < 0.0001$) [55].

APOE, mainly produced in the liver, mediates the clearance of lipoprotein from circulation through interacting with different receptors. APOE has three common variants, ε2, ε3, and ε4, which

affect LDL metabolism and therefore influence the pathogenesis of atherosclerosis and other cardiovascular diseases. In addition, APOE produced by astrocytes in the brain also participates in cholesterol and lipoprotein metabolism in central nervous system. It can bind with Aβ and tau proteins and affect the clearance of Aβ peptides [56,57]. Above all, ε4 allele of APOE is a major genetic risk factor for the late onset familial and sporadic AD, which has been widely acknowledged since its first discovery in 1993 [58]. APOE ε4 allele is involved in the pathogenesis of AD both dependent and independent of Aβ peptides [59]. APOE ε4 allele carriers make up 65%–80% of all AD patients, and the risk for AD increases from 20% to 90% with increased number of ε4 alleles. Heterozygous APOE ε4 allele carriers display 2∼3 times higher risk for AD, and homozygous ones exhibit 8∼10 times more risk when compared with individuals without APOE ε4 allele. Individuals with ε4 allele also exhibit a faster memory decline with advanced age [57]. Further study showed that APOE ε4 allele was related to higher risk for AD, while APOE ε2 allele was related to lower risk because of differential influence on Aβ aggregates in the brain [60]. Moreover, a study including 75,708 participants also showed that low plasma levels of APOE were associated with increased risk of AD (HR: 2.68; 95% CI: 2.04–3.52) and all types of dementia (HR: 1.80; 95% CI: 1.52–2.13), regardless of ε2/ε3/ε4 APOE genotype [61].

In a study with 1-year follow-up, AD patients with faster cognitive decline had platelet overactivation comparing to those with slow decline, which was indicated by significantly higher levels of biomarkers glycoprotein IIb-IIIa complex and P-selectin. Therefore, platelet overactivation may serve as the likely missing link between vascular pathology and AD [62].

In the meantime, more attention is being paid to the role of inflammation during the onset and development of AD. Too much accumulation and infiltration of immune cells in the brain and overactivation of neuroinflammation system are suggested in the cerebrovascular pathogenesis and deposition of Aβ aggregation, resulting in the progression of dementia [63].

Conclusion and Perspective

Both cardiovascular diseases and dementia are widely acknowledged as age-related diseases. With extended human life expectancy, both pathologies are becoming increasingly devastating public health problems, imposing major physical harm and financial burden to the society. To make things even worse, AD patients display a much higher prevalence of cardiac dysfunction. As summarized in **Fig. 1**, most studies have shown that patients with AD exhibit a much higher risk for diastolic dysfunction despite apparent differences in race, age, gender, and other demographical characteristics, possibly due to abnormal Aβ protein aggregation and PSEN gene mutations. Therefore, AD was considered to be more of a systemic disease with multiorgan involvement in the past decades.

On the other hand, patients with AF, heart failure, hypertension, and other confounding cardiovascular risks develop a much higher prevalence of dementia compared with healthy aged-matched individuals, a term sometimes being referred to as 'cardiogenic dementia'. At the same time, cardiac dysfunction also increases the incidence of vascular dementia and AD with or without clinical stroke, since reduced cardiac output results in cerebral pathologies including neurovascular hypoperfusion, neuroinflammation, neuronal degradation, and white matter lesion. Despite intense efforts over the past decades, the relationship between cardiac defects and dementia still remains unclear. This is partially due to the limited sample size in these studies, and larger population of patients is warranted. In addition, most studies were carried out in humans and fewer in animals. **Figure 2** illustrates some of the common soils behind proteotoxicity and aberrant protein deposition in the pathogenesis of both neurological diseases and cardiovascular anomalies. Pathogenic variation of PSEN may lead to either neurological or cardiovascular pathologies. Therefore, transgenic murine models with PSEN mutations are vital for AD research, which can mimic the pathologies of both AD and cardiovascular diseases (**Fig. 2**).

Importantly, AD and some cardiac abnormalities are both age-related and share many common features, including similar risk factors, protein aggregation, and genetic mutations. There seems to be a 'heart–brain continuum', referring to a vicious cycle between cardiac dysfunction and dementia, which is becoming a serious problem and deserves much more attention. We are also curious about whether Ca^{2+} dysfunction is the common regulatory mechanism behind the convergence of dementia and cardiac diseases, since Ca^{2+} plays a detrimental role in maintaining normal cardiac function, and Ca^{2+} dysregulation also affects various neural functions, much more beyond synaptic transmission and cell death [64].

Other than dementia, in particular AD, patients with other neurological diseases including Parkinson's disease (PD) and Huntington's disease (HD) also display much higher risk of cardiovascular abnormalities. Cardiovascular diseases are among the leading causes of death in elderly patients with PD and HD. A cross-sectional study including 50 PD patients and matched controls showed that PD patients had a higher incidence of left ventricular hypertrophy, diastolic dysfunction, and heart failure [65]. These patients also commonly suffer from cardiovascular autonomic abnormalities such as orthostatic hypotension [66]. Epidemiological surveys have shown that HD patients also have an increased incidence of cardiovascular dysfunction leading to heart failure. A study including 32 subjects with confirmed Huntington gene mutations showed that patients with autonomic nervous system dysregulation had increased risk to suffer from cardiac electrical remodeling and malignant arrhythmias such as increased Q-T interval [67]. Bacterial artificial chromosome HD mouse model was used to study the underlying mechanisms, showing age-related decline in myocardial function and increased cardiac fibrosis, with altered expression of genes clustered in cardiovascular diseases, cellular transport, and metabolism [68]. Another study using R6/2 transgenic and HdhQ150 knock-in mouse models of HD indicated that alteration of central autonomic pathways was involved in HD-related cardiomyopathy [69]. Central nervous and cardiovascular systems are strongly interconnected, since cardiovascular system may work as a senor and effector for the central nervous system, whereas the neurons tightly control the cardiovascular function [70].

The increasing incidence of cardiovascular and neurological diseases are heavy burden to modern society, and a better understanding of the interrelationship will help discover new approaches to delay or reverse the pathology in both heart and brain. Besides epidemiological surveys, novel genetically engineered murine models are needed to mimic the disease pathology to better clarify the underlying mechanisms such as abnormal protein aggregates, altered gene expressions, and Ca^{2+} dysregulation. New and novel drugs and therapeutic targets should also be explored to improve the prognosis of intervening the neurological pathological processes.

Funding

This study was supported in part by the grant from the National Natural Science Foundation of China (No. 91749128).

References

1. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, *et al.* Dementia prevention, intervention, and care. *Lancet (London, England)* 2017, 390: 2673–2734.
2. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 2015, 11: 718–726.
3. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet* 2016, 388: 505–517.
4. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement* 2016, 2016, 12: 459–509.
5. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013, 9: 63–75.e2.
6. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: past, present and future. *Neuropharmacology* 2014, 76(Pt A): 27–50.
7. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers* 2015, 1: 15056.
8. Turdi S, Guo R, Huff AF, Wolf EM, Culver B, Ren J. Cardiomyocyte contractile dysfunction in the APPswe/PS1dE9 mouse model of Alzheimer's disease. *PLoS One* 2009, 4: e6033.
9. Ohsawa I, Nishimaki K, Murakami Y, Suzuki Y, Ishikawa M, Ohta S. Age-dependent neurodegeneration accompanying memory loss in transgenic mice defective in mitochondrial aldehyde dehydrogenase 2 activity. *J Neurosci* 2008, 28: 6239–6249.
10. Bilkei-Gorzo A. Genetic mouse models of brain ageing and Alzheimer's disease. *Pharmacol Ther* 2014, 142: 244–257.
11. O'Brien JT, Thomas A. Vascular dementia. *Lancet* 2015, 386: 1698–1706.
12. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res* 2017, 120: 573–591.
13. Morra LF, Donovick PJ. Clinical presentation and differential diagnosis of dementia with Lewy bodies: a review. *Int J Geriatr Psychiatry* 2014, 29: 569–576.
14. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 2007, 64: 1734–1740.
15. Wu L, He Y, Jiang B, Liu M, Wang J, Yang S, Wang Y. The association between the prevalence, treatment and control of hypertension and the risk of mild cognitive impairment in an elderly urban population in China. *Hypertens Res* 2016, 39: 367–375.
16. Tublin JM, Adelstein JM, Del Monte F, Combs CK, Wold LE. Getting to the heart of Alzheimer disease. *Circ Res* 2019, 124: 142–149
17. Calik AN, Ozcan KS, Yuksel G, Gungor B, Arugarslan E, Varlibas F, Ekmekci A, *et al.* Altered diastolic function and aortic stiffness in Alzheimer's disease. *Clin Interv Aging* 2014, 9: 1115–1121.
18. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, *et al.* Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke* 2005, 36: 2193–2197.
19. Belohlavek M, Jiamsripong P, Calleja AM, McMahon EM, Maarouf CL, Kokjohn TA, Chaffin TL, *et al.* Patients with Alzheimer disease have altered transmitral flow: echocardiographic analysis of the vortex formation time. *J Ultrasound Med* 2009, 28: 1493–1500.
20. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction—Alzheimer's disease of the heart? *N Engl J Med* 2013, 368: 455–464.
21. Gianni D, Li A, Tesco G, McKay KM, Moore J, Raygor K, Rota M, *et al.* Protein aggregates and novel presenilin gene variants in idiopathic dilated cardiomyopathy. *Circulation* 2010, 121: 1216–1226.
22. Troncone L, Luciani M, Coggins M, Wilker EH, Ho CY, Codispoti KE, Frosch MP, *et al.* Abeta amyloid pathology affects the hearts of patients with Alzheimer's disease: mind the heart. *J Am Coll Cardiol* 2016, 68: 2395–2407.
23. Jensen BC, Willis MS. The head and the heart: the Alzheimer's connection. *J Am Coll Cardiol* 2016, 68: 2408–2411.
24. Subramanian K, Gianni D, Balla C, Assenza GE, Joshi M, Semigran MJ, Macgillivray TE, *et al.* Cofilin-2 phosphorylation and sequestration in myocardial aggregates: novel pathogenetic mechanisms for idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2015, 65: 1199–1214.
25. Sandri M, Robbins J. Proteotoxicity: an underappreciated pathology in cardiac disease. *J Mol Cell Cardiol* 2014, 71: 3–10.
26. McLendon PM, Robbins J. Proteotoxicity and cardiac dysfunction. *Circ Res* 2015, 116: 1863–1882.
27. Sanna GD, Nusdeo G, Piras MR, Forteleoni A, Murru MR, Saba PS, Dore S, *et al.* Cardiac abnormalities in Alzheimer disease: clinical relevance beyond pathophysiological rationale and instrumental findings? *JACC Heart failure* 2019, 7: 121–128.
28. Stamatelopoulos K, Sibbing D, Rallidis LS, Georgiopoulos G, Stakos D, Braun S, Gatsiou A, *et al.* Amyloid-beta (1-40) and the risk of death from cardiovascular causes in patients with coronary heart disease. *J Am Coll Cardiol* 2015, 65: 904–916.
29. Shi J, Tian J, Pritchard A, Lendon C, Lambert JC, Iwatsubo T, Mann DM. A 3'-UTR polymorphism in the oxidized LDL receptor 1 gene increases Abeta40 load as cerebral amyloid angiopathy in Alzheimer's disease. *Acta Neuropathol* 2006, 111: 15–20.
30. Li D, Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, Partain J, *et al.* Mutations of presenilin genes in dilated cardiomyopathy and heart failure. *Am J Hum Genet* 2006, 79: 1030–1039.
31. Song XW, Yuan QN, Tang Y, Cao M, Shen YF, Zeng ZY, Lei CH, *et al.* Conditionally targeted deletion of PSEN1 leads to diastolic heart dysfunction. *J Cell Physiol* 2018, 233: 1548–1557.
32. Nakajima M, Moriizumi E, Koseki H, Shirasawa T. Presenilin 1 is essential for cardiac morphogenesis. *Dev Dyn* 2004, 230: 795–799.
33. Takeda T, Asahi M, Yamaguchi O, Hikoso S, Nakayama H, Kusakari Y, Kawai M, *et al.* Presenilin 2 regulates the systolic function of heart by modulating Ca2+ signaling. *FASEB J* 2005, 19: 2069–2071.
34. Li A, Zhou C, Moore J, Zhang P, Tsai TH, Lee HC, Romano DM, *et al.* Changes in the expression of the Alzheimer's disease-associated presenilin gene in drosophila heart leads to cardiac dysfunction. *Curr Alzheimer Res* 2011, 8: 313–322.
35. Jin WS, Bu XL, Wang YR, Li L, Li WW, Liu YH, Zhu C, *et al.* Reduced cardiovascular functions in patients with Alzheimer's disease. *J Alzheimers Dis* 2017, 58: 919–925.
36. Jabir NR, Firoz CK, Baeesa SS, Ashraf GM, Akhtar S, Kamal W, Kamal MA, *et al.* Synopsis on the linkage of Alzheimer's and Parkinson's disease with chronic diseases. *CNS Neurosci Ther* 2015, 21: 1–7.
37. Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, Testa G, *et al.* Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev* 2014, 18: 41–52.
38. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, *et al.* Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010, 7: 433–437.
39. de Bruijn RFAG, Heeringa J, Wolters FJ, Franco OH, Stricker BHC, Hofman A, Koudstaal PJ, *et al.* Association between atrial fibrillation and dementia in the general population association between atrial fibrillation and dementia association between atrial fibrillation and dementia. *JAMA Neurol* 2015, 72: 1288–1294.
40. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Tuan TC, Lin YJ, *et al.* Risk and prediction of dementia in patients with atrial fibrillation—a nationwide population-based cohort study. *Int J Cardiol* 2015, 199: 25–30.
41. Rusanen M, Kivipelto M, Levalahti E, Laatikainen T, Tuomilehto J, Soininen H, Ngandu T. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis* 2014, 42: 183–191.

42. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, *et al.* Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012, 9: 1761–1768.
43. Aldrugh S, Sardana M, Henninger N, Saczynski JS, McManus DD. Atrial fibrillation, cognition and dementia: a review. *J Cardiovasc Electrophysiol* 2017, 28: 958–965.
44. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013, 158: 338–346.
45. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol* 2019, 73: 612–619.
46. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006, 166: 1003–1008.
47. Adelborg K, Horvath-Puho E, Ording A, Pedersen L, Toft Sorensen H, Henderson VW. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *Eur J Heart Fail* 2017, 19: 253–260.
48. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail* 2009, 15: 1–10.
49. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med* 2015, 277: 406–425.
50. de la Torre JC. Vascular basis of Alzheimer's pathogenesis. *Ann NY Acad Sci* 2002, 977: 196–215.
51. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, Wolf PA, *et al.* Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham heart study. *Circulation* 2015, 131: 1333–1339.
52. dB RF, ML P, MJ L, MJ B, A H, vdL A, WJ N, *et al.* Subclinical cardiac dysfunction increases the risk of stroke and dementia: the Rotterdam study. *Neurology* 2015, 84: 833–840.
53. Thorin E. Hypertension and Alzheimer disease: another brick in the wall of awareness. *Hypertension* 2015, 65: 36–38.
54. Xu X, Hueckstaedt LK, Ren J. Deficiency of insulin-like growth factor 1 attenuates aging-induced changes in hepatic function: role of autophagy. *J Hepatol* 2013, 59: 308–317.
55. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 2005, 65: 545–551.
56. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. *Pathology* 2019, 51: 165–176.
57. Rasmussen KL. Plasma levels of apolipoprotein E, APOE genotype and risk of dementia and ischemic heart disease: a review. *Atherosclerosis* 2016, 255: 145–155.
58. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993, 261: 921–923.
59. Huang Y. Mechanisms linking apolipoprotein E isoforms with cardiovascular and neurological diseases. *Curr Opin Lipidol* 2010, 21: 337–345.
60. Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol* 2011, 10: 241–252.
61. Rasmussen KL, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Plasma levels of apolipoprotein E and risk of dementia in the general population. *Ann Neurol* 2015, 77: 301–311.
62. Stellos K, Panagiota V, Kogel A, Leyhe T, Gawaz M, Laske C. Predictive value of platelet activation for the rate of cognitive decline in Alzheimer's disease patients. *J Cereb Blood Flow Metab* 2010, 30: 1817–1820.
63. Takeda S, Sato N, Morishita R. Systemic inflammation, blood-brain barrier vulnerability and cognitive/non-cognitive symptoms in Alzheimer disease: relevance to pathogenesis and therapy. *Front Aging Neurosci* 2014, 6: 171.
64. Alzheimer's Association Calcium Hypothesis Workgroup. Calcium hypothesis of Alzheimer's disease and brain aging: a framework for integrating new evidence into a comprehensive theory of pathogenesis. *Alzheimers Dement* 2017, 13: 178–182.e17.
65. Piqueras-Flores J, Lopez-Garcia A, Moreno-Reig A, Gonzalez-Martinez A, Hernandez-Gonzalez A, Vaamonde-Gamo J, Jurado-Roman A. Structural and functional alterations of the heart in Parkinson's disease. *Neurol Res* 2018, 40: 53–61.
66. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. *Neurobiol Dis* 2012, 46: 572–580.
67. Cankar K, Melik Z, Kobal J, Starc V. Evidence of cardiac electrical remodeling in patients with Huntington disease. *Brain Behav* 2018, 8: e01077.
68. Schroeder AM, Wang HB, Park S, Jordan MC, Gao F, Coppola G, Fishbein MC, *et al.* Cardiac dysfunction in the BACHD mouse model of Huntington's disease. *PLoS One* 2016, 11: e0147269.
69. Mielcarek M, Inuabasi L, Bondulich MK, Muller T, Osborne GF, Franklin SA, Smith DL, *et al.* Dysfunction of the CNS-heart axis in mouse models of Huntington's disease. *PLoS Genet* 2014, 10: e1004550.
70. Critchley BJ, Isalan M, Mielcarek M. Neuro-cardio mechanisms in Huntington's disease and other neurodegenerative disorders. *Front Physiol* 2018, 9: 559.