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REVIEW TOPIC OF THE WEEK

Heart Failure-Induced Brain Injury

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ABSTRACT

Heart failure (HF) is a systemic illness with grave implications for bodily functions. The brain, among other vital organs, often suffers insults as a result of HF, and both anatomic and functional brain abnormalities were found in the HF population. This injury was demonstrated across a wide range of clinical conditions and cardiac functions and was shown to affect patients' outcomes. Although reduced cardiac output and high burden of cardiovascular risk factors are the prevailing explanations for these findings, there are data showing the involvement of neurohormonal, nutritional, and inflammatory mechanisms in this complex process. Here, the authors review the suggested pathophysiology behind brain injury in HF, describe its effect on patients' outcomes, offer a diagnostic approach, and discuss possible therapeutic options.
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The impact of heart failure (HF) on bodily functions is widespread; thus, other important organs interact with the failing heart to produce what are now known as the cardiorenal syndrome (1) and the cardiohepatic syndrome (2). Another vital, although less well-defined interaction, is the interface between the failing heart and the brain. Central nervous system (CNS) symptoms and signs are well established as part of HF presentation (3). These findings are demonstrable in HF patients with either reduced or preserved ejection fraction (HFrEF and HFpEF, respectively), and can be found in severely symptomatic, as well as in stable, community-dwelling HF patients. This interaction is further emphasized by specific findings encountered while evaluating both organs, and by the reciprocal improvement in their performance when the failing heart recovers. Furthermore, in this era of ever-growing therapeutic options, where patients' adherence and comprehension are imperative for therapeutic success, the importance of impaired cognition on HF patients' outcomes cannot be underestimated.

Here, we review the interaction between HF and the brain, describe typical anatomic and physiological brain changes, discuss potential mechanistic factors, and offer a practical diagnostic approach towards HF-induced brain injury.

CEREBRAL BLOOD FLOW

An early attempt to measure cerebral blood flow (CBF) in humans was performed in 1941 by evaluating the oscillations in cerebrospinal fluid following the intermittent obstruction of both jugular veins (4). Fortunately, other less invasive, yet more accurate methods (e.g., nuclear and magnetic resonance imaging [MRI]) were later implemented (5,6) to show that CBF is approximately 50 ml/min/100 g brain tissue (7), and is maintained at a wide range of mean arterial pressures. This stability is achieved by the sophisticated autoregulation of the CNS (8,9), and is maintained through a series of vascular and neurogenic factors, including the release of vasoactive compounds, the response to changing carbon dioxide

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ABBREVIATIONS AND ACRONYMS

CBF = cerebral blood flow

CF-LVAD = continuous-flow left ventricular assist device

CI = cognitive impairment

CNS = central nervous system

CO = cardiac output

GM = gray matter

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IHD = ischemic heart disease

IL = interleukin

LVAD = left ventricular assist device

MRI = magnetic resonance imaging

S1R = sigma-1 receptor

tHcy = total plasma homocysteine

WM = white matter

levels, and the unique response of CNS vasculature to fluctuating intraluminal pressures (7,10,11). Contemporary data have shown that CBF is jeopardized in chronic HF conditions, which is suggested to be associated with CNS-related symptoms (12). This hypoperfused state is not caused merely by the low cardiac output (CO) found in HF, because cerebral autoregulation is also compromised in these patients (13). Carbon dioxide levels were shown to fluctuate in both patients with acute and with chronic HF, and are inversely related to left ventricular end-diastolic pressures, with resultant constriction and dilatation of CNS blood vessels (14,15). Additionally, cerebrovascular reactivity, as measured by the response of cerebral vasculature to high levels of carbon dioxide, was also shown to be abnormal. Using transcranial Doppler to estimate CBF velocities, Georgiadis et al. (13) demonstrated that whereas HF patients had baseline flow-velocities comparable to those of normal controls, their response to the hypercapneic state (which typically produces significant vasodilation and increased flow) was blunted.

Heart transplantation was shown to result in a significant improvement in CBF, which was often accompanied by improved cognitive performance in heart transplant patients (5,16). A more complex interaction exists between CBF and left ventricular assist device (LVAD) implantation. LVADs provide circulatory support, either through volume-shift pulsatile or continuous-flow pumps (CF-LVAD). The effect of the nonphysiological CF-LVADs has been a controversial subject, because it was found to impair endothelial function and to significantly reduce levels of nitric oxide, a key modulator of cerebral autoregulation (17). However, in a study in which Doppler CBF velocity was measured in steady-state and after sit-stand maneuvers in pulsatile-flow LVADs, CF-LVADs, and controls, Cornwell et al. (18) demonstrated that CBF flow velocities showed significant variations in the pulsatile-flow LVADs, as opposed to the CF-LVADs or normal controls, and dynamic cerebral autoregulation was maintained with both devices. These findings are reinforced by the comparable arteriolar histological findings in autopsied cerebral arteries from patients implanted with pulsatile versus CF-LVADs (19). A possible explanation might be found in the complex interaction between the high sympathetic tone found in patients with CF-LVADs and its effect on the cerebral vasculature (18). Animal models have shown that an abrupt elevation in blood pressure causes a significant increase in CBF, yet, counterintuitively, when this hypertension was accompanied by increased sympathetic tone, the augmentation in CBF was attenuated (20). The hypothesized mechanism for this response is the selective constriction of large CNS arteries in the presence of increased sympathetic tone, consequently causing an increase in total CNS vascular resistance while maintaining adequate perfusion (21). Because CF-LVAD patients were shown to have relatively high sympathetic tone (22), it can be speculated that this has a protective effect on their CBF.

BRAIN ANATOMIC AND COGNITIVE CHANGES

Prevalent mental disturbances associated with HF encompass multiple processes including: attention and learning deficits; reduced psychomotor speed; diminished executive function; specific subtypes of memory dysfunctions; and, to a lesser degree, language impairment and reduced visuospatial performance (23,24). Although these findings were originally thought to be limited to older, debilitated HF patients, current data show that they are also found in young, stable individuals (23,24). HF patients have worse degrees of cognitive impairment (CI) compared with matched controls (23,25), and have worse cognitive performances after adjustment for age, socioeconomic status, and education, and also when compared with patients with significant comorbidities (e.g., hypertension, ischemic heart disease [IHD]) other than HF (23,26). Interestingly, Athilingam et al. (27) showed that although HFrEF patients experienced more executive dysfunction and attention deficit, HFpEF patients had delayed recall and reduced abstraction abilities. HF patients' quality of life and risk of complications were shown to be influenced by CI. Cameron et al. (28) reported that CI predicted poor self-care in HF patients, and Hawkins et al. (29) showed that HF patients with CI were less likely to adhere to their medical regimens. Consequently, CI was found to be a risk factor for HF decompensation, increased rate of readmissions, and even increased mortality (30). In a recent study examining risk prediction models for short-term HF-related outcomes, Huynh et al. (31) reported that CI and depression were strong predictors of hospital readmissions and 30-day mortality.

Investigating the anatomic aspect of these findings, both gray matter (GM) and white matter (WM) changes were demonstrated in HF patients (23,32). These structural changes can be diffuse, but were usually localized and related to specific brain dysfunctions (23,32,33). Again, such changes were not

limited to severely decompensated individuals, but were also found in stable, ambulatory HF patients with subtle CI revealed only through focused cognition tests. Almeida et al. (23) showed that the impaired executive functions demonstrated in independent community-dwelling HF patients were related to GM loss in the anterior cingulate, and lateral and medial frontal cortex, regions that have an important role in strategic thinking. Similarly, Vogels et al. (32) showed that HF patients free from stroke, dementia, or depression had a higher prevalence of WM hyperintensities on brain MRIs.

THE PATHOPHYSIOLOGY BEHIND FUNCTIONAL AND ANATOMIC BRAIN CHANGES

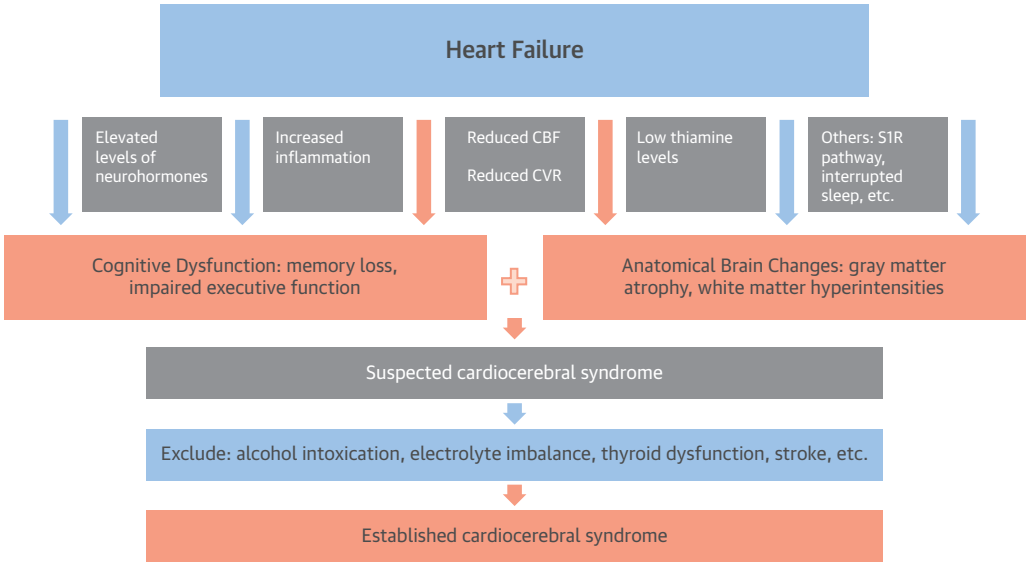
REDUCED CBF AND HIGH CARDIOVASCULAR RISK BURDEN. The mechanism proposed for brain injury in HF is multifactorial and not well understood (**Central Illustration**). Deep brain structures lack collaterals, are irrigated by deep penetrating arteries, or are located at the junction supplied by both middle and anterior cerebral arteries, and hence are exposed to watershed phenomena. They consequently become prone to ischemic assault under hypoperfused conditions, usually found in reduced CO states (34). Accordingly, different investigators considered jeopardized CBF to be the main causative factor (32,35). However, WM lesions (36) and CI (37) were also reported in HFpEF patients. Data on CBF in these patients are currently lacking. Considering the increased arterial stiffness and reduced vasodilatory reserve found in HFpEF (38), one might speculate that CBF would be reduced. However, given the normal CO found in the HFpEF population (39), it is also possible that CBF might be preserved. Additionally, reduced CBF cannot serve as the key explanation in the case of cortical GM loss, where the vasculature is rich and instead, cardiovascular risk burden is considered the main offender (23). For example, HF patients and IHD patients have a similar pattern of GM loss compared with individuals with no heart disease, implying that these structural changes are related to shared risk factors (23). Nevertheless, in a study conducted as early as 1991, MRI brain scans of dilated cardiomyopathy patients showed significant structural brain changes compared with normal controls, even though patients with IHD risk factors were specifically excluded from the study (40). Furthermore, despite the similar pattern of brain injury, contemporary data showed that HF patients had GM loss in specific regions that was much more extensive than that observed in either IHD patients or healthy controls (23). In addition, although WM hyperintensities were previously considered the result of aging or increased cardiovascular risk burden (41), they remained significantly more prevalent in HF patients, even after correction for age, and the presence of IHD and its risk factors (32). And so, it seems that although there is a strong association between reduced CBF or increased cardiovascular risk burden and the observed high prevalence of brain injury seen in HF, they do not fully explain these findings.

THE NEUROHORMONAL AXIS. The neurohormonal axis in HF has been discussed extensively before, and probably has a role in the interaction between HF, cognition, and structural brain changes. Cortisol, a known stress-related hormone, was found to influence cognitive performance. Newcomer et al. (42) showed cortisol levels to be elevated in the saliva of healthy volunteers who had poorer results in a cognitive stress test. Furthermore, matched participants treated with cortisol performed worse on specific cognitive assessments compared with those treated with placebo (43). Although the results of these trials imply that transient high levels of cortisol directly impair cognitive function, other studies showed that prolonged exposure to high levels of cortisol can cause atrophy of specific brain regions through decreased neurogenesis (44). In this regard, HF patients were found to have elevated serum levels of cortisol compared with normal controls (45), and significantly higher levels of cortisol were found in HF patients who experienced depression and CI, but not in those free from these symptoms (46), suggesting that cortisol levels in HF might influence the development of CI.

Catecholamine levels are known to be elevated in HF patients, with deleterious effects on heart function (47). The effect of sustained elevated levels of epinephrine on cognitive function has been studied by Karlamangla et al. (48), who reported that in elderly men, higher levels of urine epinephrine were related to poorer performance on cognitive tests. Interestingly, epinephrine does not usually cross the blood-brain barrier, and its effect on brain function is thought to be mediated mainly through an inverse U-shaped relationship between glucose levels and memory (49).

THE INFLAMMATORY AXIS. HF is considered a state of increased inflammation and immune response that is usually triggered by myocardial injury (50). In trials conducted by Ferketich et al. (51) and Parissis et al. (52), high levels of interleukin (IL)-6 and tumor necrosis factor-alpha were measured in HF patients with CI and depressive disorders, but not in HF patients

CENTRAL ILLUSTRATION **HF-Induced Brain Injury: Characteristics, Pathophysiology, and Approach**



Havakuk, O. et al. J Am Coll Cardiol. 2017;69(12):1609–16.

The pathophysiology of brain injury in heart failure (HF) is multifactorial. Once functional and/or anatomic brain changes are demonstrated in an HF patient, exclusion of other offenders should be pursued before classifying this brain injury as HF-induced. CBF = cerebral blood flow; CVR = cerebrovascular reactivity; S1R = Sigma 1 receptor.

free from these findings. These results remained significant after adjustment for patients' left ventricular systolic function and the severity of HF symptoms. Evidence suggesting a cause-and-effect mechanism can be derived from studies showing impaired cognitive performance in healthy individuals who were exposed to bacterial endotoxins versus placebo in a randomized, double-blind fashion (53). These trials showed an inverse relationship between the levels of IL-6 and the cognitive performance of the subjects (53). Additionally, in other chronic inflammatory states, such as rheumatoid arthritis, higher levels of circulating cytokines were related to significantly worse cognitive functions (54). Almeida et al. (23) reported that, compared with normal controls, high levels of IL-6, total plasma homocysteine (tHcy), and more extensive brain changes were found in HF patients, but not in IHD patients. High levels of tHcy were shown to produce brain atrophy and cognitive decline through brain cell apoptosis (55), and interventions aimed at reducing the levels of tHcy were shown to delay brain atrophy (56). Notably, IL-6 receptors were found to reside specifically in areas such as the hippocampus and cerebral cortex, and, once activated by their ligand, can trigger an intracellular cascade resulting in subsequent neuronal loss (57).

NUTRITIONAL DEFICIENCY. A study conducted by Hanninen et al. (58) showed that approximately one-third of hospitalized HF patients suffer from thiamine deficiency. This deficiency is probably significant, because thiamine-deprived rats develop brain atrophy and WM changes that coincide with their impaired learning capabilities (59). Similarly, autopsied brains from thiamine-deficient patients demonstrated histological changes in regions functionally related to memory (i.e., the mammillary bodies and hippocampus) (60). MRI brain scans conducted in thiamine-deficient patients showed a similar pattern of brain atrophy (61). It should be mentioned that most of these studies were conducted in alcoholic patients; however, not all alcoholic patients show these abnormalities (62) and, as mentioned, comparable changes were demonstrated in animal models of thiamine deficiency without alcohol exposure. Considering the data showing that thiamine deficiency was suspected in only 20% of patients with histologically proven Wernicke-Korssakof brain changes (60), it might be

hypothesized that the deleterious effect of thiamine deficiency is similarly underdiagnosed in the HF population. More conclusive data on the role of thiamine deficiency in brain changes of HF patients are currently lacking and await future investigation.

DEPRESSION. A complex interaction exists between HF, CI, and depression. Depression was shown to be associated with reduced cognitive function (63) and anatomic brain changes (64), and was also shown to be related to higher levels of inflammatory (65) and neurohormonal (66) biomarkers. However, depression is also prevalent among HF patients (30). These data can be interpreted in 2 ways. First, because depression was suggested as a possible cause for an increased risk of CI, it might present an important confounder in the suggested association between HF and CI. Alternatively, depression might also serve as an important mechanistic link between HF and CI.

An improvement in cognitive functions was noted in patients who were medically treated for their depression (67). Currently, however, no such data exist specifically for the HF population. It seems that given the high prevalence of depression in HF, along with the association of both HF and depression with inflammation, increased neurohormonal activity, and CI, a clear causality would be challenging to demonstrate.

OTHER PATHWAYS. Sigma receptors participate in different bodily functions, including of the heart and the brain, and have recently been found to participate in the suggested link between HF and depression. The importance of the sigma-1 receptor (S1R) in depression has been well described (68), and specific drug therapy has been introduced (69). In the context of HF, Ito et al. (70) demonstrated that in a laboratory model of HF, lower brain S1R levels were correlated with signs of depression. To further emphasize this point, animals who were treated with the S1R agonist, PRE084, showed a decrease in depressive behavior, with concomitant improvement in cardiac function.

DEFINITION OF CARDIOCEREBRAL SYNDROME

The term *cardiocerebral syndrome* was loosely used by previous investigators (71–73). Indeed, this lack of unifying terminology withheld universal acceptance. We suggest that the term cardiocerebral syndrome should be redefined as follows: a state of cognitive impairment of undefined cause in HF patients, beyond that anticipated in age-matched controls, and typically accompanied by anatomic brain changes (**Table 1**). The patient may exhibit a wide variety of neurobehavioral symptoms, and a focused examination might be required in order to recognize subtle changes (74). MRI studies will typically show WM hyperintensities, particularly periventricular (32), and GM atrophy, particularly involving the hippocampus and frontal cortex (23,33). A laboratory investigation is anticipated to show high levels of neurohormones and inflammatory markers. Clinicians should also rule out other possible offenders that may cause similar results (**Table 1**, **Figure 1**) before suggesting cardiocerebral syndrome as the generator of the brain injury.

TABLE 1 HF-Induced Brain Injury: Characteristics and Basic Approach

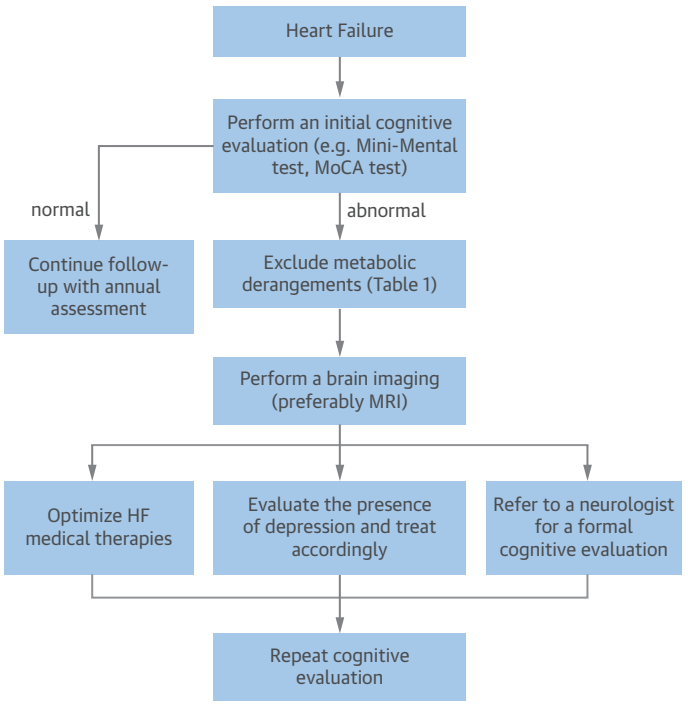
Definition	A state of cognitive impairment of undefined cause in HF patients, beyond the one anticipated in age-matched controls, typically accompanied by anatomic brain changes
What should be looked for?	1. Cognitive functions: impaired memory and executive functions 2. Anatomic brain changes: white matter hyperintensities; medial temporal atrophy; frontal lobe and hippocampal atrophy 3. Serum markers: elevated levels of IL-6; TNF-α; cortisol; and epinephrine
What should be ruled out?	1. Electrolyte imbalance, hypothyroidism, nutritional deficiency, alcohol intoxication, stroke, infection 2. Other causes for dementia: Alzheimer disease; Parkinson disease; Lewy body dementia; normal pressure hydrocephalus, among others

HF = heart failure; IL = interleukin; TNF = tumor necrosis factor.

SUGGESTED THERAPEUTIC OPTIONS

Improved cardiac performance and systemic hemodynamics have a positive impact on the brain. Cognitive function improves after cardiac transplantation and following LVAD implantation (16,75). In this regard, denying advanced HF therapies to HF patients solely on the basis of CI may be erroneous, given its potential reversibility. However, less aggressive therapeutic options were also shown to be beneficial. Zuccalà et al. (76) demonstrated that HF patients receiving angiotensin-converting enzyme inhibitors had an improvement in cognitive performance that was enhanced with higher dosages and prolonged treatment. This favorable effect was probably not limited to improved cardiac function; angiotensin-converting enzyme resides in major cerebral arteries, and hence, despite the reduction in systemic blood pressure, an increase in cerebral perfusion was shown (77,78). Digoxin's positive effect on cognition (79) might be even more complex. Endogenous sodium-potassium adenosine triphosphatase (Na^+/K^+ATPase) blockers (e.g., ouabain, endobain) were found to influence the release of

FIGURE 1 Suggested Diagnostic Approach to HF-Induced Brain Injury



A suggested practical approach for identifying HF-induced brain injury. A simple, user-friendly screening test should be applied in order to detect a possibly overlooked cognitive impairment. An abnormal test result should trigger a search for other potential offenders, followed by brain imaging, a formal neurological evaluation, including depressive disorder assessment, and optimization of HF therapies. HF = heart failure; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging.

brain acetylcholine and catecholamines, and to affect N-methyl-D-aspartate (NMDA) receptors, which are involved in memory processing (80,81). Putting this together, the improved cognitive function demonstrated in digoxin-treated patients is probably not limited to increased contractility alone. The effects of other measures, including pacemaker implantation and cardiac resynchronization therapy, are probably related to the improvement in cardiac function (82). Importantly, and considering the prevalence of HF in the elderly, more directed approaches, such as the use of exercise programs (83) and nurse-enhanced memory interventions (84), were also shown to delay or reverse cognitive impairment.

AREAS OF EQUIPOISE AND FUTURE PERSPECTIVES

Most of the data described earlier were derived from single-center trials, databases, and observational studies. Accordingly, the conclusions drawn here can be generally referred to as experts' opinions or consensuses (Level of Evidence: C). At the same time, the bulk of evidence connecting HF to brain injury seems beyond dispute. The purposes of this review were to present the data accumulated thus far on this important topic and, by doing so, to increase the awareness of the medical community to its presence and trigger future research that will allow more firm conclusions in the evaluation of this disease to be presented. Further elaboration of the information on the relationship between CBF, inflammatory, nutritional, and neurohormonal pathways, as well as other specific mechanisms, and their interplay with HF subtypes and brain injury will make our future attempts to cope with this problem more evidence-based, accurate, and comprehensive.

APPROACH TO CARDIOCEREBRAL SYNDROME

Acute HF may present as significant cerebral dysfunction (3). However, other explanations for these findings must be ruled out first. Considering the high prevalence of comorbidities and frequent use of antithrombotic therapy in the HF population, both acute cerebral ischemic and hemorrhagic events should always be included in the differential diagnosis. Similarly, metabolic and electrolyte imbalances should be considered, and the susceptibility of these patients to infection and sepsis cannot be ignored. Alcohol toxicity deserves special consideration because it may produce both cardiac and brain injury (**Table 1**). Stabilization of acute HF with attempted normalization of blood pressure while avoiding possible damage to cerebral perfusion and function is therefore recommended. A recent study has shown that post-discharge 30-day mortality and readmission rates were strongly influenced by the presence of CI (31). Accordingly, overlooking the presence of this correctable condition might impact patients' adherence to therapy, which could have a deleterious effect on outcomes.

Because considerable data have shown that cerebral dysfunction can be present in ambulatory, stable HF patients, a more challenging case might be the diagnosis of brain injury in chronic HF. We suggest that a short, simple cognitive test (e.g., the Mini-Mental test [MMSE], the Montreal Cognitive Assessment [MoCA]) (Online Appendix) should be conducted in all HF patients, either by the referring physician or by a member of the HF team during the patient's first clinic visit and yearly thereafter, in order to recognize possible subtle cognitive changes that might be otherwise overlooked. In the case of an

abnormal result, metabolic derangements should be excluded, followed by brain imaging (preferably MRI). The patient should then be referred for a formal neurological evaluation (including the investigation and treatment of possible depression), and the evaluation should be repeated after optimization of HF therapy (**Figure 1**). The use of the MMSE and MoCA tests has been suggested by the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of HF (85). This approach is anticipated to increase the diagnosis rates of HF-induced brain injury and might also improve patients' outcomes.

CONCLUSIONS

There are significant data supporting the presence and importance of brain injury in the HF population, and there are also measures to diagnose, sustain, or even reverse this injury. As always, the first step is awareness.

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KEY WORDS cerebral blood flow, cognitive impairment, depression

APPENDIX For examples of the Mini-Mental test and the Montreal Cognitive Assessment, please see the online version of this article.