Emerging Role of Combined Brain/Heart Magnetic Resonance Imaging

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Heart failure (HF) patients frequently develop brain deficits that lead to cognitive dysfunction (CD), which may ultimately also affect survival. There is an important interaction between brain and heart that becomes crucial for survival in patients with HF. A combined magnetic resonance imaging of brain/heart can reveal early pathophysiologic changes.

Keywords: brain magnetic resonance imaging ; cardiac magnetic resonance imaging ; MRI

1. Brain Anatomy and Function in HF

The critically attained threshold of cerebral hypoperfusion ('CATCH') theory supports the fact that aging in conjunction with vascular risk factors leads to chronic cerebral hypoperfusion and increased risk of Alzheimer's disease (AD) [1]. Reduced myocardial contractility, commonly found in Heart failure (HF), leads to a decreased forward flow with concurrent decline in brain perfusion. Cerebral blood flow (CBF) reduction is further compounded by the negative action of other co-morbidities, such as hypertension, diabetes, sleep apnea and depression [2]. In HF patients, there is evidence of reduced CBF to bilateral hippocampus, parahippocampal gyrus and right posterior cingulate cortex [3][4], regions usually associated with AD. Furthermore, HF patients have up to 31% reduction in resting CBF compared with age-matched healthy controls [5]. Finally, patients with mild-to-moderate HF had reduced blood flow velocity of the middle cerebral artery, compared to healthy controls (47.3 versus 56.1 cm/s, respectively) [6]. However, the reasons of brain hypoperfusion in HF include not only the low cardiac output, due to HF, but also the compromised cerebral autoregulation [1]. Carbon dioxide levels were fluctuated in patients with either acute or chronic HF and were inversely related to left ventricular end-diastolic pressures, leading to constriction/dilatation of central nervous system (CNS) blood vessels [2]. Additionally, cerebrovascular reactivity, measured by the response of cerebral vasculature to high levels of carbon dioxide, becomes abnormal. Using transcranial Doppler to estimate CBF velocities, it was demonstrated that, whereas HF patients had baseline flow velocities comparable to normal controls, their response to the hypercapneic state, which produces vasodilation and increased flow, was decreased. Furthermore, alterations in cardiac hemodynamics, irrespective of cardiovascular risk factors and co-morbidities, are linked to reduced brain function. Interventions to maintain cardiac function in old age might have implications for preservation of brain function; therefore, physicians in charge of HF treatment should also take under consideration patients' brain status and cognitive function. This is in agreement with recent recommendations by the AHA that cardiovascular risk factors lead to vascular cognitive impairment [3]. Finally, Heart Transplantation leads to a significant improvement in CBF, which is usually accompanied by improved cognitive performance in heart transplant patients [4].

The mental disturbances associated with HF include attention and learning deficits, memory loss, cognitive dysfunction (CD) and, to a lesser degree, language impairment and reduced visual–spatial performance [5][7]. Furthermore, HF patients have reduced cognitive function compared with matched controls [8][9][10], which remains reduced after adjustment for age, socioeconomic status and education [10][11]. CD predicted poor self-care in HF patients [11], and these patients are less likely to follow their medical regimens [12][13]. Therefore, CD is a risk factor for HF decompensation, increased readmissions and mortality [13].

The evaluation of brain anatomy showed that both gray matter (GM) and white matter (WM) alterations are common in HF [14][15] and can be either diffuse or, most commonly, localized, leading to specific brain dysfunction [10][14][15][16][17][18][19]. These changes were not limited only to severely decompensated HF, but they were also seen in stable HF, with subtle CD that was detectable only through specific cognition tests [10].

2. Pathophysiology of Brain Dysfunction in Heart Failure

2.1. The Role of Reduced CBF

Although CBF has been considered as the main causative factor of brain lesions in HF, reduced CBF cannot serve as the only explanation for cortical GM loss, where the vasculature is rich. In contrast, cardiovascular risk burden is the main cause for this [7]. HF and ischemic heart disease [IHD] patients have a similar pattern of GM loss compared with individuals with no heart disease, proving that these structural changes are related to common risk factors [18]. Furthermore, despite the similar pattern of brain injury, recent data showed that HF patients suffered GM loss in specific regions that was much more extensive than that observed in either IHD patients or healthy controls [7]. In addition, white matter hyperintensities [WMH] remained significantly more common in HF patients, even after correction for age, IHD and coronary artery disease (CAD) risk factors [14]. Therefore, it seems that, although there is a strong association between reduced CBF, increased CVD risk burden and high prevalence of brain injury found in HF, brain damage cannot be explained exclusively by these factors.

2.2. The Neurohormonal Axis

The neurohormonal axis in HF has a role in the interaction between HF, cognition and structural brain changes. Cortisol, a stress-related hormone, can influence cognitive function. Cortisol levels were found to be increased in the saliva of healthy volunteers with poor results in cognitive stress tests [20]. Furthermore, patients treated with cortisol performed worse in specific cognitive tests, compared with those treated with the placebo [21]. Although the results of these trials show that transient high levels of cortisol can directly impair the cognitive function, other studies showed that prolonged exposure to high cortisol levels can cause atrophy of specific brain regions, due to decreased neurogenesis [22]. In this context, significantly higher levels of cortisol were found in HF patients who experienced depression and CD, but not in those free from these symptoms [23], suggesting that cortisol levels in HF might influence the development of CD.

2.3. The Inflammatory Axis

HF is a situation of increased inflammation and immune response that is usually triggered by myocardial injury [24]. In relevant trials [25], high levels of interleukin (IL)-6 and tumor necrosis factor-alpha were found in HF patients with CD and depression, but not in HF patients free from these symptoms. Additionally, in other chronic inflammatory states, such as rheumatoid arthritis, higher levels of circulating cytokines were related to significantly worse cognitive functions [26]. Notably, IL-6 receptors were found to reside specifically in areas such as the hippocampus and cerebral cortex and can trigger an intracellular cascade, resulting in subsequent neuronal loss [27].

2.4. The Nutritional Deficiency

Keith et al. [28] showed that approximately one-third of hospitalized HF patients present thiamine deficiency. Additionally, thiamine deficiency was suspected in only 20% of patients with histologically proven Wernicke-Korsakoff brain changes [29] and the same might be hypothesized in HF. However, conclusive data regarding the role of thiamine deficiency in brain involvement of HF patients are currently missing.

2.5. The Role of Depression

A complex interaction exists between HF, CD and depression. It was found that depression is associated with CD [30] and anatomic brain changes [31] and is also related to higher levels of inflammatory [32] and neurohormonal [33] biomarkers that are also prevalent in HF patients. Furthermore, an improvement in CD was noted in patients who were medically treated for their depression [34]. However, further studies are needed to fully clarify the role of depression in CD presented in HF.

2.6. The Role of Atrial Fibrillation (AF)

There is evidence that AF is associated with a higher risk of cognitive impairment and dementia, with or without a history of clinical stroke. AF increases the risk of clinical stroke by four- to five-fold, and patients with a clinical history of stroke are at increased risk of developing dementia. However, AF is also associated with cognitive dysfunction, ranging from mild impairment to overt dementia, independently of clinical stroke as well as multiple shared risk factors. It is also well established that AF and cognitive impairment share common risk factors, including advanced age, diabetes, hypertension, sleep apnoea and chronic heart failure. Moreover, a significant increase of 34% was found in the risk of cognitive impairment in patients with AF in the absence of clinical stroke, even after adjustment for shared risk factors [35].

2.7. The Role of Myocardial Infarction (MI)

The recently identified association between unrecognized MI and cerebral infarction suggests that unrecognized MI may be a novel risk factor for cardiac embolism and cerebral infarction [36].

2.8. The Role of Heart Failure (HF)

HF is linked to an increased risk of thrombosis, leading to sudden death, stroke, systemic thrombo-embolism and/or venous thrombo-embolism. There is the risk of stroke, possibly silent, in patients with HF, even in the absence of atrial fibrillation, which may lead to cognitive dysfuncion in patients with atrial fibrillation.

In HF patients with reduced left ventricular ejection fraction who are in sinus rhythm, there is no evidence of an overall benefit of vitamin K antagonists (e.g., warfarin) on mortality, with risk of major bleeding. In contrast, risk factors associated with increased risk of thrombo-embolic events should be identified and the decision about the use of anticoagulation should be individualized. New oral anticoagulants that offer a different risk-benefit profile compared with warfarin may be an interesting alternative, but this would need to be confirmed in clinical trials [37].

3. Brain Imaging in Heart Failure

Neuroimaging includes the application of various modalities to directly or indirectly image the structure, function or pharmacology of the brain [14] and falls into two broad categories:

1. Structural imaging

This deals with brain structure and the diagnosis of large-scale intracranial disease, such as tumor or injury.

2. Functional imaging

This is used to diagnose metabolic diseases and fine lesions such as those found in AD as well as for neurological and cognitive-psychology research. Functional imaging allows the direct visualization of brain information processing through the “lights up” of the involved area.

The commonest methods to evaluate the brain include:

- Electroencephalography (EEG)

EEG is used to show brain activity in certain mental states, such as alertness or drowsiness. It is useful in the diagnosis of seizures and other medical problems involving an overabundance or lack of activity in certain parts of the brain [38].

- Positron Emission Tomography (PET)

Positron emission tomography (PET) scan measures the glucose levels in the brain to illustrate where neural firing is present and is based on the fact that active neurons use glucose as fuel. During the scan, a tracer attached to radioactive isotopes is injected into the blood, and when parts of the brain become active, blood containing the tracer is sent to deliver oxygen. This creates visible spots, which are collected by detectors and used to create images of the brain, while the patient performs a particular task. However, PET can detect only generalized areas of brain activity and not specific locations and is very expensive. A study assessing the heart–brain axis with cardiac and brain ^{18}F-FDG PET/CT imaging in HF patients showed that the global and regional brain metabolic activity was significantly associated with the extent of hibernated myocardium (HM) and cardiac function [39].

- Magnetic Resonance Imaging (MRI)

MRI and functional magnetic resonance imaging (fMRI) are the most commonly used modalities in neuropsychology. MRI uses strong magnetic fields to align spinning atomic nuclei (usually hydrogen protons) within body tissues, then disturbs the axis of rotation of these nuclei and observes the radiofrequency signal generated as the nuclei return to their baseline status. Through this process, MRI creates images of the brain structure. It is noninvasive and can be used safely in patients with MRI compatible devices, cardiac valves and coronary artery stents. The most important disadvantage is that the patient has to stay still for long periods of time in a noisy, narrow space until the imaging has been accomplished.

It has been found that the CD, demonstrated in HF patients, is related to gray matter density (GMD) loss in the anterior cingulate, lateral and medial frontal cortex, regions that play an important role in strategic thinking [36]. Furthermore,

despite the similar pattern of brain injury, recent data showed that HF patients had GM loss in specific regions that was much more extensive than that observed in either CAD patients or healthy controls [40]. In addition, Vogels et al. [13] showed that HF patients free from stroke, dementia or depression had a higher prevalence of WMH on brain MRI. Although WMH were previously considered the result of aging or increased cardiovascular risk burden [17][18], they remained significantly more prevalent in HF patients, even after correction for age, IHD and its risk factors [16]. Cardiac dysfunction contributes independently to the development of cerebral MRI abnormalities in patients with HF. Age and low left ventricular ejection fraction (LVEF) are the principal predictors of WMH in patients with HF and in cardiac controls [17]. Furthermore, MRI brain scans, performed in 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 [19]. Finally, diminished GMD was found in wide brain regions, including the whole fronto-median cortex as well as hippocampus and precuneus, that might promote CD development [13]. This reduced GMD was correlated with decreased LVEF and increased NTproBNP [14].

References

1. Georgiadis, D.; Sievert, M.; Cencetti, S.; Uhlmann, F.; Krivokuca, M.; Zierz, S.; Werdan, K. Cerebrovascular reactivity is impaired in patients with cardiac failure. Eur. Heart J. 2000, 21, 407–413.
2. Lorenzi-Filho, G.; Azevedo, E.R.; Parker, J.D.; Bradley, T.D. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. Eur. Respir. J. 2002, 19, 37–40.
3. Sabayan, B.; van Buchem, M.A.; Sigurdsson, S.; Zhang, Q.; Harris, T.B.; Gudnason, V.; Arai, A.E.; Launer, L.J. Cardiac hemodynamics are linked with structural and functional features of brain aging: The age, gene/environment susceptibility (AGES)-Reykjavik Study. J. Am. Heart Assoc. 2015, 4, e001294.
4. Gruhn, N.; Larsen, F.S.; Boesgaard, S.; Knudsen, G.M.; Mortensen, S.A.; Thomsen, G.; Aldershvile, J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke 2001, 32, 2530–2533.
5. Vogels, R.L.; Oosterman, J.M.; Laman, D.M.; Gouw, A.A.; Schroeder-Tanka, J.M.; Scheltens, P.; van der Flier, W.M.; Weinstein, H.C. Transcranial Doppler blood flow assessment in patients with mild heart failure: Correlates with neuroimaging and cognitive performance. Congest. Heart Fail 2008, 14, 61–66.
6. Scherbakov, N.; Doehner, W. Heart-brain interactions in heart failure. Card. Fail. Rev. 2018, 4, 87–91.
7. Almeida, O.P.; Garrido, G.J.; Beer, C.; Lautenschlager, N.T.; Arnolda, L.; Flicker, L. Cognitive and brain changes associated with ischaemic heart disease and heart failure. Eur. Heart J. 2012, 33, 1769–1776.
8. Sauvé, M.J.; Lewis, W.R.; Blankenbiller, M.; Rickabaugh, B.; Pressler, S.J. Cognitive impairments in chronic heart failure: A case controlled study. J. Card. Fail. 2009, 15, 1–10.
9. Alagiakrishnan, K.; Mah, D.; Ahmed, A.; Ezekowitz, J. Cognitive decline in heart failure. Heart Fail. Rev. 2016, 21, 661–673.
10. Huijts, M.; van Oostenbrugge, R.J.; Duits, A.; Burkard, T.; Muzzarelli, S.; Maeder, M.T.; Schindler, R.; Pfisterer, M.E.; Brunner-La Rocca, H.P.; TIME-CHF Investigators. Cognitive impairment in heart failure: Results from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) randomized trial. Eur. J. Heart Fail. 2013, 15, 699–707.
11. Athilingam, P.; D'Aoust, R.F.; Miller, L.; Chen, L. Cognitive profile in persons with systolic and diastolic heart failure. Congest. Heart Fail. 2013, 19, 44–50.
12. Hawkins, L.A.; Kilian, S.; Firek, A.; Kashner, T.M.; Firek, C.J.; Silvet, H. Cognitive impairment and medication adherence in outpatients with heart failure. Heart Lung 2012, 41, 572–582.
13. Rutledge, T.; Reis, V.A.; Linke, S.E.; Greenberg, B.H.; Mills, P.J. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J. Am. Coll. Cardiol. 2006, 48, 1527–1537.
14. Vogels, R.L.; van der Flier, W.M.; van Harten, B.; Gouw, A.A.; Scheltens, P.; Schroeder-Tanka, J.M.; Weinstein, H.C. Brain magnetic resonance imaging abnormalities in patients with heart failure. Eur. J. Heart Fail. 2007, 9, 1003–1009.
15. Pan, A.; Kumar, R.; Macey, P.M.; Fonarow, G.C.; Harper, R.M.; Woo, M.A. Visual assessment of brain magnetic resonance imaging detects injury to cognitive regulatory sites in patients with heart failure. J. Card. Fail. 2013, 19, 94–100.
16. Schmidt, R.; Fazekas, F.; Offenbacher, H.; Dusleag, J.; Lechner, H. Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. Stroke 1991, 22, 195–199.

17. Ovbiagele, B.; Saver, J.L. Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. Cerebrovasc. Dis. 2006, 22, 83–90.
18. Mueller, K.; Thiel, F.; Beutner, F.; Teren, A.; Frisch, S.; Ballarini, T.; Möller, H.E.; Ihle, K.; Thiery, J.; Schuler, G.; et al. Brain damage with heart failure: Cardiac biomarker alterations and gray matter decline. Circ. Res. 2020, 126, 750–764.
19. Risacher, S.L.; Saykin, A.J. Neuroimaging in aging and neurologic diseases. Handb. Clin. Neurol. 2019, 167, 191–227.
20. Newcomer, J.W.; Selke, G.; Melson, A.K.; Hershey, T.; Craft, S.; Richards, K.; Alderson, A.L. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch. Gen. Psychiatry 1999, 56, 527–533.
21. Kirschbaum, C.; Wolf, O.T.; May, M.; Wippich, W.; Hellhammer, D.H. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci. 1996, 58, 1475–1483.
22. Chetty, S.; Friedman, A.R.; Taravosh-Lahn, K.; Kirby, E.D.; Mirescu, C.; Guo, F.; Krupik, D.; Nicholas, A.; Geraghty, A.; Krishnamurthy, A.; et al. Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. Mol. Psychiatry 2014, 19, 1275–1283.
23. Huffman, J.C.; Celano, C.M.; Beach, S.R.; Motiwala, S.R.; Januzzi, J.L. Depression and cardiac disease: Epidemiology, mechanisms, and diagnosis. Cardiovasc. Psychiatry Neurol. 2013, 2013, 695925.
24. El-Menyar, A.A. Cytokines and myocardial dysfunction: State of the art. J. Card. Fail. 2008, 14, 61–74.
25. Ferketich, A.K.; Ferguson, J.P.; Binkley, P.F. Depressive symptoms and inflammation among heart failure patients. Am. Heart J. 2005, 150, 132–136.
26. Wallin, K.; Solomon, A.; Kåreholt, I.; Tuomilehto, J.; Soininen, H.; Kivipelto, M. Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: A population-based study. J. Alzheimers Dis. 2012, 31, 669–676.
27. McAfoose, J.; Baune, B.T. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 2009, 33, 355–366.
28. Keith, M.E.; Walsh, N.A.; Darling, P.B.; Hanninen, S.A.; Thirugnanam, S.; Leong-Poi, H.; Barr, A.; Sole, M.J. B-vitamin deficiency in hospitalized patients with heart failure. J. Am. Diet. Assoc. 2009, 109, 1406–1410.
29. Zuccoli, G.; Santa Cruz, D.; Bertolini, M.; Rovira, A.; Gallucci, M.; Carollo, C.; Pipitone, N. MR imaging findings in 56 patients with Wernicke encephalopathy: Nonalcoholics may differ from alcoholics. AJNR Am. J. Neuroradiol. 2009, 30, 171–176.
30. Saczynski, J.S.; Beiser, A.; Seshadri, S.; Auerbach, S.; Wolf, P.A.; Au, R. Depressive symptoms and risk of dementia: The Framingham Heart Study. Neurology 2010, 75, 35–41.
31. Sheline, Y.I.; Sanghavi, M.; Mintun, M.A.; Gado, M.H. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J. Neurosci. 1999, 19, 5034–5043.
32. Schiepers, O.J.; Wichers, M.C.; Maes, M. Cytokines and major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 2005, 29, 201–217.
33. Bhagwagar, Z.; Hafizi, S.; Cowen, P.J. Increased salivary cortisol after waking in depression. Psychopharmacology 2005, 182, 54–57.
34. Halvorsen, M.; Høifødt, R.S.; Myrbakk, I.N.; Wang, C.E.; Sundet, K.; Eisemann, M.; Waterloo, K. Cognitive function in unipolar major depression: A comparison of currently depressed, previously depressed, and never depressed individuals. J. Clin. Exp. Neuropsychol. 2012, 34, 782–790.
35. Dagres, N.; Chao, T.F.; Fenelon, G.; Aguinaga, L.; Benhayon, D.; Benjamin, E.J.; Bunch, T.J.; Chen, L.Y.; Chen, S.A.; Darrieux, F.; et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: What is the best practice? Europace 2018, 20, 1399–1421.
36. Merkler, A.E.; Sigurdsson, S.; Eiriksdottir, G.; Safford, M.M.; Phillips, C.L.; Iadecola, C.; Gudnason, V.; Weinsaft, J.W.; Kamel, H.; Arai, A.E.; et al. Association between unrecognized myocardial infarction and cerebral infarction on magnetic resonance imaging. JAMA Neurol. 2019, 76, 956–961.
37. Lip, G.Y.; Ponikowski, P.; Andreotti, F.; Anker, S.D.; Filippatos, G.; Homma, S.; Morais, J.; Pullicino, P.; Rasmussen, L.H.; Marin, F.; et al. Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. Eur. J. Heart Fail. 2012, 14, 681–695.
38. Aiyer, R.; Novakovic, V.; Barkin, R.L. A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry. Postgrad. Med. 2016, 128, 656–664.
39. Yun, M.; Nie, B.; Wen, W.; Zhu, Z.; Liu, H.; Nie, S.; Lanzenberger, R.; Wei, Y.; Hacker, M.; Shan, B.; et al. Assessment of cerebral glucose metabolism in patients with heart failure by 18F-FDG PET/CT imaging. J. Nucl. Cardiol. 2020, 29,

476–488.

40. Alosco, M.L.; Brickman, A.M.; Spitznagel, M.B.; Narkhede, A.; Griffith, E.Y.; Cohen, R.; Sweet, L.H.; Josephson, R.; Hughes, J.; Gunstad, J. Reduced gray matter volume is associated with poorer instrumental activities of daily living performance in heart failure. J. Cardiovasc. Nurs. 2016, 31, 31–41.