Section: Physiology

Systematic Review

COGNITIVE IMPAIRMENT IN HEART FAILURE: A SYSTEMATIC REVIEW

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Abstract

Background: Heart failure (HF) is a common illness that can lead to a number of problems, including mental decline. There may be several pathophysiological routes affecting brain shape and function in the complex link between HF and cognitive impairment. The objective is to conduct a thorough analysis and synthesis of the body of research on the cognitive deficits linked to HF, with an emphasis on known alterations in the brain. **Materials and Methods:** An extensive search was carried out for studies published between January 2000 and April 2024 using the databases PubMed, EMBASE, Cochrane Central, and PsycINFO. Studies with adult HF patients who described results pertaining to cognitive impairment and related alterations in the brain were included. A qualitative synthesis of the results was carried out, and the included studies' quality was evaluated with the use of the proper instruments. **Result:** Numerous research were included in the review, all of which pointed to abnormalities in cerebral blood flow and considerable brain shrinkage, especially in the medial temporal lobe and hippocampal regions, as major contributors to the cognitive deterioration linked to hippocampal failure. Further information about plausible causes, including cerebral venous congestion and neuroinflammation, was obtained from observations made on animal models. Nevertheless, there was a great deal of methodological and result variability among the research, which made it difficult to draw broad conclusions. **Conclusion:** Multiple brain-related alterations influence cognitive impairment in HF patients, highlighting the necessity for comprehensive management techniques that take both cardiac and cognitive health into account. To investigate causation and the effects of certain treatments on cognitive outcomes, future research should concentrate on interventional and longitudinal studies.

INTRODUCTION

A complicated clinical illness known as heart failure (HF) is brought on by the heart's incapacity to pump blood effectively enough to meet the body's demands. It affects about 26 million individuals worldwide, and as the population ages and cardiovascular disease survival rates increase, its incidence is rising.[1] Among the numerous HF-related consequences, cognitive impairment stands out as a key comorbidity that has a substantial impact on patient treatment, quality of life, and healthcare utilization.[2]

Because cognitive impairment in HF patients is common and has a significant impact, but is frequently ignored, there is increased interest in this area. The cognitive deficits associated with HF can vary in severity, ranging from moderate impairments in executive function and attention to more marked reductions typical of dementia and mild cognitive impairment.[3] In addition to being a result of HF, these cognitive problems are also thought to be directly impacted by changes in the brain brought on by the illness itself, including decreased cerebral blood flow, neuroinflammation, and brain atrophy.[4] Developing tailored therapies requires an understanding of the pathophysiological pathways that connect heart failure (HF) to cognitive impairment. Previous research has shown that the brain actively contributes to the illness process and is not merely a passive recipient of circulatory abnormalities. Alterations in brain structure and function have a direct impact on cognitive results.[5] For example, HF patients have been found to have decreased cerebral perfusion and higher white matter hyperintensities, which are linked to impaired cognitive performance.[6]

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This systematic review attempts to summarize the available data on the cognitive deficits seen in HF patients, with a particular emphasis on the underlying brain alterations reported by recent research, in light of the importance of these discoveries. To gain a better understanding of the extent and significance of cognitive deficiencies in this population, we investigate multiple aspects of this problem, such as structural brain changes, changes in cerebral blood flow, and other associated neurophysiological changes. This thorough analysis aims to draw attention to the crucial connections between neurocognitive performance and cardiovascular health, supporting an integrated treatment strategy that takes into account the patients' heart and brain health.

MATERIALS AND METHODS

Study Design: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] The aim of the study was to assemble and integrate data pertaining to the cognitive deficits linked to heart failure, with a specific emphasis on the alterations in the brain reported in scholarly works.

Data Sources and Searches: Several electronic databases, including PsycINFO, EMBASE, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL), were used to conduct a thorough search. The search approach was devised by combining MeSH terms with free text terms associated with "cerebral blood flow," "heart failure," "cognitive impairment," "brain atrophy," and "white matter hyperintensities." Only English-language articles released between January 2000 and April 2024 were included in the search.

Eligibility Criteria

Studies that fulfilled the following requirements were included: The empirical research articles on cognitive impairment in adult patients with heart failure that has been clinically identified

Research that used established diagnostic techniques to produce precise results about modifications to the brain, such as changes in cerebral blood flow, structural brain changes, and other neurophysiological data.

Studies that were both observational and interventional were taken into account.

Studies that were case reports, conference papers, editorials, or expert comments were not accepted.

Did not offer precise results regarding brain alterations or cognitive impairment.

Concentrated on congenital heart disease-related heart failure.

Study Selection: Titles and abstracts served as the initial screening criteria for all identified documents. After that, the whole texts of any studies that might qualify were obtained and their eligibility was independently determined.

Data Extraction and Quality Assessment: A standardized data extraction form was used to extract the data, which included information about the authors, the year the study was published, the design of the study, the sample size, patient demographics (age, sex), the type of heart failure, the diagnostic techniques for both heart failure and cognitive impairment, the primary outcomes linked to cognitive impairment, and any observed brain changes.

The Cochrane Collaboration's tool for evaluating the risk of bias in randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies were used to evaluate the quality of the included research. Selection bias, performance bias, detection bias, attrition bias, and reporting bias were among the important domains that were evaluated.

Data Synthesis and Analysis: Owing to the anticipated variation in research approaches and results, a qualitative synthesis was carried out. The data were arranged according to the kind of cognitive impairment and related alterations in the brain. Subgroup analyses were conducted, if feasible, according to the diagnostic techniques employed, the degree of cognitive impairment, and the type of heart failure (HFpEF vs. HFrEF).

RESULTS

Heart failure (HF) and cognitive decline were found to be significantly correlated across a number of areas in this systematic evaluation of heart failure-related cognitive impairment. We compiled data from several research that examined the effects of heart failure-related brain alterations on cognitive processes.

Patients with heart failure showed substantial local and total brain shrinkage in the parahippocampal gyrus, according to Meguro et al. Using a 1.5 T scanner and a voxel-based particular regional analysis approach for Alzheimer's disease, Magnetic Resonance Imaging (MRI) revealed that this atrophy was considerably higher in HF patients compared to controls.[8]

According to Frey et al., patients with heart failure (HF) have specific abnormalities in verbal memory and attention. These deficiencies are linked to atrophy of the medial temporal lobe, which was detected using a 3-T MRI scanner. Patients with diagnoses in accordance with the European Society of Cardiology's guidelines for chronic heart failure had a higher frequency of these structural brain alterations.[9]

Transcranial Doppler (TCD) ultrasonography was used by Alosco et al. to present the results of a cross-sectional study that showed lower global cognitive status and higher white matter hyperintensities (WMH) in heart failure patients. These findings were linked to decreased cerebral perfusion of the middle cerebral artery.[10] Reduced cerebral blood flow was also found to be a predictor of poorer attention,

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executive function, and memory over the course of a year in another study conducted by Alosco et al.[11]

The frontal, parietal, and occipital cortices, as well as the thalamus, hippocampus, and cerebellar portions of the brain, all showed decreased cerebral blood flow, according to research by Roy et al. A 3-T MRI scanner was used to measure these decreases, which were associated with worse cognitive function in HF patients.[12]

Using a 1.5 T MRI scanner, Suzuki et al. studied patients with chronic heart failure at different stages and discovered a strong correlation between the degree of cognitive impairment in patients with stage C HF and decreased cerebral blood flow in the posterior hippocampus.[13]

The substantial influence of heart failure (HF) on brain perfusion was highlighted by Leeuwis et al.'s finding that HF patients had lower whole-brain and regional cerebral blood flow when compared to patients with carotid occlusive disease and vascular cognitive impairment, as well as healthy controls.[14]

Through the use of animal models, researchers Nyul-Toth et al. and Fulop et al. connected cerebral venous congestion to the development of cerebral microhemorrhages and disruption of the blood-brain barrier, respectively. Their findings suggested underlying molecular pathways that might be applicable to human populations with heart failure.[15,16]

The abnormalities in brain energy metabolism and decreased brain activity that lead to cognitive impairment in HF were further described by Yang et al. and Ichijo et al. Yang et al. used PET imaging and Nissl staining in their research.[17,18]

This review adds credence to the increasing amount of data showing that major alterations in brain structure and function are linked to heart failure, and that these alterations ultimately lead to the cognitive deficiencies seen in this patient population. These results highlight the significance of taking cognitive health into account while managing heart failure and point to possible intervention avenues to lessen cognitive impairment in these patients.

Table 1: Summary of Studies Investigating Cognitive Impairment Due to Brain Changes in Heart Failure Patients.

Authors	Study design	Participants	Diagnosis and type of HF	Cognitive tools	Tools to measure mechanism	Main findings
Meguro et al.	Case control	37	Framingham criteria, mainly non-ischemic, NYHA Class II, EF 46.1%	MMSE	1.5 T MRI, Voxel-based analysis	Significant brain atrophy in parahippocampal gyrus in HF patients
Frey et al.	Case control	432	ESC guidelines, chronic HF, mainly ischemic, EF <35-45%, NYHA I-III	Neuropsychological tests, MMSE	3-T MRI	Deficits in attention and verbal memory; medial temporal lobe atrophy in HF patients
Alosco et al.	Cross sectional	69	NYHA, chronic HF, EF 42.39%, NYHA II & III	MMSE, AMNART	1.5 T MRI, TCD ultrasonography	Greater white matter hyperintensities and reduced cerebral perfusion associated with worse cognitive status
Alosco et al.	Cross sectional	100	NYHA, chronic HF, EF 40.6% HFrEF/59.4% HFpEF, NYHA II & III	Neuropsychological tests, MMSE	TCD ultrasonography	Reduced cerebral blood flow linked to decreased cognitive functions over 1 year
Roy et al.	Cross sectional	48	NYHA, 100% HFrEF, NYHA II & III, mainly non-ischemic	MoCA	3-T MRI	Reduced cerebral blood flow in multiple brain regions, associated with poorer cognitive function
Suzuki et al.	Cross sectional	80	ESC/ACC/AHA guidelines, chronic HF, EF 43.1% for Stage C, ischemic and non-ischemic	MMSE, Wechsler Memory Scale	1.5 T MRI	Lower CBF in posterior hippocampus in Stage C HF linked to cognitive impairment
Leeuwis et al.	Cohort	439	ESC guidelines, mixed patient group including HF and others	Neuropsychological tests including VAT, RAVLT, TMT	3 T MRI	Reduced whole-brain and regional CBF in HF patients compared to others
Nyul-Toth et al.	Case control	9 mice	Animal model	Daily neurological examination	Histological analysis, Image J software	Central venous congestion exacerbates genesis of cerebral microhaemorrhages

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Fulop et al.	Case control	40 mice	Animal modesl	Neurological examination, Raial Arm Water Maze	Immunofluorescent labelling, confocal microscopy	BBB disruption and neuroinflammation in mouse model of cerebral venous congestion
Yang et al.	Case control	39 rats	Animal model	Morris water maze	PET imaging, Nissl staining, Transmission Electron Microscopy	Disorders in brain energy metabolism and neuronal structure contribute to cognitive impairment in HF
Ichijo et al.	Cross sectional	63	ESC/ACC/AHA guidelines, mainly Non ischaemic, HF varies, NYHA I&II.	MMSE, Verbal Fluency test	Near-Infrared spectroscopy	Reduced brain activity and cognitive function in HF patients compared to controls
Ferro et al.	Cohort	278	ESC guidleines, Wide range of EF	Neuropsychological tests, MMSE	3-T MRI	No link between cerebral cortical microinfarcts and cognitive impairment in HF
Toledo et al.	Case control	12 rats	Animal model	MWM, Memory Flexibility test	Immunoblots	Altered Wnt/β-catenin pathway in hippocampus linked to cognitive impairment in HF rats
Feng et al.	Case control	Various datsets	NA	NA	Functional Enrichment Analysis, GSEA software	hsa-miR-933/RELB/CCL21 regulatory axis implicated in HF and cognitive disorders

DISCUSSION

The results of numerous research that have looked into the connection between heart failure (HF) and cognitive impairment are compiled and discussed in this systematic review, which focuses on the corresponding alterations in the brain. The data shows that HF affects the structure and function of the brain in multiple important ways, which may result in cognitive deficiencies.

Brain Atrophy and Structural Changes: Multiple studies have consistently found that patients with HF have a significant amount of brain atrophy, especially in areas important for memory and executive function. Research such as that conducted by Meguro et al. and Frey et al. have shown significant atrophy in the medial temporal lobe and parahippocampal gyrus, respectively.[2,19] These regions are well-known to be crucial for memory processing, and their impairment is consistent with the symptoms of memory impairment that HF patients frequently experience. Advanced imaging methods, such 3-T and 1.5 T MRI, offer strong proof of these structural alterations, highlighting the necessity of frequent neuroimaging in HF patients exhibiting cognitive symptoms.

Cerebral Blood Flow and White Matter Changes: According to the results of Alosco et al. and others, changes in cerebral blood flow (CBF) and white matter hyperintensities (WMH) are especially significant. Microvascular brain injury is indicated by decreased CBF and increased WMH, which is probably made worse by the HF-related reduced cardiac output. Studies demonstrating a connection between lower CBF in different brain regions and subpar cognitive function provide credence to this vascular concept. These results imply that vascular health is important for HF patients' cognitive function and could be a target for therapeutic approaches.[10]

Mechanistic Insights from Animal Studies: Animal research, like that done by Nyul-Toth et al. and Fulop et al., is included because it offers important mechanistic insights into how HF may cause cognitive impairment. According to these research, the pathophysiology of cognitive decline may involve disturbance of the blood-brain barrier and cerebral venous congestion. Prior to human trials, these animal models are essential for testing prospective therapies and comprehending the underlying biological processes.[16,20]

The evidence suggests that there are multiple implications for clinical practice here. In the first place, there is an undeniable requirement for cognitive screening in patients with heart failure, particularly those who have chronic or severe heart failure. This is because the early discovery of cognitive impairment can lead to improved management and outcomes. Furthermore, the significance of controlling cardiovascular health in order to prevent or minimize cognitive loss is highlighted by these findings.

Studies that follow participants over time are required for future study in order to have a better understanding of the causal linkages and the potential reversibility of cognitive impairment in heart failure. In addition, intervention studies that concentrate on

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both cognitive and cardiac rehabilitation have the potential to offer insights into successful strategies that might be utilized to improve cognitive results in this population.

CONCLUSION

The examined research collectively highlight the intricate relationship between heart failure and brain function. Given the persistent links between HF and modifications to the structure and function of the brain, managing cognitive impairment in patients with HF should be a key priority. Acknowledging and treating cognitive deficits in heart failure patients not only enhances quality of life but also aids in more efficient heart failure management because cognitive function is essential for both drug adherence and self-care practices. In order to optimize outcomes for patients with heart failure, this data synthesis emphasizes the necessity of integrated treatment approaches that address both the neurological and cardiovascular facets of health, possibly requiring multidisciplinary teams.

Future perspectives

Although thorough, there are a few limitations to this systematic study that should be noted: There are substantial differences among the included studies in terms of design, patient demographics, heart failure and cognitive impairment assessment methodologies, and imaging modalities utilized to measure alterations in the brain. It is difficult to draw broad generalizations from this variation across various contexts and demographics.

The majority of the research that make up this review are observational. These studies can point to correlations, but they cannot prove a link between heart failure and cognitive decline. Confounding variables impacting the associations that have been detected cannot be ruled out.

Studies with definitive or favorable results are more likely to be published than those with negative or inconclusive outcomes, suggesting the possibility of publication bias. This bias may have impacted the studies that were eligible for inclusion, distorting our collective knowledge of the connection between heart failure and cognitive decline.

The impact of therapies intended to enhance heart function on cognitive outcomes has not been extensively studied. There is still a lack of research in the literature regarding how heart failure treatment affects cognitive decline.

Older persons, who are generally more susceptible to heart failure and cognitive decline, are the subject of the majority of research. Younger populations or those with early-stage heart failure might not be immediately affected by the findings.

In light of the aforementioned limitations, the following avenues for future research are recommended to improve our comprehension and treatment of heart failure patients' cognitive impairment:

- To evaluate how patients with heart failure's cognitive performance varies over time, longitudinal studies should be given priority in future research. To prove causation and investigate potential therapeutic advantages, interventional trials evaluating the impact of particular heart failure medications on cognitive results are also required.
- It is possible to lessen study heterogeneity by standardizing the techniques for identifying and gauging the severity of heart failure and cognitive impairment. More trustworthy comparisons and data synthesis would be made easier by this standardization.
- Learning more about how heart failure affects cognitive impairment in different populations will be made easier by including research on a wider range of demographic groupings, such as younger patients and those from different ethnic backgrounds.
- To clarify the molecular processes that connect heart failure to cognitive decline, more investigation is required. Research examining cerebral blood flow, neuroinflammatory pathways, and metabolic alterations may yield important insights.
- The creation and evaluation of integrated care models that target cognitive function and cardiovascular health may enhance the prognosis of heart failure patients. Ideally, these models would involve multidisciplinary teams made up of rehabilitation specialists, neurologists, cardiologists, and psychologists.
- Research can advance toward more potent methods for anticipating, preventing, and treating cognitive impairment in patients with heart failure by addressing these constraints and concentrating on the proposed future perspectives. This will ultimately improve these patients' quality of life and therapeutic outcomes.

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