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Review · **Open Access** ·

Cognitive impairment in heart failure patients

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Abstract

Cognitive damage in heart failure (HF) involves different domains thus interfering with the ability for single patient to self-care and to cope with treatment regimens, modifying symptoms and health behaviours. Many cerebral and functional changes were detected in brain imaging, involving areas of both grey and white matter deputed to cognition. Although various instruments are available to explore cognition, no consensus was obtained on better tools to be used in HF population. Reduction in cerebral blood flow, decreased cardiac output, alterations of cerebrovascular reactivity and modification of blood pressure levels are the main features involved in the etiopathogenetic mechanisms of cognitive deficit. Several cardiac variables, laboratory parameters, demographic and clinical elements were studied for their possible relation with cognition and should be properly evaluated to define patients at increased risk of impairment. The present review gathers available data pointing out assured information and discussing possible areas of research development.

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1 Introduction

Heart failure (HF) is a major health problem in developed countries that affects approximately 1%–2% of the adult population with a rising prevalence to 6%–10% in people over 65 years and to ≥ 10% among persons 70 years of age or older.[1] HF is associated to increased mortality and morbidity, frequent hospital admissions and reduced quality of life and functional status.

As HF incidence increases according with aging, also geriatric conditions must be taken in account in the evaluation of cognitive impairment in HF population. Cognitive impairment is one of the most common co-occurring chronic conditions among elderly people with HF. Its incidence varies widely from 25% to about 70%–80% depending on the characteristics of the sample and of the disease, instruments used to assess cognition and study design.[2–7]

Several cerebral areas and different cognitive domains can be involved in patients with HF developing deficits in cognition. Furthermore, different pathophysiological processes like cerebral hypoperfusion due to alteration of cardiac output or cerebrovascular reactivity, arterial hypotension, production of proinflammatory cytokines or depressed mood are called into question in the determination of cognitive impairment.

Presence of cognitive impairment may interfere with self-care that is the active decision-making process aimed to maintain health, deal with incident disease and operate changes in personal behaviours or specific treatment if necessitated by worsening symptoms. Deficits in cognition may be related also to increased mortality, higher rates of hospital admission and functional impairment. Some studies focused on the role of pharmacological and non-pharmacological interventions in reversing cognitive impairment even if no absolute consensus was reached.

The present review gathers available evidence on epidemiology of cognitive impairment in patients with HF, on brain and cognitive areas affected, on the tools to be used to assess cognition. Moreover, pathophysiological processes of cognitive impairment and finally the impact of such deficit in HF population were discussed.

2 Cognition: definition, single domains and testing

Cognition is a superior cortical function involving multiple brain processes that allows an individual to perceive information, learn and remember specific knowledge and use them for problem solving and plan actions in the challenges of daily life. Cognitive functioning covers different specific aspects known as cognitive domains that include

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memory, attention/working memory, executive function, psychomotor speed, language/speech and visuospatial ability.

Various neuropsychological instruments are available to evaluate and measure different cognitive domains. Table 1 summarizes principal measures as well as the tasks involved for each cognitive domain.

2.1 Memory

Memory is a basic cognitive function that involves the registration, storage and retrieval of information. According to a temporal point of view, memory can be divided into an immediate memory (information stored for only a few minutes) and delayed memory (information stored for a longer period, at least 15 min). Cerebral regions related to memory are the medial temporal lobe area (such as the hippocampal region, the enthorinal, peririnhal and parahippocampal cortex), the diencephalic area (including thalamic nuclei and mammillary bodies) and prefrontal areas.

Table 1. Cognitive domains, neuropsychological tests used to assess them and tasks involved in single examination.

Cognitive domain	Neuropsychological test	Task or tasks involved
Episodic memory	Verbal learning tests	Listen to lists of unrelated words and repeat as many words as one can remember immediately and after some time has elapsed
Semantic memory	Category fluency tests	List as many elements as possible in a given category (e.g., animals, vegetables)
	Picture-naming test	Tell the examiner the name of each picture
	Word-picture matching test	Match word and picture in given categories
Attention	Trail making test A	Connect a series of numbers
	Attentional matrices	Identifying a missing part of a series
Working memory	Digit span backwards	Repeat a series of numbers in the reverse order they were given by the examiner
	Corsi's block tapping test	Tapping on a series of blocks in the order they are tapped by the examiner
	Short category test	State the principles that relate a series of figures and lines in a given order
Psychomotor speed	Digit symbol substitution test	Write down corresponding symbol beneath each digit according to a combination of symbols and digits given by the examiner
	Trail making test A	Connect a series of numbers
	Trail making test B	Connect a series of numbers alternating with letters (1 to A, A to 2, 2 to B and so on)
	Stroop color word test	Read a list of color names, say the name of the color of some spots, sat the name of the color in which some names are printed
Executive function	Stroop color word test	Read a list of color names, say the name of the color of some spots, sat the name of the color in which some names are printed
	Trail making test B	Connect a series of numbers alternating with letters (1 to A, A to 2, 2 to B and so on)
	Raven's progressive matrices	In each form of increasing difficult, complete a series of figures with the missing one
	Letter fluency	List in 1 min as many words as possible that begin with a given letter
	Wisconsin card sorting test	Match different cards according to specific criteria, not known by the subject, and determine the criteria depending on specific examiner feedback
Language	Boston naming Test	Tell the examiner the name of 60 different picture
	Benton controlled oral word association test	List as many words beginning with letters "F", "A" and "S" during three 1-min trials
	Token test	Perform verbal orders acting on various tokens
	Semantic fluency	List as many elements as possible in a given category
Visuospatial/ construction	Benton facial recognition test	Find target face in a series of six
	Judgement of line orientation test	Indicate which two lines from an array are in the same position and in the same direction as the two lines given to compare
	Block design test	Arrange blocks with different colored sides according to a given pattern
	Clock drawing test	Draw numbers in a given circle to make the circle look like the face of a clock and then draw the hands of the clock to read a precise hour

2.2 Attention and working memory

Attention is the skill to focus selectively on a stimulus and it's essential also for performance in different cognitive tasks. Cerebral areas involved in attention are many cortical and subcortical structures such as the frontal and parietal association cortex, basal ganglia, anterior cingulated cortex and the cerebellum. Working memory is the ability to actively hold multiple image and verbal information in mind, integrate and manipulate them and then retrieve them if necessary in a short time. The prefrontal cortex is crucial for the control of working memory but also parietal cortex, anterior cingulate, basal ganglia and cerebellar regions participate.

2.3 Executive functions

Executive function comprehends a various range of different cognitive processes, including working memory, verbal reasoning, problem solving, task flexibility, planning and execution. The areas primarily involved in the control of executive functions are the frontal and prefrontal cortex but also other cortical and subcortical regions are recognized to enter a role.

2.4 Language

In this cognitive domain, we comprehend not only verbal expression but also reading and writing. The two main cerebral regions dedicated to language are the Broca's area, in the frontal lobe, a motor area connected to speech production and the Wernicke's area, in the superior temporal gyrus, related to language perception.

2.5 Visuospatial and constructional function

Visuospatial function allows a correct identification of objects in the surrounding environment and of their spatial relation and, consequently, a proper use of them. Impairment in visuospatial function limits topographical orientation, localization of points in space and judgement of direction and distance, cause visual object agnosia with difficulty to cope with facial or color recognition and alter visuoconstructive abilities (graphomotor performance). Several areas of parietal lobes, lateral prefrontal cortex, occipital cortex, medial and inferior temporal cortex, basal ganglia and white matter regions form a complex network that control visuospatial function.

3 Cognitive impairment in HF patients: epidemiology

Incidence of cognitive damage in HF patients varies widely depending on the studied population (outpatients or inpatients, age, sample sizes), features of disease (subtypes or severity of disease, diagnostic criteria), the neuropsychological tests used to define cognitive impairment and the different study designs.

In a cross-sectional descriptive study on forty-four HF outpatients ≥ 65 years, 52% of whom in New York Heart Association (NYHA) class III or IV, mean age 76 years and mean left ventricular ejection fraction (LVEF) 37%, cognitive impairment, defined as a score on montreal cognitive assessment (MOCA) test < 26, was detected in > 70% of the sample.[2] Similar results were obtained in a randomized controlled trial aimed to assess the effects of a tailored intervention on self care in 176 patients hospitalized for acute heart failure: 74% of them screened positive for mild cognitive impairment (MCI) defined as score on MOCA test of 17–25, 9% scored < 17 points and 17% proved to have normal cognition.[3] In a group of twenty patients with previous myocardial infarction, symptoms of HF in NYHA III-IV and a LVEF < 40%, a moderate or severe episodic long-term memory impairment, evaluated with the Rivermead Behavioural memory test, in 25% of patients emerged.[4] The mini mental state examination (MMSE) revealed cognitive impairment in 54% in a group of fifty patients (mean age: 67.3 years) who were admitted for acute decompensation and without a history of myocardial infarction/stroke during the previous 6 months and with LVEF lower than 45%.[5] In a longitudinal study on 140 outpatients, 35.7% females, mean age 68.9 years with no previous history of neurological or psychiatric disease, 62% of the sample demonstrated some degree of cognitive impairment assessed through different tools.[6] Finally, the systematic review of Vogels compared the risk of cognitive impairment in a pooled sample of 2937 HF patients to 14,848 controls (healthy subjects or with other cardiovascular disease) and underlined as cognitive impairment was 1.62 times greater in HF group.[7]

4 Cognitive impairment in HF patients: cognitive areas and cerebral regions involved

Cognitive damage in HF involves different domains,[8,9] in particular HF adversely affects learning memory and delay recall, attention, executive function, psychomotor speed and working memory. Language and visuospatial ability are less affected in patients with HF even if very few studies assessed them in these patients.

In a cross-sectional study involving 249 patients with chronic systolic HF compared to age and education-matched 63 healthy people and 102 participants with major chro-

nic disease other than HF, HF patients showed worse score in memory ($P < 0.0001$), psychomotor speed ($P < 0.0001$) and executive functions ($P < 0.0002$) assessed through validated tools (Hopkins verbal learning test for memory, digit symbol and trail making test A (TMT-A) for psychomotor speed and TMT-B and controlled oral word association (COWA) for executive function).[10] In the systematic review by Vogels pooled analysis showed diminished performance in memory, psychomotor speed/attention (assessed with TMT-A) and global cognition (tested with MMSE) when comparing HF patients to healthy subjects.[7] Also in 577 hospitalized patients with acute HF, mean age 71 years, females about 50% of the sample, 33% showed memory problems, 40% slower processing speed and 56% impairment in executive tasks.[11]

A global deterioration test as MOCA was frequently used to assess cognition as in the cross-sectional study by Harkness, *et al*.[2] that analysed forty-four outpatients ≥ 65 years with HF: cognitive domains showing significant differences ($P < 0.01$) in subscores were short-term memory, visuospatial ability, executive function and language. Athilingham, *et al*.[12] performed MOCA test in a group of 90 community-dwelling adults, 76.6% of whom with systolic HF: mean MOCA score was lower in the systolic group than in diastolic patients with statistically significant difference (22.9 ± 2.31 *vs*. 24.8 ± 2.76, $P = 0.03$); visuospatial/executive function and attention subtests score were significantly lower in patients with systolic dysfunction ($P = 0.026$ and $P = 0.049$, respectively) while abstraction and delayed recall were more compromised in patients with diastolic HF ($P = 0.014$ and $P = 0.048$, respectively).

Did cognitive function decline over time in HF populations tested regularly? In a cohort of 702 community-dwelling people, 80 years of age and older (mean age at baseline 83.5 years) who were tested five times in a period of eleven years through selected tools assessing processing speed (symbol digit test, perceptual speed), visuospatial abilities (block design test), short-term (digit span), episodic (prose recall, picture memory) and semantic memory (verbal meaning): 13% of the sample presented HF, spatial abilities and episodic memory were the most compromised tasks in patients with HF compared to other people and measures of episodic memory declined more over time compared to other cognitive domains.[13]

Trying to summarize the interesting data regarding the cognitive areas affected in HF patients, most of the studies on the relation between memory tasks and HF reveal deficits both on immediate and delayed recall, while semantic memory is less compromised.[2,7,9–11,13] Attention and psychomotor speed seemed to be impaired in most studies,[5,7,9,10,12] but not in all ones.[2] Data on working memory are instead more conflicting.[4,5] Measurements of the executive function were impaired in most of the available studies.[2,9,10]

Neuroanatomical damages may concern both grey and white matter and they can be studied through magnetic resonance imaging (MRI) with several methods such as T1 or T2-weighted images, voxel-based morphometry, diffusion technique, functional MRI.

In 1991, Schmidt, *et al*.[14] found a higher rate of cerebral infarcts (20% *vs*. 0%, $P < 0.05$) and cortical (50% *vs*. 5%, $P < 0.01$) and ventricular (55% *vs*. 15%, $P < 0.02$) atrophy at brain MRI in twenty patients with idiopathic dilated cardiomyopathy and no neurological symptoms compared to twenty age-matched controls determining a worse cognitive performance. Woo, *et al*.[15] analysed changes in regional grey matter volumes of areas deputed to specific role in cognition (e.g., parahippocampal gyrus, frontal cortex), CO_2 regulation (e.g., cerebellar nuclei) and sympathetic and parasympathetic control (e.g., insula) in nine patients with HF NYHA class III-IV patients and 27 healthy controls obtaining a significant grey matter loss in both left and right insular cortex (larger in the right side) in HF patients. Both cerebellar cortex and deep cerebellar nuclei involved in the autonomic and respiratory control, were affected thus compromising response to CO_2 and increasing the risk to develop a Cheyne-Stokes breathing pattern. The authors stated that ischemia processes with consequent reduction in perfusion, impaired effectiveness of neural autoregulation and diminished cerebral blood flow may play a role in the origin of grey matter loss and such damage can cause cognitive impairment, autonomic disturbances and sleep-disordered breathing.

Kumar, *et al*.,[16] studied the mamillary body volumes and cross-sectional fornix areas, which are involved in spatial and working memory processes, using high-resolution T1-weighted MRI in chronic HF patents, revealing reduced dimensions with hypoxic/ischemic processes and thiamine deficiency. High-resolution T1-weighted MRI scans detected significantly lower left ($P = 0.014$) and right ($P = 0.014$) global putamen volumes, particularly in bilateral rostral, mid-dorsal and medial caudal regions in 16 HF patients (mean age: 54.1 years, 75% male) compared to 32 controls (mean age: 52.4 years, 75% male); however, no neuropsychological evaluation was taken into account.[17] Putamen is a basal ganglia structure playing a significant role in motor function, motivation, emotional regulation, language processing and memory function, which are often impaired in HF patients; hypoxic or ischemic processes are called into question in determining such damages.

Cerebral metabolic changes can be detected in patients with HF. In fifty adult patients with advanced clinically stable HF (LVEF ≤ 35%, mean age 41.8 years), and in twenty healthy controls proton magnetic resonance spectroscopy was obtained by specific regions of occipital grey matter and parietal white matter calculating absolute levels of four metabolites (*N*-acetylaspartate, creatine, choline, and myo-inositol): in parietal region creatine levels decreased more in HF patients than in controls, while in occipital region all metabolites reached lower levels engendering the hypothesis that distinct brain areas show a different susceptibility to chronic hypoperfusion; creatine levels significantly correlated with peak oxygen consumption ($P < 0.01$), half-recovery time, NYHA functional class ($P < 0.05$) both in occipital and parietal regions, with duration of symptoms and LVEF ($P = 0.05$) in parietal and with serum sodium concentration ($P < 0.01$) in occipital area and significantly improved in both brain regions after successful heart transplantation occurred in ten patients.[18] Finally, in a murine model of congestive HF, the expression of molecules involved in β-amyloid metabolism, apoptosis and inflammation was impaired and cognitive behaviour was altered three months after induction of cardiac failure thus providing the hypothesis that congestive HF increases the risk of cognitive impairment and changes in Alzheimer disease related protein markers.[19]

5 Cognitive impairment in heart failure: pathophysiology

Reduction in cerebral blood flow (CBF) is often referred as a determinant in brain changes affecting people with HF. In 17 HF patients, NYHA class II or III compared with 18 elderly healthy volunteers, a reduction of CBF, evaluated with ^{99m}TC-HMPAO single photon emission computed tomography (SPECT) was detected involving in particular the left and right precuneus and cuneus and the right lateral temporoparietal cortex and posterior cingulated gyrus; furthermore, reduction in posterior cortical areas was directly correlated with cognitive deficits measured with the cambridge mental disorders of the elderly examination (CAMDEX).[20]

CBF depends on several variables such as cardiac output, blood pressure and cerebrovascular reactivity; low cardiac output, low systolic blood pressure and impaired autoregulatory mechanisms might impair CBF determining neuroanatomic and neuropsychological changes.[8]

Cerebrovascular reactivity was measured with transcranial Doppler using a hypercapnic gas mixture as a vasodilating agent, demonstrating a significant reduction of blood flow velocity at middle cerebral arteries after carbon dioxide in HF patients compared to all the controls, correlated to the severity of NYHA class and to left ventricular ejection fraction.[21]

Cardiac output is another important determinant of CBF. First studies about systemic hypoperfusion and cognition focused on pre- and post-heart transplantation patients; in small samples of subjects with end-stage HF, candidate to transplantation, a certain degree of impairment in cognitive function, especially memory tasks, was documented and, furthermore, the transplanted patients demonstrated significantly improved cognition.[22,23] These data, though limited by the confounding role of psychological conditions such as anxiety or depression, seemed to confirm the hypothesis that decreased cardiac function can cause chronic hypoperfusion and consequent cerebral damage. To avoid confounding factors, subsequent studies considered patients with a less severe stage of HF disease measuring the cardiac pump function as LVEF or cardiac output (CO).

In 1504 community-dwelling subjects from the Framingham Heart Study (mean age: 61 years), free of clinical dementia or stroke and only 7% of whom suffering from prevalent cardiovascular disease, cardiac index, measured with cardiac MRI, was independently related to neuroimaging markers of preclinical dementia and accelerated brain aging such as total brain volume (positive relation, $P = 0.03$) and lateral ventricular volume (inverse relation, $P = 0.048$) and, in *post-hoc* analysis, low cardiac index (< 2.5 L/min per m^2) was seen to be significantly correlated with poorer performance at TMT-A evaluating psychomotor speed.[24] The authors speculated that decreased cardiac output can lower systemic blood flow thus reducing cerebral perfusion and impairing autoregolatory mechanisms so that affected brain blood flow homeostasis may lead to clinical or subclinical damages by exacerbating microvessel changes or Alzheimer disease neuropathology.

Cognitive evaluation was performed in seventy-two geriatric subjects, mean age 69.1 years (range 56–85 years), with stable cardiovascular disease further divided into two groups according to CO non-invasively measured through transthoracic echocardiogram: in tests of executive function, including sequencing and planning, but not in other cognitive domains such as memory or visuospatial task,[25] patients with lower CO (< 4.0 L/min) seemed to performed worse than the normal CO group (≥ 4.0 L/min). Moreover, arterial hypotension can be coupled with cognitive impairment in older patients with HF. In a large Italian study involving 13,635 patients without clinical cerebrovascular disease or dementia (1583 of whom affected by HF), cognitive impairment was detected in 26% of HF subjects and in

19% of remaining population; systolic blood pressure below 130 mmHg predicted cognitive impairment only in patients with HF and, in multiple logistic regression, any increase of 10 mmHg had a protective effect against cognitive impairment with a OR = 0.78 (95%CI: 0.71– 0.86).[26]

In summary, the research of a correlation between neuroimaging, hemodynamic changes and cognitive function seemed to reach conflicting results. There are clinical experience in which a poorer performance in neuropsychological tests correlated with neuroanatomical or functional cerebral damage;[20] conversely, in 58 patients with HF only medial temporal lobe atrophy correlated with memory ($P < 0.01$), executive functions ($P < 0.01$) and MMSE score ($P < 0.05$) while total and deep white matter hyperintensities only correlated with depression and anxiety scores, but not with cognitive measures.[27]

Recently, obesity and depression of mood were added as additional risk factors for poor cognitive performance in older adults with HF. An interaction between hypoperfusion and obesity was especially recorded for its adverse effect on attention/executive function.[28,29] Depression of mood might play an interactive role in determining changes of cognitive function in patients with HF. Both depression and cognitive impairment proved to be associated with neuroanatomical changes as WMH or brain grey matter reduction in subcortical and cortical regions so that it can be assumed that they are the result of structural change due to HF; furthermore, relevant data to explain the relationship between HF, depression of mood and cognitive impairment seem to derive from studies about neurohormones as cortisol or about pro-inflammatory cytokines (i.e., IL-6, TNF-α, C-reactive protein).[30] The relation between depression (assessed by the Beck Depression Inventory II), cognitive impairment (measured with neuropsychological tests) and cerebral perfusion (through transcranial Doppler) was investigated in a group of 89 patients with HF: depression was associated with impairment in attention/executive function, language and motor function ($P < 0.05$) while global CBF was related with memory performance ($P = 0.04$).[31]

6 Cognitive impairment in HF: related variables

Several experiences focused their attention on cardiac variables, laboratory parameters and demographic and clinical elements that can be related with HF. The results are often conflicting due to different methodologies, variety in the choice of the sample, variable aims of single studies.

The role of left ventricular ejection fraction (LVEF) has been explored by Zuccalà, *et al*.[32] in a small sample of older adults (mean age 76.6 years) with chronic heart failure (NYHA class III, LVEF 44%) obtaining a non-linear positive correlation between LVEF and MMSE global score, being cognitive performance significantly lower in subjects with LVEF ≤ 30%. Other experiences, involving outpatients with known chronic HF (age: 55–77 years), stated a relationship between neuropsychological functioning (measured through different tools such as global tests like MMSE, Repeatable battery for the assessment of neuropsychological status or the cambridge cognition test or specific scales for individual domains) and LVEF.[33–37] In fifty-five patients with HF NYHA class I-III, mean age 55.3 years, predominantly men, LVEF, measured with equilibrium radionuclide ventriculography performed with a multicrystal gamma camera in the left anterior oblique view, was related to subjective cognitive impairment, assessed through Cerebral Insufficiency Self Report Inventory while peak oxygen uptake, obtained by cardiopulmonary exercise testing, was correlated with objective cognitive impairment.[34] In the study by Festa, *et al*.[35] that analyzed 207 patients with HF (range of age 17–72 years), the effect of ejection fraction on memory varied with age: in fact subjects younger than 63 years showed no variation in memory function across LVEF levels, while people older than 63 years presented a significant decrease in memory performance (especially verbal delayed recall and recognition) when LVEF was lower than 30% ($P < 0.02$). In a larger study on 1114 persons of the Framingham Heart Study offspring Cohort,[36] with not known diagnosis of HF and no history of clinical stroke or dementia (mean age 67 years, more than half female), LVEF as a continuous variable was not related to any brain aging features, such as pre-clinical brain MRI changes or deficits in neuropsychological tests linked to vascular or degenerative cognitive impairment. However, when LVEF levels were divided into quintiles, the lowest quintile (Q1), with an ejection fraction < 62%, showed a poorer performance of delayed memory. Finally, also in the absence of neuropsychological evaluation, a modest dose response relationship between cerebral grey matter volume and LVEF ($r = 0.51$, $P = 0.06$), such that the lesser the LVEF, the greater the grey matter volume loss, but not between white matter volume and ejection fraction, is recorded in a small sample of patients with transient ischemic attack undergoing an MRI and a transthoracic echocardiogram.[37]

In other experiences, considering outpatients with chronic HF or hospitalized patients for exacerbation of HF (mean age: 55–70 years and a variable value of LVEF between 25.7% and 63%), the hypothesis of a correlation between ejection fraction and cognition, assessed through global tests or specific scales was not verified.[38,39] The

large population of the Hoorn Study was studied with echocardiography to evaluate systolic and diastolic function at baseline and at follow-up (after a mean period of 5.9 years), while cognitive tests for processing speed, memory, attention and executive functioning were administered at follow-up.[39] In a standardized regression model, after adjustment for age, sex, estimated intelligence quotient, presence of an impaired glucose metabolism or type 2 diabetes and markers of left ventricular function at baseline, no association was found between LVEF at follow-up and any of the assessed cognitive areas ($P > 0.05$).

Blood pressure variations might play an important role in HF both for prognosis and for the risk of cognitive impairment: in fact, according to available data, lower systolic pressure seemed to be related with increased mortality but also with an elevated risk of cognitive deficits due to cerebral hypoperfusion, chronic hypotension and excessive use of antihypertensive drugs [32,40,41] although not all data are in agreement on this aspect. [33,42,43] In a sample of 1075 Italian older adults, 8.2% with congestive heart failure and 23% with a score < 24 at MMSE, systolic blood pressure was negatively related with NYHA classes only in subjects with cognitive impairment ($r = –0.981$, $P < 0.02$). [41]

Regarding diastolic blood pressure, the proof on its influence in the relationship between HF and cognitive impairment are poorer.[44] In a community-based cohort of 1301 individuals ages 75 years or older followed for a period of nine years to examine the presence of dementia or Alzheimer disease, 205 subjects claimed HF at enrollement while 440 developed dementia. Heart failure was linked with an increased risk of dementia (HR: 1.84, 95%CI: 1.35–2.51); antihypertensive drug use lowered the risk of developing cognitive impairment in patients with HF (HR: 0.97, 95%CI: 0.78–1.20) with the tendency to gain a protective role even if non-significant; patients with high systolic blood pressure and HF showed a reduced risk of dementia compared with subjects with HF only but normal blood pressure values (HR: 1.84, 95%CI: 1.19–2.84 *vs*. 2.53, 95%CI: 1.48–4.31). Low diastolic blood pressure seemed to play an additive role in term of developing dementia in individuals with HF and diastolic blood pressure values < 70 mmHg (HR: 3.07, 95%CI: 1.67–5.61 *vs*. 1.55, 95%CI: 1.13–2.13).[44]

Among laboratory tests, B-type natriuretic peptide (BNP) has the most consistent data regarding the relationship with cognitive impairment in a general elderly population,[45,46] in individuals with cardiovascular disease[47] and in patients with HF.[39,48] In a cohort of 464 individuals, mean age 79 years, MMSE was administered at baseline and after a follow-up period of five years: BNP was the only variable connected with decline of MMSE over time and it was associated with new diagnosis of dementia, defined according to diagnostic and statistical manual of mental disorders (DSM)-IV criteria and to guidelines with an OR: 1.53 (95%CI: 1.09–2.16, $P = 0.013$) together with length of education and diagnosis of hypertension that showed a protective influence.[45] In the Rancho Bernardo Study, a population-based study, elevated NT-proBNP values were independently associated with poor cognitive function on MMSE (OR: 2.0, 95%CI: 1.1–3.6, $P = 0.02$) and on measures of psychomotor speed (TMT-B, OR: 1.7, 95%CI: 1.2–2.7, $P = 0.01$), but not with test of semantic memory (category fluency, $P = 0.19$).[46] Also in a group of 56 adults with cardiovascular disease (27% suffering from HF, 34% from myocardial infarction), with a mean age of 70 years, a LVEF 58% and an average BNP of 122 pg/mL, BNP levels predicted Dementia Rating Scale score after adjusting for several demographic and medical confounders.[47] Regarding individuals with HF, in sixty patients hospitalized for exacerbation of HF (mean age 65.5 years, mean LVEF 32.9 and average BNP plasma level 683.3 pg/mL), BNP was related with MMSE ($r = 0.12$, $P = 0.02$) but not with other memory and learning test.[48]

More consistent data linked cognition and functional status assessed by NYHA class or 6 min walking test.[32,34,38,42–45,49,50] More severe degree of HF status, expressed by a NYHA class III-IV was an independent correlate of an impaired performance on at least baseline examination ($P < 0.001$).[45] In fact, in 83 patients hospitalized for HF, exacerbation revealed that NYHA class IV was associated with a MMSE < 24 with an OR = 4.1 (95%CI: 1.0–16.4) in a multivariate model.[49] In eighty elderly outpatients with stable HF, the distance walked at 6 min test and MMSE score were positively associated even after adjustment for demographic features, indexes of disease severity, comorbidities, level of disability and quality of life.[50]

7 The clinical impact of cognitive impairment in HF patients

Impairment of memory, attention, executive function and psychomotor speed can affect the ability of patients with HF to manage their disease, to recognize symptoms of worsening, to make appropriate choices about their health and to adhere to specific, often complex therapeutic regimens.[51]

Self-care is an active decision-making process aimed to maintain health through treatment and advice adherence, management and recognition of symptoms, implementation of changes in the event of worsening and evaluation of cor-

rect personal behaviours. When considered as a neural process, self-care decision making involves the same cerebral areas that are often compromised in subjects with HF such as the prefrontal, frontal and temporal cortex; brain damage alter the ability of perceiving, interpreting and processing information thus impairing self-care.[52]

The self-care heart failure index (SCHFI) was created to assess self-care maintenance, self-care management and self-care self-confidence in people with HF.[53] Self-care maintenance is the ability of performing those behaviours aimed to maintain a stable state such as daily control of weight, take medications according to a given scheme or adhere to a low sodium diet regimen. Self-care management reflects the ability of recognizing changes in steady state, modify behaviours according to changes and to verify the therapeutic effectiveness. Self-care confidence reflects one's confidence in practice self-care. A scale score ≥ 70 is the cut-point to judge adequate self-care. A later version with additional items and standardized scores was developed.[54] In a sample of 93 hospitalized patients with congestive HF, predominantly male, with an average age of 70 years and half of whom in NYHA class III-IV, according to SCHFI, 46% of subjects had an inadequate self-care maintenance, 63% inadequate self-care management and 56% inadequate self-care confidence; compared with subjects with normal cognition, people with mild cognitive impairment, evaluated with MMSE and MOCA test (75% of the sample) had lower self-care management ($P \leq 0.01$) and self-confidence ($P < 0.02$) scores while no significant difference in self-care maintenance was recorded; in multivariate analysis, mild cognitive impairment made the largest contribution in explaining variance in self-care management score ($\beta = -0.25$, $P < 0.01$).[55] The relationship between cognitive impairment and poor self-care, even if evaluated with different assessment tools, was confirmed in further studies.[16,56,57]

Furthermore, the treatment adherence has been obviously influenced by self-care; in fact, in twenty-two elderly HF patients (average age 79 years), 30 days after having been prescribed medications and after having received verbal and written information on therapeutic regimen, only 55% of patients could remember the name of prescribed drugs, 50% were unable to state the exact doses and 64% could not tell when the drugs were to be taken, the rate of non-compliance was elevated.[58] In 251 outpatients with stable HF, cognitive impairment was revealed in 58% of the sample, verbal learning, immediate and delayed memory were the most affected domains; mild cognitive impairment was significantly associated with poor medication adherence measured through pill counts ($P = 0.017$).[59]

The presence of cognitive impairment seemed to be important in determining mortality, hospital admission and functional decline. In 1113 patients admitted for heart failure in 81 Italian hospital, mean age 78 years, in-hospital mortality occurred in 18% of subjects with cognitive impairment (defined as an Hodkinson AMT score < 7) versus 3% of patients with normal cognition ($P < 0.0001$) while 1-year mortality was 27% among patients with cognitive impairment and 15% in other participants ($P < 0.0001$); in multivariate models, cognitive deficit was associated with an almost fivefold increase of mortality (RR: 4.9, 95%CI: 2.9–8.3) also after adjustment for Angiotensin Converting Enzyme Inhibitor (ACEI) use or dosage, therapy with spironolactone, body weight, depression or pulse pressure.[60] Other clinical experiences confirmed these results.[61–63] In 166 stable outpatients with chronic HF and a LVEF < 40%, average age 65.6 years, predominantly men, about half in NYHA class III-IV, 1-year all-cause mortality was 13% and, in logistic regression analyses, poorer global cognitive score assessed by MMSE, working memory, memory, psychomotor speed and executive function were significant predictors of mortality.[63] Assessment and documentation of cognitive impairment seemed to be important to improve patient care. A group of 282 patients hospitalized for HF, average age 80 years, more than half of the sample female, was studied in search of cognitive impairment through MMSE and physician documentation of cognitive impairment at the time of discharge was recorded: cognitive impairment was present in 46.8% of the subjects and, among those with cognitive deficits, only 22.7% were reported as such by physician; patients without documented cognitive impairment had significantly more 6-month mortality or hospital readmission than patients without cognitive impairment (HR: 1.53, 95%CI: 1.06–2.20, $P = 0.02$) while HR was not significantly higher in patients whose cognitive impairment was correctly reported.[64]

8 Longitudinal changes and therapeutic strategies

Patterns of cognitive changes over the time in patients with cardiovascular disease or HF have been already described. In 172 community-dwelling adults suffering from cardiovascular disease (age 69 years, average LVEF 59%) the temporal course of cognitive decline was studied through MMSE, the Dementia Rating Scale and specific neuropsychological tests administered at baseline and after 12 and 36 months: trajectory of cognitive decline was linear for language and attention-executive function-psychomotor and was curvilinear, with a gradual recovery over time, for visuospatial skills, memory and overall cognition. No dif-

ferences in the trajectories of decline depending on the presence of HF emerged.[65]

Available experiences reported, unfortunately, conflicting data in HF patients. In fact, while in 40 HF patients an improvement on dementia rating scale and especially on subscales of attention, initiation/perseveration and conceptualization was noted over a 12-month follow-up,[66] in a larger series of 702 octogenarians did not.[13] On the contrary, attention/executive function and language showed a stable slope over a period of one year in 115 HF patients, while memory performance improved.[67] No change on digit symbol substitution test was recorded over a period of 6 months in 279 patients with chronic systolic or diastolic HF (76.3% in NYHA class III-IV).[68] A recent systematic review involving 15 studies, published from 1980 and 2012, assessed cognitive function using validated tools at least twice in patients with HF and highlighted a significant decline in cognitive function among HF patients followed for more than one year, but an improvement in cognition in patients undergoing intervention to ameliorate cardiac function such as heart transplantation emerged.[69] No significant correlations were found between changes in HF severity (measured as NYHA class, NT-proBNP levels, fatigue and exercise tolerance) and changes in cognition (severe cognitive impairment defined as a AMT < 7) over a period of 18 months in 611 patients from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure.[70]

Other studies pointed their attention on the effects that pharmacological aids, rehabilitation programs, counselling interventions and education demonstrated in HF patients with cognitive impairment. In a cohort of 1220 hospitalized patients from the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA) study, with a confirmed diagnosis of HF (age 79 years) showed an improvement of cognitive impairment measured with Hodkinson AMT (30% *vs*. 22% of those who did not start taking, $P = 0.001$) confirmed also on multivariate analysis (OR = 1.57, 95%CI: 1.18–2.08). This amelioration seemed to be independent to the baseline or discharge blood pressure levels; furthermore, the benefit proved to be greater for dosages above the median (P for trend = 0.001) and for longer duration of treatment (P for trend = 0.007).[71] In another large sample of patients from the GIFA study, cognitive impairment improved in 25% of 1172 patients with HF receiving digoxin against 16% of subjects who did not take it ($P < 0.0001$), as confirmed by logistic regression analysis after adjusting for several confounders (OR: 1.69, 95%CI: 1.20–2.38); also in patients without HF, cognitive impairment ameliorated in digoxin users ($P < 0.0001$) but the data was not significant in multivariate analysis (OR = 1.13, 95%CI: 0.98–1.31).[72] Beneficial role of pharmacological therapies on cognitive impairment was underlined in fifty patients over 60 years old admitted to hospital for HF NYHA class IV: the introduction of effective treatment according to need for diuretics, ACEI, cardiotonic or antiarrhythmic drugs, improved cognitive performance at 6-month follow-up.[5]

The role of non-surgical device treatment and mechanical circulatory support in the relationship between HF and cognitive impairment has not yet been clearly established according to the very few data available. In a prospective cross-sectional study, memory, processing and motor speed were assessed with validated scales in 252 patients with advanced HF who were potential heart transplant candidates, divided into three groups according to disease severity (outpatients, inpatients requiring inotropic support and inpatients not responding at inotropes infusion likely requiring mechanical cardiac assist devices): the third group showed more severe deficits across all the three domains; in the conclusions, the authors postulated the need to study the role of mechanical supports in arresting cognitive decline also considering the role of cognitive impairment as a contraindication to heart transplant or implantation of devices as destination therapy.[73] A small study of only thirty-six HF patients in NYHA class II-III investigated the effect of enhanced external counterpulsation on cognitive performance showing an improvement in the treatment group (that involved half of the sample) in naming ($P = 0.011$), attention ($P = 0.02$) and executive function ($P = 0.012$) domains.[74] In a recent systematic review on the impact of cardiac resynchronization (CRT) on cognition based on only three studies, CRT demonstrated a non significant overall effect on cognition.[75]

HF patients ICD-implanted for primary prevention, studied in a large single-centre observational study, demonstrated a similar anxiety/depression of mood and cognitive performance in comparison with a non-ICD implanted subjects.[76]

The role of decreased physical activity in the determination of cognitive impairment in HF was investigated in a recent work by Alosco in 65 HF patients physical inactivity and was associated with worse performance in executive function and attention and with a reduced cerebral perfusion within one year of follow-up.[77] In a sample of twenty patients with HF in NYHA class III and LVEF ≤ 35%, mean age 63 years, the majority of whom suffering from ischaemic disease, the participation in an exercise training program of 40 min, twice a week for 18 weeks, compared with five controls, was related to a significant improvement in measures of attention and psychomotor speed (TMT-A, $P =$

0.02, TMT-B, $P = 0.002$, Stroop test, $P = 0.04$), in exercise capacity (6 min walking test, $P < 0.001$, Bruce exercise test, $P < 0.001$) but not in cerebral vasomotor reactivity.[78]

In the relationship between cognitive impairment and HF, some counselling and educational interventions proved their efficacy in older adults. However, obtained data are poorly comparable for the varied organization of such interventions. In a sample of 72 HF outpatients, mean age 76 years, mostly in NYHA class II, a nurse-based program of education conducted with verbal and written information and with computerised and video support, was able to improve patient's knowledge of disease and self-care (assessed through a specific questionnaire) especially in women and among people with cognitive dysfunction (MMSE < 24). In fact, men knew more as compared to female at baseline ($P < 0.01$) but their knowledge did not increase after 6 months of follow-up, female who took part in the intervention program ameliorated compared to those who did not ($P < 0.05$) and subjects with cognitive impairment presented poorer scores on knowledge as compared with persons with MMSE > 24 at baseline ($P < 0.01$) but this difference disappeared after the intervention.[79] Role of patients' education and telemonitoring in improving self-care knowledge and management of disease in older adults with HF was analysed in an integrative review on studies published from 2002 to 2012.[80] On the contrary, a targeted intervention based on cognitive training improved significantly knowledge of the disease (evaluated with the Dutch HF Knowledge Scale) but not self-care (assessed with SCHFI) or readmission rates at 30 days post-discharge in 63 HF patients with mild cognitive impairment at MOCA test compared with 62 controls.[3] Prognostic importance of mild cognitive impairment, even in presence of a specialized education intervention, was further demonstrated in a randomized study that compared 100 HF patients who received a management program by nurses added to usual care and 100 HF controls: cognitively impaired subjects had similar adjusted risk of death and readmission in both groups and also in the intervention group adjusted risk of death was higher in patients with cognitive impairment (RR: 2.33, 95%CI: 1.10–4.92, $P = 0.027$).[81] Finally, cognitive dysfunction should be considered to predict poor participation in an outpatient treatment program: in fact, in 78 patients nonparticipation in such intervention was associated with an MMSE score below the median.[82]

9 Conclusions

In HF patients, the challenges for clinicians will be not only the treatment of cardiac disease itself but also the identification and the management of associated conditions such as cognitive impairment, in order to prevent major complications. Impaired cognition was recorded among older inpatients with acute HF, suggesting that many of them may have experienced delirium, a potential reversible condition, but also among subjects with chronic and stable cardiac disease: it will be important to correctly identify delirium, through validated tools such as the confusion assessment method scale, in hospitalized patients and differentiate it from chronic cognitive impairment or dementia that will further affect patients' outcomes.

Unfortunately, no definitive consensus was, however, achieved about optimal method to indentify changes in cognition in patients with HF. The mechanism of cognitive dysfunction is multifactorial and several cardiac variables, laboratory parameters and demographic and clinical elements are related with cognitive impairment in HF: a correct evaluation of all elements can help identifying a potential profile for mild cognitive impairment risk in patients with HF. Treating HF patients with ACE inhibitors or digoxin seemed to improve neuropsichological functions but all mechanical support or CRT might be useful in ameliorating cognitive impairment through an increase of cardiac output.

Furthermore, more randomized controlled trials might provide additional data to implement strategies to treat or even prevent cognitive decline in elderly patients with HF.

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