Heart failure and cognitive impairment: Challenges and opportunities

George A Heckman
Christopher J Patterson
Catherine Demers
Joye St.Onge
Irene D Turpie
Robert S McKelvie

Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Abstract: As populations age, heart failure (HF) is becoming increasingly common, and in addition to a high burden of morbidity and mortality, HF has an enormous financial impact. Though disproportionately affected by HF, the elderly are less likely to receive recommended therapies, in part because clinical trials of HF therapy have ignored outcomes of importance to this population, including impaired cognitive function (ICF). HF is associated with ICF, manifested primarily as delirium in hospitalized patients, or as mild cognitive impairment or dementia in otherwise stable outpatients. This association is likely the result of shared risk factors, as well as perfusion and rheological abnormalities that occur in patients with HF. Evidence suggests that these abnormalities may be partially reversible with standard HF therapy. The clinical consequences of ICF in HF patients are significant. Clinicians should consider becoming familiar with screening instruments for ICF, including delirium and dementia, in order to identify patients at risk of nonadherence to HF therapy and related adverse consequences. Preliminary evidence suggests that optimal HF therapy in elderly patients may preserve or even improve cognitive function, though the impact on related outcomes remains to be determined.

Keywords: heart failure, mild cognitive impairment, delirium, dementia, elderly

Introduction

The term "cardiogenic dementia" was introduced in 1977 and although the concept was poorly developed at that time, it did identify a link between impaired cognitive function and cardiac disease (Lancet Editorial 1977).

The worldwide burden of cardiovascular disease is substantial and now accounts for approximately 30% of deaths from chronic illness globally (Strong et al 2005). Despite a decline in cardiovascular mortality in developed countries over the last three decades, the burden of heart failure (HF) has risen (Rich 2001; Strong et al 2005). HF develops when cardiac output is insufficient to meet metabolic requirements, usually in the setting of functional or structural cardiac defects (Colluci and Braunwald 2005). HF occurs primarily in patients aged 55 years and over, and its prevalence rises with increasing age (American Heart Association 2002; Bleumink et al 2004; Lee et al 2004). In the prospective cohort Rotterdam study, the prevalence of HF rose from 0.9% in persons aged 55 to 64 years, to 4% in persons aged 65–74 years, 9.7% in persons aged 75–84 years, and 17.4% in persons aged 85 years and over (Bleumink et al 2004). The lifetime risk of developing HF is approximately 20% in men and women who reach the age of 80 years (American Heart Association 2002). The rising prevalence of HF is driven in large part by population aging and the longer survival of adult patients with hypertension and ischemic heart disease (Rich 2001; Strong et al 2005). Between 2001 and 2030, the number of elderly persons over the age of 65 will double, with the greatest proportional increase occurring among octogenarians (Statistics Canada 2001). Over that thirty-year span, the prevalence of HF will likely quadruple (Rich 2001).

Correspondence: George A Heckman
Hamilton General Hospital, 4 East Room 419, 237 Barton Street East, Hamilton, Ontario, Canada, L8L 2X2
Tel +1 905 527 4322 44760
Email heck0@sympatico.ca

Despite advances in management, HF remains associated with substantial mortality, morbidity, and economic impact, particularly among elderly persons (Rich 2001). Elderly HF patients are less likely to receive recommended therapies, in part due to their under-representation in clinical trials, as well as excessive concerns about adverse drug events (Fuat et al 2003). In addition, by focusing on mortality and hospitalization, HF trials have neglected outcomes of relevance to the frail elderly, such as impaired cognitive function (ICF.) There are two predominant syndromes of ICF. Acute and fluctuating ICF, known as delirium, can be precipitated by an underlying medical illness. Delirium may be present in as many as one quarter of elderly patients presenting to hospital and may develop in over 50% during hospitalization, and is therefore most likely to occur in the setting of decompensated HF (Pi-Figueras et al 2004; Inouye 2006). Chronic ICF can be recognized in patients with stable HF and is referred to as dementia if it interferes with a person's independent function. Mild cognitive impairment (MCI) or cognitive impairment but no dementia (CIND) are considered to be borderzone conditions between normality and dementia, if independent function is retained despite documented cognitive deficits (Petersen and O'Brien 2006). Dementia affects approximately 8% of the Canadian population and, as with HF, its prevalence increases with age (Canadian Study on Health and Aging 1994). The prevalence of CIND is approximately twice that of dementia and is associated with higher mortality and a greater likelihood of developing dementia (Tuokko et al 2003). An important distinction between delirium and dementia is that delirium is often reversible if the underlying precipitant is diagnosed and treated (although recovery may be delayed for weeks or even months), while dementia is chronic and usually progressive (Inouye 2006).

As populations age, with the prevalence of both HF and ICF rising with age, the simultaneous occurrence of these two conditions in the same individual will become more frequent. Furthermore, recent studies have identified a strong and possibly causal relationship between HF and ICF. The purpose of this review is to describe the epidemiology of this association, outline potential underlying mechanisms, and discuss the relevance of ICF to the clinical management of HF, primarily focusing on elderly patients.

Epidemiology of impaired cognitive function in older persons with heart failure

An association between HF in older persons and ICF has been described in several recent studies, though few have attempted to distinguish delirium from dementia. In a review of 156 acute HF episodes occurring in a cohort of patients aged 83.2 ± 9.0 years and admitted to convalescence homes in five US states, acute confusion consistent with delirium was a presenting feature in 35.3% of cases (Hutt et al 2003). A high prevalence of ICF has been documented in older patients hospitalized or recently discharged from acute care facilities with HF. In a cross-sectional study of 57 consecutive inpatients with no prior history of dementia, with a mean age of 76.7 years, New York Heart Association (NYHA) class II-III HF symptoms, and mean left ventricular (LV) ejection fraction of 44.7 ± 0.6%, 53% scored below the commonly accepted cut-off for dementia of 24/30 on the Mini Mental State Examination (MMSE) (Folstein et al 1975; Zuccala et al 1997). Lower MMSE scores were associated with more severe LV systolic dysfunction. In a case-control study, the neuropsychological battery of the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG) was administered to 50 consecutive hospitalized patients aged 67.3 ± 0.9 years and with NYHA III-IV HF and (Almeida and Tamai 2001a). Thirty outpatients aged 76.7 ± 1.5 years without HF and with normal LV function served as controls. None of the participants had a prior diagnosis of dementia. Despite their lower age, a greater number of HF patients scored below the threshold for dementia than did controls (74% vs. 30%, $p < 0.001$), and the severity of CI was related to the severity of LV systolic dysfunction. In a study of 515 elderly patients aged 75 ± 7 years, with no prior diagnosis of dementia, who were hospitalized with a primary cardiac diagnosis, cognition was worse among those with HF compared with those without (Trojano et al 2003). The severity of CI correlated with the severity of NYHA symptoms.

The studies described above suggest that ICF is common in older patients with acute HF, and that the severity of cognitive dysfunction is related to the severity of HF symptoms and LV systolic dysfunction. The presence of ICF in so many older patients soon after an episode of acute HF suggests that many may have been experiencing delirium. However, a number of studies of nonhospitalized and presumably stable community-dwelling elderly persons suggest that a history of HF is also associated with a greater risk of chronic ICF or dementia. In a randomly selected sample, 1075 elderly Italians aged 73.9 ± 6.2 years were assessed clinically for a history of HF and ICF as indicated by a MMSE score of less than 24/30 (Cacciatore et al 1998). Those with a history of HF were more likely to have ICF than those without (adjusted OR 1.96; 95% CI 1.07–3.58). The Berlin Aging Study assessed 516 randomly community-dwelling

persons with a mean age of 84.9 ± 8.6 years, 206 of which were followed over four years (Verhaeghen et al 2003). HF was associated with poorer cognition at baseline. The rate of cognitive decline over four years was not significantly different among persons with HF, coronary artery disease, diabetes, or controls without clinical cardiovascular disease, likely reflecting attrition of very elderly persons with severe HF and thus more severe ICF. The Helsinki Aging Study followed a randomly selected sample of 650 community-dwelling seniors stratified at inception into three groups: aged 75 years (239 persons), aged 80 years (212 persons), and aged 85 years (199 persons) (Tilvis et al 2004). A neurologist assessed baseline cognition and cognitive decline was defined either as deterioration of 4 or more points on the MMSE or a worse classification in the Clinical Dementia Rating scale (Morris 1993). A history of HF was associated with cognitive decline and mortality over five years (Relative risk [RR] 1.83, 95% CI 1.02–3.27, and RR 1.76, 95% CI 1.23–2.51, respectively). Cardiovascular disorders did not predict cognitive decline over ten years, though by the end of the study 61% of participants had died. The Kungsholmen project followed 1301 community-dwelling seniors aged 81.5 ± 4.9 years with no prior history of dementia, 205 of whom had a history of HF (Qiu et al 2006). After an average follow-up of 5 years, those with a history of HF were more likely to develop dementia, including Alzheimer's disease (Hazard ratio [HR] 1.84, 95% CI 1.35–2.51, and 1.80, 95% CI 1.25–2.61). In a cross-sectional analysis of baseline cognitive assessments of 3425 elderly persons aged 74.0 ± 5.6 years in the Italian Longitudinal Study, those with a history of HF were more likely to be classified as having CIND (OR 1.73, 95% CI 1.11–2.68) (DiCarlo et al 2000).

The data presented above supports an association between ICF and a history of HF in elderly persons, and suggests that both acute delirium and chronic ICF, including CIND and dementia, can occur in these patients.

Pathophysiology of impaired cognitive function in older patients with heart failure

Shared risk factors

The association between ICF and HF in older persons is multifactorial and includes shared risk factors for both chronic ICF and delirium, as well as factors arising from LV dysfunction per se. Risk factors for HF, such as atherosclerosis, hypertension, and diabetes mellitus, can also lead to chronic ICF (Breteler et al 1994; Skoog et al 1996; Ott et al 1999; Heckman and McKelvie 2000; Roman 2004; Whitmer et al 2005; Cukierman et al 2005). In patients with vascular risk factors, ICF can develop as a result of strokes affecting key cerebral structures (strategic strokes), multiple strokes, or periventricular ischemic leukoencephalopathy (Roman 2003a). Vascular risk factors have also been implicated in the development of Alzheimer's disease (Skoog et al 1996; Hofman et al 1997; Ott et al 1999).

Older patients with decompensated HF are also at risk for delirium. Risk factors that predispose to delirium in hospitalized elderly patients include pre-existing chronic ICF, visual or hearing impairment, dehydration, and illness severity, while precipitants of delirium include the use of urinary catheters and other forms of restraint, malnutrition, the introduction of three or more new medications, and iatrogenic events (Inouye et al 1993; Inouye and Charpentier 1996). The occurrence of one or more of these risk factors is common in older patients hospitalized with HF (Zuccala et al 2005a). Furthermore, medications used to manage HF may also increase the likelihood of delirium. Furosemide and digoxin have measurable anticholinergic activity, and an elevated anticholinergic burden from prescribed medications has been associated with postoperative delirium (Tune et al 1993; Tune 2001). Digoxin can cause delirium at serum concentrations generally considered therapeutic and in the absence of classical electrocardiographic abnormalities (McDonnell Cooke 1993). In a cross-sectional study of hospitalized patients with NYHA II-IV HF, the use of digoxin and furosemide was associated with memory difficulties, though it is unclear whether these reflected illness severity or adverse drug events (Antonelli Incalzi et al 2003). Other cardiovascular medications that may be prescribed to elderly HF patients, including β-blockers, nondihydropyridine calcium-channel blockers, amiodarone and other antiarrhythmic agents, have been associated with the occurrence of neuropsychiatric disturbances, including delirium (Keller and Frishman 2003).

Heart failure and cerebral perfusion

There is mounting evidence that the association between HF and ICF reflects more than shared risk factors. HF is a risk factor for stroke, which may complicate as many as 5% of hospitalizations of patients with HF, and which can result from a number of mechanisms (Kannel et al 1983; Brown and Cleland 1998; Loh et al 1999). Patients with HF are predisposed to cardiogenic thromboembolism. In the setting of severe LV dysfunction and dilation of cardiac chambers, sluggish blood flow may promote thrombus formation (Lip and Gibbs 1999). HF is associated with impaired endothelial function, which may promote platelet adhesion to the endothelium and thus

facilitate thrombosis (Kubo et al 1991; Lip and Gibbs 1999). Rheological abnormalities in patients with HF include activation of platelets and of the coagulation cascade, and are most pronounced in the setting of severe LV systolic dysfunction (Jafri et al 1993; Sbaroumi et al 1994; Hoffmeister et al 1999; Gibbs et al 2001; Chin et al 2003). The combination of abnormal intracardiac blood flow, endothelial dysfunction, and rheological abnormalities satisfy Virchow's triad and suggest that HF, particularly in the setting of LV systolic dysfunction, is a hypercoagulable state (Lip and Gibbs 1999). Furthermore, as many as 20% of strokes in HF patients may occur when transient myocardial ischemia or arrhythmias cause sudden reductions in cardiac output, leading to watershed infarction of cerebral territories with precarious blood supply, or of major arterial territories already compromised by coincident arterial stenosis (Howard et al 1987; MacKenzie 2000). The consequences of strokes are more significant in patients with a history of HF. Imaging studies reveal that patients with impaired LV systolic function suffer larger infarcts as well as more symptomatic watershed infracts than controls with preserved LV systolic function (Pullicino et al 2001). HF has been identified as a risk factor for the development of post-stroke dementia (Leys et al 2005).

In addition to stroke, HF can lead to more diffuse brain injury. Using magnetic resonance imaging (MRI), the brains of nine stable HF patients aged 50 ± 10 years and with LV systolic dysfunction were compared with those of twenty-seven healthy and matched controls (Woo et al 2003). Significant cerebral atrophy, affecting the deep and inferior temporal lobes, parahippocampal gyrus, and frontal lobes, particularly of the right cerebral hemisphere, was observed in the patients with HF, though no cognitive testing was performed to assess the clinical significance of these findings. In another MRI study, twenty patients with HF due to idiopathic dilated cardiomyopathy aged 40.5 ± 7.8 years were compared with twenty healthy matched controls (Schmidt et al 1991). Patients with HF had more severe cortical atrophy and enlargement of cerebral ventricles than controls, with the duration of HF predicting the severity of the lesions. Morphological abnormalities detected by MRI correlated with worse performance in cognitive tests for memory, learning, and vigilance. Finally, a history of HF has been associated with the development of periventricular leukoaraiosis, an established risk factor for ICF (Tarvonen-Schröder et al 1996; Roman 2003b).

In summary, HF is associated with various forms of brain injury. Acute strokes can result from cardiogenic embolism or transient hemodynamic disturbances and have more significant clinical consequences, including a greater risk of ICF. HF is also associated with more widespread and diffuse lesions. These lesions may develop gradually from chronic ischemia due to cerebral perfusion abnormalities (Roman 2003a). Thus far, the literature has largely attributed cerebral hypoperfusion to the hemodynamic consequences of HF, such as reduced effective circulating volume and relative hypotension (Zuccala et al 2001; Bennet et al 2005). However, the regulation of cerebral perfusion also depends on neurohormonal and humoral factors, some of which are potentially reversible.

Cerebral hypoperfusion in patients with heart failure

Cerebral hypoperfusion is associated with ICF in patients with HF. Using single-photon emission computed tomography (SPECT), cerebral perfusion in seventeen stable HF patients aged 73.7 ± 5.4 years, with LV ejection fraction less than 50%, and NYHA II-III functional capacity, was compared with that of eighteen age-matched healthy controls (Alves et al 2005). Patients with HF demonstrated reduced perfusion in a number of regions including the posterior cortices, which appeared to correlate with impaired visual memory. Studies of younger patients demonstrate that cognition often improves following cardiac transplantation, and that these improvements are associated with increased cerebral perfusion as measured by transcranial doppler assessments of middle cerebral arterial flow and cerebral SPECT (Gruhn et al 2001; Bennet and Sauvé 2003; Massaro et al 2006). A study of 29 patients aged 52 ± 12 years and with severe LV systolic dysfunction demonstrated near-normalization of cognitive evoked potentials following implantation of LV assist devices, correlating with improvements in cardiac index (Zimpfer et al 2006).

In addition to cardiac output, cerebral perfusion is mediated by a number of other factors, including blood pressure, blood vessel radius and length, and blood viscosity η, and which are described by Poiseuille's law (Román 2003a):

$$Flow = \frac{\pi \times pressure \times radius^4}{8 \times \eta \times length}.$$

A number of studies have suggested that in comparison with age-matched controls, blood viscosity is elevated in patients with HF (Sbarouni et al 1994; Hoffmesiter et al 1999; Gibbs et al 2001). Viscosity is greatest among patients with more severe NYHA functional capacity and LV systolic dysfunction.

Another important determinant of cerebral perfusion is vessel radius, which is regulated by a number of neurohormonal mechanisms and humoral factors. Mediators of vasodilation include cholinergic neurons arising from the nucleus basalis of Meynert, bradykinin, nitric oxide, potassium, and

magnesium (Román 2003a). Mediators of vasoconstriction include norepinephrine, serotonin, calcium, arterial hypocapnea and hyperoxia. In healthy individuals, an autoregulatory mechanism exists to balance these mediators and thus maintain perfusion over a wide range of systemic blood pressure and cerebral metabolic demands. In older patients, vascular architecture is disrupted through a combination of age-associated changes and vascular risk factors, resulting in narrower, longer and more tortuous vessels, and increased susceptibility to hypoperfusion resulting from systemic hemodynamic disturbances (Román 2003a). The frontal lobes are particularly vulnerable to these changes. The capacity for cerebral autoregulation appears to be further reduced in patients with HF. Cerebrovascular reactivity, as measured by changes in middle cerebral arterial flow in response to hypercapnea, was studied in a cohort of 50 patients with HF, aged 59 ± 11 years, LV ejection fractions ranging from 12 to 54%, and NYHA II-IV symptoms (Georgiadis et al 2000). In comparison to 20 age-matched and 20 younger healthy controls, cerebrovascular reactivity was impaired in patients with HF. The severity of LV systolic dysfunction and the severity of NYHA functional capacity, were both independent predictors of impaired cerebrovascular reactivity.

Another recently hypothesized mechanism leading to impaired cerebral perfusion in some HF patients is the development of CSF effusions, in an analogous fashion to the development of pleural effusions (Caplan 2006). This syndrome may present with reduced spontaneous behaviour and apathy, and appears to be reversible following the withdrawal of cerebrospinal fluid by lumbar puncture.

Can HF therapy improve cerebral perfusion and cognitive function?

A number of neurohormonal axes are activated in patients with chronic HF which, when left unchecked, eventually result in clinical deterioration. The most important of these neurohormonal axes are the renin-angiotensin-aldosterone (RAA) axis and the adrenergic system (Colluci and Braunwald 2005). Medications that antagonize these neurohormonal mechanisms, such as ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers, exert beneficial effects on mortality and morbidity in patients with chronic HF, particularly in the setting of LV systolic dysfunction (Arnold et al 2006). Activation of the RAA axis has been implicated in abnormal regulation of cerebral perfusion in the setting of hypertension and HF, often resulting in a righward shift of cerebral perfusion autoregulation towards higher blood pressures and increasing brain susceptibility to ischemia (Saavedra et al 2006). Increased circulating angiotensin II and aldosterone may impair cerebral perfusion by reducing large artery compliance and causing endothelial dysfunction as well as cerebral vasoconstriction, the latter being mediated directly by angiotensin II and indirectly by activation of the sympathetic nervous system and altered metabolism of vasodilatory kinins (Saavedra and Nishimura 1999; Stier et al 2002; Moreau et al 2005; Saavedra et al 2006).

A number of small studies suggest that ACE inhibitors may have beneficial effects on cerebral perfusion. In two of these studies, patients with HF primarily due to LV systolic dysfunction and NYHA class III and IV functional capacity were treated with captopril (Paulson et al 1984; Rajagopalan et al 1984). While mean arterial blood pressure fell by 10% to 26%, cerebral blood flow, as measured by functional imaging, either remained unchanged or increased. In contrast, control patients in one of the studies experienced both a fall in mean arterial pressure and a reduction in cerebral perfusion (Paulson et al 1984). These observations may extend to patients with HF with preserved LV systolic function. In a double blind randomized controlled trial of 24 stable patients aged on average 74 years, a mean EF of 53 ± 2%, and NYHA II to III functional capacity, and who had not been taking any cardiovascular medications for two weeks, initiation of diuretic therapy with furosemide increased the likelihood of post-prandial hypotension associated with a reduction in frontal lobe oxygenation, as measured by near-infrared spectroscopy (Mehagnoul-Schipper et al 2002). In contrast, patients randomized to initiation of captopril therapy experienced no significant changes in frontal lobe oxygenation. These observations suggest that the administration of ACE-inhibitors can maintain or improve cerebral perfusion. Furthermore, angiotensin converting enzyme (ACE) inhibitors and β-blockers may improve blood viscosity in patients with HF (Turchetti et al 2002). Preliminary evidence also suggests that ACE inhibitors may improve cognition in patients with HF. In an uncontrolled prospective cohort study of 31 patients aged 67.3 years who were hospitalized with severe HF and who were well enough to undergo repeat cognitive testing over a 6-week interval, treatment with ACE inhibitors and the judicious use of diuretics was associated with improvement in measures of attention (Almeida and Tamai 2001b). In a retrospective database analysis of 1220 patients hospitalized with HF, aged 79 ± 9 years, none of whom received ACE inhibitors prior to admission, ACE inhibitor use was associated with greater improvements in cognition throughout the hospital stay (OR 1.57, 95% CI 1.18–2.08)

(Zuccala et al 2005b). Furthermore, a dose-response relationship was observed between improvements in cognition and higher ACE inhibitor doses (p value for trend = 0.001). It remains unclear whether the improvements observed in these two studies can be attributed to ACE inhibitors per se, reflect the natural history of delirium or better tolerance of these medications by relatively less frail individuals. Similar data on the effect of angiotensin receptor blockers and aldosterone antagonists are lacking at this time.

The effect of other HF therapies on cerebral perfusion and cognitive function remain to be evaluated. Modest improvements in LV systolic function may result from use of β-blockers, aldosterone antagonists, digitalis, and cardiac resynchronization, though whether these are associated with improved cognition remains to be determined (Kirkwood et al 2002; Cleland et al 2005; Frigerio and Roubina 2005). Similarly, while circulating norepinephrine levels are elevated in patients with HF, particularly in the setting of LV systolic dysfunction, it remains to be determined whether β-blockers, particularly nonselective β-blockers such as carvedilol, can improve cerebral perfusion and cognitive function (Court and Perry 2003; Kohno et al 2005; Culluci and Braunwald 2005).

HF, sleep quality, and cognition

Sleep disturbances may result in daytime cognitive dysfunction (Bedard et al 1991). Cheyne-Stokes respiration during sleep is common in patients with advanced HF, though it remains unclear whether this phenomenon is related to the ICF seen in these patients, or whether treating them with nocturnal oxygen or continuous positive airway pressure can improve cognitive function (Andreas et al 1996; Staniforth et al 1998, 2001). Improved alertness resulting from better sleep has been hypothesized as the reason for the beneficial effects on cognition observed in a trial in which a supervised exercise program was administered over eighteen weeks to twenty HF patients aged 63 ± 13 years, with NYHA III symptoms and LV ejection fraction 35% or less (Tanne et al 2005). Compared with matched control patients who did not exercise, those who completed the exercise program experienced improvements in psychomotor speed and general attention.

Clinical implications of impaired cognitive function in older persons with heart failure

The impact of CI in patients with HF is substantial and includes an increased risk of rehospitalization, progressive physical disability, and higher mortality (Zuccala et al 2001b, 2003; Hutt et al 2003; Rozzini and Sabatinin 2004). In community-dwelling elderly patients, ICF may lead to nonadherence to recommended therapy, medication mismanagement, failure to recognize early symptoms and seek timely medical attention, and HF hospitalization (Vinson et al 1990; Bennett et al 1997; Chin and Goldman 1997; Cline et al 1999; Ekman et al 2001). These adverse outcomes may arise through a number of mechanisms. Delirium can develop early in the course of any acute illness, in patients with previously normal cognition as well as those with dementia (Inouye 2006). Delirium is a nonspecific syndrome that can be triggered by a number of medical conditions, leading to delays in the recognition of HF as the underlying precipitant and the initiation of appropriate therapy. Furthermore, the development of delirium in acute HF may jeopardize the ability even for previously cognitively intact patients to recognize their illness and make appropriate health care decisions.

Adverse outcomes can also result from the specific types of cognitive deficits that occur in older patients with HF. A systematic review of cognitive testing in patients with HF identified impairments in global measures of cognition, and deficits in short term memory and the ability to sustain attention (Almeida and Flicker 2001). Other studies have demonstrated impairments in immediate and delayed memory, executive function, verbal fluency, attention, processing speed, and learning (Antonelli Incalzi et al 2003; Trojano et al 2003; Verhoeghen et al 2003; Alves et al 2005; Tanne et al 2005; Jefferson et al 2006). Executive dysfunction is associated with injury to frontal lobe system which occurs commonly in patients with cardiovascular disease, and is characterized by difficulties with disorganized thinking, formulating and achieving goals, and problem-solving (Goetz 2003; Roman 2003b). Clearly, deficits in one or more of these domains has the potential to impair a patient's ability to master the complex tasks involved in the management of HF, including complying with dietary restrictions, prescribed medications, monitoring of fluid balance and weights, and taking appropriate and timely action when symptoms of decompensated HF develop.

Clinicians looking after elderly persons with HF should maintain a high index of suspicion for the presence of ICF, as data suggest that it is frequently under-diagnosed. Despite its high prevalence and incidence among elderly hospitalized patients, as many as two thirds of cases of delirium may remain unrecognized by physicians (Inouye 2006). ICF is also underdiagnosed in stable outpatients with HF. In a cohort of 88 consecutive stable outpatients attending a specialized hospital-based HF clinic with a mean age of 76 years and a mean LV ejection fraction of 35%, and only two

of whom had been previously diagnosed with ICF, cognitive deficits were identified in 39% (St.Onge et al 2004). One important reason for the underdiagnosis of ICF in HF patients is that commonly used screening tests such as the MMSE are insensitive to executive dysfunction (Roman 2003a). ICF should be strongly considered when caregivers report cognitive difficulties, changes in personality and behaviour, incontinence or gait difficulties, all of which may suggest executive dysfunction in elderly HF patients (Patterson and Gass 2001; Roman 2003a).

The most important step in the evaluation of ICF in a hospitalized patient is to determine its onset with a focused history (Inouye 2006). Acute cognitive decline suggests delirium and requires that physicians undertake a careful assessment for possible HF, as well as for other occult medical illness or medication side effects. Clinicians should consider becoming familiar with the CAM, a simple yet powerful screening instrument for delirium (Inouye et al 1990). Furthermore, while delirium usually improves when the underlying causes are identified and treated, the associated cognitive deficits may persist for weeks to months, well beyond hospital discharge (Cole et al 2003; McCusker et al 2003). Consequently, even a patient whose dyspnea and oedema have improved sufficiently to consider discharge from hospital may remain too cognitively impaired to benefit from educational efforts designed to prevent rehospitalization. In order to assess executive function, which is associated with the ability to perform instrumental daily activities, and is likely to be important in strategies to prevent rehospitalization, clinicians should consider becoming familiar with brief screening tests for executive dysfunction. These include the Trail Making B Test (Tombaugh 2004; Lavery et al 2006), CLOX (Royall et al 1998), Executive Interview (EXIT-25)(Royall et al 1992), or Frontal Assessment Battery (FAB)(Dubois et al 2000). In patients presenting with either acute delirium or chronic ICF, referral for further cognitive assessment should be considered (Arnold et al 2006).

Therapies shown to be effective in younger patients with HF are often withheld from elderly patients. Evidence derived from a small number of randomized trials, as well as substantial observational data, is consistent in supporting the benefits of standard HF therapies, and particularly ACE inhibitors and β-blockers, in elderly patients (Arnold et al 2006). The discussion above suggests that ACE inhibitors may be particularly effective in protecting cognitive function. Care should be taken to avoid over-diuresis, and digoxin should be used sparingly due its potential for side effects such as delirium in older patients (McDonnell Cooke 1993). For patients with ICF, clinicians should consider directing educational interventions for HF management to cognitively intact caregivers (Arnold et al 2006). Adherence to prescribed therapy may be improved through the use of pill boxes filled weekly and supervised by a pharmacist or caregiver, and ensuring adequate social support through family members or visiting nurses (Papaioannou and Uppaluri 2003). Referral of elderly patients with ICF to multidisciplinary HF management programs should be considered, and involvement of primary care physicians is essential (Gonseth et al 2004; Arnold et al 2006). In hospitalized patients with HF, risk factors predisposing to the development of delirium should be identified, as simple and cost-effective maneuvers targeting these risk factors have been shown to prevent up to 40% of incident cases of delirium in at-risk medical patients (Inouye et al 1999).

Conclusion

The coming decades will see a substantial rise in the number of elderly patients with HF, many of whom will also suffer from concomitant ICF. The challenges facing clinicians will be to identify and manage patients with HF who develop ICF, hopefully to prevent their associated complications. Optimizing HF therapy in elderly patients may be beneficial for cognitive function. Many opportunities exist for clinician scientists to determine optimal methods of identifying and managing elderly patients with HF, developing strategies for treating and perhaps even preventing the development of cognitive deficits in this growing vulnerable population.

Acknowledgment

The authors would like to thank Dr. Neil Gillespie from the University of Dundee, Scotland, for his comments on a previous version of this manuscript.

Disclosures

Dr. Heckman has received speaker and consultant fees from Pfizer, Novartis, and Janssen-Ortho, travel allowances from Astra-Zeneca and Bristol-Meyers-Squibb, and research funding from Novartis. Dr. Patterson has received research funding from Pfizer and Janssen-Ortho, speaker fees from Pfizer, and consultant fees from Hoescht. Dr. Demers has received grant in aid funding from Merck and Eli Lilly Canada, and speaker fees from Astra-Zeneca. Dr. St.Onge has no disclosures to make. Dr. Turpie has received research funding from Sanofi-Synthelabo Canada, Pharmacia UpJohn, as well

as consultant fees Janssen-Ortho and Pfizer. Dr. McKelvie has received research support from Astra-Zeneca, Bristol-Meyers-Squibb/ Sanofi/Aventis and Scios, and speaker fees from Astra-Zeneca, Bristol-Meyers-Squibb/ Sanofi/Aventis, and Merck Frosst.

References

Adams KF, Gheorghiade M, Uretsky BF, et al. 2002. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol*, 39:946–53.

Almeida OP, Tamai S. 2001. Congestive heart failure and cognitive functioning amongst older adults. *Arq Neuropsiquiatr*, 59(2-B):324–9.

Almeida OP, Tamai S. 2001. Clinical treatment reverses attentional deficits in congestive heart failure. *BMC Geriatr*, 1:2.

Almeida OP, Flicker L. 2001. The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. *Intern Med J*, 31:290–5.

Alves TCTF, Rays J, Fráguas R, et al. 2005. Localized cerebral blood glow reductions in patients with heart failure: A study using ^{99m}Tc-HMPAO SPECT. *J Neuroimaging*, 15:150–6.

Andreas S, Clemens C, Sandholzer H, et al. 1996. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol*, 27:1486–90.

American Heart Association. 2002. Heart disease and stroke statistics – 2003 update. Dallas, Texas: American Heart Association.

Antonelli Incalzi R, Trojano L, Acanfora D, et al. 2003. Verbal memory impairment in congestive heart failure. *J Clin Exp Neuropsychol*, 25:14–23.

Arnold JMO, Liu P, Demers C, et al. 2006. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol*, 22:23–45.

Bedard MA, Montplaisir J, Richer F, et al. 1991. Obstructive sleep apnoea syndrome: pathogenesis of neuropsychological deficits. *J Clin Exper Neuropsychol*, 13:950–64.

Bennett SJ, Pressler ML, Hays L, et al. 1997. Psychosocial variables and hospitalization in persons with chronic heart failure. *Prog Cardiovasc Nurs*, 12:4–11.

Bennett SJ, Sauvé MJ. 2003. Cognitive deficits in patients with heart failure. *J Cardiovasc Nurs*, 18:219–42.

Bennett SJ, Sauvé MJ, Shaw RM. 2005. A conceptual model of cognitive deficits in chronic heart failure. *J Nurs Scholarsh*, 37:222–8.

Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. 2004. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. *Eur Heart J*, 25:1614–9.

Breteler MMB, Claus JJ, Grobbee DE, et al. 1994. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. *BMJ*, 308:1604–8.

Brown AM, Cleland JGF. 1998. Influence of concomitant disease on patterns of hospitalization in patients with heart failure discharged from Scottish hospitals in 1995. *Eur Heart J*, 19:1063–9.

Cacciatore F, Abete P, Ferrara N, et al. 1998. Congestive heart failure and cognitive impairment in an older population. *J Am Geriatr Soc*, 46:1343–8.

Canadian Study on Health and Aging Study Group. 1994. Canadian Study on Health and Aging: study methods and prevalence of dementia. *Can Med Assoc J*, 150:899–912.

Caplan LR. 2006. Cardiac encephalopathy and congestive heart failure. *Neurology*, 66:99–101.

Chin BSP, Blann AD, Gibbs CR, et al. 2003. Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure. *Eur J Clin Invest*, 33:941–8.

Chin MH, Goldman L. 1997. Factors contributing to the hospitalization of patients with congestive heart failure. *Am J Public Health*, 87:643–8.

Cleland JGF, Daubert J-C, Erdmann E, et al. 2005. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*, 352:1539–49.

Cline CM, Bjorck-Linne AK, Israelson BY, et al. 1999. Non-compliance and knowledge of prescribed medications in elderly patients with heart failure. *Eur J Heart Fail*, 1:145–9.

Cole M, McCusker J, Dendukuri N, et al. 2003. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *J Am Geriatr Soc*, 51:754–60.

Colluci WS, Braunwald E. 2005. Pathophysiology of heart failure. In: Zipes DP (ed). Braunwald's Heart Disease: A textbook of cardiovascular medicine. 7th ed. Philadelphia: W.B. Saunders.

Court JA, Perry EK. 2003. Neurotransmitter abnormalities in vascular dementia. *Int Psychogeriatr*, 15(Suppl 1):81–7.

Cukierman T, Gerstein HC, Williamson JD. 2005. Cognitive decline and dementia in diabetes – systematic review of prospective observational studies. *Diabetologia*, 48:2460–9.

Di Carlo A, Baldereschi M, Amaducci L, et al. 2000. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *J Am Geriatr Soc*, 48:775–82.

Dubois B, Slachevsky A, Litvan I, et al. 2000. The FAB: a frontal assessment battery at bedside. *Neurology*, 55:1621–6.

Editorial, 1977. Cardiogenic dementia. *Lancet*, 1:27–8.

Ekman I, Fagerberg B, Skoog I. 2001. The clinical implications of cognitive impairment in elderly patients with chronic heart failure. *J Cardiovasc Nurs*, 16:47–55.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-Mental State". A practical method for grading cognitive state of patients for the clinician. *J Psychiatr Res*, 12:189–98.

Frigerio M, Roubina E. 2005. Drugs for left ventricular remodeling in heart failure. *Am J Cardiol*, 96(suppl):10L–8L.

Fuat A, Hungin APS, Murphy JJ. 2003. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *BMJ*, 326:196–201.

Georgiadis D, Sievert M, Cencetti S, et al. 2000. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J*, 21:407–13.

Gibbs CR, Blann AD, Watson RDS, et al. 2001. Abnormalities of hemorheological, endothelial, and platelet function in patients with chronic heart failure in sinus rhythm. *Circ*, 103:1746–51.

Goetz CG (ed). 2003. Textbook of clinical neurology, 2nd Ed. St.Louis, Elsevier Pr. p. 546.

Gonseth J, Guallar-Castillon P, Banegas JR, et al. 2004. The effectiveness of disease management programmes in reducing re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. *Eur Heart J*, 25:1570–95.

Gruhn N, Larsen FS, Boesgaard S, et al. 2001. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*, 32:2530–3.

Heckman G and McKelvie RS. 2000. Prevention of congestive heart failure and treatment of asymptomatic left ventricular systolic dysfunction in the elderly. *Clinical Geriatrics*, 8:76–85.

Hoffman A, Ott A, Breteler MM, et al. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet*, 18:151–4.

Hoffmeister A, Hetzel J, Sander S, et al. 1999. Plasma viscosity and fibrinogen in relation to haemodynamic findings in chronic congestive heart failure. *Eur J Heart Fail*, 1:293–5.

Howard R, Trend P, Russel RW. 1987. Clinical features of ischemia in cerebral arterial border zones after periods of reduced cerebral blood flow. *Arch Neurol*, 44:934–40.

Hutt E, Frederickson E, Ecord M, et al. 2003. Associations among processes and outcomes of care for medicare nursing home residents with acute heart failure. *J Am Med Dir Assoc*, 4:195–9.

Incalzi RA, Chiappini F, Fuso L, et al. 1998. Predicting cognitive decline in patients with hypoxaemic COPD. *Respir Med*, 92:527–33.

Inouye SK, van Dyck CH, Alessi CA, et al. 1990. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*, 113:941–8.

Inouye SK, Viscoli CM, Horwitz RI, et al. 1993. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med*, 119:474–81.

Inouye SK, Charpentier PA. 1996. Precipitating factors for delirium in hospitalized elderly persons. *JAMA*, 275:852–7.

Inouye SK, Bogardus ST, Charpentier PA, et al. 1999. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*, 340:669–76.

Inouye SK. 2006. Delirium in older persons. *N Engl J Med*, 354:1157–65.

Jefferson AL, Poppas A, Paul RH, et al. 2006. Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. *Neurobiol Aging*, doi:10.1016/j.neurobiolaging.2006.01.001; available online February 15, 2006.

Jafri SM, Ozawa T, Mammen E, et al. 1993. Platelet function, thrombin and fibrinolytic activity in patients with heart failure. *Eur Heart J*, 14:205–12.

Kannel WB, Wolf PA, Verter J. 1983. Manifestations of coronary disease predisposing to stroke. The Framingham study. *JAMA*, 250:2942–6.

Keller S and Frishman WH. 2003. Neuropsychiatric effects of cardiovascular drug therapy. *Cardiol Rev*, 11:73–93.

Kohno T, Yoshikawa T, Yoshizawa A, et al. 2005. Carvedilol exerts more potent antiadrenergic effect than metoprolol in heart failure. *Cardiovasc Drugs Ther*, 19:347–55.

Kubo SH, Rector TS, Bank AJ, et al. 1991. Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation*, 84:1589–96.

Lavery L, Vander Bilt J, Chang C-CH, et al. 2006. The association between congestive heart failure and cognitive performance in a primary care population of elderly adults: the Steel Valley Seniors Survey. *Int Psychogeriatr*, doi:10.1017/S1041610206003449; available online May 10, 2006.

Lee DS, Johansen H, Gong Y, et al. 2004. Regional outcomes of heart failure in Canada. *Can J Cardiol*, 20:599–607.

Leys D, Henon H, Mackowiak-Cordoliani MA, et al. 2005. *Lancet Neurol*, 11:752–9.

Lip GYH, Gibbs CR. 1999. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol*, 33:1424–6.

Loh E, St. John Sutton M, Wun CCW, et al. 1997. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med*, 336:251–7.

MacKenzie JM. 2000. Are all cardio-embolic strokes embolic? *Cerebrovasc Dis*, 10:289–92.

Massaro AR, Dutra AP, Almeida DR, et al. 2006. Transcranial doppler assessment of cerebral blood flow: effect of cardiac transplantation. *Neurology*, 66:124–6.

McCusker J, Cole M, Dendukuri N, et al. 2003. The course of delirium in older medical inpatients. *J Gen Intern Med*, 18:696–704.

McDonnell Cooke D. 1993. The use of central nervous system manifestations in early detection of digitalis toxicity. *Heart Lung*, 22:477–81.

Mehagnoul-Schipper DJ, Colier WNJM, Hoefnagels WHL, et al. 2002. Effects of furosemide versus captopril on postprandial and orthostatic blood pressure and on cerebral oxygenation in patients 70 years of age with heart failure. *Am J Cardiol*, 90:596–600.

Moreau ME, Garbacki N, Molinaro G, et al. 2005. The kallikrein-kinin system: current and future pharmacological targets. *J Pharmacol Sci*, 99:6–38.

Morris JC. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, 43:2412–4.

Ott A, Stolk RP, van Harskamp E, et al. 1999. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*, 53:1937–42.

Papaioannou A, Uppaluri A. 2003. Pharmacological issues in the very old: the treatment of heart diease. In: Turpie ID, Heckman GA (eds). Aging Issues in Cardiology. Boston: Kluver Acad Pub.

Patterson CJS, Gass DA. 2001. Screening for cognitive impairment and dementia in the elderly. *Can J Neurol Sci*, 28 (Suppl 1):S42–S51.

Paulson OB, Jarden JO, Godfredsen J, et al. 1984. Cerebral blood flow in patients with congestive heart failure treated with captopril. *Am J Med*, 76:79–85.

Pereira AA, Weiner DE, Scott T, et al. 2005. Cognitive dysfunction in dialysis patients. *Am J Kidney Dis*, 45:448–62.

Petersen RC and O'Brien J. 2006. Mild cognitive impairment should be considered for DSM-V. *J Geriatr Psychiatry Neurol*, 19:147–54.

Pullicino P, Mifsud V, Wong E, et al. 2001. Hypoperfusion-related cerebral ischemia and cardiac left ventricular systolic dysfunction. *J Stroke Cerebrovasc Dis*, 10:178–82.

Pi-Figueras M, Aguilera A, Arellano M, et al. 2004. of delirium in a geriatric convalescence hospitalization unit: patient's clinical characteristics and risk precipitating factor analysis. *Arch Gerontol Geriatr Suppl*, 9:333–7.

Qiu C, Winblad B, Marengoni A, et al. 2006. Heart failure and the risk of dementia and Alzheimer disease. *Arch Intern Med*, 166:1003–8.

Rajagopalan B, Raine AEG, Cooper R, et al. 1984. Changes in cerebral blood flow in patients with severe congestive heart failure before and after captopril treatment. *Am J Med*, 76:86–90.

Rich MW. 2001. Heart failure in the 21st century: a cardiogeriatric syndrome. *J Gerontol A Biol Sci Med Sci*, 56:M88–M96.

Román G. 2003a. Managing Vascular Dementia. London: Science Pr.

Román GC. 2003b. Vascular dementia: distinguishing characteristics, treatment, and prevention. *J Am Geriatr Soc*, 51:S296–04.

Román GC. 2004. Brain hypoperfusion: a critical factor in vascular dementia. *Neurol Res*, 26:454–8.

Royall DR, Cordes JA, Polk M. 1998. CLOX: an executive clock drawing test. *J Neurol Neurosurg Psychiatry*, 64:588–94.

Royall DR, Mahurin RK, Gray KF. 1992. Bedside assessment of executive cognitive impairment: the executive interview. *J Am Geriatr Soc*, 40:1221–6.

Rozzini R, Sabatani T, Trabucchi M. 2004. Cognitive impairment and mortality in elderly patients with heart failure. *Am J Med*, 116:137–8.

Saavedra JM and Nishimura Y. 1999. Angiotensin and cerebral blood flow. *Cell Mol Neurobiol*, 19:553–73.

Saavedra JM, Benicky J, Zhou J. 2006. Angiotensin II: multitasking in the brain. *J Hypertens*, 24(suppl 1):S131–7.

Statistics Canada. 2005. Census 2001 [online]. Accessed on December 13, 2005. URL: http://www.statcan.ca/english/census01/home

Stier CT, Chander PN, Rocha R. 2002. Aldosterone as a mediator in cardiovascular injury. *Cardiol Rev*, 10:97–107.

Staniforth AD, Kinnear WJM, Starling R, et al. 1998. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. *Eur Heart J*, 19:922–8.

Staniforth AD, Kinnear WJM, Cowley AJ. 2001. Cognitive impairment in heart failure with Cheyne-Stokes respiration. *Heart*, 85:18–22.

St.Onge J, Heckman G, Tait P, et al. 2004. Unrecognized cognitive impairment is common in heart failure outpatients. Poster presentation, AHA Scientific Sessions.

Strong K, Mathers C, Leeder S, et al. 2005. Preventing chronic diseases: how many lives can we save? *Lancet*, 366:1578–82.

Tanne D, Freimark D, Poreh A, et al. 2005. Cognitive functions in severe congestive heart failure before and after an exercise program. *Int J Cardiol*, 103:145–9.

Tarvonen-Schroder S, Roytta M, Kurki T, et al. 1996. Clinical features of leukoaraiosis. *J Neurol Neurosurg Psychiatry*, 46:942–8.

Tilvis RS, Kahonen-Vare MH, Jolkkonen J, et al. 2004. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol Med Sci*, 59A:268–74.

Tombaugh TN. 2004. Trail making test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*, 19:203–14.

Trojano L, Antonelli Incalzi R, Acanfora D, et al. 2003. Cognitive impairment: a key feature of congestive heart failure in the elderly. *J Neurol*, 250:1456–63.

Tune L, Carr S, Cooper T, et al. 1993. Association of anticholinergic activity of prescribed medications with postoperative delirium. *J Neuropsychiatry Clin Neurosci*, 5:208–10.

Tune LE. 2001. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry*, 62(suppl 21):11–4.

Tuokko H, Frerichs R, Graham J, et al. 2003. Five-year follow-up of cognitive impairment with no dementia. *Arch Neurol*, 60:577–82.

Turchetti V, Bellini MA, Boschi L, et al. 2002. Haemorheological and endothelial-dependent alterations in heart failure after ACE inhibitor, calcium antagonist and beta blocker. *Clin Hemorheol Microcirc*, 27:209–18.

Verhaeghen P, Borchelt M, Smith J. 2003. Relation between cardiovascular and metabolic disease and cognition in very old age: cross-sectional and longitudinal findings from the Berlin Aging Study. *Health Psychology*, 22:559–69.

Vinson JM, Rich MW, Sperry JC, et al. 1990. Early readmission of elderly patients with congestive heart failure. *J Am Geriatr Soc*, 38:1290–5.

Whitmer RA, Sidney S, Selby J, et al. 2005. Midlife cardiovascular risk factors and risk f dementia in late life. *Neurology*, 64:277–81.

Woo MA, Macey PM, Fonarow GC, et al. 2003. Regional brain gray matter loss in heart failure. *J Appl Physiol*, 95:677–84.

Zimpfer D, Wieselthaler G, Czerny M, et al. 2006. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. *ASAIO Journal*, 52:24–7.

Zuccala G, Cattel C, Manes-Gravina E, et al. 1997. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry*, 63:509–12.

Zuccala G, Onder G, Pedone C, et al. 2001a. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology*, 57:1986–92.

Zuccala G, Onder G, Pedone C, et al. 2001b. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results from a multicentre survey. *J Neurol Neurosurg Psychiatry*, 70:109–12.

Zuccala G, Pedone C, Cesari M, et al. 2003. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med*, 115:97–103.

Zuccala G, Marzetti E, Cesari M, et al. 2005a. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. *Am J Med*, 118:496–502.

Zuccala G, Onder G, Marzetti E, et al. 2005b. Use of angiotensin-converting enzyme inhibitors and variations in cognitive performance among patients with heart failure. *Eur Heart J*, 26:226–33.