

CATHY A. SILA, MD\*

Cerebrovascular Center, Neurological Institute  
Professor of Medicine, Cleveland Clinic Lerner College of Medicine  
Cleveland Clinic  
Cleveland, OH

## Cognitive impairment in chronic heart failure

**A**dvances in the treatment of ischemic heart disease have resulted in the survival of an increasingly elderly population with chronic heart failure (CHF). Approximately 5 million Americans suffer from CHF, and an additional 20 million are presymptomatic with a reduced ejection fraction.<sup>1</sup> As the heart fails, so do other organs; renal failure and the profound weight loss of cardiac cachexia are significant determinants of mortality. However, it is the decline in cognitive functioning that can significantly reduce patients' quality of life at a time when physical abilities are limited. This article reviews patient characteristics associated with cognitive impairment in CHF as well as conditions that may contribute to it.

### ■ THE SCOPE OF THE PROBLEM: IMPACT ON OUTCOMES AND PATIENT CARE

Within the past several decades, awareness of the presence and impact of cognitive impairment in patients with CHF has grown. Most of our understanding is derived from the detailed study of small numbers of patients or limited testing in larger groups participating in epidemiologic studies or clinical trials. A literature review of heart failure studies from 1966 to 2000 revealed only 13 that reported on the cognitive status of 907 patients.<sup>2</sup> From these data, the message is that some degree of cognitive impairment is common, affecting about half of all patients with CHF.

The presence of cognitive impairment in patients with CHF is significantly associated with increasing age, impaired activities of daily living, reduced independence in daily living, and worsening heart failure.<sup>3,4</sup>

The risk of CHF also increases with age, affecting 10% of those older than 70 years, and is a major cause of hospitalization among the elderly. Cognitive impairment in this group is particularly common. In a study of 92 consecutive patients with CHF admitted to a geriatric unit over a 6-month period, cognitive screening with the Mini Mental State Examination

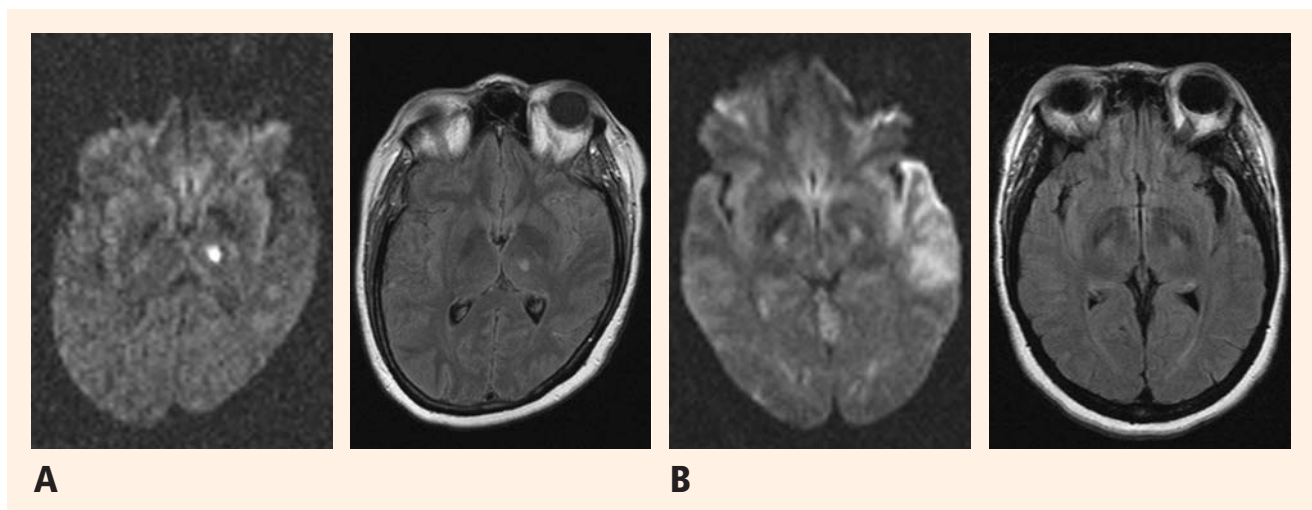
(MMSE) was performed prior to discharge.<sup>5</sup> Confounding causes of dementia, such as Alzheimer disease, vascular dementia, psychiatric disorders, or substance abuse, were excluded, leaving 57 patients (mean age: 77) available for the final analysis. MMSE scores less than 24, consistent with dementia, were present in 53% of patients, with the worst performance observed on tests of complex reasoning. In addition to advanced age, an association between MMSE and left ventricular ejection fraction (LVEF) was evident: subjects with LVEF of 30% or less had worse cognitive scores than those with higher LVEF.<sup>5</sup>

Although age is an important risk factor, cognitive impairment in CHF patients is not exclusive to the elderly. In small studies employing detailed neuropsychological testing in a pretransplant assessment, approximately 50% of patients fulfilled criteria for cognitive impairment.<sup>6-8</sup> In one study, the 62 patients were an average age of 44.7 years.<sup>6</sup> Overall cognitive impairment was documented in 58%, and 13% to 66% of individual test items were abnormal. Most difficulties were observed in reasoning and concept formation, attention, and psychomotor skills.<sup>6</sup> Within this young age group, the older patients (> 50 years) fared worse, as did those with worse CHF as indicated by greater right atrial pressures and lower stroke volume, cardiac output, and cardiac index.<sup>6-8</sup>

In a large pharmacoepidemiologic study, cognitive screening was performed at the time of discharge in 13,635 patients, including 1,583 with CHF.<sup>4</sup> Cognitive dysfunction in patients with CHF was independently associated with disability, as it was present in 57% of those who were disabled vs 13% of those who were independent.<sup>4</sup> Disability in CHF patients is predictive of poorer quality of life, higher medical resource consumption, increased mortality, and more frequent hospitalizations.

Approximately 50% of hospital admissions for heart failure are associated with poor compliance with a prescribed treatment plan. Among patients hospitalized for decompensated CHF, 42% to 80% were noncompliant with medications and 49% to 78% were noncompliant with diet.<sup>9</sup> Addressing these

\* Dr. Sila reported that she has no financial relationships that pose a potential conflict of interest with this article.



**FIGURE 1.** (A) A 53-year-old woman with a left ventricular ejection fraction (LVEF) of 20% presented with a sudden onset of hypersomnolence, abulia, and short-term memory loss. She repeated questions and confabulated answers. These effects were persistent and disabling. An acute left mesial thalamic lacunar infarct was identified on diffusion-weighted magnetic resonance imaging (MRI) (left) and T<sub>2</sub>-weighted fluid-attenuated inversion recovery (FLAIR) MRI (right). (B) A 43-year-old woman with LVEF of 10% presented with a sudden onset of agitated delirium with memory loss, dysnomia, and poor comprehension. Diffusion-weighted MRI (left) demonstrated an acute left temporal lobe infarct. On follow-up, she had persistent cognitive residual. Follow-up T<sub>2</sub>-weighted FLAIR MRI (right) depicts the evolution to temporal atrophy.

issues through intensive postdischarge disease management programs can reduce rehospitalization rates, although the cost to implement these programs exceeds hospitalization cost savings.<sup>10</sup> As cognitive impairment has a significant impact on patients' ability to understand and comply with treatment plans that may be complicated, an improved understanding of this issue could lead to more targeted, and perhaps more cost-effective, treatment of these patients.

#### ■ FACTORS CONTRIBUTING TO COGNITIVE IMPAIRMENT IN CHF

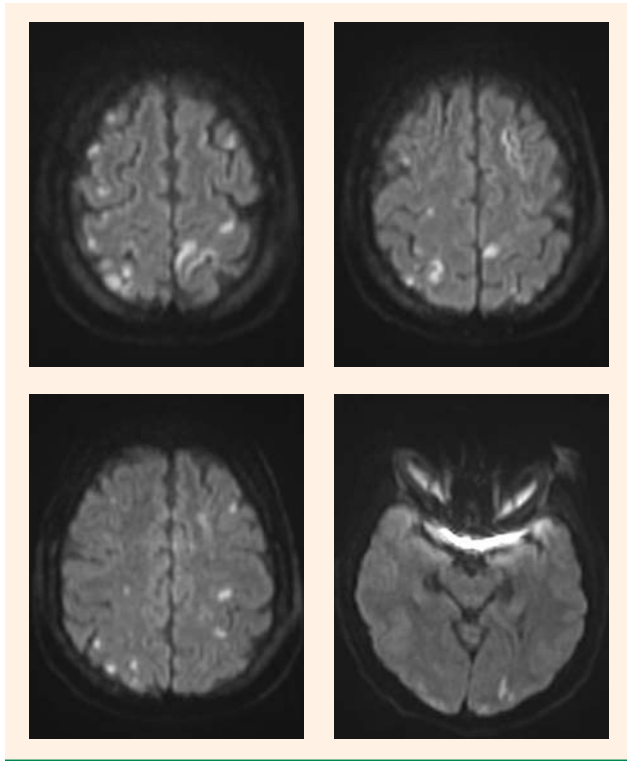
A number of potential mechanisms have been identified by which CHF can lead to cognitive impairment. These include vascular injury from ischemic or hemorrhagic stroke, injury after cardiac arrest or cardiac surgery, and chronic cerebral hypoperfusion. Brain atrophy, disordered cerebral metabolism, and neurotransmitter dysfunction have also been described as pseudodementia related to depression and sleep deprivation from sleep-related breathing disorders. In addition, it is likely that multiple mechanisms can interact in individual patients.

#### Stroke

CHF has emerged as the second most common cardiac condition leading to stroke.<sup>11</sup> More than 90% of heart failure is caused by dilated cardiomyopathy, in which the risk of stroke is increased two- to three-

fold.<sup>11</sup> The development of cognitive impairment after stroke (ie, vascular dementia) is related to the size and location of cerebral injury. Strategic damage to the dominant medial thalamus or temporal lobe will manifest primarily as cognitive impairments, whereas dominant frontal or posterior temporal lesions result in the language impairments so critical to cognitive testing (**Figures 1A and 1B**).

**Most have a cardioembolic mechanism.** A multiplicity of infarcts can also produce a subcortical pattern of cognitive inflexibility and prolonged cognitive processing. This pattern may also be a result of a series of inapparent infarcts. Silent cerebral infarcts are common and have been identified in 34% of patients undergoing neuroimaging prior to transplantation.<sup>12</sup> Most of the strokes are ischemic and consistent with a cardioembolic mechanism, which is supported by the relationship between stroke risk and severity of CHF. The overall annual risk of stroke is relatively low, at 1.3% to 3.5%, but certain subsets of patients, such as the elderly, women, those with prior stroke or diabetes, and especially those with worse LVEF, are at increased risk.<sup>13</sup> Stroke risk increases by 18% for every 5% decline in LVEF, from an incidence of 1.5% to 2% with LVEF of 30% to 35%, to an incidence of 2% to 4% with LVEF less than 10%.<sup>14</sup> Worsening left ventricular function leads to increased end-diastolic volume, which, in turn, results in intracardiac stasis and thrombus formation.<sup>1,15</sup>



**FIGURE 2.** A 37-year-old man with a left ventricular ejection fraction of 20% and a 7-year history of ischemic heart disease sustained an acute myocardial infarction with cardiogenic shock requiring intra-aortic balloon support and urgent coronary revascularization. He was slow to awaken after minor sedation, abulic, and disoriented, and had impaired memory but no other focal sensorimotor or visual abnormalities. Note the multifocal infarcts on diffusion-weighted magnetic resonance imaging throughout the cortex.

In elderly patients with CHF, atrial fibrillation is independently associated with cognitive decline, increasing the risk 3.4-fold. This relationship is lost, however, if patients with a history of cerebrovascular events are excluded, implying that the contribution to cognitive impairment is largely exerted through damage from cardioembolic stroke.<sup>3,4</sup>

**Other stroke subtypes.** Although most strokes are cardioembolic, this population is also at risk for other stroke subtypes. Atherosclerotic risk factors for coronary heart disease, such as hypertension, hyperlipidemia, diabetes, and cigarette smoking, are also risk factors for cerebrovascular disease, resulting in artery-to-artery embolism or stenosis, or occlusion of large cervicocephalic arteries, intracranial arteries, or small perforating arterioles. Intracranial hemorrhage is an established complication of antithrombotic therapies used to prevent ischemic stroke, particularly with anticoagulant use in the elderly.

The risk of stroke after acute myocardial infarction

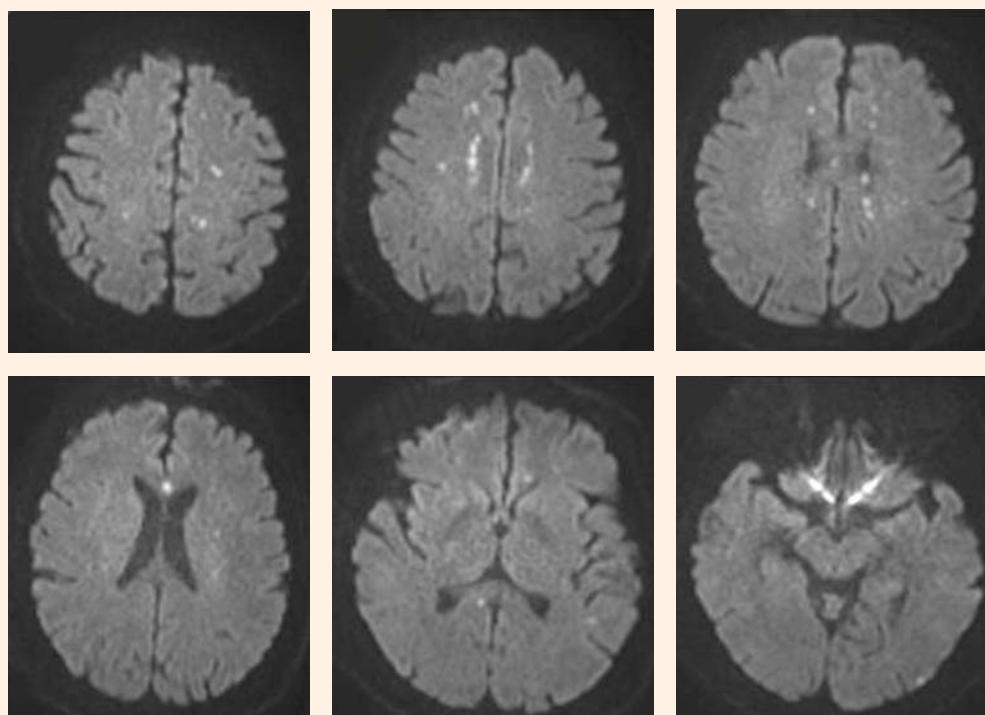
(MI) is 2% to 4%, and is particularly high in the elderly with CHF. Transcranial Doppler (TCD) monitoring of patients within 72 hours of an acute MI detected cerebral microembolism in 17% of patients, with the greatest risk in patients with LVEF less than 65%, akinetic left ventricular segments, and left ventricular thrombus.<sup>16</sup> Of these 17%, 3% had a symptomatic cerebral embolism (**Figure 2**).

Patients with CHF are likely to undergo various cardiac interventional procedures that can be complicated by cerebral embolism.<sup>17</sup> Stroke complicates less than 0.1% of diagnostic cardiac catheterizations and 0.3% of coronary endovascular interventions. Cardiac surgery risks include a 2% to 5% risk of stroke with coronary bypass alone and a 5% to 10% risk when coronary bypass is combined with valvular surgery (**Figure 3**).<sup>17</sup>

**Optimal prevention therapy unknown.** In the absence of atrial fibrillation, the optimum antithrombotic therapy to prevent stroke in patients with reduced LVEF is unknown. When the Warfarin and Antiplatelet Therapy in Heart Failure (WATCH) trial was terminated for poor recruitment, the available data did not demonstrate a significant difference in the primary end point of stroke, MI, or death among those randomized to treatment with warfarin (target International Normalized Ratio [INR]: 2.5 to 3.0), aspirin (160 mg/day), or clopidogrel (75 mg/day). Patients randomized to warfarin, however, experienced fewer strokes but more bleeding complications compared with the antiplatelet regimens, and patients randomized to aspirin had more hospitalizations for heart failure.<sup>18</sup> The ongoing Warfarin Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial continues to compare warfarin (target INR: 2.5 to 3.0) to aspirin (325 mg/day).<sup>19</sup> WARCEF was prospectively designed, and its end points are the same as those in WATCH. These data will hopefully clarify the best therapy for a large range of patients with CHF, and result in guidelines similar in scope to those that emerged from trials of patients with atrial fibrillation.<sup>20</sup>

### Cerebral hypoperfusion

In the normal state, resting cerebral blood flow (CBF) is optimized within rather narrow parameters throughout a wide range of systemic blood pressures, a process known as cerebral autoregulation. In CHF, declines in cardiac output result in a redistribution of blood flow to favor the heart and brain at the expense of the skeletal muscle and the cutaneous, splanchnic, and renal vascular beds.<sup>21</sup> As cardiac output continues to decline, however, the capacity of cerebral autoregulation to maintain CBF is exhausted. CBF will begin



**FIGURE 3.** After an urgent, but otherwise uncomplicated, coronary artery bypass operation, this patient was abulic with poor attention, concentration, and memory. Encephalopathy following open-heart surgery was diagnosed. The patient had poor memory and exhibited poor attention and concentration. Diffusion-weighted magnetic resonance imaging depicted acute, multifocal ischemic injuries, which have been related to multifocal embolism or reduced clearance of emboli.

to decline when mean arterial pressures decrease to 80% of baseline, or approximately 60 mm Hg. In normal subjects, a 30% decline of CBF results in mild symptoms of cerebral hypoperfusion, and a 50% to 60% decline produces mental confusion.

As part of a pretransplant evaluation, CBF was assessed by  $^{133}\text{Xe}$  single photon emission computed tomography (SPECT) and TCD in 12 CHF patients and matched controls.<sup>21</sup> In the CHF patients, resting CBF was 36 mL/min/100 g, which represented a significant 31% reduction compared with 52 mL/min/100 g in the control patients. Resting mean arterial pressures were also significantly lower in the CHF group (76 mm Hg vs 95 mm Hg). CBF and mean arterial pressure values normalized within 1 month of transplantation in the five patients who underwent follow-up testing. In this study, TCD values were somewhat more variable (lower) than SPECT values, but not significantly so, at 36 cm/sec vs 49 cm/sec. However, in another study of 22 patients who underwent heart transplant, TCD velocities increased 53% postoperatively, including 117% in one patient whose increase in CBF was associated with symptoms of hyperperfusion related to impaired cerebrovascular reactivity (an inability to rapidly vasoconstrict when impaired CBF has been rapidly corrected).<sup>22</sup>

The association of cognitive impairment with

reduced LVEF is not linear but rather declines sharply with LVEF less than 30%.<sup>5</sup> In young patients with end-stage CHF, cognitive impairment is associated with elevated right atrial pressure, low stroke volume, and low cardiac index.<sup>6</sup> These data support the theory that cognitive impairment in CHF results from cerebral hypoperfusion. The cerebral autoregulatory mechanisms that maintain CBF will begin to fail in the setting of severe hypoperfusion.

It is not clear how the autoregulatory curve shifts in the setting of CHF and chronic hypotension.<sup>23</sup> It is likely to be affected by diseases that alter the function of arteriolar resistance vessels, such as hypertension and diabetes (the classic risk factors for “small vessel disease”), as well as advanced age. The capacity for cerebral vasodilation is an important compensatory mechanism to maintain CBF in the setting of reduced cardiac output. The point at which this capacity becomes exhausted would likely lead to ischemic injury. This capacity, or cerebrovascular reactivity, can be assessed by administering inhaled  $\text{CO}_2$ . As a potent cerebral vasodilator,  $\text{CO}_2$  normally induces immediate increases in CBF that can be measured with TCD monitoring. Cerebrovascular reactivity was demonstrated to be impaired in a group of 50 patients with CHF compared with age-matched and normal controls, an impairment that was also signifi-

cantly related to LVEF and New York Heart Association (NYHA) class.<sup>24</sup>

### Cerebral abnormalities

Brain atrophy on magnetic resonance imaging (MRI) studies is more common in CHF patients and correlates with disease duration and cognitive performance. In several small neuroimaging studies of patients with CHF, brain atrophy was present in 77%. In a comparison of 20 CHF patients and 20 age-matched controls, brain atrophy affected cortical structures in 50% of CHF patients vs 5% of controls, ventricular enlargement occurred in 55% of the cases and 15% of the controls, and cerebral infarcts were evident in 20% of the cases and 0% of the controls.<sup>25</sup> Wasting of other tissues—fat, muscle, and bone—occurs in cardiac cachexia, but whether brain atrophy is part of this wasting syndrome is unknown.<sup>26</sup> However, brain atrophy has been demonstrated in other similar chronic illnesses as well as in starvation and eating disorders.

Hydrocephalus can result from the global loss of tissue or specific loss of periventricular white matter tissue in patients with CHF. This hydrocephalus has also occasionally been associated with a fluctuating abulic syndrome similar to normal-pressure hydrocephalus syndrome. It is related to increased central venous hydrostatic pressure and delayed resorption of cerebrospinal fluid within the intracranial cavity during or after treatment of an episode of cardiac decompensation.<sup>27</sup> The importance of recognizing this behavioral and motor syndrome is that therapeutic lumbar punctures can result in rather rapid improvement with more gradual improvement in the neuroimaging abnormalities.

The volume loss exhibited in CHF patients does not appear to occur in a random fashion. Volumetric analyses have demonstrated significant, largely lateralized loss of gray matter in areas related to the control of autonomic and respiratory functions.<sup>28</sup> In a follow-up study, functional MRI was used to image the sympathetic outflow response to a cold pressor test.<sup>29</sup> Aberrant responses in deep and cortical structures were documented, many overlying or neighboring the previously demonstrated regions of gray matter damage. The authors postulated that the aberrant functional neural responses identified in CHF patients could contribute to the progression of the pathology of CHF.<sup>29</sup>

Cerebral metabolic abnormalities have also been demonstrated on magnetic resonance spectroscopy imaging, affecting the gray matter earlier and progressing more rapidly than similar changes in periventricu-

lar white matter. Loss of a specific neuronal marker, N-acetylaspartate, in the occipital lobe was associated with duration of CHF symptoms and CHF mortality.<sup>30</sup>

### Sleep-disordered breathing

Half of CHF patients have sleep-disordered breathing, 40% due to Cheyne-Stokes respiration and central apneas and 10% to obstructive apneas.<sup>31</sup> The disruption of sleep cycles leads to a reduction of restorative sleep with daytime somnolence and cognitive impairment. This pattern is important to recognize because effective treatment for 1 to 3 months has been demonstrated to improve quality of life and reduce symptoms of daytime fatigue, inattention, and memory complaints, as well as improving LVEF by 5% to 10%.<sup>32</sup>

The presence of central breathing abnormalities may also be an indicator of impending exhaustion of CBF autoregulatory mechanisms. Cerebrovascular reactivity was assessed by TCD monitoring during hypocapnia (voluntary hyperventilation) and hypercapnia (20-second breath-holding) in CHF patients with and without central sleep apnea.<sup>33</sup> Apnea patients had poorer cerebrovascular reactivity, primarily due to poor vasoconstrictor response during hypocapnia, and smaller CBF surges after breath-holding. This impairment was proposed to be the cause of the breathing instability by causing ventilatory overshooting with high  $PCO_2$  and undershooting during low  $PCO_2$ .

### Depression and pseudodementia

Depression is reported by about half of CHF patients and correlates with NYHA class and perceived control of their illness.<sup>34</sup> Depression is significantly associated with abnormalities on neuropsychological testing, and may contribute to cognitive impairment through poor attention and effort. Among young patients with end-stage CHF, 37% reported depressive symptoms in a pretransplant evaluation.<sup>6</sup> Those who went on to transplantation experienced some reduction in anxiety, but both transplanted and non-transplanted patients exhibited increased depression over a mean follow-up of 3 years.<sup>6</sup>

### Concomitant dementias

Cognitive impairment has been described in patients after heart surgery, particularly those procedures that require cardiopulmonary bypass or opening the cardiac chambers. A clinically apparent confusional state or encephalopathy identified by simple cognitive screening persists to the fourth postoperative day in 5% to 12% of patients, but 80% of cases resolve by discharge.<sup>17</sup> However, detailed neuropsychological testing reveals cognitive deficits in 35% to 75% of

patients, strongly linked to age.<sup>17</sup> Persistent coma or “failure to awaken” after heart surgery is fortunately rare, at 0.2%.<sup>17</sup> Patients with advanced CHF are also at increased risk for malignant arrhythmias and cardiac arrest. Overall, about 20% of CHF patients have another cause for dementia, such as Alzheimer disease, with or without an element of vascular dementia.<sup>5</sup>

## CONCLUSION

Cognitive impairment in CHF is common, affecting half of all patients, and increases with the severity of heart disease and advanced age. It is an important predictor of disability, poorer quality of life, increased frequency of hospital admissions, and mortality. Cognitive screening should be routinely incorporated into patient evaluations, particularly when poor compliance is identified. The mechanism of cognitive impairment is multifactorial, and multiple causes may be present in any individual patient, which increases the complexity of the evaluation but also offers the possibility of multiple avenues for improvement.

## REFERENCES

- Pullicino PM, Halperin J, Thompson J. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000; 54:288–298.
- Almeida OP, Flicker L. The mind of a failing heart: a systematic review of the association between cognitive functioning. *Intern Med J* 2001; 31:290–295.
- Sabatini R, Barbisoni P, Rozzini R, Trabucchi M, Zuccalà G. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology* 2002; 59:651.
- Zuccalà G, Onder G, Pedrone C, et al on behalf of the GIFA (SIGG-ONLUS) Investigators. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results of a multicentre survey. *J Neurol Neurosurg Psychiatry* 2001; 70:109–112.
- Zuccalà G, Cattell C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997; 63:509–512.
- Bornstein RA, Starling RC, Myerowitz P, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. *Acta Neurol Scand* 1995; 91:260–265.
- Putzke J, Williams MA, Rayburn BK, Kirklin JK, Boll TJ. The relationship between cardiac function and neuropsychological status among heart transplant candidates. *Card Fail* 1998; 4:295–303.
- Schall RR, Petrucci RJ, Brozena SC, Cavarocchi NC, Jessup M. Cognitive function in patients with symptomatic heart dilated cardiomyopathy before and after cardiac transplantation. *J Am Coll Cardiol* 1989; 14:1666–1672.
- Evangelista LS, Dracup K. A closer look at compliance research in heart failure patients in the last decade. *Prog Cardiovasc Nurs* 2000; 15:97–103.
- Gregory D, Kimmelstiel C, Perry K, Parikh A, Konstam V, Konstam MA. Hospital cost effect of a heart failure disease management program: The Specialized Primary and Networked Care in Heart Failure (SPAN-CHF) Trial. *Am Heart J* 2006; 151:1013–1018.
- Hays AG, Sacco RL, Rundek T, et al. Left ventricular systolic dysfunction and the risk of stroke in a multiethnic population. *Stroke* 2006; 37:1715–1719.
- Siachos J, Vanbassel A, Feldman DS, Uber W, Simpson KN, Pereira NL. Silent strokes in patients with heart failure. *Card Fail* 2005; 11:485–489.
- Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial dysfunction. *N Engl J Med* 1997; 336:251–257.
- Dries DL, Rosenberg YD, Waclawiw MA, Domanske MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm. *J Am Coll Cardiol* 1997; 29:1074–1080.
- Kalaria VG, Passannante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. *Am Heart J* 1998; 135:215–220.
- Nadareishvili ZG, Choudary Z, Joyner C, Brodie D, Norris JW. Cerebral microembolism in acute myocardial infarction. *Stroke* 1999; 30:2679–2682.
- Sila CA. Cardiac catheterization, angiography and surgery. In: Noseworthy J, ed. *Neurological Therapeutics: Neurologic Complications of Systemic Illness*. London, UK: Martin Dunitz; 2006:1383–1388.
- Massie BM, Krol WE, Ammon SE, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. *J Card Fail* 2004; 10:101–112.
- Pullicino P, Thompson JL, Ammon SE, et al. Warfarin Aspirin in Reduced Cardiac Ejection Fraction (WARCEF): rationale, objectives, and design. *J Card Fail* 2006; 12:39–46.
- Pullicino PM, Hart J. Cognitive impairment in congestive heart failure? Embolism vs hypoperfusion. *Neurology* 2001; 57:1945–1946.
- Gruhn N, Larsen FS, Borsgaard S, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001; 32:2530–2533.
- Massaro AR, Dutra AP, Almeida DR, Diniz RV, Malheiros SM. Transcranial Doppler assessment of cerebral blood flow: effect of cardiac transplantation. *Neurology* 2006; 66:124–126.
- Ackerman RH. Cerebral blood flow and neurological changes in chronic heart failure. *Stroke* 2001; 32:2462–2464.
- Georgiadis D, Sievert M, Cencetti S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J* 2000; 21:407–413.
- Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. *Stroke* 1991; 22:195–199.
- Steinborn W, Anker SD. Cardiac cachexia: pathophysiology and clinical implications. *Basic Appl Myol* 2003; 13:191–201.
- Caplan LR. Cardiac encephalopathy and congestive heart failure. *Neurology* 2006; 66:99–101.
- Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol* 2003; 95:677–684.
- Woo MA, Macey PM, Keens PT, et al. Functional abnormalities in brain areas that mediate autonomic nervous system control in advance heart failure. *J Card Fail* 2005; 11:437–446.
- Lee CW, Lee JH, Lim TH, et al. Prognostic significance of cerebral metabolic abnormalities in patients with congestive heart failure. *Circulation* 2001; 103:2784–2787.
- Javaheri S, Parker TJ, Wexler L, et al. Occult sleep-disordered breathing in stable congestive heart failure. *Ann Intern Med* 1995; 122:487–492.
- Cormican LJ, Williams A. Sleep disordered breathing and its treatment in congestive heart failure. *Heart* 2005; 91:1265–1270.
- Xie A, Skatrud JB, Dempsey JA, Morgan B, Russell D. Cerebrovascular response to carbon dioxide in patients with congestive heart failure. *Am J Respir Crit Care Med* 2005; 172: 371–378.
- Westlake C, Dracup K, Fonarow G, et al. Depression in patients with heart failure. *J Card Fail* 2005; 11:30–35.

**Address:** Cathy A. Sila, MD, Neurological Institute, Cleveland Clinic, 9500 Euclid Avenue, S91, Cleveland, OH 44195; silac@ccf.org.