

**MEMORY PERFORMANCE AMONG TAIWANESE POSTMENOPAUSAL WOMEN
WITH HEART FAILURE**

By

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DEDICATION

To my parents, parents-in-law, husband, and children

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ABSTRACT

Memory deficits have been reported in patients with chronic HF (heart failure). However, little is known about memory performance and the factors that explain memory performance in women with HF. The purposes of this study were to (a) examine the memory performance among Taiwanese postmenopausal women with heart failure (HF) compared to age- and education-matched healthy women, and to determine the factors that explain memory performance in women with HF, (b) evaluate the validity of the Chinese version of the CogState battery among women with HF in Taiwan, and (c) examine type, frequency, and severity of menopausal symptoms in women with HF, compared with healthy participants, and to explore the association between menopausal symptoms and memory performance among Taiwanese postmenopausal women with HF.

A cross-sectional design was used in this study. Seventy-six women with HF and 64 healthy women were recruited from one medical center in Taipei, Taiwan. Women completed memory tests and measures of demographic variables, menopausal symptoms, HF severity symptoms, and global cognitive function. Clinical variables were obtained from medical records. Descriptive statistics, comparative statistics, exploratory factor analysis, Pearson product-moment correlation coefficients, and multiple regression analyses were used.

Women with HF performed significantly worse than healthy women on working and verbal memory tests. Among women with HF, older age explained working memory; older age, higher HF severity, more comorbidities, and systolic HF explained verbal memory. In addition, the Chinese CogState Battery had satisfactory construct and c

onvergent validity. Furthermore, women with HF had worse menopausal symptoms on subscales for psychological (anxiety and depressive), somatic, and vasomotor symptoms compared with healthy women. Anxiety and sexual symptoms were significantly associated with visual and verbal memory performance. In summary, the Chinese CogState Battery is a valid measure of memory performance in Taiwanese women with HF. Women with HF had poorer memory performance and more severe menopausal symptoms compared with healthy women. Nurses and health care professionals should assist women with HF by early assessment and recommendations regarding compensation for memory deficits. Interventions tailored to these identified factors can be developed to improve memory performance for Taiwanese postmenopausal women with HF.

Key words: Heart failure, Memory, Postmenopausal, Women

Word: 348 ---max is 350

CHAPTER I

Introduction

Heart failure (HF) affects 6.6 million people, with 670,000 new cases diagnosed annually in the United States (Roger et al., 2012). The prevalence of HF rises with increasing age due to long-standing cardiovascular abnormalities. The most common causes of HF include coronary artery disease, hypertension, and valvular heart disease. The affected heart is unable to pump vigorously enough to support the needs of the body (Brozena & Jessup, 2003). In particular, the brain is a critical organ that requires oxygen to function (Lezak, 2004). Moreover, as cardiac output continues to decline, the neurohormonal counter-regulatory response to HF leads to deterioration of cardiac function and a decrease in the autoregulation mechanisms and may increase vascular resistance, which contributes to the reduction of cardiac output to the brain (Choi et al., 2006; Gruhn et al., 2001; Sila, 2007). Heart failure is, however, a chronic condition in which the body has time to activate compensatory mechanisms for improving cardiac performance (Davis, 2002).

Cognitive deficits, including memory changes, resulting from cardiovascular diseases are a matter of increasing interest. Memory is a set of functional systems that is supported by distinct and interrelated regions of the brain. Research has indicated that there are neurobiological changes and brain abnormalities that occur in the hippocampus in HF, which may affect memory functioning (Gruhn et al., 2001; Kumar et al., 2009; Vogels, & Flier, et al., 2007; Vogels, Oosterman, van Harten, & Gouw, et al., 2007). Evidence supports the biological hypothesis that HF has an adverse effect on memory performance. Research related to memory deficits in HF

shows deficits in working memory and episodic long-term memory (Hawkins et al., 2012; Kindermann et al., 2012; Pressler et al., 2010; Sauvé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009; Vogels, Oosterman, van Harten, Scheltens, van der Flier, Schroeder-Tanka, et al., 2007). Importantly, cognitive deficits in patients with HF have been found to be associated with disability, decreased quality of life, increased frequency of hospital readmissions, and mortality (Sila, 2007).

Recent review of the literature demonstrated a prevalence rate of cognitive deficits ranging from 25%-50% in patients with chronic HF (Pressler et al., 2010; Sauvé et al., 2009; Vogels, Oosterman, van Harten, Scheltens, et al., 2007). In a study conducted to explore hypotension and cognitive impairment, women with HF (n=836) had an increased probability of cognitive impairment compared to men (n=747), as assessed by the Hodkinson Mental Test (Zuccala et al., 2001). Altimir et al. (2005) evaluated 360 HF patients (27.5% women) using the Pfeiffer Test and found more frequent abnormal cognitive testing scores in women than men (15.2 % vs. 5 %, $p = 0.003$). Bennett, Baker and Huster (1998) used a self-report measure of cognitive function among 30 women with HF and found that cognitive deficits were a problem for over one third of them. Moreover, female gender was associated with poorer memory performance on the tasks of attention, early recall, and delayed recall (Sauvé et al., 2009).

Approximately 46% of HF cases are estimated to be women (Roger, et al., 2012). Women with HF exhibit more physiological and psychological symptoms than men but are less likely to be referred for treatment and clinical trials (Frazier et al., 2007; Stromberg & Martensson, 2003). Moreover, women with HF experience more hospital discharges and have longer hospitalizations than men, leading to increased costs (Roger et al., 2012; Frazier et al., 2007). Most research

involving HF has been studied predominantly in men, with results generalized to women. Women have been under-represented in cardiovascular research (Klabnik & Murin, 2012).

Of women diagnosed with HF, 70% are older than 50, the average age of menopause (Schocken, Arrieta, Leaverton, & Rosse, 1992; Roger et al., 2012). Some studies have demonstrated that estrogen acts as a neuroprotector in maintaining cognitive function among healthy elderly women (Lebrun et al., 2005; Heys et al., 2012), perhaps related to the fact that there are multiple sites of estrogen receptors in the brain, including the hippocampus (the main structure for memory) (Ancelin & Ritchie, 2005). With their current life expectancy, women are more likely to live one third of their lives in the postmenopausal stage, a state of relative estrogen deficiency (Lebrun et al., 2005). The possible acceleration of memory decline in postmenopausal women with HF may lead to difficulties in regard to maintenance of functional ability for successful living. However, despite the importance of estrogen in maintaining cognitive function, results from studies of cognition and HF have failed to provide information about memory performance in postmenopausal women.

Overall, almost all studies of memory function in the HF population have combined results for men and women (Hawkins et al., 2012; Kindermann et al., 2012; Pressler et al., 2010; Pressler et al., 2011; Sauvé et al., 2009; Vogels, Oosterman, van Harten, Scheltens, et al., 2007), thus, we know little about gender specific differences. Only one study addressed women with memory deficits, using self-report methods (Bennett et al., 1998). Importantly, no studies were found that investigated the association between menopausal symptoms related with estrogen decline and memory function. Although memory function in HF has been studied in the western countries, no data were available for Asian countries, including Taiwan.

Statement of the Problem

Evidence suggests that HF has an adverse effect on memory performance and the neurobiological changes and brain abnormalities that appear in areas involved in memory function (Vogels, Oosterman, van Harten, & Gouw, et al., 2007; Woo et al., 2009). To our knowledge, no published studies have explored the nature of memory performance and related factors among women with HF. Although literature suggests estrogen influences memory function (Luine & Frankfurt, 2010; Heys et al., 2011), no study has been identified that examines menopausal symptoms associated with estrogen decline in relation to memory performance in women with HF. Furthermore, little is known about the nature of memory performance among postmenopausal Taiwanese women with HF. One reason is likely due to lack of the valid psychometric instruments for detecting memory decline in Chinese-speaking populations such as Taiwan.

Structure of the Dissertation

This is a three-manuscript format dissertation. The chapters include the introduction, three manuscript-style papers, and a conclusion. The first chapter provides a brief background, statement of the problem, and theoretical perspectives. Chapter 2 presents the first paper which examines memory performance in Taiwanese postmenopausal women with HF and possible influencing factors. Chapter 3 is the second paper, which examines validity of the Chinese Version of the CogState computerized cognitive assessment battery. Chapter 4 is the third paper, which addresses results for menopausal symptoms and their relationships to memory performance among Taiwanese postmenopausal women with HF. Chapter 5, the final chapter, presents a summary of the findings, strengths, weaknesses, limitations, and implications of the three papers and directions for future research.

Theoretical Perspectives

The theoretical perspectives for the study link the neurobiological theory of heart failure, the biological theory of menopausal-related estrogen loss in post-menopausal women, and the neurobiological theory of estrogen to the neurobehavioral theory for memory functioning, specifically working memory and episodic memory.

Memory Functioning

Memory, a critical aspect of cognition, is the way the human brain processes information for later usage (Budson, 2009), or the mental ability to encode, store, and retrieve information (Sherwin & Henry, 2008). These processes ensure that knowledge is gained and recalled for use in our environment. Memory is necessary for high level cognitive functions such as language processing, visuospatial thinking, reasoning, problem solving, and decision making (Kandel, Kupfermann, & Iversen, 2000). Human memory consists of several functional systems that contribute to the encoding, storing, and retrieving of information (Giovanello & Verfaellie, 2001). A major aspect of memory relates to duration of retained information, such as working memory or short-term memory and long-term memory (Giovanello & Verfaellie, 2001). Memory can additionally be categorized by the material sources to be remembered, such as verbal or visual memories (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). For example, verbal memory refers to memory for words and verbal items. It is the ability related to use of words, such as recall of words or materials that can be mediated verbally (Kimura, 1999).

Working memory refers to the cognitive ability to temporarily store and manipulate limited amounts of information for use in guiding behavior (Baddeley, 2000). The characteristics of working memory are applicable to more complex mental tasks that maintain information in the service of ongoing cognitive activities (Baddeley, 2000). According to Baddeley and Hitch (1974), working memory is composed of the central executive system and two short-term storage

systems. The central executive system is a control system of limited attentional capacity that is responsible for manipulating information and coordinating information flow to and from short-term memory systems (Repov & Baddeley 2006). The short-term storage systems store and maintain different types of information (phonological and spatial). The core working memory system is prefrontal cortex (Budson, 2009). The rate of decline of working memory has been shown to be equivalent decade by decade (Park et al., 2002); deficits for working memory among individuals at age 70 and older are greater than for other ages in both verbal and visuospatial memory (Conner, 2001). Impairment of working memory may present in different ways. For example, because attention control has the ability to inhibit irrelevant information, decreased attentional capacity may lead to cognitive and behavioral manifestations such as distractibility, impulsivity, and irritability (Chiu, 2002). Patients with impaired working memory show an inability to pay attention, which leads to the problem of holding new or modified information for short-term, which cannot later be encoded into episodic long-term memory (Budson, 2009; Fletcher & Henson, 2001).

Episodic memory is a declarative long-term memory system for personally experienced events (Budson, 2009; Tulving, 2002). Episodic memory processes include the encoding, storage, and retrieval processes that mediate different forms of memory (Mayes & Roberts, 2001). The process of storing information as long-term memory, or consolidation, is the processing of encoded information from hippocampal and medial temporal lobes to the neocortex for long-term memory storage (Lezak, 2004). The episodic memory system is dependent on the medial temporal lobes, including the hippocampus. Other structures involved in episodic memory are the prefrontal cortex, the fornix, the mammillary body, and the anterior thalamus nucleus (Budson, 2009). Episodic memory declines moderately under 50 years of age; age-related

decline accelerates significantly over 50 years of age (Verhaeghen & Salthouse, 1997). Memory declines associated with aging are found in encoding and retrieving of information; storage of information is least affected (Price, Said, & Haaland, 2004).

Neural Processes in Heart Failure and their Effect on Memory

Although the causes for heart failure that result in neurobiological change that may contribute to memory deficits are not known, factors that might be associated include decreased cerebral blood flow leading to deprivation of oxygen and glucose supply, or to metabolic disturbances and HF-related cerebral embolism (Alves & Busatto, 2006). There is evidence of neurological change including neurobiological damage, cerebral circulation reduction, and brain abnormalities in relation to cerebral hypoperfusion in animal models and heart failure patients; some studies also included memory function measures and are described in the following section.

Neurobiological damage in chronic cerebral hypoperfusion. Given that HF is accompanied by reduced cerebral blood flow, animal models showing chronic cerebral hypoperfusion have been applied to humans to examine neuropathologic changes in the hippocampus, one of the brain regions most sensitive to decreased oxygenation (Farkas et al., 2007). Neurobiological damage includes loss of neurons and reduction of dendritic arborizations and synaptic contacts and is hypothesized to be related to spatial learning and memory (Bennett, Tenniswood, Chen, Davidson, & Keyes, 1998; Liu, Zhang, Zheng, & Zhang, 2005). Moreover, some studies in animals have reported that the severity and extent of brain damage depend on the degree and duration of hypoperfusion (Farkas et al., 2007; Kaplan et al., 1991).

Cerebral circulation reduction in heart failure. Studies investigating HF influences on cerebral circulation and glucose metabolism have been established. Global and regional cerebral blood flow reductions were found in HF studies (Choi et al., 2006; Gruhn et al., 2001; Vogels et

al., 2008). Some evidence showed that decreased cerebral blood flow was related to cognitive deficits in HF patients (Alves et al., 2005; Jesus et al., 2006).

Brain abnormalities in heart failure. Studies have reported structural brain abnormalities such as brain atrophy and volume loss in HF patients, as assessed by use of magnetic resonance imaging (MRI). Heart failure patients showed significant medial temporal lobe atrophy as compared to other cardiac patients and healthy controls (Vogels, Flier, et al., 2007). The medial temporal lobe atrophy was significantly negatively correlated with memory (Vogels, Oosterman, van Harten, & Gouw, et al., 2007). Reduced gray matter in the brain presented in areas related to short-term memory and learning, such as the hippocampus and hippocampus output fibers that project to the anterior thalamus, caudate nuclei, anterior fornix, and corpus callosum in HF patients (Woo et al., 2009). A past study found that mammillary body volumes and cross-sectional fornix areas fibers (which are essential to the route signals between areas integrating memory formation) were significantly reduced in HF (Kumar et al., 2009).

Menopause

Menopause is characterized by the cessation of menstruation for twelve months or more; the average age of menopause is 51 years old. Sex hormone levels, such as those for estrogen and progesterone, are reduced because of decreased ovarian activity after menopause (Lokken & Ferraro, 2006). Although ovarian production of estrogen ceases after menopause, postmenopausal women continue to register detectable concentrations of circulating estrogen. Estrogen (estradiol, E2) is primarily produced by aromatization of testosterone and reduction of estrone (E1), in turn arises through aromatization of androstenedione in peripheral adipose tissue (Judd, Shamonki, Frumar, & Lagasse, 1982; McTiernan et al., 2008). Estradiol levels rise and fall throughout the menstrual cycle, with the average estradiol level being approximately 100 to

110 pg/ml (Berga, 2002). After menopause, estrogen levels drop markedly and frequently are below the detection limits of the assay (Al-Azzawi & Palacios, 2009). By three years after postmenopausal decline, estrogen levels attain relative stability to the normal postmenopausal values of 13.3 pg/ml (SD=24.7 pg/ml). Several factors are associated with estrogen concentrations. For example, postmenopausal women with increased body mass index (BMI) show higher levels of serum estradiol and estrone (Rannevik et al., 1995). One study found that the passage of time after menopause was negatively associated with estradiol concentrations (Chubak et al., 2004).

Menopausal symptoms are those that directly result from estrogen decrease as women go through menopausal stages (Rahman, Zainudin, & Mun, 2010). Symptoms can be grouped into vasomotor symptoms such as hot flushes (also referred to as hot flashes) and night sweats, physical symptoms (dizziness tightness in head or body, parts of body feeling numb, headaches, muscle and joint pains, loss of feeling in hands or feet, and breathing difficulties), psychological symptoms (anxiety and depression) and sexual complaints (loss of interest in sex) (Greene, 1998). Symptoms in women at the post-menopause stage are variable due to diverse biological and psychosocial factors. Estrogen decline is the most important factor that might explain the symptom differences (Malacara, Prez-Luque, Martnez-Garza, & Snchez-Marn, 2004).

Studies indicated that symptom severity correlates with estrogen changes. In longitudinal studies of the menopausal transition in early postmenopausal women, low estrone levels (highly correlated with serum estradiol levels) have been associated with higher hot flash severity and decreased sexual desire (Woods, Mitchell, & Smith-Dijulio, 2010; Woods, Smith-Dijulio, Tao, & Mitchell, 2007). Moreover, a study of 88 symptomatic menopausal women showed relief from vasomotor symptoms, psychological disturbances, genital symptoms, and urinary

symptoms after using hormone therapy (HT) (Akhila & Pratapkumar, 2006). Other studies also reported that HT was associated with significant improvements in hot flushes, and quality-of-life scores in symptomatic postmenopausal women (Lobo et al., 2009; Pinkerton, Pickar, Racketta, & Mirkin, 2012).

Neurobiological Effects of Estrogen on Memory

Estrogen in the central nervous system. Estrogen potentially affects cognitive function by means of mechanisms that influence the structure and function of the brain. There are two types of estrogen receptors, ER- α and ER- β , localized in the hypothalamus, hippocampus, cerebral cortex, midbrain, and brainstem (Sherwin & Henry, 2008). Estrogen acts on the central nervous system by modulating the synthesis, release, and metabolism of neurotransmitters and neuropeptides. It also exerts effects on neuron excitability, morphological structure, and synaptic functionings through plasma membrane-associated estrogen receptors (Genazzani, Pluchino, Luisi, & Luisi, 2007). Estrogen additionally affects neurotransmitters such as in the serotonergic, cholinergic, dopaminergic, and nonadrenergic systems that can contribute to numerous cognitive functions (McEwen, 2002). Moreover, estrogen exerts neurotrophic effects because estrogen-binding sites co-localize and facilitate neurotrophins such as the brain-derived neurotrophic factor (BDNF) (Scharfman & Maclusky, 2005). Estrogen may also have neuroprotective effects in reducing cell apoptosis (Nilsen, Mor, & Naftolin, 2000) and modulating neuronal growth and synaptic plasticity (Woolley & McEwen, 1998).

Estrogen reflected brain areas and domains. Post-mortem studies in brain areas have shown that estradiol concentrations were significantly higher in brains of fertile women as compared to postmenopausal women, which indicates that peripheral serum levels of estradiol are reflected in the brain (Bixo et al., 1995). Fluctuating levels of estrogen change structure and

functional plasticity in the adult hippocampus in animal models (Woolley, 1998). Studies have found that estrogen treatment increased dendritic spine density on CA1 pyramidal neurons in the hippocampus (Gould, Woolley, Frankfurt, & McEwen, 1990) as well as enhancing N-methyl-D-aspartate (NMDA) receptors binding in the CA1, which related to increased dendritic spine density and sensitivity in CA1 (Cyr et al., 2001). Finally, hippocampus-dependent cognitive function may be affected, such as in memory and learning (Sherwin & Henry, 2008).

In summary, theoretical perspectives suggest that HF and estrogen decline after menopause may influence memory performance-associated areas of the brain, including the hippocampus. Postmenopausal women with HF may have poorer working memory and episodic memory (verbal memory, and visual memory) compared to healthy postmenopausal women. Age, HF severity, and postmenopausal symptoms associated with estrogen decline that may affect memory performance are hypothesized to explain working memory and episodic memory deficits among postmenopausal women with HF. To understand memory performance and possible influencing factors in postmenopausal women with HF, this study provides a scientific basis to explore mechanisms of memory performance and develop effective nursing interventions for improving memory among postmenopausal women with HF.

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CHAPTER II

Memory Performance among Taiwanese Postmenopausal Women with Heart Failure

Abstract

Background: There are limited data describing the nature of memory deficits in women with HF.

Objectives: The aims of this study were to examine the memory performance among Taiwanese postmenopausal women with HF compared to age- and education-matched healthy women, and to determine the factors that explain memory performance in women with HF.

Methods and Results: Seventy-six women with HF and 64 healthy women were recruited from Taiwan. Women completed memory tests; measures of the postmenopausal symptoms associated with estrogen decline and HF severity were collected. Women with HF performed significantly worse than healthy women on tests of working memory and verbal memory. Among women with HF, older age explained poorer working memory; older age, higher HF severity, more comorbidities, and systolic HF explained worse verbal memory.

Conclusion: The study provides important insights into poor memory performance in Taiwanese postmenopausal women with HF and significant factors associated with performance.

Interventions focusing on those factors should be tested to prevent memory loss in women in HF.

Key words: Heart failure, Memory, Postmenopausal, Women

Word: 172 --JCF --max is 200

Introduction

Heart failure (HF) affects more than 6.6 million adults in the United States.¹ Of patients with heart failure, approximately 46% are estimated to be women, and at least 70% of those women are above 50 years of age.^{1,2} Although women with HF have been less studied than men,³ they have reported worse physiological and psychological symptoms,^{4,5} more hospital discharges¹ and longer hospitalizations than men, leading to increased costs for HF care.^{4, 6}

Cognitive deficits have been reported in patients with HF.^{7, 8} Patients with HF have more than a 4-fold increased risk for development of cognitive impairment compared to persons without HF.⁹ According to past studies, the prevalence of cognitive dysfunction is estimated to be 25% to 50% among the HF population.^{7,9,10} The most frequently affected cognitive domain found in HF patients is memory.¹¹ Past studies have indicated that HF patients experienced impaired working memory, verbal memory and visual memory.¹²⁻¹⁵ Memory deficits in HF patients indicate difficulties in learning, storing, and retrieving new information. Individuals with decreased memory function are unable to effectively function in daily life, are more likely to have difficulties in learning, retaining, and recalling information in understanding and participating in treatment decisions, and adhering to long-term self-care management programs.¹¹⁻¹³

Almost all studies of cognitive deficits in the HF population have included samples with more men than women, and few studies have reported cognitive results separately for women with HF. In a study that included 1583 hospitalized patients with HF, investigators assessed cognitive impairment using the Hodkinson Abbreviated Mental Test. The results indicated that being female and having HF (n=836) was associated with an increased probability of cognitive impairment.¹⁶ One study examined cognitive function using the Pfeiffer Short Portable Mental

Test; 360 patients (mean age 65.2 years, 41.7% \geq 70 years, 27.5% women) were evaluated. Scores on the Pfeiffer Test were abnormal in 7.8% of patients, and an abnormal score was more frequent in older patients (14% vs. 3.3%, $p < 0.001$) and in women (15.2% vs. 5%, $p = 0.003$).¹⁷ Bennett, Baker, and Huster¹⁸ used a self-report measure of cognitive impairment, the Alertness Behavior Scale (ABS) of the Sickness Impact Profile, among 30 women with HF. The ABS describes problems patients experience in memory, attention and concentration. Over one third of the women reported that cognitive deficits were a problem. However, the above studies used a screening or self-report questionnaire to assess cognitive function, rather than using valid neuropsychological tests. Moreover, study participant groups were selective: two of the studies included only elderly patients and two studies recruited hospitalized patients. There are little data on memory function in the population of women with HF.

Although the underlying mechanism for memory loss in HF remains unclear, the most widely accepted potential etiologies are brain injury from multiple cerebral emboli and decreased cerebral blood flow caused by low cardiac output, leading to impaired cerebral autoregulation, cerebral hypoperfusion, and deprivation of oxygen to the brain.¹⁹⁻²³ Studies have suggested that global cerebral blood flow was reduced in HF patients. Gruhn et al.²¹ documented that global cerebral blood flow measured by single photon emission computed tomography was significantly reduced by 31% in patients with New York Heart Association (NYHA) functional Class III and IV (n=12) compared to a healthy group (n=12). Choi et al.²⁴ found that global cerebral blood flow was 19% less in HF patients (n=52) than in age-matched healthy participants (n=10). Global cerebral blood flow was related to severity of HF measured by NYHA functional class, serum B-type natriuretic peptide level and duration of HF. Some evidence showed that decreased cerebral blood flow was related to cognitive deficits in HF. Alves et al.²⁵ found

significant reductions of cerebral blood flow in HF patients compared to age-matched elderly healthy control participants. The degree of cognitive deficits, assessed by the Cambridge Mental Disorders of the Elderly Examination (CAMCOG), was correlated with cerebral blood flow in the posterior cingulate cortex and precuneus (areas involved in tasks including episodic memory retrieval, spatial orientation and memory). Jesus et al.²⁶ also reported that decreased cerebral blood flow velocity in the right middle cerebral artery was significantly related to lower Mini-Mental Status Examination (MMSE) score in patients with HF ($n=83$) ($r = 0.231$ $p = 0.039$).

Evidence from animal models suggests that inadequate cerebral perfusion and cerebral hypoxia result in neuronal damage and loss of dendritic structure and synaptic contacts in the hippocampus that may prove to be one of the mechanisms of memory impairment.²⁷ The hippocampus is one of the regions of the brain most vulnerable to reduced blood flow.²⁸ The hippocampus, located within the medial temporal lobe, is essential in the acquisition of new information, and consolidating items from short-term to long-term memory. Conjecturally, then, the damage in affected brain areas such as the hippocampus may lead to learning difficulties and short-term and long-term memory problems.

Studies using magnetic resonance imaging (MRI) support that structural changes such as brain atrophy and volume loss appear in areas involved in memory loss. Schmidt et al.²⁹ demonstrated that HF patients with a significantly higher rate of cortical and ventricular atrophy performed worse on verbal memory and learning, and vigilance tests. Vogels et al.³⁰ identified more medial temporal lobe atrophy in HF patients ($n=58$) as compared to healthy control participants ($n=42$). In their further study,³¹ the investigators also found medial temporal lobe atrophy to be significantly and negatively correlated with memory. Brain volume loss was demonstrated in HF patients. Woo et al.³² reported reduced gray matter in the brain in areas

related to short-term memory and learning, including the hippocampus and hippocampus output fibers that project to the anterior thalamus, caudate nuclei, anterior fornix, and corpus callosum in HF patients (n=13) compared to age-matched healthy control participants (n=49). Additionally, women with HF (n=5) had more injured areas, although the sample was small. Moreover, Kumar et al.³³ found that mammillary body volumes and cross-sectional fornix areas were significantly reduced in HF patients (n=17) as compared to control participants (n=50). The authors suggested that the injured mammillary body and fornix fibers may contribute to impaired spatial and working memory because of their important roles to memory processing.

Some evidence revealed that memory performance decreases with increasing age in HF.^{13,}
^{34, 35} Others reported that years of education are positively related to memory function.^{13, 36} Multiple comorbidities are common in patients with HF and their combined etiology has been related to deficits in verbal learning.¹³ One study demonstrated that some chronic conditions such as hypertension are independent predictors of cognitive impairment.³⁷ Increased severity of HF has been related to more deficits in verbal^{13, 37, 38} and working memory.³⁷ Almost all studies of memory function in the HF population have combined men and women; thus, we know little about gender-specific factors that may influence memory in women with HF.

The relationship between memory deficits and their contributing factors has not been examined fully in women with HF. One factor that may be related to memory function in women with HF is estrogen level. Estrogen potentially affects cognitive function by means of mechanisms that influence the structure and function of the brain. The hippocampus, one of the brain areas with many estrogen receptors, is known to be the main structure for memory.^{39, 40} Studies have shown that endogenous estrogen has a positive association with verbal memory in healthy postmenopausal women.⁴¹⁻⁴³ Although estrogen levels have been associated with

menopausal symptoms,⁴⁴ no studies were found in the literature that have examined menopausal symptoms or effects of estrogen decline after menopause, such as menopausal status, use of hormone replacement therapy,¹⁴ and duration of menopause, that may contribute to memory deficits in women with HF.

In summary, although nearly half of the patients with HF are women, most studies of cognitive function in HF patients have combined men and women. There are limited data describing the nature of memory deficits in women with HF. In addition, no studies were found that considered the gender-specific factors that may influence memory function and examined memory performance in a sample of women with HF who were postmenopausal. Therefore, the primary aim of this study was to examine memory performance among Taiwanese postmenopausal women with HF compared with age- and education-matched healthy control participants. The secondary aim was to evaluate factors that explain memory performance among women with HF. Hypotheses were (1) Taiwanese postmenopausal women with HF have poorer working memory, verbal memory, and visual memory performance in comparison with age- and education-matched healthy women participants and (2) age, HF severity, and postmenopausal symptoms associated with estrogen decline explain working memory, verbal memory, and visual memory performance among Taiwanese postmenopausal women with HF.

Method

Design and Procedures

This cross-sectional study used a convenience sample. Approvals for protection of human subjects were obtained from the University of Michigan, Health Science Human Subject Review Committee, and Institutional Review Board of the Tri-Service General Hospital in Taipei,

Taiwan. Patients were recruited from the Tri-Service General Hospital from November 2010 to October 2011.

After obtaining written informed consent, a registered nurse with neuropsychological assessment training collected the data. Participation included face-to-face interviews for both HF and non-HF groups and medical records review for the HF group. The interviews took place in private rooms at hospital outpatient clinics. Baseline data including demographic and clinical information, postmenopausal symptoms associated with estrogen decline, HF severity, and global cognitive function were collected by the investigator using questionnaires. After completing questionnaires, the investigator explained and administered computerized neuropsychological tests with a laptop computer. Participants were not required to have prior computer experience to take the computerized tests. The administration time of the interview was about 60 to 90 minutes. To ensure a quiet environment with minimal distractions, the participants used noise cancelling headphones to minimize distraction noise. Participants were requested to turn off their cell phones and their family and friends were required to wait outside the room during the neuropsychological tests. There was a sign on the door that read “Testing- Please Do Not Disturb”. Participants were paid \$10 (NT300) in the form of a gift card for participating in the entire interview session. The investigator abstracted data about HF conditions from medical records using a structured checklist.

Sample

Seventy-six women with chronic HF were recruited from cardiovascular clinics and 64 age- and education- matched healthy women were recruited from among outpatients of the gynecology clinic, the women’s health center, and volunteers in the same hospital. Eligibility criteria for women with HF were: 1) age 50 years and older; 2) fluent in Mandarin; 3) naturally

postmenopausal based on the women's self-report and last menstrual cycle having been completed more than 12 months earlier; and 4) having a documented diagnosis of HF of duration at least 6 months. Women were excluded if they had one of the following conditions that may cause cognitive deficits: 1) a documented history of neurological disease or condition (such as stroke, Alzheimer's disease, epilepsy, head injury with loss of consciousness longer than 30 minutes, dementia, or Parkinson's disease); 2) history of recurrent mental disorders diagnosis or undergoing treatment with psychotropic medication; 3) history of drug/ alcohol abuse; 4) renal failure requiring hemodialysis and terminal cancer; 5) diagnosed encephalopathy; and 6) impaired sensory problems such as hearing loss and visual problems.

For age- and education- matched healthy women, eligibility criteria were: 1) age 50 years and older; 2) fluent in Mandarin; 3) naturally postmenopausal, as above; and 4) no major medical condition. Women who had cardiovascular risk factors controlled by medication (such as hypertension with blood pressure less than 140/90 mmHg or hyperlipidemia with cholesterol less than 200 mg/dl) were eligible for the healthy group. Women were excluded if they met any of the exclusion criteria described for the HF group.

Measures

Demographic and clinical data included personal information (age, race, education, marital status, employment status, and blood pressure) and menopausal history (age when menstruation began, number of pregnancies, number of live births, age at menopause, duration of menopause, hysterectomy and ovariectomy, and estrogen replacement therapy) that were obtained at interview. The number of comorbidities and HF condition such as left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, heart failure duration, and type of HF) were also collected from medical records for the HF group.

The Montreal Cognitive Assessment (MoCA) was used to measure global cognitive function.⁴⁵ The MoCA is a one-page 30-point test that takes 10 minutes to administer. It has eight subscores: visuospatial abilities (5 points); naming (3 points); short-term memory recall task (5 points); attention task (6 points); language (3 points); verbal abstraction task (2 points); memory (0 points); and orientation (6 points). One point is added if the participant has less than 12 years of education. The total score of the MoCA ranges from 0 to 30, with higher scores indicating better global cognitive function. The MoCA is a test with high sensitivity (90%) and specificity (87%) for detecting possible mild cognitive impairment (MCI).⁴⁵ Using the cutoff score of 23/24 to detect possible MCI, the Chinese version of the MoCA had an excellent sensitivity of 92% and specificity of 78% to detect possible MCI.⁴⁶ The criterion validity, internal consistency and test-retest reliability were satisfactory in the Chinese version of MoCA among 40 Chinese patients with cerebral small vessel disease and 40 matched controls.⁴⁷

Menopausal symptoms have been associated with estrogen levels.⁴⁴ The Greene Climacteric Scale (GCS) was used to measure postmenopausal symptoms associated with estrogen decline. The 21 items in the questionnaire reflect symptom groups for women during different menopausal stages: 2 items for vasomotor symptoms (hot flushes and night sweats); 11 items for psychological symptoms (anxiety and depression); 7 items for somatic symptoms (physical); and 1 item for loss of interest in sex (libido).⁴⁸ Each item is rated by participants according to its severity using a four-point scale as “not at all” (0), “a little” (1), “quite a bit” (2), and “extremely” (3). Factor analyses have established construct validity of the 21 symptom items.⁴⁸ Test-retest correlations range from 0.82-0.94 among menopausal women.⁴⁹ The Chinese version of the GCS has been used in postmenopausal women with satisfactory construct validity and reliability (Cronbach’s $\alpha=0.93$).^{50,51} In this study, five items that often occur in Chinese menopausal

women were added to the questionnaire: cold sweats (night or day), waking up during the night, vaginal dryness, backache, and forgetfulness.^{52,53} The total score of the questionnaire is the sum of the 26 items, ranging from 0 to 78. Higher scores indicate more symptoms or more severe symptoms. In this sample, the Cronbach's alpha was 0.90.

The NYHA functional classification and the Duke Activity Status Index (DASI) were used as two measures of perceived functional capacity to evaluate severity of HF symptoms.⁵⁴ Patients were assigned values of 1 (no symptoms of HF upon ordinary physical activity) to 4 (symptoms of HF at rest).⁵⁵ Validity and reliability of the NYHA classes have been reported.⁵⁶ The DASI is a 12-item questionnaire with 4-point response scales that measures perceived functional capacity and correlates well with peak oxygen uptake. This instrument is based on a patient's ability to perform common activities of daily living.⁵⁷ The activities in the questionnaire include personal care, ambulation, household tasks, sexual function, and recreation.⁵⁸ Each item is weighted by metabolic cost, and the total score is calculated by multiplying the weights of the 12 items. Possible scores range from 0 to 58.2. Higher scores represent better perceived functional capacity. The Cronbach's α reliability coefficient for DASI scores was high (0.87) in a chronic HF population.⁵⁹ This questionnaire has been validated in the Chinese language.⁶⁰ In the present sample, the Cronbach's alpha was 0.69.

Six tasks from the CogState neuropsychological test battery were administered to measure memory performance and other cognitive abilities. Reviews of each test have been described in detail.^{61, 62, 63} Although the primary outcomes of the study relate to memory performance, we also included measures of psychomotor speed (Detection task, DET) and attention (Identification Task, IDN). On the CogState tests, each task had an instructional part and a scored part presented on the computer screen for participants to complete. The DET assesses psychomotor

speed by measuring speed of performance. Participants respond to the face-up card as soon as possible in the task. The Identification Task assesses working memory by measuring speed of performance. Participants are asked to press different keys as soon as possible if the card that appears in the center of the computer screen is red or black.⁶⁴ A lower score for performance speed indicated better performance.

Working memory refers to the cognitive ability to temporarily store and manipulate limited amounts of information for use in guiding behavior.⁶⁵ Working memory was measured by the One Back Task (OBK). The OBK assesses working memory by measuring accuracy of performance. The participant responds according to whether the new card is the same as or different from the previously presented card.⁶⁶ Higher score indicates better working memory performance.

Verbal memory refers to memory for words and verbal items. It is the ability related to use of words, such as recall of words or materials that can be mediated verbally.⁶⁷ Verbal memory was measured by the International Shopping List Task (ISLT). The International Shopping List Task is the verbal memory task that consists of immediate free recall for a series of 12-word lists for three trials, followed by recall of the word list after a 20-minute delay. The scores of the ISLT are the total number of words correctly recalled in the sum of trials 1 to 3 and the correct number of recalled words after a 20-minute delay. The range of correct scores is 0-36 in ISLT and the range of correct scores is 0-12 in ISLT-DR (Delayed Recall). A higher score indicates better verbal memory performance.

Visual memory refers to the ability to explicitly remember visual episodic information that was seen previously.⁶⁸ This was measured by the One Card Learning Task (OCL) and the Continuous Paired Associate Learning Task (CPAL). The One Card Learning Task assesses

visual memory by measuring accuracy of performance. The participants respond using different keys depending upon whether the face-up card has appeared before or not.⁶¹ A higher accuracy score indicated better performance. In the Continuous Paired Associate Learning Task, the participants were required to remember the pictures hidden beneath the peripheral location on the screen first, and asked to determine whether a single picture presented in the center of the screen was the same as any one of the peripheral pictures and tap the same one in the peripheral location.⁶⁹ It is scored as the total number of errors across five rounds, with a lower score reflecting better visual memory performance.

Tasks were selected from the CogState Battery because of their brevity, good usability,⁶¹ and demonstrated validity and reliability that has sensitivity for detection of decline over time in older adults.^{62,63} All tasks in the Chinese version were translated using a linguistically validated process to produce an instrument that is conceptually equivalent to the English version. The validation process included seven steps: conceptual definition, forward translation, backward translation, pilot testing, international harmonization, proofreading, and report.⁷⁰ The method for using the Chinese version of the CogState is the same as English version. It is easy to administer and scoring is completed within the program. The battery requires approximately 20 minutes for completion. For these CogState tests, the score of a speed test was computed as the mean log₁₀ transformed reaction time for correct response and the score of an accuracy test was computed as the arcsine transformation of the proportion of the correct response. Transformations were applied to normalize the distribution.

Statistical analyses

Descriptive statistics such as mean, medians, standard deviation, and percentages were used to describe the demographics, clinical characteristics, and measures of the sample. The HF and

healthy groups were compared using independent t-tests, chi-square tests, or Fisher's exact tests. Cronbach's alpha was calculated to estimate internal consistency reliability for the GCS and the DASI. For hypothesis one, analysis of covariance (ANCOVA) was used for each test of memory performance to evaluate differences in means adjusting for age and education between the HF group and the healthy comparison group. Each subtest of the CogState battery was standardized by creating z scores whereby the healthy control mean was set to zero and the standard deviation set to one.^{71, 72}

For hypothesis two, Pearson product-moment correlation coefficients were computed to examine multicollinearity and to assess the association between continuous variables and each memory outcome; independent t-test and ANOVA analyses were used to examine differences in memory performance for categorical variables. A series of multiple linear regression analyses using simultaneous methods were performed in the HF group. Three explanatory variables were entered in the regression model based on sample size. Each dependent memory task (OBK, ISLT, ISLT-DR) was entered in separate regression equations. Independent variables were age, heart disease severity (DASI and NYHA Class entered in separate equations), and postmenopausal symptoms associated with estrogen decline. The covariate was years of education, which influences cognitive function. Finally, additional regression models were examined to evaluate variables that were significant in univariate analyses (comorbidity and HF type). First, age was entered because it is known to affect memory performance.^{13, 34, 35} Next, comorbidity and HF type were entered.

For hypothesis one, power analyses indicated that a sample size of 64 participants in each group was required to detect the mean difference between the two groups with a power of 0.8. The sample size was 64 for each group, totaling a sample size of 128. For hypothesis two, the

sample size needed was 76 in the HF group to obtain a power of 0.80 with a medium effect size and alpha at 0.05, as determined by inclusion of 3 explanatory variables in the regression model.

⁷³ Regression diagnostics were carried out to test the assumptions underlying regression analysis (independence, normal distribution, linearity, homoscedasticity). ⁷⁴ All analyses were conducted using SPSS version 17.

Results

Characteristics of sample

During the recruitment, 108 women with HF met the inclusion criteria and 76 of them (70%) were enrolled in the study. Reasons for not participating were: lack of availability, not interested, too sick, aversion to memory testing, disapproval of family member. No significant differences were found between women with HF who did and did not participate the study in terms of age, postmenopausal period, NYHA functional class, and HF duration. A total of 140 participants were included in the current study, including 76 women with HF and 64 healthy women. The characteristics of the participants are presented in Table 2.1. The demographic characteristics of the two groups were comparable: the sample was primarily Taiwanese; there were no group differences in age, marital status, years of education, and whether participant lived alone or not. More healthy participants were employed.

Compared with healthy women, women with HF had significantly higher systolic blood pressure, more comorbid diseases, worse perceived functional capacity and poorer mental status. The women with HF also had more postmenopausal symptoms associated with estrogen decline. No differences were found between the groups in terms of other variables related to menopause, including age at menopause, duration of menopause, ever taking hormone replacement therapy (HRT), and taking HRT now.

Memory performance in HF

The neuropsychological test scores of women with and without HF are presented in Table 2.2. Reaction times for DET were significantly longer among women with HF, indicating a slower psychomotor response in this group. There were no differences between women with HF and healthy women on tests of IDN. The scores in women with HF were significantly lower than healthy women on two of four memory outcomes. Women with HF had significantly worse scores on tests of working memory (OBK) and verbal memory (ISLT and ISLT-DR). The scores of visual memory (OCL and CPAL) in women with HF were lower compared with healthy women, but the difference did not reach significance. Of the memory domains tested, ISLT and ISLT-DR had lower mean z scores (z score= -.74 and -.77) compared to DET, IDN, OBK, OCL, and CPAL tasks (z score= -.61, -.15, -.44, -.40, and -.38), indicating that the verbal memory was the most affected (Figure 2.1). Hypothesis one was supported in the study.

Factors associated with memory performance in HF

In univariate analyses, age was significantly correlated with OBK ($r = -.56, p < .001$), ISLT and ISLT-DR ($r = -.62, p < .001$; $r = -.64, p < .001$). Women in more severe NYHA Classes performed significantly worse in verbal memory recall tasks ($F = -3.28, p = .026$). However, HF severity (DASI) and postmenopausal symptoms associated with estrogen decline were not associated with any memory tasks. In addition, associations between demographic and clinical variables and memory outcomes were small to moderate. Duration of menopause was significantly correlated with OBK ($r = -.50, p < .001$), ISLT and ISLT-DR ($r = -.52, p < .001$; $r = -.52, p < .001$). Comorbidity was significantly correlated with OBK ($r = -.23, p < .05$), ISLT and ISLT-DR ($r = -.37, p < .01$; $r = -.32, p < .01$). Moreover, women with systolic HF had significantly worse performance in working memory tasks ($t = -2.39, p < .05$) and verbal memory

tasks ($t = -2.67, p < .01$; $t = -3.12, p < .01$) compared to women with diastolic HF. Finally, age and duration of menopause were highly correlated ($r = .85, p < .05$), so duration of menopause was not entered into multiple regression equations. Comorbidity and HF type were further evaluated in additional multiple regression models.

Hypothesis two was only partially supported in the study. The results of simultaneous multiple regression analyses for tasks in working memory (OBK) in the HF group are presented in Table 2.3. Age was the only significant explanatory variable in all of the models. Thus, older age was associated with worse working memory scores (OBK, $p < 0.001$). Heart failure severity (DASI and NYHA Class), postmenopausal symptoms associated with estrogen decline, comorbidity, and HF type did not significantly contribute to performance of working memory.

For verbal memory tasks (Table 2.4 and Table 2.5), age and comorbidity significantly influenced ISLT (total recall) scores. Thus, being older and having more comorbidities were associated with worse ISLT (total recall) scores. Age and comorbidity accounted for 46% of variance in ISLT (Total Recall, $R^2 = .46$). Age, NYHA Class IV, comorbidity, and HF type were significantly related to poor verbal memory performance on ISLT-DR. In separate models, age and NYHA Class IV explained ISLT-DR ($R^2 = .46$); age, comorbidity, and HF type accounted for 48% of variance in ISLT-DR ($R^2 = .48$). Another heart failure severity measure (DASI) and postmenopausal symptoms associated with estrogen decline were not significant explanatory variables in any of the models of verbal memory.

Finally, all regression models were rerun with years of education entered as a covariate. In models for working memory, years of education was a significant covariate (OBK; $t = 2.18, p = 0.033$; $t = 2.01, p = 0.049$). In models for verbal memory, years of education was a significant explanatory variables for ISLT (Total recall, $t = 2.36, p = 0.021$).

Discussion

This is one of the first studies to examine memory performance and its associated factors in Taiwanese postmenopausal women with HF. The results provide important insights into memory performance in Taiwanese postmenopausal women with HF. First, this sample of 76 women with HF had poorer performance in working memory and verbal memory compared with 64 healthy women. Second, age was significantly associated with working memory; age, HF severity, comorbidity, and HF type were significant explanatory variables for verbal memory.

In the current study, women with HF had poorer performance on tests of working memory and verbal memory compared with healthy women. These results are consistent with and extend the work of past HF studies that combined men and women participants.^{9, 11, 13, 30, 34, 38} As few studies have reported gender difference in cognitive deficits in HF, our study extends previous work by focusing on women, using valid objective neuropsychological tests to measure memory performance, and including a comparison group matched on age and education. Furthermore, the current results were obtained from a culturally different sample than other studies, and consequently validate findings observed in patients from the United States and Europe. Poor memory performance may be related to difficulties in daily living activities and adhering to long-term self-care behaviors.^{11, 12} Therefore, it is important for nurses to identify memory deficits and assist healthcare providers in referring patients for advanced assessment.

Although memory deficits associated with systolic HF have been extensively studied, less is understood about the memory performance for patients with diastolic HF. In this study, most of the women with HF had diastolic HF (n=65, 85%). Memory deficits in these women were similar to memory deficits in patients with systolic HF in past studies.^{9, 38, 57, 75} In diastolic heart failure, left ventricular compliance is decreased. As there is a decrease in left ventricular filling,

stroke volume and cardiac output are reduced.⁷⁶ This finding is important because it supports the theory that decreased cardiac output leading to inadequate cerebral perfusion and oxygenation is associated with memory deficits in diastolic HF. Working memory and episodic memory deficits are consistent with multiple brain structure damage in patients with HF, including loss of gray matter in the frontal cortex and parahippocampal areas,⁷⁷ reduced gray matter in the areas of hippocampus and hippocampus output fibers,³² and reduced mammillary body volume and cross-sectional areas of the fornix fibers.³³

As hypothesized, age was significantly negatively related to all memory measures, including working, verbal, and visual memory. This is consistent with past HF studies relating age to decline in different domains of memory.^{7, 9, 13} The age-related memory decline was associated with anatomical, electrophysiological, and synaptic plasticity changes in the hippocampus.^{78, 79} This finding is particularly important to clinical practice because most patients with HF are elderly. Interventions to improve memory deficits in older patients with HF, such as cognitive training or exercise, have not been tested.

HF severity was significantly associated with verbal memory performance, consistent with previous studies.^{13, 37, 80} In the current study, most women had diastolic HF. More severe NYHA Class was associated with poor verbal memory as measured by ISDL-DR. We are uncertain as to why there was no association between NYHA class and working or visual memory, in contrast to previous studies.^{13, 37} It is possible that results were due to the heterogeneous measures that were used for assessing working memory and visual memory. Another explanation may be that most of the participants (75%) were NYHA functional class II. Further analyses should use another indicator for HF severity (ejection fraction, EF) to explore the association between HF severity and memory performance.

No association was found between estrogen decline and memory performance in the current study. One possible explanation is that measurement issues limited the ability to detect relationships by using self-reported postmenopausal symptoms related to estrogen decline without measuring serum estrogen level. Moreover, it is possible that estrogen levels had remained low for a time period after menopause,⁸¹ which may have limited impact on memory function in postmenopausal women with HF. Further studies are needed that include serum estrogen concentrations and recruitment of women with HF in different menopausal stages in order to understand the impact of estrogen decline on memory function.

This study provides evidence that comorbidities have a small detrimental influence on measures of verbal and visual memory. This effect is present and beyond the influences of age, education, and HF type. These findings contrast with a previous study that included 249 HF patients, where multiple comorbidities as measured by the Charlson Comorbidity Index were not associated with cognitive deficits.³⁸ The score was weighted by disease severity using one, two, three or six points; total comorbidity scores were not related to cognitive deficits. However, our study examined comorbidity using number of medical diseases rather than using severity level. A previous study found that patients with HF had a high rate of chronic diseases (an average of 5 chronic diseases), with hypertension, cardiac arrhythmias, hyperlipidaemia, and diabetes mellitus most frequently reported.⁸² These heart and circulation comorbidities were known to be related to cognitive function.^{9,37} It is not surprising that our HF sample, which had more comorbidities, would present with poorer memory performance.

The association between HF type and verbal memory (ISLT-DR) was unexpected. The findings indicate that women with systolic HF had poorer verbal memory compared with women with diastolic HF. To our knowledge, no studies have reported the relationship between HF type

and memory function. The sample size of women with systolic HF in our study was small (n=11). Considering that this association was not included in our original hypothesis, further work is needed to examine the possible impact of HF type on memory performance.

Limitations

This study has a number of limitations. First, estrogen decline was measured by self-reported menopausal symptoms that may not actually reflect estrogen condition. Further studies should collect blood estrogen samples that can directly confirm the relationship between estrogen level and memory outcomes. In addition, results could not be generalized to all women with HF because we included only postmenopausal women without other conditions that may cause cognitive deficits or psychiatric problems.

Conclusion

In conclusion, results indicated that working memory and verbal memory are poorer in women with HF compared to healthy participants. Several factors, such as age, HF severity, comorbidity, and HF type, which affect memory performances, were identified. Further studies are needed to determine mechanisms of memory deficits in women with HF and how these influence women's lives and self care, and to develop interventions such as cognitive training. This study has important clinical implications. Women with HF who have significant memory decline may be compromised in their ability to learn to adhere to such things as complex medication schedules and dietary therapies in ways that interfere with the goal of successful living with this illness. Nurses and health care providers should assess women with HF at risk of poor memory (ex., older patients, patients with severe HF, and patients with more chronic diseases), educate health and self-care behaviors to reduce risk of memory decline, and develop novel interventions to maintain cognitive function.

Table 2.1. Demographic and Clinical Variables by Groups (n=140)

Characteristics	Total (n=140)	HF (n = 76)	Healthy (n = 64)	t-test, χ^2 or Fisher's exact test	P-value
Age, mean (SD)	69.4 (8.9)	69.7 (10.2)	68.9 (7.1)	t=0.53	0.59
Race, n (%)				Fisher's exact test	0.02*
Taiwanese	104 (74.3)	49 (64.5)	55 (85.9)		
Mainland China	26 (18.6)	19 (25)	7 (10.9)		
Hakka	8 (5.7)	6 (7.9)	2 (3.1)		
Aborigine	2 (1.4)	2 (2.6)	0 (0)		
Marital status, n (%)				Fisher's exact test	0.16
Married	102 (72.9)	61 (80.3)	41 (64.1)		
Single	3 (2.1)	1 (1.3)	2 (3.0)		
Divorced	6 (4.3)	2 (2.6)	4 (6.3)		
Widowed	29 (20.7)	12 (15.8)	17 (26.6)		
Education, mean (SD)	7.6 (3.2)	7.3 (3.3)	8.0 (3.1)	t=-1.31	0.19
Employment, n (%)				$\chi^2=11.25$	0.001**
No	115 (82.1)	70 (92.1)	45 (70.3)		
Yes	25 (17.9)	6 (7.9)	19 (29.7)		
Live alone, n (%)				$\chi^2=1.28$	0.52
No	115 (82.1)	64 (84.2)	51 (79.7)		
Yes	25 (17.9)	12 (15.8)	13 (20.3)		
Systolic blood pressure, mean (SD)	129.5 (15.8)	135.5 (17.5)	122.3 (9.5)	t=5.34	< .001***
Diastolic blood pressure, mean (SD)	75.3 (8.9)	76.1 (10.2)	74.4 (6.9)	t=1.1	0.27
Comorbidity number, mean (SD)	1.1 (1.0)	1.8 (0.9)	0.2 (0.4)	t=12.16	< .001***
Age at menopause, mean (SD)	50.0 (5.1)	50.4 (5.8)	49.6 (4.1)	t=0.83	0.407
Months since menopause, Mean (SD)	232 (116)	232 (133)	231 (94)	t=0.08	0.929
Ever take HRT, n (%)				$\chi^2=0.00$	0.983
No	95 (67.9)	51 (67.1)	44 (68.8)		
Yes	43 (30.7)	23 (30.3)	20 (31.2)		
Take HRT now, n (%)				Fisher's exact test	0.12

No	136 (97.1)	72 (94.7)	64 (100)		
Yes	4 (2.9)	4 (5.3)	0 (0)		
MoCA, mean (SD)	26.2 (3.3)	25.1 (3.7)	27.5 (2.1)	t=-4.54	< .001***
Duke Activity Status Index, mean (SD)	30.8 (15.1)	21.6 (11.3)	41.7 (11.5)	t=-10.29	< .001***
The Greene Climacteric Scale , mean (SD)	14.6 (9.5)	17.9 (10.4)	10.8 (6.8)	t=4.69	< .001***
Left Ventricular Ejection Fraction, mean (SD)		60.9 (3.8)			
NYHA class, n (%)					
Class I		6 (7.9)			
Class II		57 (75)			
Class III		11 (14.5)			
Class IV		2 (2.6)			
Month of HF, mean(SD)		35.7 (28.4)			
Type of HF, n (%)					
Systolic HF		11 (14.5)			
Diastolic HF		65 (85.5)			

Note. HRT= Estrogen replacement therapy; MoCA= Montreal Cognitive Assessment; NYHA=New York Heart Association; HF=heart failure; Values are expressed as numbers (%). Percentage is expressed as valid percentage, which excludes missing data

Note. *P < .05 **P < .01 ***P < .001

Table 2.2. Means and Standard Deviations for CogState tests

	HF (n=76) (Mean ± SD)	Healthy (n=64) (Mean ± SD)	F	P ^c	HF z score ^d
DET, speed ^a	2.7 ± 0.1	2.6 ± 0.1	7.6	0.007	-0.61**
IDN, speed ^a	2.7 ± 0.09	2.7 ± 0.0	0.2	0.65	-0.15
OBK, accuracy ^b	1.0 ± 0.2	1.1 ± 0.1	4.3	0.04	-0.44*
ISDL, total ^b	20.2 ± 5.7	23.4 ± 4.4	14.7	< .001	-0.74***
ISDL, delayed recall ^b	6.8 ± 2.8	8.3 ± 1.9	13.9	< .001	-0.77***
OCL, accuracy ^b	0.9 ± 0.1	0.9 ± 0.09	3.6	0.06	-0.40
CPAL, error ^a	96.7 ± 61.3	79.3 ± 40.3	2.8	0.10	-0.38

Note. . *P < .05 **P < .01 ***P < .001, HF=heart failure; DET= Detection task; IDN= Identification task; OBK= One Back Task; ISLT= the International Shopping List Task, total; ISLT-DR= the International Shopping List Task, delayed recall; OCL= One Card Learning Task; CPAL= Continuous Paired Associate Learning

^aLower score=better performance.

^bHigher score=better performance.

^cP value for analysis of covariance adjusting for age and education.

^dPerformance of Patients with HF on CogState scores Standardized to Healthy Control Women

Table 2.3. Multiple Regression Analysis: Explanatory Variables for Working Memory (One Back Task, Accuracy) in Women with HF

Models	Variables	B	SE B	Beta	<i>t</i>	P value
1 ^a	Age	-0.02	0.003	-0.65	-5.96	<0.001
	GCS	-0.001	0.002	-0.06	-0.56	0.58
	DASI	-0.01	0.002	-0.21	-1.92	0.06
2 ^b	Age	-0.01	0.002	-0.57	-5.59	<0.001
	GCS	0.00	0.002	-0.01	-0.08	0.94
	NYHA IV	0.08	0.16	0.05	0.54	0.59
3 ^c	Age	-0.01	0.002	-0.50	-5.08	<0.001
	Comorbidity	-0.04	0.03	-0.14	-1.41	0.16
	HF type	0.10	0.07	0.15	1.5	0.14

Note: HF=Heart Failure; GCS= the Greene Climacteric Scale; DASI= Duke Activity Status Index; NYHA=New York Heart Association.

^a $R^2 = .35$, Adjusted $R^2 = .32$

^b $R^2 = .31$, Adjusted $R^2 = .29$

^c $R^2 = .35$, Adjusted $R^2 = .32$

Table 2.4. Multiple Regression Analysis: Explanatory Variables for Verbal Memory (International Shopping List Task, Total Recall) in Women with HF

Models	Variables	B	SE B	Beta	<i>t</i>	P value
1 ^a	Age	-0.35	0.06	-0.63	-5.94	<0.001
	GCS	0.02	0.05	0.04	0.44	0.66
	DASI	-0.02	0.05	-0.05	-0.43	0.67
2 ^b	Age	-0.33	0.05	-0.59	-6.22	<0.001
	GCS	0.03	0.05	0.05	0.52	0.60
	NYHA IV	-3.81	3.33	-0.11	-1.15	0.26
3 ^c	Age	-0.30	0.05	-0.54	-6.06	<0.001
	Comorbidity	-1.59	0.53	-0.26	-3.00	0.004
	HF type	2.78	1.42	0.17	1.96	0.05

Note: HF=Heart Failure; GCS= the Greene Climacteric Scale; DASI= Duke Activity Status Index; NYHA=New York Heart Association.

^a $R^2 = .38$, Adjusted $R^2 = .36$

^b $R^2 = .40$, Adjusted $R^2 = .37$

^c $R^2 = .48$, Adjusted $R^2 = .46$

Table 2.5. Multiple Regression Analysis: Explanatory Variables for Verbal Memory (International Shopping List Task, Delayed Recall) in Women with HF

Models	Variables	B	SE B	Beta	<i>t</i>	P value
1 ^a	Age	-0.20	0.03	-0.72	-7.06	<.001
	GCS	-0.03	0.03	-0.12	-1.31	0.20
	DASI	-0.03	0.03	-0.12	-1.18	0.24
2 ^b	Age	-0.18	0.03	-0.63	-7.10	<.001
	GCS	-0.03	0.02	-0.10	-1.20	0.24
	NYHA IV	-4.27	1.54	-0.24	-2.77	0.007
3 ^c	Age	-0.16	0.02	-0.56	-6.49	<.001
	Comorbidity	-0.63	0.26	-0.21	-2.42	0.02
	HF type	1.72	0.69	0.21	2.49	0.02

Note: HF=Heart Failure; GCS= the Greene Climacteric Scale; DASI= Duke Activity Status Index; NYHA=New York Heart Association.

^a R²= .43, Adjusted R² = .41

^b R²= .48, Adjusted R² = .46

^c R²= .50, Adjusted R² = .48

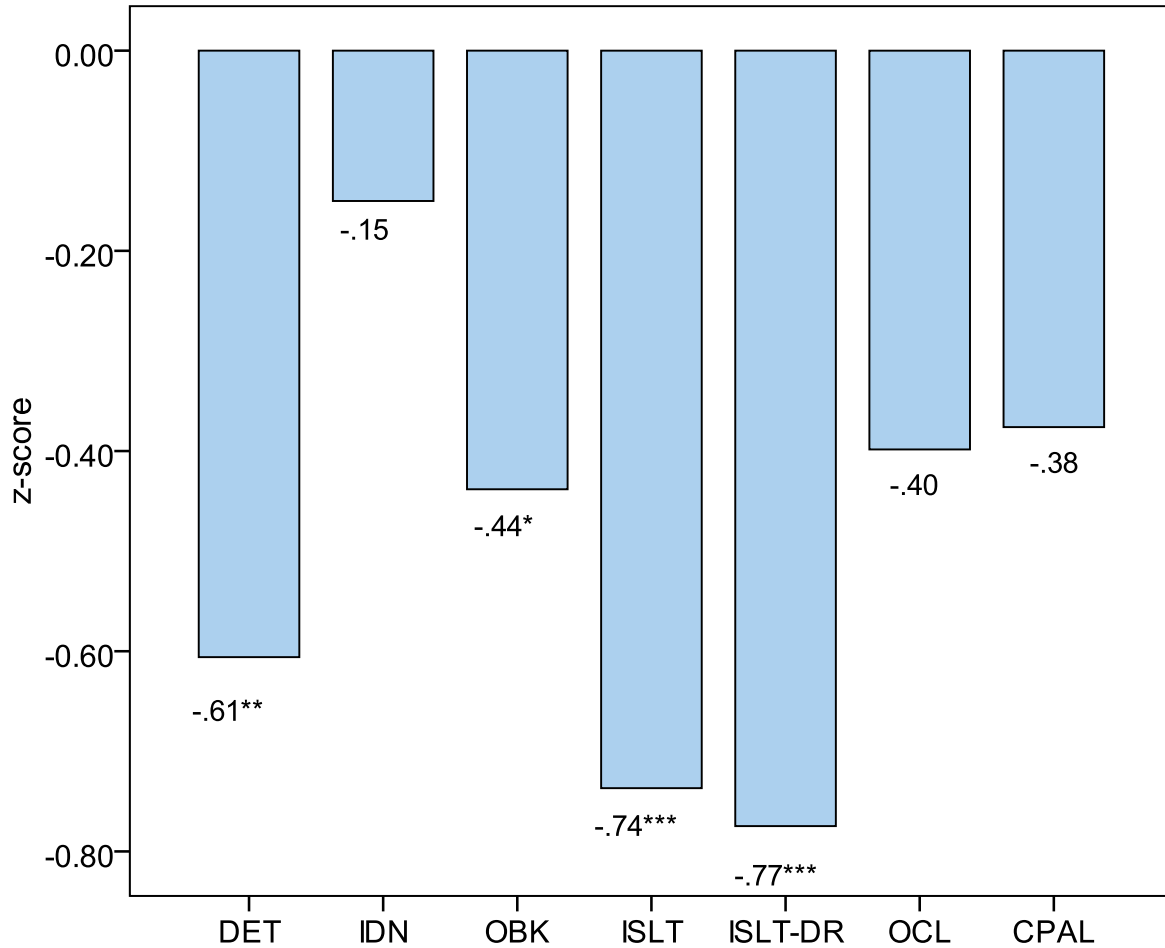


Figure 2.1. Performance of Patients with HF on CogState scores Standardized to Healthy Control Women

Note. *P < .05 **P < .01 ***P < .001; HF=heart failure; DET= Detection task; IDN= Identification task; OBK= One Back Task; ISLT= the International Shopping List Task, total; ISLT-DR= the International Shopping List Task, delayed recall; OCL= One Card Learning Task; CPAL= Continuous Paired Associate Learning

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CHAPTER III

Validation of the Chinese Version of the CogState Computerized Cognitive Assessment Battery in Taiwanese Patients with Heart Failure

Abstract

Aims and objectives: To evaluate the validity of the Chinese version of the CogState battery, a computerized neuropsychological test battery among women with heart failure (HF) in Taiwan.

Background: The CogState computerized battery has been validated in many countries, but not in Taiwan.

Design: A cross-sectional descriptive study.

Methods: A convenience sample consisted of 76 women with HF and 64 healthy women from one medical center in Northern Taiwan. Participants completed the Chinese version of the CogState battery and the Montreal Cognitive Assessment (MoCA). Construct validity of the Chinese version of the battery was evaluated by exploratory factor analysis and known-group comparisons. Convergent validity of the CogState tasks was examined by Pearson correlation coefficients.

Results: Principal components factor analysis with promax rotation showed two factors reflecting the speed and memory dimensions of the tests. Scores for CogState battery tasks showed significant differences between the HF and healthy control groups. The convergent validity of the CogState significantly associated with MoCA in the HF group ($P < 0.05$).

Conclusion: The Chinese CogState Computerized Cognitive Assessment Battery has satisfactory validity. It has potential use with HF patients for both research and practice.

Key words: Heart failure, CogState Computerized Cognitive Assessment Battery, factor analysis

Word: 199 --JCN --max is 300

Introduction

Heart failure is a major and growing problem worldwide and is associated with significant mortality and frequent hospitalizations (Gwadry-Sridhar, Flintoft, Lee, Lee, Guyatt, 2004). Cognitive deficits are common in patients with HF; prevalence ranges from 25% to 50% among this population (Bennett & Sauvé, 2003; Pressler, 2008; Vogels, Oosterman, et al., 2007). Compared to healthy persons, patients with HF have shown cognitive deficits in areas including attention and concentration, memory, psychomotor speed, and executive function (Bennett, Sauvé, & Shaw, 2003). One of the most likely etiologies of cognitive decline in HF is inadequate cerebral perfusion and cerebral hypoxia caused by low cardiac output (Bennett & Sauvé, 2005; Pullicino, & Hart, 2001; Taylor & Stott, 2002). Studies report that HF patients are at four times increased risk for cognitive deficits compared with matched controls (Sauvé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009). Qiu et al. (2006) have demonstrated that people with HF have twice the risk of dementia and Alzheimer disease over 9 years.

Complaints of memory impairment are among the most frequently reported cognitive deficits in HF patients, affecting approximately 40% of them (Hawkins et al., 2012; Pressler, Subramanian, et al., 2010; Putzke et al., 1997; Sauvé et al., 2009). Recently, researchers found that 48% of HF patients had impaired memory, but with preserved performance in other cognitive domains (Miller et al., 2012). Evidence supports that HF is associated with changes in brain structures which are critical for memory functioning. For example, HF patients had gray matter loss in brain areas involving cognition, including the prefrontal cortex areas critical to working memory (Woo, Macey, Fonarow, Hamilton, & Harper, 2003). Brain injuries emerged in several areas in HF patients, including the hippocampus, fornix, thalamus, mammillary body and fornix fibers (Kumar et al., 2009; Woo, Kumar, Macey, Fonarow, & Harper, 2009), which serve

important roles in episodic memory (Budson, 2009). Moreover, studies demonstrated that HF patients showed significant medial temporal lobe atrophy that was significantly negatively correlated with memory performance (Vogels, Flier, et al., 2007; Vogels, Oosterman, et al., 2007).

Empirical studies have consistently demonstrated the significant impacts of memory on daily activities, HF self-care, and mortality. For example, researchers reported verbal memory has been found to successfully explain performing instrumental activities of daily living (Hammers, Jung, et al., 2012). In addition, patients with poor HF self-care had impaired memory (Riegel, Dickson, Goldberg, & Deatrack, 2007). The deficits in memory may result in forgetfulness and poor learning ability that lead to failure to adhere to treatment regimens (Dickson, Tkacs, & Riegel, 2007). In a study among 166 HF patients, memory loss as measured by verbal list-learning was the most significant cognitive deficits to predict 12-month mortality (Pressler, Kim, et al., 2010). Although memory deficits have consistently been reported by patients who suffer from HF, there are no generally accepted measures for memory screening in them.

The CogState battery is a standardized, computerized neuropsychological test battery that was developed to measure cognitive function in large samples (Fredrickson et al., 2010). It is comprised of subsets that tasks assess psychomotor speed, attention, working memory, visual and verbal memory, executive function, and social cognition (Maruff et al., 2009). The battery has demonstrated sound psychometric properties. Test-retest reliability has been shown to be satisfactory, with 6-day test-retest correlations in patients with coronary surgery ranging from 0.61 to 0.92. In a recent HF study, eight-week test-retest correlations ranged from 0.53 to 0.78 among 17 HF patients (Hammers, Jung, et al., 2012). Validity has been demonstrated between

CogState tests and traditional neuropsychological measures; most of the correlations are moderate to large (De Jager et al., 2009; Pietrzak et al., 2009; Yoshida et al., 2011). The CogState test battery significantly differentiated cognitive performance between persons with schizophrenia (n=121) and matched participants in the control groups (n=120) (Pietrzak et al., 2009). Stability was acceptable, with intra-class correlation coefficients ranging from 0.65 to 0.91 in older adults over 12 months (Fredrickson et al., 2010). The battery identified mild cognitive impairment with good sensitivity (78%) and specificity (90%) among older adults (De Jager et al., 2009). The International Shopping List (ISL) subtest of the computerized CogState battery has performed comparably with the Hopkins Verbal Learning Test-Revised and significantly predicted daily functioning, indicating it could be a sensitive tool for evaluating cognitive change in HF (Hammers, Jung, et al., 2012).

Most evidence has shown that subsets of the CogState tasks are sensitive to cognitive changes in groups such as those with schizophrenia (Maruff et al., 2009; Pietrzak et al., 2009), mild traumatic brain injury (Maruff et al., 2009), dementia or Alzheimer's disease (Hammers, Spurgeon, et al., 2012; Lim, Ellis, et al., 2012; Maruff et al., 2009), and mild cognitive impairment (Darby, Maruff, Collie, & McStephen, 2002; De Jager et al., 2009). However, only one study with a small sample size evaluated the utility of the CogState verbal memory subset in an HF population (Hammers, Jung, et al., 2012).

Given the high prevalence and importance of memory deficits in HF, the routine use of validated and brief, but sensitive, assessment instruments is needed for early detection of memory impairment in this population. Moreover, despite that the CogState computerized battery has been evaluated in languages other than English, including French, Korean (Lim, Pietrzak, et al., 2012), and Japanese (Yoshida et al., 2011), the validation of the CogState tasks in

a Chinese population has not yet been examined. Therefore, the purpose of the current study was to evaluate the validity and reliability of the Chinese version of the CogState tests in Taiwanese patients with HF. The hypotheses were that the Chinese version would demonstrate validity as evaluated by: (1) exploratory factor analysis to investigate the internal structure of CogState tests; (2) differences between patients with HF and healthy control groups; and (3) correlations with a standard measure of global cognitive function.

Methods

Participants

A cross-sectional design was used. The study was conducted in a hospital in Taipei, Taiwan during November 2010 through October 2011. A convenience sample of 76 women with chronic HF was recruited from cardiovascular clinics and 64 age- and education- matched healthy women were recruited from outpatients of the gynecology clinic, the women's health center, and volunteers in the same hospital. Women with HF were eligible for participation in the study if they were age 50 years and older, their last menstrual cycle was completed more than 12 months previously, had a diagnosis of HF of at least 6 months, and could read and speak Mandarin. Women were eligible for participation in the age- and education- matched healthy group if they fulfilled the same criteria and had, no major medical conditions. Exclusion criteria for the two groups included having conditions known to cause cognitive deficits or the presence of impaired sensory problems. Women who had hypertension with blood pressure less than 140/90 mmHg or hyperlipidemia with cholesterol less than 200 mg/dl were eligible for the healthy group.

Procedures

After obtaining approval from the Institutional Review Board of the University of Michigan and the Taipei Tri-Service General Hospital, the investigator approached potential participants at

the hospital who met inclusion criteria and explained the purpose and procedures of the study. Written consents were obtained from all participants; data were collected by face-to-face interviews. The entire time for data collection was approximately 60 to 90 minutes. Demographic and clinical information was collected using questionnaires and from medical records. The MoCA and the computerized CogState tests were administered by an experienced nurse who was trained by a neuropsychologist.

The tasks in the Chinese CogState battery were translated from English version and provided by CogState Company using a linguistically validated process to produce an instrument that is conceptually equivalent to the English version. The validation process included seven steps: conceptual definition, forward translation, backward translation, pilot testing, international harmonization, proofreading, and report (MAPI Institute, 2011).

Measures

The MoCA was used to measure global cognitive function. It was developed as a screening tool for mild cognitive impairment (MCI) and early dementia (Nasreddine et al., 2005). The MoCA is a 10-minute test and includes items on visuospatial abilities, naming, short-term memory recall, attention, language, verbal abstraction, memory, and orientation. The MoCA was selected as a measure of global cognitive function because it has been demonstrated to be more sensitive in detecting cognitive impairment in HF patients than another commonly-used instrument, the Mini-Mental Status Examination (MMSE) (Athilingam et al., 2011). Possible MoCA scores range from 0 to 30; higher scores indicate better global cognitive function. Using a cutoff score of 26 to identify MCI, a sensitivity of 90% and a specificity of 87% were found among 93 patients with mild Alzheimer's disease (AD) and 90 healthy elderly controls in the original study in Canada (Nasreddine et al., 2005). Similar results were found in studies

conducted in Japan and Taiwan. Using a cut-off point of 25/26, a study in Japan reported a sensitivity of 93% and a specificity of 87% in detecting MCI in 96 older adults (Fujiwara et al., 2010). A Taiwan study reported a sensitivity of 92% and specificity of 78% for MCI by using an optimal cut-off score of 23/24 among 98 patients with AD, 71 with MCI, and 38 normal controls (Tsai et al., 2012). The criterion validity, internal consistency and test-retest reliability were satisfactory in the Chinese version of MoCA (Wong et al., 2009).

The Chinese version of the CogState computerized memory subtests was used by the authors to measure memory function in a study of Taiwanese women with HF (Table 3-1), described elsewhere (De Jager et al., 2009; Fredrickson et al., 2010; Lim et al., 2009). This test battery was selected because of its brevity, good usability, culture-free stimuli (i.e., playing cards) and because it was valid, reliable, and sensitive in detecting decline over time in older adults (Table 3-2) (Cysique, Maruff, Darby, & Brew, 2006; Pietrzak et al., 2009; Darby et al., 2002). Six tasks were selected from the battery, including four measuring working and episodic memory.

Two CogState tasks measuring psychomotor speed and attention were evaluated. The Detection task (DET) is a psychomotor speed task that requires participants to respond as soon as possible when a playing card in the center of the computer screen flips over. The Identification task (IDN) is a measure of visual attention that assesses speed of performance. Participants are asked to press the 'yes' button if the card appearing in the center of the computer screen is red and the 'no' button if the card is black as soon as possible (Collie et al., 2007). The task ends when 30 correct trials have been completed. A lower score indicated better performance.

Working memory was measured by OBK. The One Back Task (OBK) is a measure of working memory that assesses accuracy of performance. The participant presses the 'yes' button if a playing card is the same as the immediately previous card and the 'no' button if the card is

different (Cysique et al., 2006). Thirty correct trials were required for completion. A higher score indicates better performance

Verbal memory was measured by International Shopping List Task (ISLT), which included a 3-trials immediate free recall of a series of 12-word lists, followed by 20-minute delayed recall for the word list. The individuals are required to remember a list of shopping items that are relevant to their culture. Studies have reported that performance is equivalent among English, French, Malay, and Mandarin Chinese versions of the ISLT (Lim et al., 2009). The ISLT has been shown to correlate with the Hopkins Verbal Learning Test-Revised (HVLT-R) ($r = .47$ to $.75$) and has adequate stability in 40 patients with chronic HF ($r = .53$ to $.68$) (Hammers, Jung, et al., 2012). The test-retest correlations in 50 patients with mild AD were 0.85 for ISLT and 0.45 for ISLT delayed recall trail (ISLT-DR) (Thompson et al., 2011). Possible scores range from 0 to 36 in the ISLT first 3 trails and 0-12 in the ISLT-DR. A higher score indicates a better verbal memory performance.

Visual memory was measured by the One Card Learning Task (OCL) and the Continuous Paired Associate Learning Task (CPAL). The OCL assesses accuracy of performance. Similar in presentation to the ONB task, the participants press the “yes” button if the card has appeared before or the “no” button if it has not appeared. The OCL ends after 42 trials are completed (Fredrickson et al., 2010). A higher score indicates a better performance. The CPAL requires participants to learn sets of pattern–location associations in acquisition and learning phases. In the first phase, the participant is asked to remember the identical shape patterns hidden beneath the peripheral locations. In the learning phase, each pattern is presented in the centre of the screen and the participant is required to select the correct pattern presented in the peripheral

location (O'Donnell, Pietrzak, Ellis, Snyder, Maruff, 2011). It is scored as the total number of errors across seven rounds, with lower scores indicating better visual memory performance.

Statistical Analysis

SPSS 17.0 software was used for statistical analysis. Descriptive statistics (proportions, means, medians, and standard deviations) were used to summarize demographic and clinical variables, scores for CogState computerized tasks and MoCA results. Student's t-tests, chi-square tests, and Fisher's exact tests were used to examine differences between groups.

For hypothesis one, the factor structure of the CogState tasks was determined by performing exploratory factor analysis using principal components analysis with varimax rotation. The Kaiser–Meyer–Olkin (KMO) test and Bartlett's test of sphericity were used to examine sampling adequacy and model appropriateness for performing factor analyses. The following criteria were used for factor extraction: having eigenvalues greater than 1, factor loadings higher than 0.30, and interpretability (Field, 2005). For hypothesis two, analysis of covariance (ANCOVA) were used for each test of CogState battery (DET, IDN, ONB, ISLT, ISLT-DR, OCL, and CPAL) to compare differences in means adjusting for age and education between the HF and healthy groups. For hypothesis three, the correlation was examined by calculating Pearson correlation coefficients for CogState tasks (DET, IDN, ONB, ISLT, ISLT-DR, OCL, and CPAL) and the MoCA.

Results

Sample Characteristics

Table 3.3 shows characteristics of the study participants. The sample was composed of 76 women with HF and 64 healthy women. Mean age of participants was 69.4 years (SD=8.9). The mean education level was 7.6 years (SD=3.2). The majority of participants were married (72.9%)

and were not employed (82.1%). Women with HF had significantly higher systolic blood pressures and more comorbid diseases compared to healthy women. Moreover, most women with HF had diastolic HF (85.5%) and were in New York Heart Association (NYHA) class II (75%).

Performance in CogState tasks and MoCA

The score mean and standard deviation of the tasks in CogState battery among groups were presented in Table 3.4 and Figure 3.1. Compared with healthy participants, women with HF had lower scores in the tests of OBK (mean=1.0; SD=0.2), ISLT (mean=20.2; SD=5.7), and ISLT-DR (mean=6.8, SD=2.8). The scores of the IDN and OCL tests were similar between two groups. Women with HF also had higher score in the tests of DET (mean= 2.7; SD=0.1), and CPAL (mean=96.7; SD=61.3). The mean MoCA scores were 25.1 (SD=3.7) in HF group and 27.5 (SD=2.1) in healthy group (Table 3-3).

Exploratory Factor analysis

An exploratory factor analysis using principal components analysis was performed to determine the number and the content of factors underlying the CogState tasks (Table 3.5). The Kaiser–Meyer–Olkin test measure for the data was 0.724, indicating sampling adequacy and compact patterns of correlation; the factor analysis produced distinct and reliable factors (Field, 2005). Bartlett’s test of sphericity reached statistical significance ($p < .001$), which supported that some relationships between the variables existed (Field, 2005). Oblique promax rotations were used because the CogState factors were assumed to be correlated. This showed the presence of two factors with eigenvalues > 1 , explaining 64.6% of the total variance. The first factor accounted for 44.95% of the total variance and contained ISLT, ISLT-DR, CPAL, OBK, and OCL and was labeled “memory”, with factor loadings ranging 0.61-0.81. The second factor

accounted for 19.69 % of the total variances and contained two tests (DET and IDN); it was labeled “speed” . Factor loadings ranged from 0.90-0.91.

Group comparison

The ANCOVA resulted in statistically significant differences ($p < 0.05$) for CogState scores between the HF and healthy groups (Table 3.4). Women with HF reported higher psychomotor speed score than did healthy women (DET, $p < 0.01$) and lower scores on working memory (OBK, $p < 0.05$) and verbal memory tasks (ISLT, $p < 0.001$; ISLT-DR, $p < 0.001$), after controlling for age and education years, providing evidence that further supported the construct validity of the CogState battery. In addition, the HF group showed higher scores in CPAL performance than the healthy group, but the difference did not reach significance. No difference was found in the tests of the IDN and OCL between women with HF and healthy women.

Correlation between CogState tasks and MoCA

The relationship between each individual test score of the CogState and MoCA are presented in Table 3.6. Significant correlations were also shown between MoCA and the OBK ($r = 0.42$, $p < 0.001$), ISLT ($r = 0.57$, $p < 0.001$), ISLT-DR ($r = 0.64$, $p < 0.001$), OCL ($r = 0.40$, $p < 0.001$), CPAL ($r = 0.40$, $p < 0.01$), which demonstrate convergent validity of these CogState tests in this population. In addition, the DET and IDN score of the CogState battery and MoCA were not significantly correlated in both HF and healthy control group.

Discussion and Conclusion

This is the first study to report use of the Chinese version of a computerized neuropsychological test battery in an HF population. Results supported the hypothesis that the Chinese CogState subtests demonstrated good convergent validity and construct validity among Taiwanese HF patients and healthy women.

Findings of the exploratory factor analysis pointed to the common features of the selected CogState battery tasks, namely speed and memory, which support construct validity of the selected CogState battery items in this population. The OBK, OCL, and CPAL present visual stimuli in the center of the computer, and participants must memorize presentations to perform adequately. The ISLT, on the other hand, provides verbal stimuli that participants need to recall immediately or later and performance is based on how many words can be recalled correctly. For the remaining measures, such as DET and IDN, although the visual stimuli are presented in the middle of the computer screen, the participants are required to respond as quickly as possible. Four tasks loaded on a factor that labeled as memory, which included working memory (i.e., OBK) and episodic memory tasks (i.e., OCL, ISLT, and CPAL). Our findings are similar to those of Yoshida et al. (2011), who conducted a factor analysis for the CogState Schizophrenia Battery in 40 Japanese patients with schizophrenia. In our study, however, OBK was included in the memory factor, while Yoshida et al. (2011) found the OBK was not associated with any factor solution. This may be due to the small sample size of that study (N=40).

This is the first study to compare CogState results from HF population to those from a healthy control group. Results showed that HF patients scored significantly lower than the healthy controls group, which is consistent with previous findings using other standard neuropsychological tests (Pressler, Subramanian, et al., 2010; Sauvé et al., 2009; Vogels, Oosterman, et al., 2007). Women who have HF are more likely to demonstrate poor performance on most of the CogState memory tasks when compared to a healthy female control group. Although CPAL task results were not significantly different in the two groups, the HF group had more CPAL errors compared to the control group. These results are congruent with findings that HF patients show increased injury in brain regions associated with the working memory system

(Schmidet, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Woo et al., 2003) as well as in brain regions associated with episodic memory (Woo et al, 2009; Kumar et al., 2009).

The Chinese CogState subtests were significantly correlated with MoCA in HF and control groups. The MoCA is considered to evaluate different cognitive abilities, including memory (Nasreddine et al., 2005), thus these results provided evidence that supports validity in the Chinese CogState memory subtests. The English version of the selected CogState tests (DET, IDN, OBK, ISLT) was significantly correlated with standard neuropsychological tests and only ISLT was significantly correlated with MMSE in a small HF sample (N=40) (Hammers, Jung, et al., 2012). Interesting, no association was found between the global cognitive measure (MMSE or MoCA) with DET or IDN in this current study or previous HF study (Hammers, Jung, et al., 2012). This may be because the DET and IDN are measures of psychomotor speed and the MMSE or MoCA did not measure any speed of response. The current study additionally found that memory subtests such as OBK, ISLT, OCL and CPAL had significant correlations with a global cognitive measure (MoCA). Compared to MMSE, the MoCA is a sensitive cognitive screening measure that can identify possible MCI in patients with HF (Cameron, Worrall-Carter, Page, Stewart, & Ski, 2012). Future study is needed to compare correlations among the Chinese CogState subtests using standard neuropsychological tests in HF population.

There are some limitations of the study, including that a gold standard neuropsychological test was not to use to measure cognitive impairment. More research is needed to validate our results against such a gold standard neuropsychological testing. Although the study did not evaluate test-retest reliability of the Chinese CogState, other studies have reported acceptable test-retest reliability for its subtests in non-Chinese older adults and HF patients (Fredrickson et al., 2010; Hammers, Jung, et al., 2012). Future study is needed to evaluate test-retest reliability

of the Chinese CogState. Another limitation is that participants included only women with HF. It is not clear whether these results would be the same for men. Although the battery was constructed for self-administration, some patients with HF had difficulties using a mouse to complete the CPAL task and required help from the investigator. For example, help to hold her hand with mouse together and move to the location she pointed. Use of a laptop with a touch screen is suggested to-validate the CPAL task in future studies.

This study demonstrated that the CogState is a valid and reliable instrument to assess memory performance in women with HF in Taiwan, where we believe until now there has no research examining memory assessment and management. The current study showed that the CogState memory subtests were significantly correlated with MoCA tasks; were sensitive to memory impairment in Taiwanese patients with HF; loaded on a factor labeled as memory by a principal components analysis, and had acceptable internal consistency, suggesting that it could be a valid instrument for detecting memory impairment in this population. Future research is needed to address memory impairment in those with HF and to develop protocols for management of memory decline.

Implications for clinical practice

As clinicians have a better understanding of memory deficit patterns in patients with HF, it is important that they provide improved care and treatment. Nurses play a critical role in assisting patients to plan long-term treatments toward the goal of successful living with HF. The CogState battery could be used to help detect memory deficits that may be subtle in the early stages of HF, and identify changes that provide insights into patients' abilities to implement treatment accurately and consistently. Better interventions tailored to the needs of the HF population can be developed.

Table 3.1. Tasks in the CogState Computerized Cognitive Assessment Battery

Test	Abbreviation	Domain	Outcome measure
Detection task	DET	Psychomotor speed	Average log10 reaction times of correct responses
Identification Task	IDN	Attention	Average log10 reaction times of correct responses
One Back Task	OBK	Working memory	Arcsine percentage of correct responses
International Shopping List Task	ISLT	Verbal memory	Number of words recalled in 3 trials
International Shopping List Task : Delayed recall	ISLT-DR	Verbal memory	Number of words recalled after 20 minutes
One Card Learning Test	OCL	Visual memory	Arcsine percentage of correct responses
Continuous Paired Associate Learning Task	CPAL	Visual memory	Number of errors made across learning trails

Table 3.2 Pearson's Product-moment Correlations between CogState Tasks and Neuropsychological Tests in Previous Publications.

Study	DET	IDN	OBK	ISLT	ISLT-DR	OCL	CPAL
Hammers et al., 2012 (n=40)	-0.35	-0.37	0.33-0.43	0.46-0.7	0.45-0.75		
Hammers et al., 2012 (n=22)	0.50	0.45	0.47-0.52			NS	
Yoshida et al., 2012 (n=80)	0.34		NS	0.71			0.34
Pietrzak et al., 2009 (n=121)	0.56-0.79	0.57	0.56-0.75	0.78		0.76	
Maruff et al., 2009 (n=253)	0.52-0.81	0.49-0.78	0.54-0.81			0.57-0.83	
Cysique et al., 2006 (n=60)	-0.29-0.60	-0.26-0.62					

Note. NS= not significant correlation; DET= Detection task; IDN= Identification task; OBK= One Back Task; ISLT= the International Shopping List Task, total; ISLT-DR= the International Shopping List Task, delayed recall; OCL= One Card Learning Task; CPAL= Continuous Paired Associate Learning.

Note. Neuropsychological Tests with detail available in previous publications.

Table 3.3. Demographic and Clinical Variables by Groups (n=140)

Characteristics	Total (n=140)	HF (n = 76)	Health (n = 64)	t-test, χ^2 or Fisher's exact test	P-value
Age, mean (SD)	69.4 (8.9)	69.7 (10.2)	68.9 (7.1)	t=0.53	0.59
Race, n (%)				Fisher's exact test	0.02*
Taiwanese	104 (74.3)	49 (64.5)	55 (85.9)		
Mainland China	26 (18.6)	19 (25)	7 (10.9)		
Hakka	8 (5.7)	6 (7.9)	2 (3.1)		
Aborigine	2 (1.4)	2 (2.6)	0 (0)		
Marital status, n (%)				Fisher's exact test	0.16
Married	102 (72.9)	61 (80.3)	41 (64.1)		
Single	3 (2.1)	1 (1.3)	2 (3.0)		
Divorced	6 (4.3)	2 (2.6)	4 (6.3)		
Widowed	29 (20.7)	12 (15.8)	17 (26.6)		
Education, mean (SD)	7.6 (3.2)	7.3 (3.3)	8.0 (3.1)	t=-1.31	0.19
Employment, n (%)				$\chi^2=11.25$	0.001**
No	115 (82.1)	70 (92.1)	45 (70.3)		
Yes	25 (17.9)	6 (7.9)	19 (29.7)		
Live alone, n (%)				$\chi^2=1.28$	0.52
No	115 (82.1)	64 (84.2)	51 (79.7)		
Yes	25 (17.9)	12 (15.8)	13 (20.3)		
Systolic blood pressure, mean (SD)	129.5 (15.8)	135.5 (17.5)	122.3 (9.5)	t=5.34	< .001***
Diastolic blood pressure, mean (SD)	75.3 (8.9)	76.1 (10.2)	74.4 (6.9)	t=1.1	0.27
Comorbidity number, mean (SD)	1.1 (1.0)	1.8 (0.9)	0.2 (0.4)	t=12.16	< .001***
Age at menopause, mean (SD)	50.0 (5.1)	50.4 (5.8)	49.6 (4.1)	t=0.83	0.407
Months since menopause, Mean (SD)	232 (116)	232 (133)	231 (94)	t=0.08	0.929
Ever take HRT, n (%)				$\chi^2=0.00$	0.983
No	95 (67.9)	51 (67.1)	44 (68.8)		
Yes	43 (30.7)	23 (30.3)	20 (31.2)		
Take HRT now, n (%)				Fisher's exact test	0.12
No	136 (97.1)	72 (94.7)	64 (100)		

Yes	4 (2.9)	4 (5.3)	0 (0)		
MoCA, mean (SD)	26.2 (3.3)	25.1 (3.7)	27.5 (2.1)	t=-4.54	< .001***
Left Ventricular Ejection Fraction, mean (SD)		60.9 (3.8)			
NYHA class, n (%)					
Class I		6 (7.9)			
Class II		57 (75)			
Class III		11 (14.5)			
Class IV		2 (2.6)			
Month of HF, mean (SD)		35.7 (28.4)			
Type of HF, n (%)					
Systolic HF		11 (14.5)			
Diastolic HF		65 (85.5)			

Note. HRT= Estrogen replacement therapy; NYHA=New York Heart Association; HF=heart failure; Values are expressed as number (%). Percentage is expressed as valid percentage, which excludes missing data

Note. *P < .05 **P < .01 ***P < .001

Table 3.4. Mean, Standard Deviation, and Group comparison for CogState tests

	HF (n=76) Mean(SD)	Health (n=64) Mean(SD)	F	P ^c
Detection, speed ^a	2.7 (0.1)	2.6 (0.1)	7.6	0.007
Identification, speed ^a	2.7 (0.1)	2.7 (0.0)	0.2	0.65
One Back, accuracy ^b	1.0 (0.2)	1.1 (0.1)	4.3	0.04*
International Shopping List, total ^b	20.2 (5.7)	23.4 (4.4)	14.7	< .001***
International Shopping List, delayed recall ^b	6.8 (2.8)	8.3(1.9)	13.9	< .001***
One Card Learning, accuracy ^b	0.9 (0.1)	0.9 (0.1)	3.6	0.06
Continuous Paired Associate Learning, error ^a	96.7 (61.3)	79.3 (40.3)	2.8	0.10

Note. HF=heart failure

Note. *P < .05 **P < .01 ***P < .001

^aLower score=better performance.

^bHigher score=better performance.

^cP value for analysis covariance adjusting for age and education.

Table 3.5. Principal Components Analysis of CogState Tests in the HF Group (n=76)

	Factor loadings	
	Factor 1	Factor 2
Factor 1: Memory		
One Back, accuracy	0.81	-0.08
International Shopping List, total	0.71	0.27
International Shopping List, delayed recall	0.77	0.24
One Card Learning, accuracy	0.74	-0.39
Continuous Paired Associate Learning, error	0.61	0.07
Factor 2 : Speed		
Detection task	-0.03	0.90
Identification task	-0.05	0.91
Eigenvalue	3.15	1.38
Explained variance	44.95	19.69
Cumulative variance	44.95	64.64

Total CogState tests

Note. HF=heart failure ; Kaiser–Meyer–Olkin (KMO) test measure of sampling adequacy = 0.724; Bartlett’s test of sphericity P < .001

Note. *P < .05 **P < .01 ***P < .001

Table 3.6 Pearson's Product-moment Correlations Between CogState Tests and MoCA.

CogState Tests	MoCA		
	HF group	Healthy group	Totals
Detection task	-0.186	0.017	-0.208*
Identification Task	-0.208	-0.115	-0.191*
One Back Task	0.417***	0.526***	0.472***
International Shopping List Task	0.565***	0.582***	0.610***
International Shopping List Task: Delayed recall	0.640***	0.647***	0.676***
One Card Learning Test	0.395***	0.330**	0.404***
Continuous Paired Associate Learning Task	-0.396**	-0.408**	-0.421***

Note. MoCA =Montreal Cognitive Assessment; HF=heart failure

Note. *P < .05 **P < .01 ***P < .001

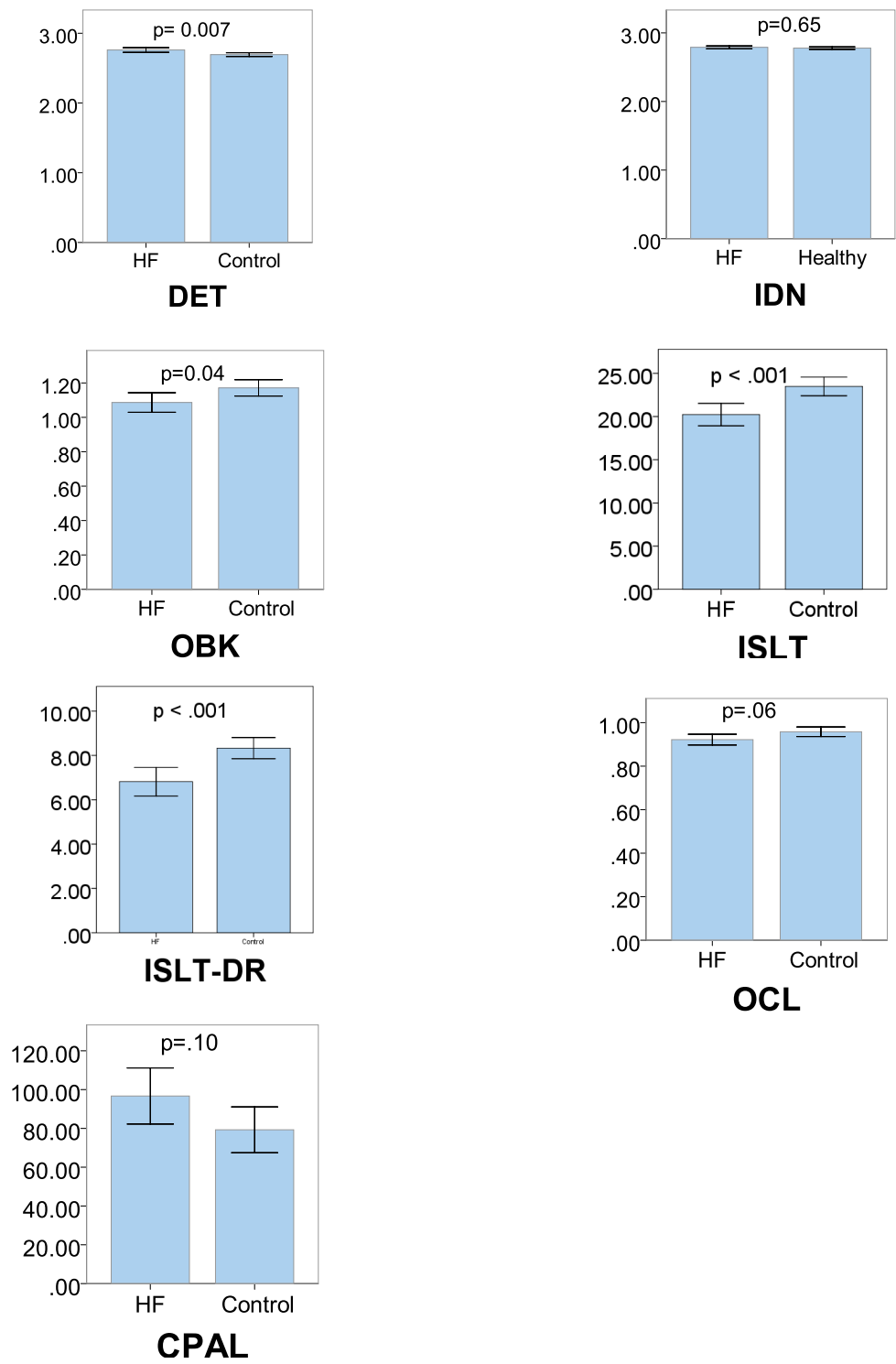


Figure 3.1. Mean and Standard Deviation for CogState Tasks. HF=Heart Failure; DET= Detection task; IDN= Identification task; OBK= One Back Task; ISLT= the International Shopping List Task, total; ISLT-DR= the International Shopping List Task, delayed recall; OCL= One Card Learning Task; CPAL= Continuous Paired Associate Learning

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CHAPTER IV

Menopausal Symptoms and Memory Performance in Women with Heart Failure

Abstract

Background: Memory deficits have been found in heart failure (HF) patients, but little is known about whether these are associated with menopausal symptoms in women with HF.

Objectives: The aims of this study were to examine type, frequency, and severity of menopausal symptoms in women with HF, compared with healthy participants, and to explore the association between menopausal symptoms and memory performance among Taiwanese postmenopausal women with HF.

Design: A cross-sectional, correlational study design was used.

Participants and settings: A total of 140 participants (76 women with HF and 64 healthy women) were recruited from an academic medical center in Taiwan.

Methods: Measures of demographic variables, menopausal symptoms, HF severity symptoms, global cognitive function, and memory were collected by self-report for women with HF. Clinical variables were obtained from medical records.

Results: Women with HF had significantly higher scores for total menopausal symptoms and subscales for psychological (anxiety and depression), somatic, and vasomotor symptoms compared with healthy women. The most prevalent symptoms in women with HF were forgetfulness, backache, waking up during the night, and feeling tired or lacking in energy. Verbal memory was significantly correlated with anxiety and sexual symptoms; visual memory was significantly influenced by anxiety and sexual symptoms. No significant association was

observed between memory performance and depressive, somatic, and vasomotor symptoms after adjustment for age, years of education, and comorbidity.

Conclusion: This study demonstrated that menopausal symptoms were worse in women with HF; anxiety and sexual symptoms were associated with memory function. Future prospective studies are needed to evaluate associations between menopausal symptoms and memory function.

Key words: Heart failure, Memory, Menopausal symptoms, Women

Word: 268 --IJNS --max is 350

1. Introduction

Heart failure (HF) is a significant health problem worldwide. The aging population and improvement in treatment of cardiovascular disease have contributed to both the increasing incidence and prevalence of HF (Lund & Mancini, 2004). Almost 46% of HF patients are women. Women with HF have more hospital discharges and longer hospitalizations than men, leading to increased costs of treatment (Roger et al., 2012; Frazier et al., 2007). Moreover, women tend to develop HF later in life and live longer after its onset (Adams et al., 1999; Frazier et al., 2007; Stromberg & Martensson, 2003). Taiwan's population is rapidly aging and the proportion of women has increased among elderly patients with HF (Tseng, 2011). The increasing prevalence of HF in Taiwan will likely be a significant burden for coming decades (Chen, Chen, & Tang, 2007).

In Taiwan, the mean menopausal age is between 48 and 50 years (Chow, Huang, & Lee, 1997; Fuh, Wang, Lu, Juang, & Chiu, 2001). Menopausal symptoms may occur in premenopausal, perimenopausal, or postmenopausal women (Blümel et al., 2012). It is well known that these symptoms have a negative effect on quality of life (Karaçam & Seker, 2007). They include vasomotor, physical, psychological, and urogenital atrophy symptoms (Greene, 1998). The types and severity of these symptoms vary by individual. Menopausal symptoms result from reduced estrogen because of decreased ovarian activity after menopause (Lokken & Ferraro, 2006; Rahman, Zainudin, & Mun, 2010). Previous research has demonstrated associations between endogenous hormone levels and menopausal symptoms. For example, vasomotor symptoms were associated with lower estradiol levels and hot flushes among women during the menopause transition (odds ratio = .77, $p < 0.001$) (Guthrie, Dennerstein, Taffe, Lehert, & Burger, 2005); urine estrone levels were positively related to sexual desire among women

during the menopausal transition and early postmenopause ($p < 0.0001$) (Woods, Mitchell , & Smith-Dijulio, 2010). Increasing estradiol levels by estrogen therapy (ET) improved depression among perimenopausal women ($r = -0.68, p = 0.001$) (Joffe et al., 2011). Most studies of menopausal symptoms have enrolled healthy women. In a literature review no studies were found on menopausal symptoms among women with HF.

The estrogen decline that accompanies menopause is thought to play a role in memory function after menopause. Studies indicate that estrogen affects the central nervous system through a variety of mechanisms to influence memory by elevating neurotransmitter levels, enhancing neuronal growth and synaptic plasticity, reducing cell apoptosis, and producing antioxidant properties (Craig & Murphy, 2007; McClure, Barha, & Galea, 2013; McEwen, 2002). It may be associated with multiple sites of estrogen receptors in the brain, including the hippocampus and prefrontal cortex, the brain regions involved in episodic and working memory (Ancelin & Ritchie, 2005). Episodic memory function concerns encoding and retrieving of conscious experiences from a person's past. The core brain region for the episodic memory system depends upon the medial temporal lobes, including the hippocampus (Budson, 2009). Working memory refers to capacity to store information for intervals of several seconds to a minute (Cown, 2008; Nichols, Kao, Verfaellie, & Gabrieli, 2006). The prefrontal cortex is the primary neural substrate responsible for working memory tasks (Budson, 2009).

The influence of estrogen decline on memory performance has been demonstrated. Pre-menopausal women who underwent oophorectomy and hysterectomy experienced significant decreases in memory tasks and had greater declines in verbal memory tasks with a greater than 50% decrease in estradiol level post-surgery (Nappi et al., 1999). Other studies have also indicated that hormone replacement therapy (HRT) improved verbal and working memory in

healthy postmenopausal women (Wroolie et al., 2011; Maki, 2012). Studies have shown that endogenous estrogen has a positive association with verbal memory in healthy postmenopausal women. One study found that older women within the lowest estradiol tertile were two times more likely than women in the highest tertile to decline on verbal memory tasks (28% versus 12%, $p=0.004$) (Yaffe et al., 2007). Others reported that high estradiol levels were related to better delayed verbal memory in healthy older women (Drake et al., 2000; Wolf & Kirschbaum, 2002). Although memory functions are particularly influenced by hormones, no prior studies have evaluated the relationship between menopausal symptoms, which may reflect the decreasing estrogen levels, and memory in HF population.

Evidence supports the biological hypothesis that HF has an adverse effect on memory performance. There are neurobiological changes and brain abnormalities that occur in the hippocampus in HF, which may affect memory functioning (Gruhn et al., 2001; Kumar et al., 2009; Vogels, Flier, et al., 2007; Vogels, Oosterman, van Harten, Gouw, et al., 2007; Woo, Kumar, Macey, Fonarow, & Harper, 2009). In one study with 251 veteran outpatients with HF, researchers reported verbal learning, immediate memory, and delayed verbal memory were most impaired (Hawkins et al., 2012). Vogels, Oosterman, van Harten and Scheltens, et al. (2007) assessed memory among 62 HF outpatients, 53 age-matched cardiac controls and 42 age-matched healthy controls. Extensive memory deficits in the HF group were found in verbal memory (delayed and immediate) compared with the other two groups. The scores for visual memory (immediate and delayed recall) were decreased on the Pattern Recognition Task in 62 outpatients with HF, although the difference did not reach significance ($p < 0.05$). Recently, another study reported that twenty-three percent of 249 HF patients had impaired scores on verbal memory (total recall task). Compared to 102 medical and 63 healthy participants, HF

patients had poor verbal memory and New York Heart Association (NYHA) Class was significantly associated with total recall score (Pressler et al., 2010a).

Studies have reported differences between men and women on cognitive screening questionnaires in the HF population. One study reported women with HF (n = 836) had an increased probability of cognitive impairment compared to men (n = 747) as assessed by the Hodkinson Abbreviated Mental Test (Zuccala et al., 2001). Researchers found more frequent abnormal scores in cognitive testing in women than men (n = 360, 27.5% women) using the Pfeiffer Test (15.2% vs. 5%, p=0.003) (Altimir et al., 2005). Moreover, a recent study with 50 HF patients and 50 healthy control subjects reported that female gender was associated with poorer memory performance on tasks of early recall, and delayed recall compared to men (Sauvé et al., 2009). These results raise questions as to whether menopause-related estrogen loss may magnify memory deficits in women with HF.

In summary, despite that emerging evidence suggests that HF has an adverse effect on memory performance and that high pre-menopausal estrogen concentrations in women are thought to be protective against memory loss, it is unknown whether the effects of estrogen decline after menopause as measured by menopausal symptoms are related to memory deficits in postmenopausal women with HF. To date, there has been no published evidence regarding menopausal symptoms and their relationship to memory performance in women with HF. Therefore, the primary aim of this study was to examine the type, frequency, and severity of menopausal symptoms in women with HF, compared with healthy participants. The secondary aim was to examine the association between menopausal symptoms and memory function among Taiwanese postmenopausal women with HF. Hypotheses were (1) Taiwanese postmenopausal women with HF have more severe menopausal symptoms compared with age- and education-

matched healthy women; and (2) menopausal symptoms are related to memory performance among postmenopausal women with HF.

2. Method

2.1 Design and Procedures

A cross-sectional, correlational study design was used for the current study. Patients were recruited from the Tri-Service General Hospital in Taipei, Taiwan from November 2010 to October 2011. HF patients were recruited from cardiovascular clinics and healthy participants were recruited from outpatients of the gynecology clinic, the women's health center, and volunteers in the same hospital. The study was performed after approval from the Institutional Review Board of the University of Michigan and the Tri-Service General Hospital. Eligible participants referred through physicians were invited to participate in the study. During face-to-face interviews at the clinics, informed consent was obtained from all participants by the investigator before data collection. Baseline data, including demographic and clinical items, menopausal symptoms, HF severity, and global cognitive function, were collected by the investigator using questionnaires and medical records reviews. After baseline data collection, computerized neuropsychological tests were administered by the investigator. Participants were not required to have prior computer experience to take the computerized tests. The time required to obtain and collect data was approximately 60 to 90 minutes.

2.2 Sample

Eligibility criteria for women with HF included having a diagnosis of HF for at least 6 months, natural menopause defined as last menstrual cycle completed longer than 12 months previously, age 50 years and older; and able to read and speak Mandarin. Eligibility criteria for age- and education- matched healthy women included having no major medical conditions and

the last three criteria listed above, as for HF patients. Women were eligible for the healthy group if they had hypertension with blood pressure less than 140/90 mmHg or hyperlipidemia with cholesterol less than 200 mg/dl. Women were excluded from the two groups if they had conditions that may cause cognitive deficit (e.g., history of neurological disease, stroke, history of recurrent mental disorders, encephalopathy or impaired sensory problems (e.g., hearing loss and visual problems)).

2.3 Measures

2.3.1. Postmenopausal symptoms associated with estrogen decline

Postmenopausal symptoms associated with estrogen decline were measured using the Greene Climacteric Scale (GCS). The GCS consists of 21 items, self-reported, divided into the following subscales: vasomotor symptoms such as hot flushes and night sweats (2 items); psychological symptoms such as anxiety and depressive symptoms (11 items); somatic symptoms (7 items); and loss of interest in sex (1 item) (Greene, 1998). Each symptom is rated by participants from 0 to 3 (0= not at all; 1=a little; 2=quite a bit; 3= extremely). Construct validity was supported in a previous study; internal consistency reliability of the GSC subscales ranged from 0.72 - 0.91 (Chen, Davis, Wong, & Lam, 2010; Greene, 1998). The GCS was translated to Chinese by two Taiwanese with Masters' degrees in Nursing. The Chinese version of GCS was translated back into English by a bilingual translator. The consistency of the back-translated English version and original version was evaluated by the research team (Pai, 2002). The construct validity and reliability of the Chinese version of the GCS were supported in postmenopausal women. Cronbach's alphas for the GCS-C were 0.86 - 0.92, and the correlation of test-retest reliability (at 2 weeks) was 0.92 (Fang, 2005; Liu, 2007; Pai, 2002). An additional five menopausal symptoms that often occur in Chinese women were added in this study,

including cold sweats (night or day), waking up during the night, vaginal dryness, backache, and forgetfulness (Chow et al., 1997; Fu, Anderson, & Courtney, 2003). Scores range from 0 to 78, with higher scores indicating more symptoms or more severe symptoms. The internal consistency reliability (Cronbach's alpha) for the present study was 0.90.

2.3.2. HF severity

Heart failure severity was assessed by the measure of perceived functional capacity, the NYHA functional classification and the Duke Activity Status Index (DASI) (Hlatky et al., 1989; New York Heart Association Criteria Committee, 1964). NYHA class was measured and confirmed by patients' physicians in outpatient clinics before the interview. Patients are assigned to 1 (no symptoms of HF upon ordinary physical activity) to 4 (symptoms of HF at rest) (New York Heart Association Criteria Committee, 1964). The validity and reliability of the NYHA classes were reported (Bennett, Riegel, Bittner, & Nichols, 2002). The DASI consists of 12 items that assess whether participants can perform daily activities with a 4-point scale. In a previous study among 50 subjects undergoing exercise testing, it significantly correlated with peak oxygen uptake in development ($r = 0.81, p < 0.0001$) and validation phases ($r = 0.81, p < 0.001$) (Hlatky et al., 1989). Possible weighted scores range from 0 to 58.2. Higher scores represent better perceived functional capacity. The reliability coefficient of the DASI score was satisfactory (Cronbach's $\alpha = 0.87$) in 249 HF patients (Pressler et al., 2010b). This questionnaire has been validated in the Chinese language (Chen, 2001). The Cronbach's alpha in this study was 0.69.

2.3.3. Global cognitive function

Global cognitive function was measured using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). This is a 10-minute test that assesses eight cognitive domains within a

series of thirteen tests: visuospatial abilities; naming; memory; attention task; language; verbal abstraction task; delayed recall; and orientation. The score of the MoCA ranges from 0 to 30, with higher scores indicating better global cognitive function. Validity and reliability were supported in previous study. The test-retest reliability was 0.92 at 35 days; the Cronbach's alpha for internal consistency was 0.83. In the original study among 94 patients with mild cognitive impairment (MCI), 93 patients with mild Alzheimer's disease (AD), and 90 healthy elderly, the MoCA had excellent sensitivity in identifying MCI and AD (90% and 100%) and normal elderly were identified with a specificity of 87% by using a cutoff score of 26 (Nasreddine et al., 2005). Criterion and concurrent validity were satisfactory for the Chinese version of MoCA. The 2-week test-retest reliability and inter-rater reliability were 0.96 and 0.87. In a study carried out in Hong Kong, the Cronbach's alpha for internal consistency was 0 (Wong et al., 2009). Using an optimal cut-off score of 23/24 in a Taiwanese population, sensitivity and specificity for MCI were 92% and 78%, respectively (Tsai et al., 2012).

3.4. Memory deficits

Memory deficits were measured using the CogState battery, a valid and reliable computerized neuropsychological test battery that is sensitive in detecting decline over time in older adults (Cysique, Maruff, Darby, & Brew, 2006; Darby, Maruff, Collie, & McStephen, 2002). The CogState Battery is standardized and easy to administer; scoring is completed within the program. Six different tests from the computerized cognitive battery considered to evaluate memory and other cognitive abilities are presented in Table 4-1, with detail available in previous publications (Darby et al., 2002; Harel et al., 2011; Lim, Peitrzak, Snyder, Darby, & Maruff, 2012). The test-retest reliability was supported in 263 older adults at 3-month intervals during 12 months (Fredrickson et al., 2010) and in 70 persons with mild Alzheimer's disease at one week

(Lim et al., 2012). The CogState battery demonstrated good sensitivity (78%) and specificity (90%) for mild cognitive impairment (MCI) (De Jager, Schrijnemaekers, Honey, & Budge, 2009).

Working memory was measured by the One Back Task (OBK). In the OBK, a card is presented in the center of the screen. The participant must indicate whether the new card is the same or different to the previously presented card when the card changes (Cysique et al., 2006). This task assesses accuracy of performance.

Episodic memory was assessed by verbal and visual stimuli. The International Shopping List Task (ISLT) and the International Shopping List Task-Delayed Recall (ISLT-DR) were used to measure verbal immediate and delayed memory. The test consists of immediate free recall for a series of 12-word lists for three consecutive trials (trials 1-3), followed by recall for the word list after a 20-minute delay (trial 4). The range of correct scores is 0-36 in ISLT and the range of correct scores is 0-12 in ISLT-DR. The One Card Learning Task (OCL) and the Continuous Paired Associate Learning Task (CPAL) were used to assess visual memory. In the OCL, the participants were instructed to respond “Yes” if the card has appeared before or “No” if it has not appeared (Fredrickson et al., 2010). This task assesses accuracy of performance. For the CPAL, the participants were asked to determine whether a single picture presented in the center of the screen was the same as any one of the pictures presented in peripheral locations and tap the same one in the peripheral location (O'Donnell, Pietrzak, Ellis, Snyder, & Maruff, 2011). It is scored as the total number of errors across five rounds, with a lower score reflecting better visual memory performance.

Speed of performance was computed as the mean of the log₁₀ transformed reaction times for correct responses. A lower score indicates better performance. Accuracy of performance was

computed as the arcsine transformation of the proportion of correct responses for total trials (Fredrickson et al., 2010; Maruff et al., 2009). Higher scores indicate better performance. The total number of words recalled in 3 trials, the number of words recalled after 20 minutes for ISLT, and total number of errors for CPAL were computed for analysis.

2.3.5. Demographic and clinical variables

Data were collected for demographic and clinical information (age, race, education, marital status, employment status, and blood pressure), and menopausal history (age when menstruation began, number of pregnancies, number of live births, age at menopause, duration of menopause, hysterectomy and ovariectomy, and estrogen replacement therapy). For HF participants, data were also collected for number of comorbid conditions and HF-related variables (i.e., LVEF, NYHA class, heart failure duration, and type of HF).

2.4 Statistical analyses

Descriptive statistics were used to compare demographics, clinical variables, and study variables among the HF and healthy groups of women. Categorical variables were examined using chi-square and Fisher's exact tests; continuous variables were examined using independent t-tests. To achieve aim one, means, medians, frequencies and standard deviations were calculated to describe the frequency and severity of postmenopausal symptoms associated with estrogen decline in the HF group. Independent t-tests were used to compare scores of menopausal symptoms between the HF and healthy groups.

To achieve aim two and test the hypothesis that menopausal symptoms are related to memory performance among postmenopausal women with HF, Pearson product-moment correlation coefficients were used to assess multicollinearity among explanatory variables and the associations between menopausal symptoms and memory scores (OBK, ISLT, ISLT-DR,

OCL, CPAL). A series of simultaneous multiple regression analyses were performed separately to explore the association between postmenopausal symptoms and memory adjusted for covariates. Regression diagnostics were carried out to test the assumptions underlying regression analysis (independence, normal distribution, linearity, homoscedasticity). In the different series, the symptom scores (which included scores for, anxiety symptoms, depressive symptoms, somatic symptoms, vasomotor symptoms, and sexual symptoms) were entered as the explanatory variables and each memory test was entered as the dependent variable in separate equations to examine memory domains in HF group. Age, years of education, and comorbid conditions were entered as covariates because they may influence memory performance (using the significance level $P < .05$). All analyses were conducted using SPSS version 17.

3. Results

3.1 Characteristics of the sample

Characteristics of the study participants are presented in Table 4-1. A total of 140 women were recruited in this study. Seventy-six postmenopausal women were in the HF group and 64 postmenopausal women were in the healthy group. The mean age of the sample was 69.4 years old (SD=8.9). There was no significant difference between the groups with respect to age, marital status, years of education, whether living alone or not, and diastolic blood pressure. In addition, menopausal variables including age at menopause, duration of menopause, ever taking HRT, and taking HRT now did not differ between the groups. Compared to healthy women, women with HF were less often employed, had higher systolic blood pressure, more comorbid conditions, worse functional capacity, and poorer global cognitive function. Most of the women with HF had diastolic HF and were NYHA class II.

3.2 Type, frequency and severity of menopausal symptoms

Scores for total GCS and its subscales for both groups are presented in Table 4-2. The total GCS score with 21 items or 26 items was significantly greater in women with HF ($p < .001$), indicating higher severity of menopausal symptoms in this group. Women with HF also had significantly higher scores on subscales for psychological ($p < .001$), somatic ($p < .001$), and vasomotor ($p < .001$) symptoms. The scores for sexual symptoms were higher in women with HF compared with the healthy women, but the difference did not reach significance. Hypothesis one was supported in the study.

In Table 4-3, mean scores and frequencies for the 21 GCS items, and additional 5 items for menopausal symptoms, are presented for women with HF. Results showed that the highest scores were reported for waking up during the night (1.56 ± 0.96), backache (1.37 ± 0.88), forgetfulness (1.20 ± 0.69), and muscle and joint pain (1.17 ± 0.99). Thirteen of 26 menopausal symptoms had a prevalence of $\geq 50\%$. Of the 26 symptoms comprising the scale the most prevalent were: forgetfulness (88.2%), backache (85.5%), waking up during the night (84.2%), and feeling tired or lacking in energy (69.7%).

3.3 Association between menopausal symptoms and memory in HF

In correlation analyses, the total score of the 21 GCS items was highly correlated with subscales of depressive and somatic symptoms ($r = .88, p < .001$; $r = .89, p < .001$). The total score for the 26 menopausal symptom items was also highly correlated with depressive and somatic symptoms ($r = .88, p < .001$; $r = .89, p < .001$). Psychological symptoms were highly correlated with anxiety and depressive symptoms ($r = .89, p < .001$; $r = .87, p < .001$). Therefore, total score for the 21 GCS items, total score for the 26 menopausal symptom items and psychological symptoms were not entered into multiple regression equations. The subscales of anxiety, depressive, somatic, vasomotor, and sexual symptoms were entered into multiple regression

equations. Vasomotor symptoms were significantly positively associated with ISLT (total recall, $r = .25, p = .03$). All other correlations between menopausal symptom variables and memory variables were not significant.

In regression models adjusted for age, education, and comorbidity, associations between GCS scores and CogState tasks in women with HF were explored. With regard to working memory, anxiety, depressive, somatic, vasomotor, and sexual symptoms were not significantly associated with OBK scores. Regarding verbal memory (Table 4-4), the anxiety ($t = -2.21, p = .03$) and sexual symptoms ($t = -2.39, p = .02$) subscales were the variables to significantly account for ISLT-DR. Women with more anxiety and sexual symptoms had worse verbal memory (ISLT-DR). However, anxiety, depressive, somatic, vasomotor, and sexual symptoms did not influence ISLT (total recall). Regarding visual memory, sexual symptom ($t = -2.59, p = .01$) was associated with OCL. Having more sexual symptom was associated with poorer OCL performance. Moreover, anxiety symptoms ($t = 2.95, p = .01$) were significantly related to more errors in CPAL performance. The hypothesis two that menopausal symptoms (anxiety and sexual symptoms) are associated with memory performance (verbal and visual memory) was partially supported.

4. Discussion

To our knowledge, this is the first study to examine menopausal symptoms and the association between them and memory performance in HF. Women with HF had significantly higher scores for total menopausal, psychological, somatic, and vasomotor symptoms than healthy women; women with HF also experienced higher severity of menopausal symptoms. Moreover, verbal memory and visual memory were significantly related to anxiety and sexual symptoms.

In the current study, women with HF had higher scores for psychological, somatic, and vasomotor symptoms than the healthy group. These group differences were expected, as other investigators have found that severity of menopausal symptoms was related to health status (Gharaibeh, Al-Obeisat, & Hattab, 2010), chronic disease history (Shu, Luh, Li, & Lu, 2007), and cardiovascular disease risk factors (Cagnacci et al., 2012). Although the main cause of menopausal symptoms is related to estrogen deficiency, women in the present study had HF and more comorbidities that may contribute to the increased risk of severe menopausal symptoms. Observed differences also may be explained by measurement issues. Some HF symptoms were similar to menopausal symptoms, for example, difficulty in sleeping is both a menopausal and HF symptom. The HF symptoms may have directly increased frequency and severity of menopausal symptoms measured by GCS and the 5 additional items. As these symptoms have a negative effect on quality of life (Karaçam & Seker, 2007), future study is needed to differentiate menopausal and HF symptoms and develop a measure of menopausal symptoms that is suitable for women with chronic disease such as HF.

Earlier studies of cognitive function in HF have not reported relationships between menopausal symptoms and memory function. Our study found that some menopausal symptoms (such as anxiety and sexuality symptoms) accounted for performance on memory tasks in women with HF. Studies of the effect of estrogen therapy on cognitive function may provide insight into the association between menopausal symptoms and memory (Yaffe, Sawaya, Lieberburg, & Grady, 1998). In a meta-analysis study on the effect of HRT on cognitive decline in healthy postmenopausal women, investigators found that HRT improved verbal memory in women with menopausal symptoms, but there was no effect on asymptomatic women. The researchers suggested that possibly because menopausal symptoms were improved (LeBlanc,

Janowsky, Chan, & Nelson, 2001). However, these studies did not directly examine the possible association between menopausal symptoms and memory.

Anxiety symptoms, one subscale of the psychological symptoms, were associated with lower memory function in women with HF, as seen in other populations (Andreoletti et al., 2006; Smeets, Otgaar, Candel, & Wolf, 2008; Wetherell, Reynolds, Gatz, & Pedersen, 2002). The relationship of anxiety symptoms to memory has not been often examined in patients with HF. A possible mechanism for the association is that psychological distress leads to increased cortisol level through activation of the hypothalamus-pituitary adrenal (HPA) axis (Wolf, 2009). A functional magnetic resonance imaging (fMRI) study revealed that increased cortisol impaired memory retrieval by reduced activation in the hippocampus (Oei et al., 2007). Future prospective studies are needed to evaluate the association between measures of anxiety and memory performance among women with HF.

Our observations of negative relationships between sexual symptoms and both verbal and visual memory have not been reported previously. Although sexual desire may not have a direct central effect on memory and the mechanisms by which it affects memory performance are unknown, previous studies have reported that decreasing estrogen levels were correlated with decreasing sexual desire (Woods et al., 2010; Woods et al., 2007). The association between sexual symptoms and memory may reflect decreasing estrogen levels. In addition, experiencing symptoms of hot flashes, fatigue, depressed mood, anxiety, and sleep problems have been significantly associated with lower sexual desire (Woods et al., 2010). Women with HF in our study showed more symptoms compared with healthy women. The effect of sexual desire on memory may be influenced by other symptoms. Future studies should explore relationships between these symptoms and memory performance.

In our study, no direct association was found between depressive, somatic, vasomotor symptoms and memory function. Similar results were found in some studies that examined memory and other perceived symptoms, such as depression (Mauro et al., 2006; Sauvé et al., 2009; Pressler et al., 2010a) and health-related quality of life (Pressler et al., 2010b). One possible explanation suggested by past research is that the objective memory measures do not correlate strongly with subjective measures (Pressler et al., 2010b). In addition, the low level of depressive symptoms (mean=0.65), somatic symptoms (mean=0.77), and vasomotor symptoms (mean=0.44) might not have been great enough to have an influence on memory performance in this sample.

Contrary to expectation, menopausal symptoms were not related to any tasks for working memory, indicating that working memory was fairly resistant to or independent of them in this sample of women with HF. It is well known that estrogen affects memory through the broader distribution of estrogen receptors in brain areas such as the hippocampus and neocortex, the brain regions involved in episodic memory and working memory (Ancelin & Ritchie, 2005). However, our findings support those of other studies. Past investigations examined effects of endogenous and exogenous estrogen exposures in postmenopausal healthy women and did not find associations between estrogen measures and working memory tasks, such as digit span backwards, Letter-Number Sequencing and serial subtraction of sevens and spelling WORLD backward (Henderson & Popat, 2011). Possible explanations are that circulating estrogen levels may not be suitable measures to use to predict neural effects on the brain (Henderson & Popat, 2011).

Furthermore, the mean age of women with HF in our study was 69.7 (SD=10.2). Findings from a previous study failed to find a neuroprotective effect for estrogen in older women

(Espeland et al., 2004). The effect of estrogen on the aging brain may be different than that on brains of younger individuals; the association between menopausal symptoms and related estrogen decline and memory might vary by age. Future studies need to include younger women with HF to clarify the relationship between menopausal symptoms and memory.

5. In conclusion

Results of this study suggest that menopausal symptoms were worse in women with HF compared to healthy women, and that anxiety and sexual symptoms were associated with poorer verbal and visual memory function. This study has limits in terms of its ability to differentiate menopausal and HF symptoms, and its ability to capture actual estrogen decline. Future studies should develop a suitable tool to evaluate menopausal symptoms in women with HF and collect serum estrogen concentrations in order to establish whether self-reported menopausal symptoms are reflected in actual estrogen concentrations. In addition, results are not generalizable to women with HF with other menopausal status or disease. Prevalence of postmenopausal women with HF is increasing. Health professionals need to be aware that women with HF who have more menopausal symptoms may be most at risk for memory deficits, develop interventions to treat symptoms and memory deficits, and assess whether their self care abilities are compromised. Future prospective studies are needed to evaluate associations between menopausal symptoms, estrogen levels, and memory function in women with HF.

Table 4.1. Demographic and Clinical Variables by Groups (n=140)

Characteristics	Total (n=140)	HF (n = 76)	Healthy (n = 64)	t-test, χ^2 or Fisher's exact test	P-value
Age, mean (SD)	69.4 (8.9)	69.7 (10.2)	68.9 (7.1)	t=0.53	0.59
Race, n (%)				Fisher's exact test	0.02*
Taiwanese	104 (74.3)	49 (64.5)	55 (85.9)		
Mainland China	26 (18.6)	19 (25)	7 (10.9)		
Hakka	8 (5.7)	6 (7.9)	2 (3.1)		
Aborigine	2 (1.4)	2 (2.6)	0 (0)		
Marital status, n (%)				Fisher's exact test	0.16
Married	102 (72.9)	61 (80.3)	41 (64.1)		
Single	3 (2.1)	1 (1.3)	2 (3.0)		
Divorced	6 (4.3)	2 (2.6)	4 (6.3)		
Widowed	29 (20.7)	12 (15.8)	17 (26.6)		
Education, mean (SD)	7.6 (3.2)	7.3 (3.3)	8.0 (3.1)	t=-1.31	0.19
Employment, n (%)				$\chi^2=11.25$	0.001**
No	115 (82.1)	70 (92.1)	45 (70.3)		
Yes	25 (17.9)	6 (7.9)	19 (29.7)		
Live alone, n (%)				$\chi^2=1.28$	0.52
No	115 (82.1)	64 (84.2)	51 (79.7)		
Yes	25 (17.9)	12 (15.8)	13 (20.3)		
Systolic blood pressure, mean (SD)	129.5 (15.8)	135.5 (17.5)	122.3 (9.5)	t=5.34	< .001***
Diastolic blood pressure, mean (SD)	75.3 (8.9)	76.1 (10.2)	74.4 (6.9)	t=1.1	0.27
Comorbidity number, mean (SD)	1.1 (1.0)	1.8 (0.9)	0.2 (0.4)	t=12.16	< .001***
Age at menopause, mean (SD)	50.0 (5.1)	50.4 (5.8)	49.6 (4.1)	t=0.83	0.407
Months since menopause, Mean (SD)	232 (116)	232 (133)	231 (94)	t=0.08	0.929
Ever take HRT, n (%)				$\chi^2=0.00$	0.983
No	95 (67.9)	51 (67.1)	44 (68.8)		
Yes	43 (30.7)	23 (30.3)	20 (31.2)		
Take HRT now, n (%)				Fisher's exact test	0.12
No	136 (97.1)	72 (94.7)	64 (100)		
Yes	4 (2.9)	4 (5.3)	0 (0)		
MoCA, mean (SD)	26.2 (3.3)	25.1 (3.7)	27.5 (2.1)	t=-4.54	< .001***
Duke Activity Status Index, mean (SD)	30.8 (15.1)	21.6 (11.3)	41.7 (11.5)	t=-10.29	< .001***

The Greene Climacteric Scale, mean (SD)	14.6 (9.5)	17.9 (10.4)	10.8 (6.8)	t=4.69	< .001***
Left Ventricular Ejection Fraction, mean (SD)		60.9 (3.8)			
NYHA class, n (%)					
Class I		6 (7.9)			
Class II		57 (75)			
Class III		11 (14.5)			
Class IV		2 (2.6)			
Month of HF, mean (SD)		35.7 (28.4)			
Type of HF, n (%)					
Systolic HF		11 (14.5)			
Diastolic HF		65 (85.5)			

Note. HRT= Estrogen replacement therapy; MoCA= Montreal Cognitive Assessment; NYHA=New York Heart Association; HF=heart failure; Values are expressed as numbers (%). Percentage is expressed as valid percentage, which excludes missing data

Note. *P < .05 **P < .01 ***P < .001

Table 4.2. Scores for Subscales and Total Greene Climacteric Scale for Two Groups

	HF (n=76) Mean (SD)	Healthy (n=64) Mean (SD)	t-test	P-value
Subscales in GCS				
Psychological (items 1-11; range 0-33)	6.96 (4.95)	4.02 (3.36)	4.04	< .001***
Anxiety (items 1-6; range 0-18)	3.71 (2.75)	2.42 (2.22)	3.01	0.003**
Depressive (items 7-11; range 0-15)	3.25 (2.77)	1.59 (1.71)	4.12	< .001***
Somatic (items 12-18; range 0-21)	5.42 (4.15)	2.73 (2.44)	4.56	< .001***
Vasomotor (items 19-20; range 0-6)	0.88 (1.14)	0.52 (0.89)	2.08	0.039*
Sexual (item 21; range 0-3)	0.30 (0.80)	0.13 (0.42)	1.60	0.112
Total score (items 1-21; range 0-63)	13.54 (9.29)	7.39 (5.56)	4.64	< .001***
Total score (items 1-26; range 0-78)	17.95 (10.40)	10.82 (6.81)	4.69	< .001***

Note. *P < .05 **P < .01 ***P < .001; GCS= the Greene Climacteric Scale; Per item score range 0 to 3; higher score in GCS= higher severity of the symptoms.

Table 4.3. Mean Scores for the Greene Climacteric Scale and Five Additional Items in Women with HF

	Women with HF (n=76) Mean \pm SD (%)
Heart beating quickly or strongly	0.62 \pm 0.77 (48.4)
Feeling tense or nervous	0.70 \pm 0.80 (53.9)
Difficulty in sleeping	0.96 \pm 1.06 (53.9)
Excitable	0.32 \pm 0.62 (23.7)
Attacks of panic	0.41 \pm 0.73 (28.9)
Difficulty in concentrating	0.71 \pm 0.78 (53.9)
Feeling tired or lacking in energy	0.96 \pm 0.81 (69.7)
Loss of interest in most things	0.64 \pm 0.80 (47.4)
Feeling unhappy or depressed	0.63 \pm 0.75 (51.3)
Crying spells	0.36 \pm 0.65 (26.3)
Irritability	0.66 \pm 0.81 (50.0)
Feeling dizzy or faint	0.74 \pm 0.84 (52.6)
Pressure or tightness in head or body	0.67 \pm 0.85 (46.1)
Parts of body feel numb or tingling	0.82 \pm 0.89 (52.6)
Headaches	0.50 \pm 0.72 (39.5)
Muscle and joint pain	1.17 \pm 0.99 (68.4)
Loss of feeling in hands or feet	0.93 \pm 0.88 (63.2)
Breathing difficulties	0.59 \pm 0.73 (46.1)
Hot flushes/sudden warmth	0.41 \pm 0.64 (34.2)
Sweating night or day	0.47 \pm 0.74 (34.2)
Loss of interest in sex	0.30 \pm 0.80 (15.8)
Five additional items:	
Cold sweats (night or day) (item22)	0.28 \pm 0.60 (21.1)
Waking up during the night (item23)	1.56 \pm 0.96 (84.2)
Vaginal dryness (item24)	0.37 \pm 0.71 (26.3)
Forgetfulness (item25)	1.20 \pm 0.69 (88.2)
Backache (item26)	1.37 \pm 0.88 (85.5)

Note. Per item score range 0 to 3; higher score in the Greene Climacteric Scale = the higher severity of symptoms.

Table 4.4. Multiple Regression Analysis: Explanatory Variables of the Greene Climacteric Subscales for Memory Performance in Women with HF

Models	Variable	B	SE B	Beta	<i>t</i>	P value
ISLT-DR ^a	Anxiety symptoms	-.24	.11	-.23	-2.21	.03
	Depressive symptoms	.23	.14	.22	1.67	.10
	Somatic symptoms	-.16	.09	-.23	-1.84	.07
	Vasomotor symptoms	.46	.25	.18	1.86	.07
	Sexual symptom	-.75	.32	-.21	-2.39	.02
OCL ^b	Anxiety symptoms	.00	.01	.00	-.02	.98
	Depressive symptoms	.00	.01	-.04	-.19	.85
	Somatic symptoms	.01	.01	.18	1.01	.32
	Vasomotor symptoms	-.01	.01	-.05	-.38	.71
	Sexual symptom	-.04	.02	-.32	-2.59	.01
CPAL ^c	Anxiety symptoms	8.79	2.98	.38	2.95	.01
	Depressive symptoms	-6.11	3.83	-.25	-1.60	.12
	Somatic symptoms	2.86	2.56	.18	1.12	.27
	Vasomotor symptoms	-1.17	7.07	-.02	-.17	.87
	Sexual symptom	12.96	9.37	.16	1.38	.17

Note: Linear regression analysis adjusted by age, years of education, and comorbidity; HF=Heart Failure; ISLT-DR= the International Shopping List Task, delayed recall; OLT= One Card Learning Task; CPAL= Continuous Paired Associate Learning

^a $R^2 = .60$, Adjusted $R^2 = .55$, $F=11.36$, $p < .0001$

^b $R^2 = .23$, Adjusted $R^2 = .12$, $F=2.14$, $p = .038$

^c $R^2 = .43$, Adjusted $R^2 = .34$, $F=4.86$, $p < .0001$

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CHAPTER V

Summary and Conclusion

Summary

The primary purpose of the study was to examine memory performance among Taiwanese postmenopausal women with HF compared with age- and education-matched healthy control participants, and to evaluate factors that explain memory performance. In addition, it examined the validity of the Chinese Version of the CogState computerized cognitive assessment battery in HF group. Finally, it focused on menopausal symptoms and their relationships to memory performance among Taiwanese postmenopausal women with HF.

The theoretical framework for the study links the neurobiological theory of HF, the biological theory of menopausal-related estrogen loss in post-menopausal women, and the neurobiological effects of estrogen to the neurobehavioral theory for memory functioning, specifically working memory and episodic memory. Cognitive deficits were examined using the CogState computerized cognitive assessment battery.

In Chapter II, hypothesis one was supported in this sample, Taiwanese postmenopausal women with HF had poorer working memory and episodic memory (verbal memory) performance than age- and education-matched healthy women participants. Verbal memory was the most affected domain in this population. Hypothesis two was partially supported. Age explained working memory; age, HF severity, comorbidity, and HF type explained verbal memory. However, postmenopausal symptoms associated with estrogen decline were not significant explanatory variables in any of the performances.

Chapter III examined the psychometric properties of the Chinese Version of the CogState computerized cognitive assessment battery used in the study. The construct validity of the Chinese CogState tests was supported by significant correlations with MoCA, significant differentiation between patients with HF and healthy control groups, and an exploratory factor analysis that pointed to two factors of the CogState battery. Findings indicated that the Chinese version of the CogState battery is a valid instrument to assess cognitive performance among women with HF in Taiwan.

In Chapter IV, severity of menopausal symptoms in women with HF was examined as well as the association between menopausal symptoms and memory function. Hypothesis one was supported: women with HF had more severe menopausal symptoms on subscales for psychological, somatic, and vasomotor symptoms compared with age- and education-matched healthy women. Hypothesis two was partially supported. After adjustment for age, years of education, and comorbidity, verbal and visual memory were significantly associated with anxiety and sexual symptoms. However, scores for depressive, somatic, and vasomotor symptoms were not correlated with any CogState tasks. This study suggested that women with HF experienced worse menopausal symptoms and anxiety and sexual symptoms may have a negative influence on memory performance.

The findings of this study are significant to the scientific body of knowledge for several reasons. First, the findings of the study showed poorer memory performance in Taiwanese women with HF compared to Taiwan healthy women with matched age and education. This result was consistent with other studies conducted in western countries, suggesting HF disease may impair memory function regardless of culture and race. Second, another important finding is that specific deficits in working memory and verbal memory were found in women with HF

compared to healthy control women. Prior HF research in western populations with men and women also showed that working memory and verbal memory were common affected domains. The results of this study provide a better understanding of the memory performance focused on women population. Third, verbal memory was the most affected memory domain in women with HF compared to other memory domains. It would be important for future research to evaluate the nature of verbal memory problems and to find ways to reduce the impact of decreased verbal memory. Fourth, an unexpected finding was that HF type was an explanatory variable for verbal memory. Women with systolic HF had worse verbal memory compared to women with diastolic HF. The effect of HF type on verbal memory was still found even when controlling for covariates such as age, education, and number of comorbidities. This finding was worthy of notice because the majority of research in HF and cognition were conducted in patients with systolic HF, and no study explored memory performance in patients with diastolic HF. The HF type may appear to influence the memory performance in women with HF. However, sample size of women with systolic HF was small and further studies need to fully examine HF type.

Strengths

This is the first study to investigate cognitive function, specifically working memory and episodic memory, in Taiwanese women with HF and explore factors associated with these deficits. Findings suggested that Taiwanese women with HF had poor memory performance compared to a healthy control group; results are similar to those from studies conducted in western countries. Moreover, this is the first study to validate the Chinese version of the CogState Computerized Cognitive Assessment Battery in Taiwanese patients with HF. This is also the first study to examine the relationship between menopausal symptoms and memory performance in women with HF.

One strength of the study is that potential covariates were controlled by study design and statistical methodology. The study design included an age- and education-matched healthy group. Moreover, potential covariates included in regression models, such as education, comorbidity, and HF type were selected based on literature review and statistical outcomes.

Another strength of the study is that a valid and reliable computerized neuropsychological test battery was used to assess specific domains of memory. It is easy to administer and scores are completed within the program, which made the battery useful in detecting memory change in clinical settings.

Furthermore, a strength is that the HF sample in this study are women and majority of them (85%) had diastolic HF. Compared to men, women tend to develop HF with preserved ventricular function (diastolic HF). Most past studies recruited patients with systolic HF, and it is not clear whether women with diastolic HF would have shown similar results. The finding indicated their performance was similar to those with systolic HF.

Limitations

The study was limited in that it had a cross-sectional design. Information on long-term cognitive performance could not be obtained and the trajectory of memory performance could not be determined. In addition, test-retest reliability of the instruments was not ascertained since it used only one-time measures.

Another design-related limitation is that a control group with major chronic diseases other than HF was not included. Findings indicated that memory deficits were found in women with HF who often had comorbid disease such as uncontrolled hypertension or diabetes. However, it is not known whether the memory deficits were associated with these major medical conditions or only affected by HF because we did not recruit a medical group for comparison.

An additional limitation of this study is that estrogen decline was measured by self-reported menopausal symptoms. As menopausal symptoms are affected by other factors, they may not reflect actual estrogen condition.

Finally, participants in this study were recruited from a medical center in Taipei, Taiwan. The sample does not necessarily represent all women with HF in Taiwan. Future studies should recruit participants from multiple sites in Taiwan.

Implications for future research

Longitudinal studies are needed to examine changes in memory performance in women with HF and to evaluate the factors that explain these memory changes. As mentioned above, a comparison group with medical conditions other than HF should be included in future studies to evaluate whether memory deficits are associated only with HF, or other major chronic diseases, as well.

Future studies should collect blood estrogen samples that can directly confirm the relationship between estrogen level and memory performance. In this study, although the total score of self-reported menopausal symptoms associated with estrogen decline was not related to memory performance, scores for subscales such as anxiety and sexual symptoms were significantly related. Future studies are needed to examine whether the estrogen levels could be a factor that influence memory function in postmenopausal women with HF.

Another recommendation is to compare memory performance in larger samples of patients with systolic and diastolic (preserved systolic function) HF. Interestingly, findings of this study showed that women with systolic HF had poor verbal memory compared to women with diastolic HF, although the sample size of the women with systolic HF was small (n=11). A larger

future study would contribute to knowledge regarding whether HF type impacts memory function.

Future research may further validate the Chinese version of the CogState battery by comparing it with a well-established standard neuropsychological test that provides a diagnosis of cognitive impairment. Stability of the instruments would also need to be established.

Future studies might also expand on the association between memory deficits and menopausal stages and younger women with HF. The sample in this study was postmenopausal; we did not recruit women with younger age, or women in pre- or peri- menopausal stages. These future studies would help to explore the possible factors that may explain memory deficits in women with HF.

Cognitive training interventions have been limited in the HF population. A preliminary study using nurse-enhanced cognitive training intervention demonstrated improved memory and conduct of daily activities in western patients with HF (Pressler et al., 2011). In that study, the nurses were not only interveners, but could monitor intervention adherence. More nurse-enhanced cognitive training interventions should be developed and modified for testing in Taiwanese women with HF.

Research on cognitive function and HF is still in development. As possible factors and mechanisms of memory change in HF are identified, more research is needed to fully explore the impact of memory declines on outcomes such as quality of life, self-care and daily activities, and mortality.

One last recommendation is to conduct direct evaluations of the influence of menopausal symptoms on patients' quality of life outcomes. This study showed that women with HF reported more menopausal symptoms compared to healthy women. However, we did not know how these

symptoms would affect their actual quality of life. An examination will provide important information about the effects of menopausal symptoms on their living in women with HF. Moreover, intervention focusing on this vulnerable population should be developed to decrease their menopausal symptoms.

Implications for nursing practice

The population has aged and the proportion of women has increased among elderly patients with HF not only in Taiwan, but also in the rest of the world. This study contributes to better understanding of memory deficit patterns in Taiwanese postmenopausal women with HF that is important to the provision of improved care and treatment. Sound memory is absolutely critical to adapting to illness, modifying one's knowledge base needed to monitor health status, and being able to incorporate new self-care practices. If women with HF experience significant memory decline, their ability to adhere to complex medication schedules and dietary therapies may be compromised because of forgetfulness and poor learning ability (Dickson, Tkacs, & Riegel, 2007). Nurses are the primary care providers who frequently observe cognitive changes in patients over time as well as receive reports of memory changes from family members (Athilingam & King, 2007). Application of these findings can help Taiwanese nurses to assist women with HF in improving treatment adherence, self-care and living with HF.

Assessment: Memory deficits are common in women with HF; researchers in western countries have used a variety of neuropsychological tests in these patients. Many may not be feasible for use in nursing practice because they need special training to administer and score. The Chinese Version of the CogState computerized cognitive assessment battery may become a reliable tool for memory assessment in Taiwan. There are no simple screening tools available to detect memory impairment in nursing clinical practice, and no routine assessment for memory

function in cardiovascular clinics in Taiwan. Our findings suggest that the International Shopping List Task (ISLT) from the Chinese CogState may be a useful tool for clinical use. It correlated well with MoCA and significantly differentiated HF and non-HF groups ($p < 0.001$). Moreover, a recently western study also suggested that ISLT may be a reliable and brief screening tool because of its cross-cultural sensitivity, and ease of administration and scoring (Hammers, Jung, et al., 2012). Routine application of the ISLT in memory screening can help in early identification of memory deficits in HF patients.

In addition, older women with severe HF, more comorbidities and menopausal symptoms may be at the risk for memory decline. These women should be assessed their memory routinely in the clinics and evaluated if their self care abilities are compromised.

Compensations and interventions: The type and severity of memory decline of women with HF were reported in this study. This is critical for health care professions to evaluate HF management and education program in acute or community settings such as outpatient clinics or community centers. The information of aging, HF severity, chronic diseases, and menopausal symptoms on cognitive function should be included in these programs for reducing the risk of memory decline, such as healthy behaviors to minimize the occurrence of chronic diseases and self-care behaviors to avoid increasing the severity of HF.

In addition, verbal memory was the most affected memory domain in our sample. The educational program providing with visual or written materials would be helpful for HF patients to remember new information. Moreover, family members are often the primary caregivers for these women with HF in Taiwan society and involve most responsibilities of care. It is important to include family member in the interventions to prevent memory decline.

Using the knowledge of brain plasticity, Pressler et al. (2011) have demonstrated that a home-based nurse enhanced cognitive training intervention was feasible and had the potential to improve memory function for HF patients. Nurses may help enhance HF patients' brain plasticity and maintain cognitive function by incorporate these novel stimulating activities into existing patient care, such as the visual (e.g., games, books, paintings, nature scenery) and auditory (e.g., music, discussions) stimulating activities.

Conclusion

In conclusion, in this sample, Taiwanese postmenopausal women with HF had poorer working memory, and episodic memory performance in comparison with age- and education-matched healthy women. Age explained working memory; age, HF severity, comorbidity, and HF type explained verbal memory; age and comorbidity explained visual memory. Although postmenopausal symptoms associated with estrogen decline were not associated with any of these performances, results indicated that subscales for anxiety and sexual symptoms significantly predicted verbal and visual memory performance. In addition, results obtained from this study provided acceptable levels of validity and reliability for the Chinese CogState using a sample of women with HF in Taiwan. By better understanding memory performance in women with HF, the healthcare provider can design and test interventions tailored to specific risk factors to improve memory deficits in Taiwanese postmenopausal women with HF.

APPENDICES

Appendix A Measures

Demographic and Clinical Data (English Version)

Personal information

1. Age _____
2. Race: 1. Taiwanese 2. From Mainland China 3 Hakka
4. Aborigine 5. Other _____.
3. Marital Status: 1. Married 2. Not married 3. Divorced 4 Widowed
5. Separated
4. What level of education have you completed?
 1. Elementary school 2. Middle school, 3. High school,
4. Vocational school, 5. Bachelor's, 6. Master's, 7. Doctorate
5. What is the actual number of years you have completed in school? _____
6. Employment status: 1. Employed, 2. Unemployed
7. Your occupation: _____ (If retired, write previous occupation)
8. Do you live alone? 1. Yes 2. No
9. Handedness: 1. Right handed, 2. Left handed

The health history

10. Height _____ cm
11. Weight _____ kg
12. BMI _____
13. Blood Pressure _____ mmHg
14. Heart Rate _____ /min
15. Smoking history:
1. Current smoker (smoking within 1 month of this encounter)
2. Recent smoker (stopped smoking between 1 month and 1 year before this encounter)
3. Former smoker (stopped more than 1 year before this encounter)
4. Never smoked
16. How often do you drink alcoholic beverages (beer, wine, or liquor)?
1. Never
2. 1 or fewer alcoholic drinks per week
3. 7 or more alcoholic drinks per week
4. Five or more drinks on one occasion

The menstrual history:

17. Age of when menstruation began? _____
18. Number of pregnancy? _____
19. Number of live? _____
20. When did your menstrual periods stop? Age: _____
- a. Time since menopause: _____ month
 - b. Did you periods stop because you went through menopause?
1. Yes 2. No
 - c. Did you have hysterectomy or ovariectomy?
1. Yes, date: _____, 2. No
 - d. If "Yes", which kind of surgery you have?
1. Surgery for uterine only
2. Surgery for one side of ovary or two side of ovary
3. Surgery for uterine and ovary
 - e. Do you take estrogen replacement therapy/hormones now?
1. Yes 2. No
 - f. If "Yes", for how long? _____
 - g. If "No", did you ever take estrogen replacement therapy?
1. Yes 2. No

The chart review information for HF condition

21. Date for HF diagnosis? _____ .
22. How long has the patient been diagnosed with heart failure ? _____ month
23. Left ventricular ejection fraction (LVEF) _____ Date: _____.
24. NYHA class by cardiologist I II III IV, Date: _____.
25. Devices: CRT ICD Other: _____.
26. Prescribed HF medications use:
- 1. Digoxin 2. Diuretic 3. ACEI 4. ARB
 - 5. Beta-adrenergic blocking agent 6. Aldosterone antagonist
27. Comorbidity:
- 1. History of MI 2. History of CABG 3. History of CAD
 - 4. Hypertension 5. Diabetes mellitus 6. Cancer
 - 7. Chronic Obstructive Pulmonary Disease
 - 8. Moderate or severe renal disease
 - 9. Hyperthyroidism
 - 10. Others: _____.
28. Type of HF: 1. Systolic HF 2. Diastolic HF

Demographic and Clinical Data (Chinese Version)

基本資料及臨床資料

請在各項符合您個人的資料“”打✓,謝謝您的合作!

基本資料

- 1.您的年齡 _____
- 2.您的籍貫: 1. 本省籍 2. 外省籍 3. 客家人 4. 原住民 5. 其它
- 3.您的婚姻狀態: 1. 已婚 2. 未婚 3. 離婚 4. 喪偶 5. 分居 6. 其它
- 4.您的教育程度?
1. 國小 2. 國中, 3. 高中(職),
4. 專科, 5. 大學 6. 碩士 7. 博士
- 5.您實際在學校接受教育的時間為幾年? _____
- 6.您目前是否仍在工作?: 1. 是 2. 否
7. 您的職業為: _____ (若您已退休,請寫下您之前的職業)
- 8.您是否獨居? 1. 是 2. 否
- 9.您的慣用手: 1. 右手, 2. 左手

健康史

- 10.身高 _____ 公分
- 11.體重 _____ 公斤
- 12.身體質量指數(BMI) _____ (由研究者計算)
- 13.血壓 #1 _____ mmHg; #2 _____ mmHg
- 14.心跳 _____ /每分鐘
- 15.抽菸史:
1. 目前抽菸者 (最近一個月內有抽菸)
2. 最近抽菸者 (未抽菸一個月以上,一年以內)
3. 之前抽菸者 (停止抽菸超過一年)
4. 從未抽菸者
- 16.您的飲酒情形 (啤酒, 或含酒精飲料)?
1. 從未飲酒
2. 一星期飲酒一杯或少於一杯
3. 一星期飲酒七杯或多於七杯
4. 每次飲酒五杯或多於五杯

停經情形:

- 17.您於 _____ 歲初經?
- 18.您的懷孕次數? ? _____

19.您的子女數? ? _____

20.您的停經年齡? _____歲

a. 停經時間; _____月

b. 請問您是自然停經嗎? 1. 是 2. 否

c. 請問您是否有接受過子宮切除或卵巢切除手術嗎?

1. 是, 日期: _____, 2. 否

d. 請問是何種手術?

1. 僅子宮切除

2. 一邊或雙邊卵巢切除手術

3. 子宮和卵巢切除皆切除

e. 請問您現在是否有接受女性賀爾蒙治療?

1. 是 2. 否

f. 如果您現在有接受女性賀爾蒙治療,請問多久時間? _____年

g. 如果您現在沒有接受女性賀爾蒙治療,請問您是否曾經接受女性賀爾蒙治療?

1. 是 2. 否

心臟疾病特性(以下由研究者查閱病歷資料填寫)

21.罹患心臟衰竭時間: _____月, (診斷日期: _____.)

22.心臟衰竭被診斷的時間有多久: _____月

23.左心室射出率 (LVEF) _____%, 檢查日期: _____.

24. NYHA 疾病分級? I II III IV, 日期: _____.

25.輔助裝置: CRT ICD Other: _____.

26.心臟疾病使用藥物 (由研究者協助填寫):

1. Digoxin 2. Diuretic 3. ACEI 4. ARB

5. Beta-adrenergic blocking agent 6. Aldosterone antagonist

27.合併其它疾病 (研究者查閱病歷資料填寫,可複選):

1. 心肌梗塞病史 2. 冠狀動脈繞道手術 3. 冠狀動脈疾病

4. 高血壓 5. 糖尿病 6. 癌症 7. 慢性阻塞性肺病疾病

8. 腎臟疾病 9. 甲狀腺亢進 10. 其它: _____.

28.心臟衰竭類型:

1. 收縮性心臟衰竭 2. 舒張性心臟衰竭

Montreal Cognitive Assessment (English Version)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Education : _____

Date of birth : _____

Sex : _____

DATE : _____

VISUOSPATIAL / EXECUTIVE							POINTS																	
		Copy cube []	Draw CLOCK (Ten past eleven) (3 points)			[] [] [] [] []	___/5																	
NAMING																								
						[] [] [] ___/3																		
MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">FACE</td> <td style="text-align: center;">VELVET</td> <td style="text-align: center;">CHURCH</td> <td style="text-align: center;">DAISY</td> <td style="text-align: center;">RED</td> </tr> <tr> <td style="text-align: center;">1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: center;">2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial						2nd trial									No points
	FACE	VELVET	CHURCH	DAISY	RED																			
1st trial																								
2nd trial																								
ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2			___/2																			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[] FBACMNAAJKLBAFAKDEAAAJAMOF AAB			___/1																			
Serial 7 subtraction starting at 100		[] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts. 2 or 3 correct: 2 pts. 1 correct: 1 pt. 0 correct: 0 pt			___/3																			
LANGUAGE	Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []					___/2																		
Fluency / Name maximum number of words in one minute that begin with the letter F		[] _____ (N ≥ 11 words)			___/1																			
ABSTRACTION	Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler					___/2																		
DELAYED RECALL	Has to recall words WITH NO CUE	FACE []	VELVET []	CHURCH []	DAISY []	RED []	Points for UNCUED recall only	___/5																
Optional	Category cue																							
	Multiple choice cue																							
ORIENTATION	[] Date [] Month [] Year [] Day [] Place [] City					___/6																		
© Z.Nasreddine MD Version 7.1		www.mocatest.org		Normal ≥ 26 / 30		TOTAL ___/30																		
Administered by: _____		Add 1 point if ≤ 12 yr edu																						

Montreal Cognitive Assessment (Chinese Version)

蒙特利爾智能測驗

中又(台灣)版蒙特利爾智能測驗MoCA

姓名：

教育程度：

出生日期：

性別：

測驗日期：

<p>視覺空間/執行</p> <p>複製立方體</p>	<p>畫時鐘 (11點10分) (3分)</p> <p>[] [] [] 形狀 數字 指針</p>	<p>分數</p> <p style="font-size: 2em;">_ / 5</p>																				
<p>命名</p> <div style="display: flex; justify-content: space-around;"> </div> <p>[] [] []</p>																						
<p>記憶</p> <p>請出右方詞語，由受測對象複述。上述步驟重複兩次。五分鐘後再測能否回憶。</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td>臉</td> <td>絨布</td> <td>教堂</td> <td>菊花</td> <td>紅色</td> </tr> <tr> <td>第一次嘗試</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>第二次嘗試</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		臉	絨布	教堂	菊花	紅色	第一次嘗試						第二次嘗試						<p>不計分</p>		
	臉	絨布	教堂	菊花	紅色																	
第一次嘗試																						
第二次嘗試																						
<p>專注</p> <p>施測者讀出右方數字 (每秒讀一個)。</p> <p>受測對象需要順序背出數字 [] 2 1 8 5 4 受測對象需要倒序背出數字 [] 7 4 2</p>																						
<p>讀出數字。當施測者讀到 1 時，受測者輕輕拍一下桌面。如錯誤兩個或以上，沒有得分。</p> <p>[] 6 2 1 3 9 8 1 1 7 6 5 2 1 6 1 6 4 5 1 1 1 7 1 9 8 6 1 1 2</p>																						
<p>從100開始連續減7</p> <p>[] 93 [] 86 [] 79 [] 72 [] 65</p> <p style="font-size: 0.8em;">4 或 5次正確: 3分, 2 或 3次正確: 2分, 1次正確: 1分, 0次正確: 0分</p>																						
<p>語言</p> <p>(國)我知道今天來幫忙的是小吳 [] (國)當狗在房間時，貓總是躲在桌子下 [] (台)我知影今日來幫忙是蔡桑 [] (台)狗那置咧房間內，貓總是密置ㄟ桌子腳 []</p>																						
<p>流暢度/一分鐘內說出最多個水果的名字 [] _____ (> 11 個即得分)</p>																						
<p>抽象概念</p> <p>共通點：例如：香蕉-橘子 = 水果 []火車-腳踏車 []手錶-尺</p>																						
<p>延遲記憶</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>在沒有提示下答出</td> <td>臉孔</td> <td>絨布</td> <td>教堂</td> <td>菊花</td> <td>紅色</td> <td rowspan="2">只有不需提示而能記得的詞語才得分</td> </tr> <tr> <td>類別提示</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>多選提示</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>			在沒有提示下答出	臉孔	絨布	教堂	菊花	紅色	只有不需提示而能記得的詞語才得分	類別提示						多選提示						
在沒有提示下答出	臉孔	絨布	教堂	菊花	紅色	只有不需提示而能記得的詞語才得分																
類別提示																						
多選提示																						
<p>定向</p> <p>[]日期 []月份 []年份 []星期 []地點 []城市</p>																						
		<p>總分</p> <p>如接受的教育 ≤ 12年則加 1分</p>																				

Duke Activity Status Index (English Version)

Now I am going to ask you about some activities that people do. Please tell me if you can do these things. The responses are:

- 1 = Yes, with no difficulty
- 2 = Yes, with some difficulty
- 3 = No, I can't do this
- 4 = I don't do this for other reasons

Can you....

- | | | | | |
|--|---|---|---|---|
| 1. Take care of yourself, that is, eating, dressing, bathing, and using the toilet? | 1 | 2 | 3 | 4 |
| 2. Walk indoors, such as around your house? | 1 | 2 | 3 | 4 |
| 3. Walk a block or two on level ground? | 1 | 2 | 3 | 4 |
| 4. Climb a flight of stairs or walk up a hill? | 1 | 2 | 3 | 4 |
| 5. Run a short distance? | 1 | 2 | 3 | 4 |
| 6. Do light work around the house like dusting or washing dishes? | 1 | 2 | 3 | 4 |
| 7. Do moderate work around the house like vacuuming, sweeping floors, carrying in groceries? | 1 | 2 | 3 | 4 |
| 8. Do heavy work around the house like scrubbing floors, or lifting or moving heavy furniture? | 1 | 2 | 3 | 4 |
| 9. Do yard work like raking leaves, weeding or pushing a power mower? | 1 | 2 | 3 | 4 |
| 10. Have sexual relations? | 1 | 2 | 3 | 4 |
| 11. Participate in moderate recreational activities, like golf, bowling, dancing, double tennis, or throwing baseball or football? | 1 | 2 | 3 | 4 |
| 12. Participate in strenuous sports like swimming, single tennis, football, and basketball or skiing? | 1 | 2 | 3 | 4 |

Total Score_____

Duke Activity Status Index (Chinese Version)

活動狀況指標

請就過去這段時間依您是否可以執行這些活動回答, 請勾選出最符合您執行時的情況:

0 為可以執行,沒有困難;

2 為不能執行這些活動;

1 為可以執行,有些困難;

3 我因其他原因並沒有做這些活動

	執行活動項目	0 為可以執行,沒有困難	1 為可以執行,有些困難	2 為不能執行這些活動	3 我因其他原因並沒有做這些活動
1	在室內行走, 例如在你的屋內走動?				
2	做一些輕度的家務, 例如,擦拭家具或洗碗?				
3	照顧自我的日常生活,路如:吃飯,穿衣,洗澡和上廁所?				
4	到戶外, 在平地行走到下一個街口或巷口?				
5	做一些中度的家務,例如:使用吸塵器,掃地或提一些雜貨食品?				
6	做庭院工作, 像是掃落葉,除雜草或操作電動割草機?				
7	從事性交活動				
8	爬一層樓梯或走上一小段上坡路				
9	參與中度的休閒活動,例如:打高爾夫球,保齡球,雙人網球,跳交際舞或投擲球?				
10	參與費勁的運動,例如:游泳,單人網球,足球,籃球,爬山,跑步?				
11	做一些重度的家務,例如:洗刷地板或搬移較重的傢俱?				
12	做短距離的跑步?				

The Greene Climacteric Scale (English Version)

Please indicate the extent to which you are bothered at the moment by any of these symptoms by placing a tick in the appropriate box.

	Symptoms	Not at all	A little	Quite a bit	Extremely	Score 0-3
1	Heart beating quickly or strongly					
2	Feeling tense or nervous					
3	Difficulty in sleeping					
4	Excitable					
5	Attacks of panic					
6	Difficulty in concentrating					
7	Fleeing tired or lacking in energy					
8	Loss of interest in most things					
9	Feeling unhappy or depressed					
10	Crying spells					
11	Irritability					
12	Feeling dizzy or faint					
13	Pressure or tightness in head or body					
14	Parts of body feel numb or tingling					
15	Headaches					
16	Muscle and joint pains					
17	Loss of feeling in hands or feet					
18	Breathing difficulties					
19	Hot flushes/sudden warmth					
20	Sweating night or day					
21	Loss of interest in sex					
22	cold sweats (night or day)					
23	waking up during the night					
24	vaginal dryness					
25	forgetfulness					
26	backache					

P (1-11) A (1-6) S (12-18) D(7-11) V(19-20) S (21)

The Greene Climacteric Scale (Chinese Version)

更年期症狀量表

以下問題是要了解您最近一個月有無下列任何身心不適的症狀?如果您有此經驗,請勾選出最適合描述您感受程度的

	症狀	沒有 0分	有一 點1 分	經常 2分	嚴重 3分	Score 0-3
1	心跳好快					
2	覺得有壓力,神經質					
3	失眠,睡得不好					
4	興奮					
5	不安感					
6	注意力不集中					
7	覺得累,沒力氣					
8	對很多事情沒興趣					
9	不快樂,鬱悶					
10	常想哭					
11	煩躁					
12	覺得頭暈					
13	覺得頭和身體很重					
14	有時身體的某部分會沒感覺或刺痛					
15	頭痛					
16	肌肉,關節痛					
17	有時手腳會沒感覺或麻麻的					
18	呼吸不順或困難					
19	熱潮紅(臉好熱)					
20	白天或夜間盜汗(白天或晚上常冒汗)					
21	性慾降低					
22	白天或夜間冒冷汗					
23	夜間醒來					
24	陰道乾燥					
25	健忘					
26	腰酸背痛					

Scripts for CogState (English Version)

Detection task: Has the card turned over?

Say: In the task, a playing card will appear in the center of the screen. Press the YES button when the card turns face-up as fast as you can. If you make a mistake you will hear an error sound. This means you have responded too soon. Try to make your responses as acute and fast as possible after a card turns face-up. Are you ready to start? Press ENTER to begin.

Identification Task: is the card red?

Say: In the task, a playing card will appear in the center of the screen. As soon as it turns face-up, you must decide: is the color of the card red? If it is red, press the YES button. If it is not red, press the NO BUTTON. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after a card turns face-up. Are you ready to start? Press ENTER to begin.

One Back Task: is the previous card the same?

Say: In the task, a playing card will appear in the center of the screen. As soon as it turns face-up you must decide: is the card exactly the same as the previous card? If it is exactly the same as the previous card, press the YES button. If it is not exactly the same as the previous card, press the NO button. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after the card turns face-up. Press ENTER to begin.

International Shopping List Task

Say: the task should start with the screen facing the supervisor so that the subject cannot see the screen. Read the following instructions out loud to them. In this task, I am going to read you a shopping list. I would like you to remember as many as items from this list as possible. Are you ready to start? Press ENTER to begin.

International Shopping List Task - Delayed Recall

Say: In this task, now we are going to go back to the shopping list I read to you earlier. I need you to try and remember the items on this list and tell me what they were. Are you ready to start? Then, press ENTER to begin. "Tell me as many of the items on the shopping list as you can remember?"

One Card Learning Task: have you seen this card before in this task?

Say: In this task, a playing card will appear face-down in the center of the screen and then turn face-up. As soon as a card turns face-up decide if you have seen it before in this task. Only a few of the face-up cards will repeat during the task. Cards seen in the practice are not used again. If you have seen the card before in this task, press the YES button. If you have not seen the card before in this task, press the NO button. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after the card turns face-up. Press ENTER to begin.

Continuous Paired Associate Learning Task: in what locations do these pictures belong?

Say: now the pictures will be presented in the center of the screen, and you must tap on the peripheral location where that picture previously appeared. Begin by tapping the target on the central location. Tap as quickly and accurately as you can. Press ENTER to begin.

Scripts for CogState (Chinese Version) 電腦測驗說明

Detection task: Has the card turned over?

檢測任務: 卡片是否已經翻轉?

在此項任務中, 螢幕中央將顯是一張遊戲卡, 請在卡片翻轉後以最快的速度按下按鈕'是', 如果回答錯誤, 你將聽到一聲錯誤提示音, 這表示你提前搶答, 請嘗試在卡面向上翻轉後盡量快而準確的回答, 你準備好了嗎? 請按下 **Enter** 鍵開始

Identification Task: is the card red?

識別任務: 卡片是紅色的嗎?

在此項任務中, 螢幕中央將顯是一張遊戲卡, 請在卡片翻轉後以最快的速度確定: 卡片顏色是否為紅色? 如果卡片顏色為紅色, 請按下按鈕'是', 如果卡片顏色不是紅色, 請按下按鈕'否', 如果回答錯誤, 你將聽到一聲錯誤提示音, 請你在卡片翻轉後盡量快而準確的回答, 你準備好了嗎? 請按下 **Enter** 鍵開始

One Back Task: is the previous card the same?

短暫記憶任務: 你是否在此項任務中見過這張卡片?

在此項任務中, 螢幕中央將顯示一張遊戲卡, 然後被翻轉, 請你在卡片翻轉後以最快的速度確定面前的卡片是否與前一張相同? 如果完全相同, 請按下按鈕'是', 如果不是完全相同, 請按下按鈕'否', 如果回答錯誤, 你將聽到一聲錯誤提示音, 請你在卡片翻轉後盡量快而準確的回答, 你準備好了嗎? 請按下 **Enter** 鍵開始

International Shopping List Task

此項任務開始前, 應使評測對象背對螢幕以免其看到螢幕內容, 同事向其大聲讀出以下說明, 在此項任務中, 我將向你讀出一份購物清單, 希望你能盡量記住清單中的項目, 你準備好了嗎? 請按下 **Enter** 鍵開始

International Shopping List Task - Delayed Recall

在此項任務中, 我們要回到我之前將你讀出的購物清單, 我需要你試著回憶清單中的項目並告訴我, 你準備好了嗎? 請按下 **Enter** 鍵開始, 請盡量告訴我你所記得的購物清單項目。

One Card Learning Task: have you seen this card before in this task?

短暫記憶任務: 你是否在此項任務中見過這張卡片?

在此項任務中, 螢幕中央將顯示一張反扣的遊戲卡, 然後被翻轉, 請你在卡片翻轉後以最快的速度確定你是否曾在在此項任務中見過面前的卡片, 在此項任務中只有部分翻轉的卡會重複出現, 如果你曾在在此項任務中見過面前的卡片, 請按下按鈕'是', 如果你未曾在在此項任務中見過面前的卡片, 請按下按鈕'否', 如果回答錯誤, 你將聽到一聲錯誤提示音, 請你在卡片翻轉後盡量快而準確的回答, 你準備好了嗎? 請按下 **Enter** 鍵開始

Continuous Paired Associate Learning Task: in what locations do these pictures belong?

連續配對關聯默記任務: 這些圖片屬於哪些位置?

現在這些圖片將顯示於螢幕的中央,請你點觸上一次顯示圖片得周邊位置,首先點觸位於中心位置的目標,請盡量又快又準地進行點觸,請按下 **Enter** 鍵開始

Appendix B Informed Consent (English Version)

Consent to Participate in a Research Study

Memory Performance in Taiwanese Postmenopausal Women with Heart Failure

Invitation to participate in a research study

Cheng-Chen Chou, PhD(c), a student at the University of Michigan in the School of Nursing, invites you to be part of a research project that she will conduct in order to complete requirements for an advanced degree. She is supervised by Dr. Susan Pressler, Ph.D. The purpose of the study is to learn more about memory change in Taiwanese postmenopausal women with HF (HF group) and without HF (healthy women group), and the possible influencing factors. Heart failure can decrease the blood flow in our body, including the brain, which may affect memory. Women who are postmenopausal may also experience memory problems because of estrogen decline. The knowledge will provide a scientific base to develop effective nursing intervention. We are asking you to participate because you recently attended an outpatient clinic of the cardiology, gynecology, or women's health clinic or you are the worker or family member of patients in Tri-service General Hospital, Taipei, Taiwan.

Description of your involvement

Healthy and HF groups:

The participation includes one face-to-face interview for both groups and chart review for only the HF group. If you agree to be part of the research study, the investigator will fully explain the study including purpose, benefits, risk, and procedures. After the informed consent is signed you will be asked to participate in one face-to-face interview in a quiet room at Tri-service General Hospital, Taipei.

The interview should take about one hour; you will be asked your background, height, weight, activity level, menopausal symptoms. You will have your blood pressure checked. The investigator will bring the computer and explain how to complete the memory testing. You will complete the computer testing around 20 minutes to look at your memory and thinking.

HF group only:

In addition, for the heart failure group, we will obtain information about your HF condition from the medical records from your physician in the clinic by using a checklist. The information we ask from medical records includes: date of HF diagnosis, echocardiography result (left ventricular ejection fraction), and New York Heart Association class, type of HF, devices, HF medicines, and comorbid conditions.

Benefits

While you may not receive a direct benefit from participating in this research, some people find it helpful to discuss their health with a nurse (the investigator) and to learn how to use the computer. We hope that this study will contribute to the improvement of memory for postmenopausal women with HF and without HF.

Risks and discomforts

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects related to your participation, even when the researchers are careful to avoid them. These risks may include the following: 1) possible frustration or becoming upset with the computer testing; and 2) possible loss of confidentiality. We will minimize these risks by making sure you are comfortable and ready to have the computer testing and keeping the files in a locked cabinet in a locked room that is only available for the investigators.

Compensation

You will be paid a \$10 (NT300) Carrefour gift card for participating in the entire interview session. You will not receive the incentive if you do not complete the study. You will need to pay for your own travel and parking expenses.

Confidentiality

We plan to publish the results of this study and your data will be kept for 6 years after the study is completed, but will not include any information that would identify you. We will plan and prepare publications of our results. To keep your information safe, the research records will be placed in a locked file cabinet in a locked room. The researchers will enter study data on a computer that is password-protected and uses special coding to protect the information. To protect confidentiality, your real name will not be used in the written copy of the discussion.

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

There are some reasons why people other than the researchers may need to see information you provided as part of the study. This includes organizations responsible for making sure the research is done safely and properly, including the University of Michigan and other government officials.

Voluntary nature of the study

Participating in this study is completely voluntary. The participation in the research does not include medical treatment for any healthcare condition. You can skip any question you want to skip. Even if you decide to participate now, you may change your mind and stop at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record.

Contact information

If you have questions about this research, including questions about the scheduling of the interview or your payment for participating, you can contact the investigator: Cheng-Chen Chou, PhD (c), University of Michigan, School of Nursing, 400 N. Ingalls, MI 48109, Telephone: 0966-827-278 (Taiwan), chenchou@umich.edu. You can also contact her faculty advisor, Susan Pressler, Ph.D., University of Michigan, School of Nursing, 400 N. Ingalls, Room 2180, Ann Arbor, MI 48109, (734) 763-5650.

If you have any questions about your rights as a research participant, please contact the University of Michigan Institutional Review Board Health Sciences and Behavioral Sciences, (734) 936-0933, 540 E. Liberty St., Suite 202 Ann Arbor, MI 48104-2210, irbhsbs@umich.edu.

Consent

By signing this document, you are agreeing to be in the study. You will be given a copy of this document for your records and one copy will be kept with the study records. Be sure that questions you have about the study have been answered and that you understand what you are being asked to do. You may contact the researcher if you think of a question later.

I agree to participate in the study.

Signature

Date

Authorization for medical records information release (HF group only)

I hereby authorize _____ to receive information from the medical records by using a checklist for the purpose of participation in this study. The records to be released are: date for HF diagnosis, echocardiography result (left ventricular ejection fraction), New York Heart Association class, type of HF, devices, HF medicines, and comorbid conditions.

Information will not be released without a valid signature below. I can cancel this authorization at any time.

I agree the person mentioned above to receive medical records information as described above.

Signature

Date

Informed Consent (Chinese Version)

參與研究同意書

臺灣停經後合併心臟衰竭的婦女的記憶研究

邀請個案參加研究

密西根大學護理學院博士班研究生周承珍邀請您成為她的研究計劃的個案。 她由 Susan Pressler 博士指導，

該研究的目的是要瞭解臺灣的停經後合併心臟衰竭的婦女與停經後健康婦女的記憶情形，我們也想知道可能影響其記憶的因素有那些。

心臟衰竭會減少到身體各部位的血液，包括我們的大腦，可能會影響我們的記憶功能。

婦女停經後由於女性荷爾蒙下降可能也會影響記憶功能。這個研究將提供未來提供護理措施的科學基礎。不論您最近參加了三軍總醫院心臟科門診，婦科門診，婦女健康門診，或您是醫院工作人員，及病患家屬，我們想請您參加本研究。

你參與的說明

心臟衰竭婦女組與一般婦女組 (兩組)

您的參與包括面對面資料收集(兩組皆要)和病歷資料收集(僅心臟衰竭婦女組)，如果您同意參與此研究，我們會與您約在三軍總醫院的房間進行資料收集。

資料收集約一個小時左右。我們會解釋包括目的、利益、可能的風險和過程的研究。

在您簽好同意書後，我們將會收集您的背景、身高、體重、

更年期症狀和活動情形，並測量你的血壓。

我們會說明及示範如何完成 20 分鐘的電腦記憶測試。

心臟衰竭婦女組

此外，我們也會從收集心臟衰竭婦女組的醫療記錄相關資料包括：心臟超音波結果、心臟功能分級、心臟衰竭型式、有無心臟輔助裝置及使用藥物、其他的健康狀況。

優點

這項研究可能不會對您有直接的好處，但其他好處包括與護理人員(研究人員)討論您的健康，並學習如何使用電腦。

我們希望這項研究將有助於改進停經後合併心臟衰竭的婦女與停經後健康婦女的記憶情形。

風險和不適

研究人員已採取步驟，這項研究的風險降至最低。即使研究人員都小心避免他們的風險，您仍可能出現參與研究有關的問題或副作用。這些可能風險包括下列: 1)

電腦測試過程中可能有挫折感； 2) 可能喪失資料機密性。

我們將確保這些風險降至最低，例如：

確定您電腦測試過程的舒適度和準備度，並將您的資料放在上鎖的房間上鎖的櫃子中，只有我們研究人員可以拿到。

補償

我們將支付 新台幣 300 元的禮卷感謝您參與整個資料收集。您需要支付自己交通和停車費用。

保密

我們計畫發表這項研究的結果，所以你的資料會我們保存 6 年的時間，但研究結果中不會包括任何會識別您的身份的資訊。

為保持您的資料安全，研究記錄將被放在上鎖的房間上鎖的櫃子中。

研究人員將使用需密碼來保護資訊的電腦上輸入研究資料。為了保密，討論會議中不會使用您的真實姓名。

簽署此同意書可以讓我們有您的許可來獲取、

使用，並分享在這研究中有關您的資訊，並且也是讓您參加本研究所必須的。我們可能會從醫院和參與您的照顧的醫生，其它健康提供者獲得有關您的資訊，包括：

醫院/醫生辦公室記錄，您的治療和您對治療的反應的記錄（血液檢查、尿液測試等）。

有些情況研究人員以外的其他人可能需要查看您提供的資訊，作為研究的一部分。這包括負責確保研究做安全和正確的包括政府官員或密西根大學相關機構。

自願性質的研究

參與這項研究是完全自願的。參與研究並不會影響您的治療，您可以挑過任何您不想做的題目，即使您現在決定參加，你可能會改變主意，並可以在任何時候停止。

如果您在資料收集完成前離開，您不會有任何的損失亦不會失去任何好處。如果你願意告訴我們為什麼要離開本研究，我們可將您離開的理由也做為研究記錄的一部分。

聯繫資訊

如果您對此研究有任何問題，您可以聯繫周承珍小姐，美國密西根大學護理學院博士候選人，電話：0966-827-278 (台灣手機)，電子信箱：

chenchou@umich.edu。您也可以聯繫她的指導教授 Susan Pressler 博士，美國

密西根大學護理學院教授，地址：400 N. Ingalls, Room 2180 電子信箱：

spressle@umich.edu

如果您對有關您作為研究參與者的權利有任何疑問，請聯繫美國密西根大學的健康科學和行為科學人體審查委員會，電話：002-1-734- 9360933，地址：540 E. Liberty St., Suite 202 Ann Arbor, MI 48104-2210，電子信箱: irbhsbs@umich.edu。

同意

簽署此同意書，您同意參加本研究。 您將保留一份同意書做記錄，另一份同意書將留在本研究中做記錄。 請確認您提出研究有關的問題已獲答覆並瞭解什麼是您需要做的。 如果您之後仍有問題，歡迎您聯繫本研究人員。

我同意參與這項研究。

簽名_____

日期_____

病歷資料給予同意

我同意_____ 因為研究的目的可以從我的病歷上資料獲得以下資訊：
心臟衰竭的時間,左心室心射出率,
心臟衰竭功能分級、心臟衰竭型式、有無心臟輔助裝置及使用藥物、其他的健康狀況。

病歷資料須有以下我的簽名才能給予, 我可以隨時終止我的同意。

我同意上述的人員獲得上述我的病歷資料,

簽名_____

日期_____