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## REFERENCES

- Lambotte O, Dautremier J, Guillet B et al. Acquired hemophilia in older people: A poor prognosis despite intensive care. *J Am Geriatr Soc* 2007;55:1682-1685.
- Bossi P, Cabane J, Ninet J et al. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med* 1998;105:400-408.
- Collins PW, Hirsch S, Baglin TP et al. Acquired hemophilia A in the United Kingdom: A 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood* 2007;109:1870-1877.
- Delgado J, Jimenez-Yuste V, Hernandez-Navarro F et al. Acquired haemophilia: Review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol* 2003;121:21-35.
- Aggarwal A, Grewal R, Green RJ et al. Rituximab for autoimmune haemophilia: A proposed treatment algorithm. *Haemophilia* 2005;11:13-19.
- Stasi R, Brunetti M, Stipa E et al. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004;103:4424-4428.
- Franchini M. Rituximab in the treatment of adult acquired hemophilia A: A systematic review. *Crit Rev Oncol Hematol* 2007;63:47-52.

## ASSOCIATION BETWEEN HEART RATE VARIABILITY AND COGNITIVE FUNCTION IN ELDERLY COMMUNITY-DWELLING MEN WITHOUT DEMENTIA: A PRELIMINARY REPORT

*To the Editor:* Prior studies have demonstrated that heart rate variability (HRV) analysis, a noninvasive approach to measuring autonomic function, is useful in assessing autonomic abnormalities in various types of dementia.<sup>1-6</sup> These reports

have supported the association between cognitive impairment and autonomic dysfunction in patients with dementia, but such association is unclear in elderly subjects without clinical dementia. Therefore, in this study, the HRV analysis was applied to examine the association between autonomic and cognitive functions in an elderly population without dementia.

Sixty-three elderly Chinese subjects without dementia were recruited from public veterans housing in the community (mean age  $\pm$  standard deviation 78.3  $\pm$  3.9, range 72-92; mean years of education 7.1  $\pm$  4.6, range 0-16). Informed consent was obtained from all subjects before commencement of the study. Each subject was carefully evaluated for medical and psychiatric illness to exclude the presence of possible dementia (Clinical Dementia Rating Scale score  $>$  0), presence of other mental illness, chronic medical illness, and neurological disorders. A group of elderly subjects without dementia and with normal function in daily activities was included in this study.

Cognitive function was assessed using the Cognitive Abilities Screening Instrument (CASI).<sup>7</sup> CASI was designed to cover a larger domain of cognitive functions and may provide more power than the Mini-Mental State Examination in identifying subtle cognitive decline in elderly subjects.<sup>8</sup> The total CASI score ranges from 0 to 100. In this study, a validated Chinese version of the CASI scale (CASI C-2.0) was employed (mean 87.0  $\pm$  5.1, range 76-97).<sup>9</sup> Electrocardiogram monitoring took place in the daytime, and participants were asked to avoid smoking and exercise. A Holter monitor (E3-8010 Portable Recorder, Microstar Inc., Taipei, Taiwan) was used to obtain 2 hours of ambulatory electrocardiogram recordings. HRV measures covering time, frequency, and nonlinear domain were used in analyzing interbeat interval time series according to international guidelines.<sup>10</sup>

Multiple linear regression analysis was applied to determine the association between HRV indices and cognitive measures with adjustment for age and education level. Partial and unadjusted Pearson correlation coefficients are shown in Table 1. Significantly positive correlations were found between adjusted CASI and standard deviation of normal interbeat intervals (SDNN, correlation coefficient ( $r$ ) = 0.37,  $P$  = .004), standard deviation of averages of normal interbeat intervals in all 5 minutes segments (SDANN,  $r$  = 0.36,  $P$  = .005), and very low frequency power (VLF,  $r$  = 0.29,  $P$  = .03). Furthermore, three components of adjusted CASI were significantly associated with certain HRV indices. Short-term memory was correlated with the root mean square of difference of consecutive interbeat intervals (RMSSD,  $r$  = 0.26,  $P$  = .04), attention was correlated with high-frequency power (HF,  $r$  = 0.27,  $P$  = .03), the fraction of consecutive interbeat intervals differed by more than 20 ms (pNN20,  $r$  = 0.28,  $P$  = .03), and list-generating fluency was correlated with SDNN and SDANN ( $r$  = 0.29,  $P$  = .03;  $r$  = 0.30,  $P$  = .02, respectively). None of the nonlinear HRV indices applied in this study were significantly correlated with cognitive measures.

This study indicated the following two key results. (1) The overall HRV, as measured using SDNN, SDANN, and VLF, was positively correlated with CASI score in elderly subjects without dementia. (2) Certain HRV variables, including RMSSD, pNN20, HF, SDNN, and SDANN, were positively correlated with individual components of CASI related to short-term memory, attention, and list-generating

**Table 1. Correlation Analysis of Cognitive Assessment and Heart Rate Variability**

Characteristic	Cognitive Abilities Screening Instrument Score			
	Adjusted		Unadjusted	
	Correlation Coefficient*	P-Value	Correlation Coefficient†	P-Value
Age			–0.28	.03
Education level, years			0.46	<.001
Time domain				
Standard deviation of normal interbeat intervals	0.37	.004	0.34	.006
Standard deviation of averages of normal interbeat intervals in all 5-minute segments	0.36	.005	0.30	.02
Root mean square of difference of consecutive interbeat intervals	0.10	.44	0.22	.09
pNN20	0.11	.40	0.08	.52
pNN50	0.14	.28	0.14	.28
Frequency domain				
VLF (0.003–<0.04 Hz)	0.29	.03	0.24	.05
LF (0.04–<0.15 Hz)	0.25	.05	0.29	.02
HF (0.15–<0.4 Hz)	0.12	.34	0.25	.05
LF/HF	0.07	.58	–0.03	.84
Nonlinear domain				
DFA $\alpha$ 1	0.14	.29	–0.005	.97
DFA $\alpha$ 2	0.04	.79	–0.05	.70
Approximate entropy	–0.15	.23	–0.19	.12

\*Partial correlation coefficient from multiple linear regression analysis with the cognitive assessment as the dependent variable, and age and education level in years as covariates.

†Pearson correlation coefficient.

pNN20, 50 = fraction of consecutive interbeat intervals differed by more than 20 or 50 ms; VLF = very low frequency power; LF = low-frequency power; HF = high-frequency power; DFA = detrended fluctuation analysis.

fluency. The novel finding of this study was that low HRV was associated with subtle cognitive decline in elderly subjects without dementia. The aging process, which is known to contribute to cognitive impairment and loss of HRV, may explain this preliminary result. Furthermore, biological mechanisms may provide an explanation of the association between essential cognitive functions (attention and short-term memory) and parasympathetic-related HRV indices, namely RMSSD, pNN20, and HF. The cholinergic system is critical to the integrity of autonomic and cognitive function. Dysfunction of the cholinergic system may not only impair cognitive functions but also decrease the cardiac innervation of the parasympathetic system.<sup>2</sup>

The relatively small sample of subjects limited this study, as did the fact that it included only men. Although cases of dementia were carefully excluded based on clinical assessment, mild cognitive impairment may have been present in this study sample. It is unclear whether subjects in this study

with mild cognitive impairment will develop dementia in the near future. Further longitudinal follow-up is needed to confirm the findings. Moreover, genetic and imaging studies are warranted to investigate the neurobiology of the cholinergic system in the association between autonomic and cognitive function during the normal aging process.

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## REFERENCES

- Zulli R, Nicosia F, Borroni B et al. QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. *J Am Geriatr Soc* 2005;53:2135–2139.
- Aharon-Peretz J, Harel T, Revach M et al. Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease. *Arch Neurol* 1992;49:919–922.
- Allan LM, Ballard CG, Allen J et al. Autonomic dysfunction in dementia. *J Neurol Neurosurg Psychiatry* 2007;78:671–677.
- Kaufmann H, Nahm K, Purohit D et al. Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies. *Neurology* 2004;63:1093–1095.

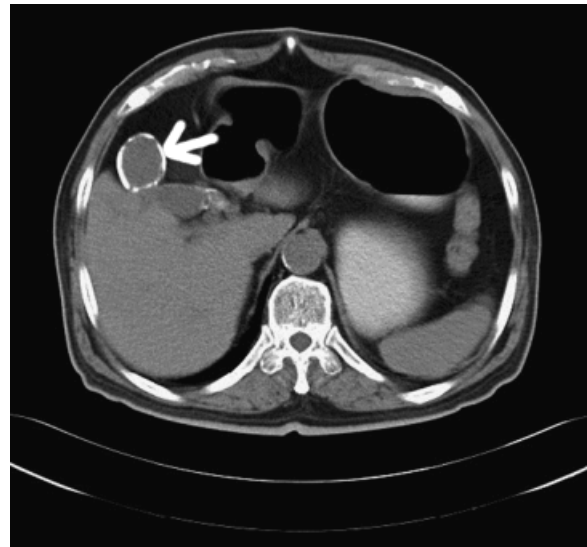
5. Wang SJ, Liao KK, Fuh JL et al. Cardiovascular autonomic functions in Alzheimer's disease. *Age Ageing* 1994;23:400–404.
6. Kim DH, Lipsitz LA, Ferrucci L et al. Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: Women's health and aging study I. *J Am Geriatr Soc* 2006; 54:1751–1757.
7. Teng EL, Hasegawa K, Homma A et al. The cognitive abilities screening instrument (CASI): A practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr* 1994;6:45–58; discussion 62.
8. McCurry SM, Edland SD, Teri L et al. The cognitive abilities screening instrument (CASI): Data from a cohort of 2524 cognitively intact elderly. *Int J Geriatr Psychiatry* 1999;14:882–888.
9. Teng EL, Lin KN, Chou P et al. The Cognitive Abilities Screening Instrument, Chinese version (CASI C-2.0) and its pilot study (in Chinese). *Psychometr Test Instrum Chin People*, Taipei 1994.
10. Task-Force. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–1065.

## PORCELAIN GALLBLADDER

*To the Editor:* An 80-year-old man came to a family medicine outpatient clinic for his annual health examination. His past history was notable for chronic cholecystitis, chronic hepatitis B carrier status, iron deficiency anemia, and chronic renal insufficiency. His chest radiography revealed a round opacity with rim and internal amorphous hyperdensities in the right upper quadrant of the abdomen (Figure 1). Laboratory values were within reference ranges except for an elevated serum creatinine level (1.6 mg/dL) and a low hemoglobin level (11.1 g/dL). Abdominal radiography 1 week later confirmed a similar finding in addition to degenerative joint disease of the spine. Computerized tomography identified a thick layer of nonuniform calcifications coating the inner wall of the Phrygian



**Figure 1.** Chest radiography revealed a round opacity (arrow) with rim and internal amorphous hyperdensities in the right upper quadrant of abdomen.



**Figure 2.** Abdominal computerized tomography showed a thick layer of nonuniform calcifications coating the inner wall of the Phrygian cap of the gallbladder as a large porcelain gallbladder.

cap of the gallbladder as a large porcelain gallbladder (Figure 2).

Porcelain gallbladder is an uncommon finding of chronic cholecystitis characterized by extensive calcification of the gallbladder wall.<sup>1</sup> The term “porcelain gallbladder” is used to describe the bluish discoloration and brittle consistency of the gallbladder wall.<sup>2,3</sup> The prevalence of porcelain gallbladder in cholecystectomy specimens has ranged from 0.06% to 0.8%.<sup>2,3</sup> In 95% of porcelain gallbladder specimens, cholelithiasis is the accompany finding.<sup>2</sup> Porcelain gallbladders are five times as common in women as in men, usually in the sixth decade.<sup>3</sup> Diagnosis is frequently made by the detection of a palpable mass in the right upper quadrant of the abdomen or incidentally in an abdominal roentgenogram.<sup>3,4</sup> The significance of porcelain gallbladder has been thought to be strongly associated with gallbladder cancer, which has a grave prognosis. The incidence of gallbladder cancer in porcelain gallbladder was reported to be 12% to 61% in an early 1960s series,<sup>3,5–10</sup> but two 2001 studies showed a lower incidence of gallbladder cancer in porcelain gallbladder (0% and 5%).<sup>6,7</sup> These results have raised the question as to whether prophylactic cholecystectomy is necessarily indicated for those who are asymptomatic or have multiple comorbidities.<sup>6,7,11</sup> Laparoscopic cholecystectomy is even suggested in the complete intramural calcification type of porcelain gallbladder, which carries a lower risk of gallbladder cancer than the incomplete mucosal calcification type.<sup>4,8,11</sup> At present, prophylactic cholecystectomy is the treatment of choice for porcelain gallbladder.<sup>11,12</sup> The natural history of porcelain gallbladder is unclear, as is the causal relationship between porcelain gallbladder and gallbladder cancer. The last report suggested that the smaller number of porcelain gallbladders and different ethnicities in the two 2001 reviews might have confounded the incidence of gallbladder cancer in porcelain gallbladders significantly.<sup>10</sup>