Published in final edited form as:

Am J Geriatr Psychiatry. 2009 October ; 17(10): 911–912. doi:10.1097/JGP.0b013e3181ad4d2f.

Better cognitive performance associated with worse cardiac functioning suggests antagonistic pleiotropy in very elderly subjects

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Keywords

Ejection fractions; left atrial diameter; cognitive functioning; oldest old; APOE genotype

This interim study describes the relationships of neuropsychological functioning with directly measured ejection fraction (EF) and left atrial diameter (LAD) in a very elderly cohort. Subjects were 196 male veterans, 75 years old and above, outpatients at the James J. Peters Veteran Administration Medical Center, Bronx, NY. All had Clinical Dementia Rating (CDR) score of zero (no dementia) at this baseline assessment. None had a history of cerebrovascular disease. All subjects provided informed consent approved by the VA IRB.

LAD (cm) and EF (%) were measured using the recommendations of the American Society of Echocardiography Committee¹. Larger LAD and lower EF reflect poor cardiac function.

The statistical analyses excluded 31 subjects with evidence of atrial fibrillation, and are based on 165 subjects who had complete data, 35 (22%) of whom had at least one APOE4 allele. Factor analysis summarized the neuropsychological measures into memory (immediate recall, delayed recall, recognition, and Savings) and executive functions (animal fluency, Trails A, Trails B, diamond cancellation, and letter cancellation) factors. Partial correlations assessed the associations between LAD and EF and these two factors controlling for age, years of education, and body surface area (BSA). Separate analyses were also performed for APOE4 carriers and non-carriers.

Subjects' mean age was 81.6 years $\pm$ 4.4, education 13.8 years $\pm$ 3.2, MMSE 28.3 $\pm$ 1.6, BSA 1.92m² $\pm$.18, LAD 4.1 cm $\pm$.70, and EF 65% $\pm$ 12. Hypertension was diagnosed for 63%, diabetes 19%, hypertension medication 70%, and diabetes medication 18%. APOE4 carriers differed significantly only in education ($p=.04$) and EF ($p=.008$) from APOE4 non-carriers (See Table).

There were significant associations of larger LAD diameter ($r=.17$, $p=.03$, $df=160$) and lower EF ($r=-.17$, $p=.03$, $df=160$) with better memory performance. The significant associations with memory were attributable to APOE4 non-carriers (LAD: $r=.25$, $p=.004$; $df=125$; EF: $r=-.25$, $p=.005$; $df=125$). Although the overall association of LAD with executive function was not significant ($r=.15$; $p=.06$; $df=160$), larger LAD diameter was associated with better executive

function among APOE4 carriers ($r=.43$; $p=.02$; $df=33$). Additionally controlling for diabetes and hypertension, and their medications, did not substantially change the results.

Larger LAD and lower EF, reflecting cardiac dysfunction, were hypothesized to be associated with worse cognitive performance, but in fact, were associated with a better one. Although the correlations for APOE4 carriers and non-carriers were not significantly different, these results suggest that APOE status be taken into account when examining the relationships between cardiac functioning and cognition.

Dementia risk and protective factors identified in younger subjects may not be relevant to the very elderly^{2, 3}. We speculate that the survival and healthy cognition of these very elderly individuals may reflect an adaptation to lower cardiac function levels. This is consistent with the antagonistic pleiotropy hypothesis of a continuous and complex reshaping of metabolism during physiological aging, likely contributing to successful aging⁴. Survival despite chronic brain hypoperfusion due to reduced cardiac output may reflect adaptively decreased cerebrovascular resistance through arteriolar dilatation⁵. Such physiologic adaptations may have far-reaching consequences in therapeutic intervention for very elderly individuals. The ongoing longitudinal examination of these participants may shed light into the inter-relationship of changes in cardiac function and cognition.

Acknowledgments

This study has been supported by NIA grants K01 AG023515-01A2 (Dr. Beeri), project 4 in P01-AG02219 (Dr. Silverman). and AG05138 (Dr. Sano).

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Table 1
Characteristics of the sample by APOE4 genotype

Characteristic	APOE4 carriers N=35	APOE4 non-carriers N=130	Total Sample N=165
Age (years)	80.9 (4.5)	81.8 (4.3)	81.6 (4.3)
Education (years)	12.8 (3.1)	14.0 (3.3)	13.8 (3.3)
Ejection Fraction (%)	60.1 (11.0)	66.0 (11.7)	64.8 (11.8)
Left Atrial Diameter (cm)	4.1 (.60)	4.1 (.72)	4.1 (.69)
BSA m ²	1.90 (.19)	1.92 (.18)	1.92 (.18)
HTN (%)	73.3	67.5	68.5
HTN medication (%)	77.0	71.0	73.0
Diabetes (%)	33.3	17.0	20.5
Diabetes medication (%)	31.0	16.0	19
MMSE	28.6 (1.4)	28.2 (1.7)	28.3 (1.6)
Memory factor	.051 (1.1)	.027 (.99)	.032 (1.0)
Executive functions factor	-.039 (.89)	.004 (1.02)	-.004 (1.0)

BSA= body surface area; HTN=hypertension; MMSE=Mini Mental State Exam