Cardiovascular Health and Cognitive Resilience

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Objectives

- To identify that the top risk factor of cognitive decline is impaired cardiovascular function;
- To describe ways to maintain and improve vascular and cardiac health;
- To review the importance of reducing cardiac & vascular risk factors (e.g., HTN, dyslipidemias, CHF & arrhythmias), on preserving the brain.

Case Presentation #1

81 yo woman with HTN, MCI, hearing loss, macular degeneration, depression.

Caregivers statement: "During the past month she has become <u>suddenly</u> <u>"demented".</u> Gets "lost" in middle of a sentence & "conversation does not make any sense. Also has <u>nausea all the time</u>, no appetite, and she is much fatigued." Prior functional status: Good. Prior cognitive status, MCI. Meds: Donepezil 5mg, Omeprazole 20mg, amlodipine 10mg, citalopram 10mg

<u>PE:</u> Vitals wnl; Reduced respiratory excursion and reduced breath sounds; Syst M 3/5 LLSB; Pedal edema 3+ bilat; Hearing loss, <u>too weak for cognitive test</u>;

Laboratory data	
H&H	13.6 / 42.5
BMP	WNL
TSH	WNL
LFTs	WNL
eGFR	52
UA	normal

Local PCP had diagnosed her as having sideeffects of donepezil because of nausea, loss of appetite and had reduced donepezil dose;

Caregivers were concerned about dementia and wanted the donepezil to be increased again.

Case #1, con'd Treatment & Outcome

Labs: Unremarkable, except **BNP** = 2749

2D-Echo: <u>LVEF 10</u>%; diffuse hypokinesis; MR; TR; PR; dilated RA and dilated LA;

Dx: Delirium, due to acute heart failure, with poor brain perfusion, hypoxemia; Predisposing factors: age, MCI, hearing loss, visual impairment, depression.

Outcome: With gradual diuresis, LVEF gradually improved to >20%, and cognition progressively returned to pt's baseline of MCI.



92 yo woman, PMH: GERD, osteoporosis, Vit D deficiency. No h/o smoking or alcohol, father died, age 68, heart attack

One evening, started having heartburn after eating at a restaurant. Took 2 aspirins. Called the PCP, was advised to go to ER. She was alone at home - heartburn continued. Called PCP again, ambulance called.

Meds: aspirin 81 mg, Vit D 50,000 IU/mo, B12 1mg injection/mo

PE: BP 109/80mmHg, pulse 85/min, weight 103 lbs, BMI 19.5 Cardiac S1 and S2 normal, no murmur or gallop. Pulses 2+ Mental status – judgment and insight intact

In ER, EKG: ST elevation, anteriolat leads CK 470, troponin 31.5, BNP 1760 Lipids 168, TG 39, HDL 53, LDL 107

Case # 2, con'd Treatment & Outcome

<u>Work-up:</u>

- Cardiac Cath: LMCA patent; LAD, 100% occlusion at ostium; Left circumflex normal; RCA 100% occlusion in proximal part and fills via collaterals from the distal portion; LVEDP 22mmHg and filling defect at apex
- S/P PCI with Placement of BMS in LAD
- Echo with LVEF 25%, severe diffuse hypokinesis with only inferior wall moving well. RV pressure 50
- Outcome: Discharged home on Plavix, carvedilol and lasix

Follow-up:

- Currently still going strong, at age 104 years old!
- BP 150/64, Pulse 94, Temp 97.1 °F (36.2 °C), Resp 20, SpO2 99%, BMI 17 kg/m²
- Cognition alert, oriented x3, conversation good. Has excellent insight
- Able to walk holding onto objects and using a cane (prefers no walker).



Beaten by an Old Heart

This is the first time I've gotten old (I think) ...

At night all night long love, my heart babbles to me of gone loves, racing with excitement and regret, my heart is beating me to death.

On my stone, they'll write "Beaten by his heart," and the space between my thoughts will be found in the closets where they hang to dry all my tangled memories.

2022-2023 Cardiology Advances

- <u>2022 AHA/ACC/HFSA Guideline for the Management of Heart</u> <u>Failure:</u>
- Prevention of HF;
- Management strategies in stage C HF, including: New treatment strategies in HF, including SGLT2i, GLP-1 and ARNi; Management of HF and atrial fibrillation (AF), including ablation of AF; Management of HF and AS and secondary MR, including TAVR and TMVR transcatheter repairs;

Specific management strategies, including: Cardiac amyloidosis; Cardio-oncology; Implantable devices. Left ventricular assist device (LVAD) use in stage D HF;

IV iron (ferric carboxymaltose or ferric derisomalotose) for HFrEF & HFmrEF and IDA

CLINICAL PRACTICE GUIDELINE 2023: AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease (CCD):

- Team-based, shared decision making;
- Non-Pharm therapies, including diet and exercise;
- Reduce sitting time, aerobic & resistance; cardiac rehab;
- Use SGLT2 I and GLP-1;
- **BB or CCB, for shorter duration**;
- Statin or adjunct agents (ezetimibe, PCSK9I, bempedoic acid);
- Antiplatelet RX for shorter duration if needed;
- No clear benefit of omega-3 or other supplements;
- No routine testing if no clinical/functional change; No e-cigs
- PCI = Med mgmt; PCI Radial ?= Femoral; BMS ?=DES
- TAVR = SAVR; TMVR ?=SMVR

CVD and ADRD, Common Risk Factors

Known

- Family history
- Age
- Atherosclerosis
- Hypertension
- Dyslipidemia
- Head injury
- Arrhythmia
- LVH
- Diabetes
- Thyroid disorder

Emerging

- ApoEe4
- Metabolic syndrome
- Fibrinogen
- Hepatic Lipase
- Oxidative stress
- C-reactive protein
- Homocysteine
- Inflammation
- Hyperinsulinemia
- Other polymorphisms

Age-related continuum from HTN to HFpEF



Signs and Symptoms of LVH, AMI, HF, TIA, CVA, AD/RD

Wei, '92, 2004; Abbate et al., 2015; Buford, 2016; Azhar et al., 2017; Kario, 2018; Huang et al., 2019; Wilson et al., 2020

HTN, LVH Linked to Early Brain Changes



Brain MRI fiber-tracking reveals white matter alterations in hypertensive patients without damage under conventional neuroimaging;
HTN in middle-age (40's-50's) predicts cognitive decline in old age (70's-80's).

This approach could identify patients at initial stages of brain damage and could gain benefit of therapies aimed at limiting the transition to cognitive decline and neurodegeneration.



High LV mass with compromised white matter microstructure



Heart-Vasculature-Brain Connections

The reins of the soul are the nerves in the thorax. - T. Willis, 1664



Memory Loss is associated with:

- Hypertension & Hypotension
- Arrhythmias & HF
- Cerebral emboli & vascular insufficiency
- CAD, CABG, stents & valves

Flacker et al, 2001; Azhar et al, 2017; Carnevale et al., 2018;

Hypoxia-reoxygenation injury:

- More injury to the brain vs heart
- Earlier DNA fragmentation in brain vs heart
- More injury in **Old** vs young adult heart, brain

Mize et al., 2021



In fixing the heart, the brain may sometimes pay the price Kennedy et al, 2013: Wang et al, 2019

Women at higher risk for HFpEF, Takotsubo & ADRD

Table 2. ADJUSTED ODD RATIOS (OR) FOR CHF WITH PRESERVED SYSTOLIC FUNCTION

Independent Risk Factor	Adjusted OR	95% CI	P Value	
Left ventricular hypertrophy	2.6	1.8-3.8	.001	
Gender (women)	2.5	1.8-3.6	.001	
Hypertension	1.6	1.1-2.3	.010	
Age (10 y)*	1.2	1.1–1.4	.003	
Diabetes	0.6	0.4-0.9	.024	
Mitral regurgitation	0.4	0.3-0.5	.001	
CAD	0.3	0.2-0.5	.001	

*The odds ratio for age is determined for a 1 decade (10 year) increment in age, e.g., a 70-year-old is 20% more likely to have CHF with preserved systolic function compared with a 60-year-old after adjusting for other factors.



Figure 4: Schematic illustrating the interactions between HF and common co-morbid conditions. There is considerable evidence for HTN, HLP and DM contributing to HF as well as dementia. The association between BMI with dementia and HF with dementia is still not well established and more studies are needed. A high incidence of Takotsubo stress cardiomyopathy in postmenopausal women may be due to cardiovascular over-activation (induced by emotional stress) in the setting of low estrogen, with reduced estrogen-mediated cardioprotection, via indirect action on the CNS as well as direct actions on the heart.

HTN and HF increase NADPH Oxidase ROS release; HTN and HF are associated with cognitive decline; Treatment of HTN and HF will improve cognition;

Samuel et al., 1999; Akashi et al., 2009; Azhar et al, 2017; Chazal et al, 2018; Wilson et al., 2020

Translational Research in Geriatrics:

New CV Risk Factors: *Psychological & psychosocial - Depression, Low self-esteem, social isolation -* Higher post-MI morbidity & mortality regardless of EF

Negative Aging Stereotypes Impair Performance on Brief Cognitive Tests Used to Screen for Predementia



Participants' scores on MMSE and MoCA tests before and after debriefing as a function of Threat condition. Bars represents standard errors of the mean. The asterisk indicates significantly different group means below .05. Positive Age Stereotypes: Enhancing Functional Independence & cardiovascular health



Skin conductance & anxiety are lower with positive priming



SBP & HR are reduced with positive priming

Hausdorff et al., 1999; Levy et al., 2000, 2008, 2016, 2022

Haslam et al., 2012; Mazerolle et al., 2017

Age Stereotypes: The Power of positive subliminal priming on physical and cognitive function



Gait speed improved with positive priming, = to that achieved post 12 wks of exercise, x 30 min x 5 days/wk



Verbal & math performance & *self efficacy* improved with positive priming Daily Consumption of Essential Amino Acid-Based Dietary Supplement reduces risk of metabolic syndrome, CVD, hypertriglyceridemia & Improves Physical Performance in elderly



changes in plasma triglyceride (TG), cholesterol, HDL, VLDL and LDL concentrations. * Indicates significant reduction from pre- to postsupplementation. * In six subjects that showed a response in TG levels after 4 weeks, the reduction was significant (95±13 mg/dl, P=0.007).

EAA

150

100-

-50

Education

n = 32) was not statistically significant.

Figure 1. Change in distance walked in 6 min at 12 wk of intervention as

compared to the preintervention value. Values are mean ± SEM. The distance

walked was significantly improved (*) in participants who consumed

daily supplements of whey protein (n = 32, p = .039) or essential amino scids (EAAs) (n = 28, p < .0001). The improvement in the EAA group was significantly greater than the improvement in the Whey Protein group (+) p = .029). The reduction below the pre-value in the Education-only group



Table 2. Anthropometrics/Body Composition

	Whey Protein $(n = 32)$		EAA $(n = 28)$		Education Only (n = 29)	
	Baseline Mean ± SEM	Baseline Final Baseline	Final	Baseline	Final	
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
Body weight (kg)	86.0 ± 2.64	85.2 ± 2.50*	82.3 ± 3.45	81.3 ± 3.50**	82.3 ± 4.36	82.8 ± 4.24=
BMI (mg/m2)	31.7 ± 1.08	31.4 ± 1.04 [*]	30.2 ± 1.11	29.9 ± 1.15**	32.7 ± 1.55	32.7 ± 1.47
Lean body mass (kg)	47.8 ± 1.60	48.3 ± 1.63*	45.7 ± 2.14	45.9 ± 2.24	44.5 ± 1.43	45.3 ± 1.54
% Body fat	39.8 ± 1.48	39.0 ± 1.37*	40.2 ± 1.21*	39.7 ± 1.25*	45.4 ± 1.81	43.7 ± 2.02**
Fat mass (kg)	33.8 ± 1.80	32.8 ± 1.61*	32.4 ± 1.75	31.6 ± 1.74**	37.4 ± 2.69	36.8 ± 2.63

Notes: BMI = body mass index; EAA = essential amino acid.

n = 22 for the education-only group's weight and % body fat at baseline and final visits; n = 25 for the EAA group's % body fat at baseline and final visits. *Statistically significant (p < .05) change from baseline at the final visit. **Statistically significant (p < .01).

Cognitive Resilience:

Definition:

<u>Cognitive Resilience</u> describes the capacity to overcome the negative effects of setbacks and associated stress on cognitive function or performance.

Characteristics:

- Positive self-image;
- Problem-solving skills;
- Self-regulation; Adaptability;
- Faith/understanding the meaning and one's purpose;
- Positive outlook;
- Skills and talents that are valued by self and community;
- General acceptance by others.

Other factors:

- Having good communication skills.
- Viewing setbacks as impermanent, opportunities for growth.

Bowles et al., 2019; Lancet Comm, 2020; Mize et al, 2021; Salinas et al, 2021



Markers of Cognitive Resilience

Network Open.

Original Investigation | Neurology Association of Social Support With Brain Volume and Cognition

Joel Salinas, MD, MBA, MSc; Adrienne O'Donnell, BA; Daniel J. Kojis, BA; Matthew P. Pase, PhD; Charles DeCarli, MD; Dorene M. Rentz, PhD; Lisa F. Berkman, PhD; Alexa Beiser, PhD; Sudha Seshadri, MD

Molecular Psychiatry (2020) 25:379-396 https://doi.org/10.1038/s41380-019-0551-9

EXPERT REVIEW

Resilience and the brain: a key role for regulatory circuits linked to social stress and support

Nathalie E. Holz¹ · Heike Tost ² · Andreas Meyer-Lindenberg²



JAMA Network Open. 2021;4(8):e2121122. doi:10.1001/jamanetworkopen.2021.21122.

Higher listening support correlated with greater cognitive resilience



Molecular Markers of Cognitive Resilience?

11/03/2021

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

NEURODEGENERATIVE DISEASES

MEF2 is a key regulator of cognitive potential and confers resilience to neurodegeneration

Scarlett J. Barker^{1,2}†, Ravikiran M. Raju^{1,3}†, Noah E.P. Milman¹, Jun Wang¹, Jose Davila-Velderrain⁴, Fatima Gunter-Rahman¹, Cameron C. Parro¹, P. Lorenzo Bozzelli¹, Fatema Abdurrob¹, Karim Abdelaal¹, David A. Bennett⁵, Manolis Kellis^{4,6}, Li-Huei Tsai^{1,2,6}* Cognitive schitty throughout life correlates with not-tage cognition (ROSMAP Brain Bank, n= 676) (ROSMAP Brain Bank, n= 676)

cognitive activity score

microRNA signatures correlate with cognition and may be future targets against cognitive decline

Cardiovascular health interacts with Cognitive health in complex ways



Top left: Quantifying the heart and brain structure and function in MRI. Top right: Examples of associations between heart MRI traits and brain white matter tracts. Bottom left: Genomic loci associated with heart MRI traits that overlapped with traits and disorders of the heart and/or brain. Bottom right: Selected genetic correlations between heart MRI traits and brain disorders.

- Multiorgan imaging data obtained from >40,000 subjects in the UK Biobank (UKB) study
- Genome-wide association analysis of heart MRI traits identified 80 associated genomic loci ($P < 6.09 \times 10^{-10}$), that shared genetic influences and colocalized with heart and brain diseases and complex traits.
- This suggests that adverse heart metrics may have implications for brain abnormalities and the risk of brain diseases.
- By understanding human health from a multiorgan perspective, we may be able to improve disease risk prediction and prevention and mitigate the negative effects of one organ disease on other organs that may be at risk.

Q: Is 99 the new 60? Prevention of HTN & HF;

Also need Sufficient Sodium and Salt Intake



Mente et al., 2014; McGreal et al., 2016; Patel et al., 202

Cognitive Resilience: Pearls

Learning Opportunities:

- Being resilient is not a trait, but a dynamic learning process.
- Focus on Progress, not Goals
- Perceive Obstacles as Challenges Rather Than Hindrances. Challenges are what make life interesting; overcoming them is what makes life meaningful.

Social Markers:

- Higher listening support from others gives greater cognitive resilience
- Feeling valued by others
- Listening to favorite music

Molecular Markers:

- Current:
 - APOe4; Abeta 42/40; NfL; p-Tau 217 & 181; a-synuclein
- New:

MEF2, SARE & TFs, microRNAs; BDNF; ADRD proteins

Bowles et al., 2019; Lancet Comm, 2020; Islam et al, 2021; Salinas et al, 2021; Barker et al., 2021; Zammit et al., 2022

CV health & Cognitive resilience: Pearls

¹/₂ - 2/3 of Alzheimer's & related dementias are preventable:

Before 65: HTN, HF, vascular disease, dyslipidemia, T2DM, homocysteine, inactivity, sleep disruption, depression, heart disease, arrhythmias, hearing loss, head trauma, pollution, isolation.



Social interactions: need listening support, feeling valued

After 65: Exercise and strength training: boost memory, maintain health and enhance longevity

Diet: MIND, veggies & fruit (eat the rainbow); low-fat, salt low carb, antioxidants, vitamins, proteins Naps & Sleep: Boosts memory and cognition



Levy et al., 2008; Coker et al., 2015; Larson-Prior, 2018; Kim et al., 2019; UC Berkley, 2019; Lancet, 2020; Wilson et al., 2020; Mize et al., 2021; Blach et al., 2023

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