Brain and Heart

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Outline

1. Fundamentals of brain-heart interaction
2. Small vessel disease
3. Takotsubo (stress) cardiomyopathy
4. Alzheimer’s disease
5. Cognitive dysfunction in heart failure
6. Conclusions
Outline

1. Fundamentals of brain-heart interaction
2. Small vessel disease
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6. Conclusions
Determinants of Optimal Brain Health

The Neurovascular Unit

Cardiac Neural Control

Intrinsic Cardiac Autonomic Nervous System: The Ganglionated Plexi

(A) High-frequency stimulation during atrial fibrillation elicits a “vagal” response, indicated by prolongation of R-R interval and drop in arterial blood pressure. (B) The anatomical location of the major atrial GP, based on the response to high-frequency stimulation, as seen in the right anterior oblique projection (left panel), anteroposterior projection (middle panel) and posteroanterior projection (right panel). ARGp = anterior right ganglionated plexus; aVL = an ECG lead; GP = ganglionated plexi; I = an ECG lead; ILGP = inferior left ganglionated plexus; IRGP = inferior right ganglionated plexus; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LOM = Ligament of Marshall; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; RV = right ventricle; SLGP = superior left ganglionated plexus.
Sympathetic Cardiovascular Control

- Arterial baroreflex
- Cardiopulmonary reflex
- CSAR
- Arterial chemoreflex

Heart
Vessels
Adrenal

Nervous Pathways Involved in the Vagal Control of the Heart

Bibevski S, Dunlap ME. Heart Fail Rev 2011; 16:129-35
Outline

1. Fundamentals of brain-heart interaction
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4. Alzheimer’s disease
5. Cognitive dysfunction in heart failure
6. Conclusions
Microvascular Disease is a Multisystem Disorder

- Vascular Dementia
- Lacunar Stroke
- White matter disease

Brain

- Chronic Kidney Disease
- Ischemic nephropathy

Kidney

- Retinopathy
- Nerve fiber disease

Retina

- Endothelial Dysfunction
- Coronary Microvascular Disease

Heart

Diagnosis of Microvascular Angina

Ford TJ, et al.  
Heart 2018; 104:284-292
Microvascular Angina and Acute Ischemic Stroke

Key Features of the Cerebral Arteriolar and Capillary Wall

Pathology Due to Small Vessel Disease in the Aging Brain

Hypertensive Small Vessel Disease: from Arteriolosclerosis to Fibrinoid Necrosis

Hypertensive Small Vessel Disease Imaging

Production, Degradation, and Deposition of Amyloid β in Cortical Arteries

Cerebral Amyloid Angiopathy
Cerebral Amyloid Angiopathy Imaging

Cerebral Amyloid Angiopathy and Atrial Fibrillation: Increased Risk of Thromboembolism and Intracerebral Hemorrhage
Outline

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The Takotsubo Cardiomyopathy

Pathophysiology of the Takotsubo Cardiomyopathy

Emotional Stress
- Negative (and positive) emotions
- Natural disasters

Physical Stress
- Trauma/Surgery
- Medications
- Intoxication
- Drug withdrawal

Hypothalamus

Pituitary

Catecholamines
Neuropeptide Y

Direct Cardio-Inhibitory Effects

Acute Microvascular Dysfunction

Stress Cardiomyopathy

Risk Factors
- Female sex
- Post-menopause
- Schizophrenia
- Anxiety/Depression
- Asthma/Chronic obstructive pulmonary disease
- Diabetes
- Chronic medications
- Substance abuse disorders

Endothelial Dysfunction

Chronic Microvascular Dysfunction

Impaired Coronary Flow Reserve

Medina de Chazal, et al.
J Am Coll Cardiol 2018; 72:1955-71
Plasma Catecholamines in Takotsubo Cardiomyopathy vs. Myocardial Infarction

Takotsubo Cardiomyopathy: Effect of Catecholamines on Myocardial Contractility

Norepinephrine-β1-Gs signalling POSITIVELY INOTROPIC PROAPOPTOTIC

Epinephrine-β2-Gi signalling NEGATIVELY INOTROPIC ANTIAPOPTOTIC

Sympathetic nerve
Structural Alterations of the Limbic System in Takotsubo Cardiomyopathy

# Takotsubo Cardiomyopathy vs. Neurogenic Stunned Myocardium

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Takotsubo CMP</th>
<th>Neurogenic stunned myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Chest pain, short of breath (pulmonary edema)</td>
<td>Chest pain may be masked by coma or altered mentation. Acute pulmonary edema is more common presentation</td>
</tr>
<tr>
<td>Age/gender</td>
<td>Overwhelming majority of females of higher age group</td>
<td>Majority are females of relatively younger age group. Also affects significant number of males</td>
</tr>
<tr>
<td>Inciting event</td>
<td>Stress (psychosocial, critical illness), no inciting event in one-third of patients</td>
<td>Acute neurologic catastrophe especially high-grade aSAH</td>
</tr>
<tr>
<td>EKG changes</td>
<td>S-T segment elevation in precordial leads are most common</td>
<td>S-T elevation in precordial leads is less common. QT prolongation and T wave inversions may be more frequent than TCM</td>
</tr>
<tr>
<td>Wall motion abnormalities</td>
<td>Apical wall motion abnormality with hypokinesia of basal segments is more common. Mid-ventricular wall motion abnormality can also be seen</td>
<td>Either of two patterns are more common (1) hypokinesia of basal and mid-ventricular segments with apical sparing, (2) global hypokinesia of LV</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Significant improvement in LV function can occur in 1–2 weeks</td>
<td>Depends on severity of primary neurologic injury. Known to adversely affect outcome from aSAH</td>
</tr>
<tr>
<td>Complications</td>
<td>Hypoxemia/hypotension/SVT</td>
<td>Hypotension and ventricular arrhythmias are more frequent</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmias are less common</td>
<td></td>
</tr>
</tbody>
</table>

*aSAH* aneurysmal subarachnoid hemorrhage, CMP cardiomyopathy, LV left ventricle, SVT supraventricular tachycardia, TCM Takotsubo cardiomyopathy

Ibrahim MS, et al. *Neurocrit Care* 2018 Nov 27
Acute Treatment of Takotsubo with Hemodynamic Compromise

Medina de Chazal, et al.
J Am Coll Cardiol 2018; 72:1955-71
Outline

1. Mechanism of death precipitated by fear
2. Fundamentals of brain-heart Interaction
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Production, Degradation, and Deposition of Amyloid β in Cortical Arteries

Normal

![Normal Neuron]

Alzheimer

![Alzheimer Neuron with Neurofibrillary Tangles and Amyloid Plaques]
Vascular Hypothesis of Alzheimer’s Disease

Cardiac Abnormalities in Alzheimer’s Disease

32 patients with AD and 34 controls matched by age and sex, all of whom were free from cardiac or systemic diseases. A clinical evaluation, an electrocardiogram, and an echocardiogram were performed in all subjects. Furthermore, patients with AD underwent genetic analyses (of the PSEN1, PSEN2, APP, and APOE genes).

### TABLE 2 Electrocardiographic Characteristics of Alzheimer Disease Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer Disease (n = 32)</th>
<th>Controls (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>30 (94)</td>
<td>32 (94)</td>
<td>0.95</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>0.95</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Low QRS voltage*</td>
<td>9 (28)</td>
<td>1 (3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total QRS score, mm</td>
<td>96.5 ± 26</td>
<td>111.6 ± 34.3</td>
<td>0.05</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Pathologic Q waves</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0.52</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>5 (16)</td>
<td>8 (24)</td>
<td>0.42</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>160 (150-180)</td>
<td>160 (160-180)</td>
<td>0.87</td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>418 ± 24</td>
<td>424 ± 30</td>
<td>0.37</td>
</tr>
<tr>
<td>Total QRS score/LVMI, mm/g per m²</td>
<td>2.32 ± 0.82</td>
<td>2.76 ± 0.87</td>
<td>0.05</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage/CSA, mm/cm²/m²</td>
<td>0.89 ± 0.36</td>
<td>1.1 ± 0.36</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are n (%), mean ± SD, or median (interquartile range). The p values in bold indicate those that are statistically significant (i.e., p value < 0.05).

*QRS amplitude =0.5 mV in all limb leads or =1 mV in all precordial leads.

CSA = cross-sectional area; LV = left ventricular; LVMI = LV mass indexed by height (m²); PR = interval; other abbreviations as in Table 1.

### TABLE 3 Echocardiographic Characteristics of Alzheimer Disease Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer Disease (n = 32)</th>
<th>Controls (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic diameter, mm</td>
<td>46 ± 4.4</td>
<td>47 ± 4.4</td>
<td>0.28</td>
</tr>
<tr>
<td>Interventricular septum, mm</td>
<td>10.1 ± 1.3</td>
<td>9.3 ± 1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum wall thickness, mm</td>
<td>10.8 ± 1.7</td>
<td>9.3 ± 1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>8.7 ± 0.9</td>
<td>8.9 ± 1.1</td>
<td>0.50</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.41 ± 0.05</td>
<td>0.39 ± 0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>LV remodeling</td>
<td>12 (39)</td>
<td>9 (26)</td>
<td>0.29</td>
</tr>
<tr>
<td>LV mass</td>
<td>145.5 ± 36</td>
<td>146.3 ± 33.7</td>
<td>0.93</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>43.4 ± 10.2</td>
<td>41.7 ± 8.6</td>
<td>0.47</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>8 (26)</td>
<td>5 (15)</td>
<td>0.26</td>
</tr>
<tr>
<td>LV myocardium cross-sectional area, cm²</td>
<td>17.9 ± 3.4</td>
<td>16.6 ± 2.8</td>
<td>0.096</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>66 ± 8</td>
<td>68 ± 2</td>
<td>0.29</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.70 ± 0.18</td>
<td>0.83 ± 0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>9.3 ± 3.1</td>
<td>7.7 ± 2.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>21 (70)</td>
<td>11 (35)</td>
<td>0.007</td>
</tr>
<tr>
<td>Left atrium enlargement</td>
<td>13 (41)</td>
<td>11 (32)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (31)</td>
<td>15 (44)</td>
<td>0.56</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Aortic valve regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11 (34)</td>
<td>9 (26)</td>
<td>0.47</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). The p values in bold indicate those that are statistically significant (i.e., p value < 0.05). E/A — early to late transmitral flow velocity ratio; E/e’ — mitral peak early filling velocity/early diastolic mitral annular velocity; other abbreviations as in Table 1.

Amyloid β Is Increased in Alzheimer's Disease Hearts

Outline

1. Mechanism of death precipitated by fear
2. Fundamentals of brain-heart Interaction
3. Takotsubo (stress) cardiomyopathy
4. Alzheimer’s disease
5. Cognitive dysfunction in heart failure
6. Conclusions
Associations of Heart Failure with Dementia and Alzheimer’s Disease

**All-Cause Dementia**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haugarvoll (2005)</td>
<td>4.54</td>
<td>[1.08; 19.11]</td>
<td>3.6%</td>
</tr>
<tr>
<td>Qiu (2006)</td>
<td>1.84</td>
<td>[1.35; 2.51]</td>
<td>24.5%</td>
</tr>
<tr>
<td>Haring (2013)</td>
<td>1.34</td>
<td>[0.42; 4.27]</td>
<td>5.3%</td>
</tr>
<tr>
<td>Noale (2013)</td>
<td>1.19</td>
<td>[0.56; 2.53]</td>
<td>10.3%</td>
</tr>
<tr>
<td>Rusanen (2014)</td>
<td>2.06</td>
<td>[1.00; 4.27]</td>
<td>10.9%</td>
</tr>
<tr>
<td>Jefferson (2015)</td>
<td>2.07</td>
<td>[1.02; 4.19]</td>
<td>11.3%</td>
</tr>
<tr>
<td>Adelborg (2016)</td>
<td>1.21</td>
<td>[1.18; 1.24]</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

Random effects model

- RR = 1.59 [1.19; 2.13] 100.0%
- $i^2 = 58\%$ [4\%; 82\%]

**Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haugarvoll (2005)</td>
<td>1.80</td>
<td>[1.25; 2.61]</td>
<td>26.5%</td>
</tr>
<tr>
<td>Qiu (2006)</td>
<td>1.03</td>
<td>[0.34; 3.19]</td>
<td>9.6%</td>
</tr>
<tr>
<td>Haring (2013)</td>
<td>1.82</td>
<td>[0.84; 3.97]</td>
<td>15.2%</td>
</tr>
<tr>
<td>Noale (2013)</td>
<td>1.00</td>
<td>[0.96; 1.04]</td>
<td>33.6%</td>
</tr>
<tr>
<td>Rusanen (2014)</td>
<td>2.10</td>
<td>[0.96; 4.61]</td>
<td>15.1%</td>
</tr>
<tr>
<td>Jefferson (2015)</td>
<td>1.44</td>
<td>[0.95; 2.16]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Random effects model

- RR = 1.44 [0.95; 2.16] 100.0%
- $i^2 = 74\%$ [35\%; 89\%]

Brain Magnetic Resonance Imaging
Abnormalities in Heart Failure

Structural Brain Abnormalities in HF Patients vs. Age- and Sex-Matched Controls

A total of 148 systolic and diastolic HF patients (mean age 64±11 years; 16% female; mean left ventricular ejection fraction 43 ± 8%) were extensively evaluated within 2 days by cardiological, neurological, and neuropsychological testing and brain magnetic resonance imaging (MRI). A total of 288 healthy, sex- and age-matched subjects sampled from the Austrian Stroke Prevention Study served as MRI controls.
Medial Temporal Lobe Atrophy vs. Cognitive Deficit

Frey A, et al. JACC Heart Fail 2018; 6:583-92
Pathogenic Links of Heart Failure and Cognitive Dysfunction

Heart Failure
- Reduced ejection fraction, cardiac output
- Impaired diastolic filling
- Low systolic blood pressure

ARterial Hypertension

COnsecutive/InTermitTent Cerebral Hypoperfusion

HyPoxia HIF-1

Disruption of Brain—Blood Barrier

Disruption of Brain—Blood Barrier

Metabolic/Humoral Abnormalities
- \( \uparrow \) elevated BNP
- Hyponatraemia
- \( \uparrow \) homocysteine

Vascular Remodeling Endothelial Dysfunction

Oxidative Damage

BRAIN-DErived Cytokines

Proinflammatory Cytokines
- IL-1, IL-6, TNF-alpha

Indirect Causes
- Diabetes
- Depression
- Anaemia
- \( \downarrow \) nutrition, etc.

Atrial Fibrillation, Atherosclerosis

Strokes

Brain

Cognitive Dysfunction

**HF-Induced Brain Injury: Characteristics and Basic Approach**

<table>
<thead>
<tr>
<th>Definition</th>
<th>A state of cognitive impairment of undefined cause in HF patients, beyond the one anticipated in age-matched controls, typically accompanied by anatomic brain changes</th>
</tr>
</thead>
</table>
| What should be looked for? | 1. Cognitive functions: impaired memory and executive functions  
2. Anatomic brain changes: white matter hyperintensities; medial temporal atrophy; frontal lobe and hippocampal atrophy  
3. Serum markers: elevated levels of IL-6; TNF-α; cortisol; and epinephrine |
| What should be ruled out? | 1. Electrolyte imbalance, hypothyroidism, nutritional deficiency, alcohol intoxication, stroke, infection  
2. Other causes for dementia: Alzheimer disease; Parkinson disease; Lewy body dementia; normal pressure hydrocephalus, among others |

HF = heart failure; IL = interleukin; TNF = tumor necrosis factor.

Management of HF Induced Brain Injury

Exercise for Cognitive Brain Health in Aging

Good quality evidence supports the use of exercise for the promotion of cognitive brain health in older adults.

Exercising for at least 52 hours in sessions lasting approximately an hour is associated with improved cognitive performance in older adults with and without cognitive impairment.

In order to achieve the exercise dose above, individuals can participate in aerobic, resistance (strength) training, mind-body exercises, or combinations of these interventions.

Improvements in processing speed/attention, executive function, and global cognition are most stable and consistently associated with exercise participation.

Outline

1. Fundamentals of Brain-Heart Interaction
2. Small vessel disease
3. Takotsubo (stress) cardiomyopathy
4. Alzheimer’s disease
5. Cognitive dysfunction in heart failure
6. Conclusions
• Brain affects the heart and vice versa. Brain and cardiac dysfunction often coexist.

• Abnormalities in cerebral blood flow are common in patients with microvascular angina and small vessel disease may be considered a multisystem disorder.

• Autonomic-limbic integration plays an important role in the pathophysiology of the Takotsubo syndrome.

• Vascular dysfunction contributes to the development of Alzheimer’s disease, the commonest cause of dementia.

• Heart failure (HF) is a risk factor for the development of dementia.

• Exercise programs on top of standard medical treatment may delay or reverse cognitive impairment in HF patients.
Components of the central autonomic network

Sagittal view

Coronal view

1 anterior cingulate; 2 insula; 3 thalamus; 4 hypothalamus; 5 amygdala; 6 periaqueductal grey; 7 parabrachial nucleus; 8 locus coeruleus; 9 rostroventrolateral medulla; 10 caudoventrolateral medulla; 11 nucleus of the solitary tract
TTS-Related Hypoconnectivity among CNS Structures

Templin C, et al. Eur Heart J 2019, 5 March
Head to Heart Connection in Alzheimer’s Disease

Aβ-Pre-amyloid Oligomers in Myocytes and Interstitial Tissue

Alzheimer’s Disease

Troncone L, et al.
J Am Coll Cardiol 2016; 68:2395-2407
Amyloid β Is Increased in Alzheimer's Disease Hearts