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Editorial

Heart and Brain: Exploring Connections and Therapeutic Opportunities Throughout the Lifespan

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Subspecialty training and practice tends to be siloed, for example, a paediatric patient "transitions" to adult care in their late teens, or a neurologist manages an embolic stroke and a cardiologist manages the atrial fibrillation (AF) that caused the event. In reality, cardiovascular and brain health are inextricably linked from the time of fetal development, a relationship that continues and modulates throughout the lifespan.

This special issue of the *Canadian Journal of Cardiology* dedicated to cardiovascular disease and the brain draws attention to how both research and clinical care related to brain health in cardiovascular disease should be refocused through an interdisciplinary lens. The connections between heart and brain health—and the role of multidisciplinary management—are conceptualized across the life course in this issue, with actionable considerations relevant to both congenital heart disease (CHD) as well as acquired cardiovascular disease.

Patt et al.[1] explore the developmental connections between heart and brain from a genetic perspective, focusing on genetic contributions to neurodevelopmental and other extracardiac disorders in children with CHD. Genetic abnormalities can include chromosomal deletions and duplications that affect multiple genes (eg, 22q11.2 deletion syndrome), single genes that affect development of both heart and brain (eg, CHD7, which leads to CHARGE syndromes), and variants that affect neurodevelopment resiliency (eg, apolipoprotein-E, which regulates cholesterol metabolism). They advocate increased use of genome sequencing technologies to improve detection of relevant genes and variants, with the ultimate goal of providing appropriate timely intervention and learning supports.

Neurodevelopmental impairment is the most common comorbidity in infants born with CHD. Peyvandi and Rollins[2] offer a comprehensive overview of the multifactorial mechanisms connecting neurodevelopmental delay with CHD, with a focus on pathophysiologic mechanisms for brain dysmaturation *in utero*. Areas of the fetal brain vulnerable to hypoxia and ischemia appear to be most affected, highlighting, along with other findings, the key role of hypoxia-ischemia in contributing to impaired fetal brain development. Complex CHD delays brain maturation. Full-term newborns with complex CHD have brain features (including lower brain volumes and less organised white matter tracts) resembling those of infants without CHD born prematurely at 34 to 36 weeks' gestation. Maternal stress and anxiety have also been associated with adverse fetal brain development, including decreased hippocampal and cerebellar volumes.

In their article, Brossard-Racine and Panigrahy[3] explore the functional implications of structural brain alterations following the neonatal phase, summarising what is known for children, adolescents, and young adults with CHD and persisting knowledge gaps. Specific techniques include conventional magnetic resonance imaging (MRI), quantitative structural MRI, and diffusion tensor imaging. Brain abnormalities are significantly more common among adolescents and adults with complex CHD compared with healthy peers. In general, smaller total and regional brain volume and lower fractional anisotropy in several brain regions were linked with poorer cognitive outcomes, including executive dysfunction and memory. They recommend that future research include multimodal imaging techniques, examine a broader range of functional outcomes, and evaluate longer-term outcomes.

Ricci et al.[4] offer 8 practical strategies to optimise neurodevelopment outcomes in children with CHD. They recommend maximising prenatal diagnosis and the detection of genetic syndromes, monitoring for brain injury, early intervention and referral to cardiac neurodevelopmental programs, collaboration with schools, and engaging and supporting patients and families in the CHD journey. Furthermore, this discussion would be incomplete without inclusion of health disparities, which are known to affect outcomes across the lifespan for individuals with CHD.[5] Jackson et al.[6] present a summary of the ways in which structural racism, social determinants of health, and provider bias both directly and indirectly affect brain development in critical CHD. Factors include, but are not limited to, socioeconomic status, access to quality prenatal and postnatal

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care, food insecurity, insurance status, distance from care centres, and the experience of interpersonal racism and bias. A multifaceted approach to address health disparities and bias is necessary and must target medical education and clinical care as well as research.

The subsequent contributions focus on brain health considerations in acquired cardiovascular disease. Still, they remain highly relevant to the CHD population, who are increasingly aging into later adulthood and remain at increased risk of stroke[7] and, based on emerging evidence, premature cognitive decline.[8]

Brain health in acquired cardiovascular disease may be compromised by the disease itself, by related medical and surgical interventions, or by both. Shoskes et al.[9] review the complications of left ventricular assist devices (LVADs), which are increasingly used as chronic therapy for prolonged support in the context of increased rates of advanced heart failure but a finite number of donor hearts. Rates of ischemic stroke and intracerebral hemorrhage have declined with use of newer-generation devices, although neurologic complications remain the second-most cause of death in this population. Beyond stroke alone, the authors review cerebral autoregulatory disturbances and dysautonomia associated with continuous-flow devices, which are additional mechanisms for neurologic morbidity with LVADs, and offer directions for future research, including optimal strategies for stroke prevention in this growing, medically complex population. Betzner et al.[10] review rates of stroke from cardiac procedures. Their review includes both overt clinical events, which range from rates of 0.1% to 1.1% in diagnostic coronary angiography to up to 1.7% to 2.9% with transcatheter aortic valve replacement, as well as covert brain infarcts (CBIs), which are an emerging area of research owing to their high frequency but less well established clinical implications. The authors review what is known about the cognitive implications of CBI, and end by discussing current preventative strategies. That discussion includes a review of risk stratification and risk factor control, optimising periprocedural antithrombotic management, and controversies around procedural considerations, including distal embolic protection devices and carotid revascularisation. In contrast to nonsurgical cardiac procedures, during cardiac surgery risks to brain health extend beyond embolic events alone. Jarry et al.[11] review current and emerging strategies to prevent cerebral hypoperfusion and desaturation, which are associated with postoperative cognitive decline, delirium, prolonged hospital stays, and additional neurologic morbidity, including stroke. Theys review cerebral near-infrared spectroscopy, processed electroencephalography, and transcranial Doppler and discuss their centre's approach with multimodal monitoring to reduce perioperative morbidity.

Cognitive deficits may result from, contribute to, or co-occur with cardiovascular disease. AF in particular is associated with increased risk of cognitive impairment. Blum and Conen[12] review mechanisms for cognitive decline in AF. Although the risk may be driven in large part by stroke, which is increased 5-fold in AF, risk of dementia is increased even in those with AF who do not have a history of clinical stroke. In addition to CBIs, potential mechanisms include concomitant cerebral small vessel disease, including microbleeds, and hypoperfusion. Although the primary strategy to reduce the risk of stroke and resultant cognitive decline is oral anticoagulation, the authors emphasise the importance of a comprehensive preventive approach, including optimisation of modifiable risk factors, such as hypertension, diabetes, and lifestyle.

Although anticoagulation remains a powerful means of risk reduction for stroke in AF, its place in secondary stroke prevention outside of AF remains uncertain, even in the era of the direct oral anticoagulants, which have favourable efficacy and safety compared with warfarin.[13] In the wake of the neutral trials examining anticoagulation for embolic strokes of undetermined source (ESUS; ie, without significant large artery stenoses or major-risk cardioembolic mechanisms), Field et al.[14] describe lessons learned regarding the patient phenotypes that composed the ESUS trials. They discuss ongoing and anticipated clinical trials to guide more personalized antithrombotic strategies in this diverse patient cohort, and review ongoing controversies related to prolonged cardiac monitoring for secondary prevention.

Management of cognitive impairment and promotion of brain health in cardiovascular disease, however, does not end with secondary prevention alone, nor with the cardiologist or neurologist. Gagnon and Bherer[15] describe the important roles that neuropsychologists, who specialise in brain-behaviour interactions, can play in assessing cognitive impairment and dementia and offering treatment recommendations. Neuropsychologists have historically been underutilised in cardiology, yet they can offer unique insights into understanding and managing cognitive decline observed in individuals with various cardiac diagnoses, including coronary artery disease, heart failure, AF, CHD, and sudden cardiac arrest.

Bherer et al.[16] review 3 specific interventions to improve cognitive function of adults with cardiovascular disease: cognitive stimulation, physical activity, and cardiac rehabilitation. Multidisciplinary cardiac rehabilitation programs have demonstrated benefits not only for cardiovascular mortality, but also for depressive symptoms, global cognition, attention, executive functions, and memory. Early studies investigating the effects of cognitive training in adults with cardiovascular disease also offer promising results.

The heart-brain connection has also been identified as a priority by the Heart and Stroke Foundation of Canada, which in 2019 released a report on heart, stroke, and vascular cognitive impairment.[17] As stated in the first 2 sentences of the introduction: "The heart, brain and mind are inextricably connected. They work together and are dependent upon each other; if something happens to one, the others are affected." As the field of cardiology progresses toward increased interdisciplinary efforts with other medical subspecialties, such as respirology and obstetrical medicine, so must it strengthen ties with neurology, neuropsychology, and mental health professions. Primary care physicians can also play a major role in optimising brain health through traditional cardiovascular prevention and risk reduction strategies, as described in a 2021 scientific statement from the American Heart Association.[18] The aim of optimising both cardiac and brain functioning across the lifespan is essential for multiple stakeholders, including patients, families, individual clinicians, health care institutions, and the broader health care system.

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