this is poorly acknowledged, those with a poor quality of venting of the cardiac cavities.

And last, but not least, even if we do admit that CPB is not harmless, we are also obliged to admit that it is still indispensable and mandatory for the most part in cardiac surgery. In the last 2 or 3 decades, many interesting interventional techniques, such as off-pump coronary surgery, transcatheter aortic valve implantation, stent grafting of the aorta, and so on, have been developed that allow the repair of many diseases and troubles without the aid of CPB. They certainly will progress and most probably reduce the need for CPB in the future. Until that time, however, CPB, adequately carried out, will remain indispensable and at the core of cardiac surgery.

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See Article page e185.

Commentary: Neurocognitive dysfunction after cardiopulmonary bypass: Multiple modalities to rescue the microglia

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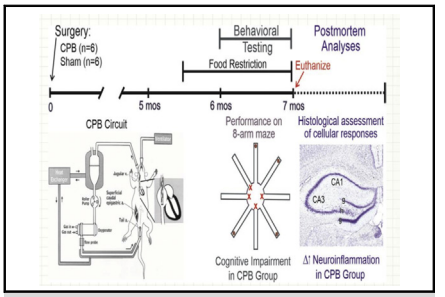

Cognitive and cellular effects of cardiopulmonary bypass.

CENTRAL MESSAGE

The microglia offer multiple therapeutic targets for neurocognitive rescue after cardiac surgery. Future trials should explore multimodal interventions, including modulation of inflammation.

Because neurocognitive dysfunction after cardiac surgery remains clinically relevant, therapeutic targets for cognitive rescue are essential.[1,2] The microglia function as resident macrophages for immune defense throughout the brain.[3] Activated microglia participate in an inflammatory cascade implicated in cognitive injury after cardiac surgery.[4,5] Furthermore, rodent models have suggested that impaired neurogenesis may also contribute to this pathogenesis.[4,5]

The study by Wang and colleagues[6] in this issue of the *Journal* highlights the central role of inflammation in this setting. In a rat model of cardiopulmonary bypass, the investigators demonstrated that persistent microglial inflammation correlated with neurocognitive dysfunction. Detailed histology also revealed decreased neurogenesis in the hippocampus.[6] These findings suggest that central inflammation and disrupted neurogenesis are likely mechanisms in cognitive injury from cardiopulmonary bypass.[4-6]

How might these observations guide further progress in cognitive rescue for our patients? Avoiding cardiopulmonary bypass in coronary artery bypass grafting has not abolished cognitive injury, despite anaortic techniques and ancillary carbon dioxide.[7] Further trials will likely refine the conduct of off-pump techniques to reduce the cognitive risk, especially in high-risk groups such as the elderly and frail.[1,2,7,8]

What are our options when cardiopulmonary bypass cannot be avoided?[1,2] In deep hypothermic circulatory arrest, recent results from rat knockout models have identified cold-inducible RNA-binding proteins as a microglial inflammatory target for cognitive rescue.[3,9] The migration

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to moderate hypothermia with anterograde cerebral perfusion in aortic arch surgery will likely mitigate cognitive injury due to microglial inflammation from hypothermia and ischemia.[10]

Furthermore, what about brain rescue in the common scenario of cardiopulmonary bypass at milder degrees of hypothermia?[1,2] The conduct of cardiopulmonary bypass likely has a major role in cognitive rescue, given that multiple factors are modifiable.[1,2] In a recent randomized trial, targeted therapy to optimize cerebral oxygenation improved memory up to 6 months after cardiac surgery with cardiopulmonary bypass.[11,12] A future focus will likely be the systematic optimization of cardiopulmonary bypass for neurocognitive rescue.[11,12]

So, where do we go from here? This elegant study has focused attention on microglial inflammation as a potent target for cognitive rescue after cardiopulmonary bypass.[6] Although inflammatory blockade can improve cognition, multiple anti-inflammatory drugs have failed in high-quality clinical trials.[1,2,13] In the case of steroids, 2 multicenter trials reported little clinical benefit in adult cardiac surgical patients, including neurocognitive function.[1,2,14] The deliberate acceleration of the active resolution process in inflammation is a new therapeutic target, because it preserves neurocognitive function in animal models.[1,2] Future trials will likely explore the role of resolution agonists to modify microglial inflammation for cognitive rescue.[1,2]

Wang and colleagues[6] are to be congratulated for highlighting microglial inflammation and neurogenesis in the pathogenesis of cognitive injury after cardiopulmonary bypass. The augmented resolution of inflammation merits further investigation. Future trials will likely address multimodal approaches for cognitive rescue, given that central inflammation is the not the only mechanism in this setting. These therapeutic investigations should also consider the dynamics of the microglial compartment because it has a major role in cognitive homeostasis.

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