**Pre-existing Heart Failure Exacerbates Neuroinflammation After Cardiopulmonary Bypass**

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**Introduction.** Postoperative neurocognitive dysfunction is a major complication of cardiac surgery, particularly in patients with pre-existing heart failure (HF). No treatments exist, and mechanistic insight has been limited by the lack of clinically relevant models.

**Aims**. To determine how pre-existing HF influences cerebral oxygenation, neuroinflammation and blood biomarkers of neuronal injury after cardiopulmonary bypass (CPB).

**Methods**. Female sheep were instrumented under isoflurane anaesthesia (2.0–2.5% in oxygen–air) for continuous monitoring of systemic haemodynamics and cerebral tissue oxygenation (PO₂) across pre-CPB (conscious), CPB (anaesthetised), and recovery (conscious). At 48 h post-CPB, frontal lobe brain tissue was collected for immunohistochemistry and microglial morphology quantified. HF was induced by progressive coronary ligation and defined by a ≥25% reduction in ejection fraction. HF (n=8) and control (n=8) animals underwent 2 h CPB with aortic cross-clamp and 48 h recovery.

**Results.** CPB caused marked reductions in systemic oxygen delivery and mean arterial pressure in both groups (both *P*time < 0.001), which were more pronounced in HF animals (both *P*group < 0.05). Despite these systemic changes, cerebral PO₂ was relatively preserved during the transition to CPB, though it declined progressively while on bypass (*P*time = 0.002), with a trend toward hypoxia in HF animals during the final 30 min (17 ± 2 vs 36 ± 10 mmHg, *P* = 0.065). Over the 48 h postoperative period, cerebral PO₂ remained near baseline in both groups, and plasma neurofilament light chain increased to ~1.5-fold baseline (*P*time = 0.008), with no group differences. The most striking finding was exaggerated microglial activation in HF animals, evidenced by shorter branches (588 ± 49 vs 903 ± 63 µm, *P* = 0.005), fewer segments (129 ± 12 vs 211 ± 20, *P* = 0.005), and fewer terminal points (71 ± 7 vs 114 ± 10, *P* = 0.006) compared with controls.

**Discussion.** Heart failure exacerbates postoperative neuroinflammation, potentially due to lower cerebral oxygenation at the end of CPB, identifying neuroinflammation as a potential therapeutic target in cardiac surgery.