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Inflammation, Oxidative Stress and Functional Decline of the Heart During Ex Situ Heart Perfusion: Are Leukocytes the Ultimate Villains?

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Normothermic ex-situ heart perfusion (ESHP) preserves the donated heart, in a perfused, dynamic status preventing the preservation-related ischemia. However, myocardial function declined during ESHP. The functional decline of the heart in this setting may be associated with the inflammation and oxidative stress related to extracorporeal circulation. To avoid inflammation, the leukocyte-depleted blood-based perfusate is utilized in clinical ESHP. There is a considerable lack of data about the contribution of leukocytes to inflammation, oxidative stress, and functional decline of the heart during ESHP.

Porcine hearts were perfused in working mode for an extended period of 12 hours using either a whole blood-based (WM, n=6) or a leukocyte-depleted blood-based perfusate (Lred-WM, n=6). Cardiac function alongside the markers of oxidative stress [malondialdehyde (MDA) and oxidized Low-density lipoprotein, (Ox-LDL)], the activity of the oxidative stress-responsive pathways [including glucose-6-phosphate dehydrogenase (G6PD), pentose phosphate pathway, and hexosamine biosynthesis pathway (O-linked N-acetylglucosamine formation, O-GlcNAc)], were compared in the left ventricular (LV) tissue of the ex-situ -perfused hearts and In vivo LV tissues (n=6) using immunoassay methods.

Myocardial functional parameters including cardiac index (CI) and LV stroke work (SW) significantly decline over the perfusion time in both WM (CI, p=0.008 and SW, p=0.019) and Lred-WM (CI, p=0.047 and SW, p=0.030). There was not a significant difference in the preserved CI and SW percentage between the two groups during the perfusion. Interestingly, despite significant depletion of leukocytes in Lred-WM group, the perfusate pro-inflammatory cytokines including interleukin 1-beta and tumor necrosis factor-alpha, and Ox-LDL (a marker of oxidative stress) significantly increased in both groups over time. There was not a significant difference in perfusate pro-inflammatory cytokines or ox-LDL between the two groups at any assessed time point. The LV tissue markers of oxidative stress including MDA and protein sulfonation, together with the activity of G6PD, and protein O-GlcNAc modification, while significantly induced in ex situ-perfused hearts compared to in vivo, were similar between WM and Lred-WM (Figure 1).

The induction of inflammatory responses and oxidative stress during ESHP may be a result of various conditions related to extracorporeal circulation, including hemolysis (free hemoglobin), depletion of tissue and perfusate antioxidants, and related metabolic alterations. Induction of these responses may play an important role in the metabolic and functional deterioration of the ex-situ perfused heart. The myocardial tissue challenged and stressed with these alterations may be a source of inflammatory cytokines, masking leukocyte-produced cytokine values.