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Piglet cardiopulmonary bypass model recapitulates dysbiosis and intestinal barrier dysfunction seen in pediatric congenital heart disease undergoing cardiopulmonary bypass

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Congenital heart disease (CHD) and cardiopulmonary bypass (CPB) have been implicated in intestinal dysbiosis development. Dysbiosis is associated with exacerbated inflammation, which is a large contributing factor to the morbidity and mortality following cardiac surgery with CPB. As our understanding of the intestinal microbiome grows, identifying animal models to reduce dysbiosis and systemic inflammation following CPB is necessary to improve clinical outcomes for this patient population. We hypothesize a CPB piglet model can be used to evaluate associations between the intestinal microbiome, metabolite profiles, barrier function, and systemic inflammation similar to those seen in pediatric patients with CHD undergoing CPB. We used 7 control piglets undergoing mechanical ventilation (MV), and 5 piglets undergoing CPB and deep hypothermic circulatory arrest (CPB/DHCA). Piglets on MV received 7 hours of ventilation before euthanasia, while the CPD/DHCA group was placed on bypass, received DHCA for 75 minutes, and were re-warmed and supported for 4 hours off bypass before euthanasia. During this process, blood and stool samples were obtained prior to intervention and at euthanasia for further analysis of the microbiome, metabolite profiles, barrier dysfunction, and inflammatory markers. Between the CPB/DHCA and MV groups, no significant differences in overall bacterial abundance were present, as measured in operational taxonomic units. Phylogenetic diversity was reduced in the CPB/DHCA group compared to the MV group ($p=0.018$). Significant differences in beta diversity between the two groups were measured ($p=0.017$). Intestinal barrier dysfunction was noted in plasma samples with elevations of tight junction proteins claudin-2 ($p<0.0001$) and claudin-3 ($p<0.01$), as well as intestinal specific fatty acid binding protein 2 ($p<0.01$). Significant reductions in three primary short chain fatty acids in the CPB/DHCA group versus MV group were observed to be similar to pediatric patients after CPB. Finally,

increased in Il-1-beta, Il-6, and TNF-alpha in CPB/DHCA piglets were noted compared to the MV group, and were similar to human levels. These results corroborate previously published findings on the microbial shifts within pediatric patients with congenital heart disease undergoing CPB, while also demonstrating evidence of intestinal barrier dysfunction, short chain fatty acid reductions, and increased systemic inflammatory cytokines. This is the first known animal model of CPB to evaluate changes in the intestinal microbiome, metabolites, and barrier dysfunction. This study sets the stage for future projects to evaluate microbiome interventions and identify mechanistic targets to reduce systemic inflammation activation.