Impaired and recovered vasorelaxation mediated by endothelium-derived hyperpolarizing factor under septic conditions

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Background: The vascular endothelium plays an essential role in maintaining tissue and organ perfusion by producing and releasing various vasodilators. Among these, nitric oxide (NO) is the most widely known and has been extensively studied. However, endothelium-derived hyperpolarizing factor (EDHF) is considered to have the most significant impact on microcirculatory regulation, particularly in small resistance arteries. EDHF induces hyperpolarization of vascular smooth muscle cells, leading to vasorelaxation and improved microvascular perfusion. Despite its importance, the precise role of EDHF in pathological conditions such as sepsis has remained unclear due to the technical difficulties associated with its experimental evaluation. Sepsis is characterized by profound microcirculatory dysfunction and endothelial injury, which contribute to organ failure and poor outcomes. Therefore, understanding the behavior of EDHF under septic conditions is crucial for developing new therapeutic strategies targeting microcirculatory disturbances.

Methods: In this study, we investigated changes in EDHF-mediated vasorelaxation and endothelial function in a rat model of sepsis induced by lipopolysaccharide (LPS). Male Wistar rats received an intraperitoneal injection of LPS at a dose of 5 mg/kg. Mesenteric arteries and right gastroepiploic arteries were harvested at baseline (Control), day 1 (24 hours after LPS administration), and day 3 (72 hours after LPS administration). Vasorelaxation responses were evaluated by measuring the relaxation induced by acetylcholine (Ach), which is known to be mediated approximately 80% by EDHF in small arteries. In addition, changes in vascular smooth muscle cell membrane potential (hyperpolarization responses) were measured. To assess the contribution of NO, experiments were also conducted in the presence of Nitro-L-arginine (L-NNA), an NO synthase inhibitor.

Results: On day 1 after LPS administration, Ach-induced vasorelaxation was significantly suppressed compared to control arteries, indicating an early impairment of EDHF-mediated relaxation. By day 3, vasorelaxation responses had recovered close to baseline levels. However, in the presence of NO inhibition by L-NNA, the recovery observed on day 3 was abolished, suggesting that NO played a compensatory role in restoring vasorelaxation when EDHF function was impaired. Similarly, endothelial hyperpolarization responses were markedly reduced on Day 1 and showed recovery by Day 3, but this recovery was delayed or absent under NO inhibition.

Conclusion: Our findings demonstrate that under normal physiological conditions, EDHF is the primary mediator of small artery vasorelaxation. However, in the early phase of sepsis induced by LPS, EDHF-mediated vasorelaxation and hyperpolarization responses are significantly impaired. During this period, NO appears to compensate for the loss of EDHF function, supporting vasorelaxation and maintaining microvascular perfusion. These results highlight a dynamic and complementary interaction between EDHF and NO under septic conditions, which may represent a potential therapeutic target for improving microcirculatory dysfunction and organ perfusion in sepsis. Further studies are needed to elucidate the molecular mechanisms underlying these interactions and to explore possible interventions that enhance endothelial function in critical illness.