NO-synthase inhibition in sepsis

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Despite major advances and novel therapeutic approaches in intensive care medicine, sepsis is still a major burden of modern medicine and the leading cause of death in non-coronary intensive care units (1). Sepsis represents a complex disease state with distinctive activation of the inflammation cascade and the coagulation system, resulting in pervasive macro- and microvascular dysfunction and subsequent impairment of organ function. Therefore, innovative strategies targeted against single components of the proinflammatory and/or coagulation cascade have been extensively investigated in the last decades. Unfortunately, many of these agents showed very promising findings in preclinical studies (2, 3), but failed to be efficacious in pivotal clinical trials (4, 5).

The gaseous molecule nitric oxide (NO) is a potent regulator of vascular tone, microvascular function and oxygen transport. During the progression of sepsis, proinflammatory cytokines like tumour necrosis factor-α and interleukin-1 stimulate the overproduction of non-specific (nNOS) and inducible NO-synthase (iNOS) throughout the organs (6), consequently leading to impairment of vasomotor function (7). As a consequence, NO inhibitors have been investigated in numerous clinical and animal studies of sepsis (8–11). Both, non-specific and iNOS-specific NOS-inhibitors indicated normalisation of cardiac indices, systemic vascular resistance and oxygen extraction by peripheral vasoconstriction in subjects with sepsis. However, a randomised phase III trial of the non-selective NOS inhibitor L-NMMA was recently discontinued after interim analysis due to a significant elevation of the mortality rate in the treatment group (12).

In this issue of *Thrombosis and Haemostasis*, Pullamsetti, et al. compare the effects of norepinephrine titration, non-selective NOS inhibition by L-NMMA and selective inhibition of iNOS by the compound 1400W on haemodynamics and in particular on the regulation of microcirculation in a rat model of endotoxic shock (13). Therefore, they quantified haemoglobin saturation spectral-photometrically in different areas of the upper intestinal tract.

The key finding of this study is that the selective iNOS inhibitor 1400W not only restores macrocirculatory dysfunction similarly to norepinephrine and L-NMMA, but as only treatment regimen does not deteriorate tissue oxygenation in the critical gut mucosal surface layer. The frequency of severely deoxygenated mucosal areas is significantly reduced in comparison to the catecholamine treatment group. Additionally, 1400W reduces plasmatic nitrite and nitrate levels similar to the non-selective NOS inhibitor L-NMMA. Hence, these results are consistent with the opinion that the endotoxin-triggered excess NO formation is largely attributable to iNOS upregulation. The different distribution of nNOS and iNOS in tissues such as the intestine (14) could explain why inhibition of the latter may be superior. If NO production is unselectively shut down by inhibition of nNOS, tissue compartments solely dependent on nNOS could become underperfused, while specific inhibition of iNOS would still allow for sufficient NO production.

The above mentioned paper by Pullamsetti, et al. focuses on the effects of NO-inhibition in a sepsis model. Alternatively, various “NO-donor” studies suggest that increased NO production may preserve or protect microvascular blood flow by counteracting “microvascular shut down” (15, 16). These diverging lines of evidence demonstrate that NO plays a complex role in microvascular homeostasis which has not yet fully been understood. For the future, studies directly comparing the effects of NO donors and selective inhibitors in sepsis models might be desirable. Thereby, one should especially focus on the microcirculation, since microcirculatory dysfunction has been identified as the key player in the pathophysiology of sepsis (17, 18).
References


18. Lam C, Tym K, Martin C, et al. Microvascular perfusion is impaired in a rat model of normotensive sep-