"AKI and endotheliopathy amplifies endogenous NO inhibition during early phase of ICU admission"

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Background

Circulatory instability is commonly observed in patients admitted to Intensive Care Units (ICU). Nitric oxide (NO) is a vasodilator and the production is upregulated during critical illness[1]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO production. Admission plasma concentrations of ADMA is increased in critically ill patients compared to healthy controls[2] and the increase is associated with mortality[2,3]. The time course needs to be further investigated to decide for clinical relevance and potential of future intervention. The aim of this research project is to determine how endogenous NO-synthase inhibition, as measured by plasma ADMA, varies over the first five days of ICU admission, and identify subgroups with distinctive patterns.

Materials and methods

We included adult patients admitted to the ICU of Copenhagen University Hospital – North Zealand from November 2016 to June 2019. We took blood samples during the first five days of admission. Plasma concentration of ADMA was analysed with enzyme-linked immunosorbent assay (ELISA). In subgroup analyses we further investigated the time course of plasma ADMA in patients with septic shock vs. without septic shock, in different stages of endotheliopathy (soluble thrombomodulin (sTM) < 4 ng/ml vs. 4-10 ng/ml vs. > 10 ng/ml), patients treated with dialysis vs. no dialysis and patients with acute kidney injury (AKI) vs. no AKI. We used linear mixed models to describe the time course of plasma ADMA and tested for subgroup effect using interaction tests.

Results

We included 567 mixed ICU patients with a total of 1933 blood samples. Median age was 71 years (interquartile range (IQR) 63-79 years) and 327 (57.7%) were male. Median SAPS 3 score was 64 (IQR 56-73). Plasma ADMA concentration increased during the first five days of ICU admission ($p < 0.001$). Patients with AKI had a more pronounced increase in ADMA vs. patients without AKI ($p < 0.001$) (fig. 1A), and likewise in patients with endotheliopathy measured by sTM ($p = 0.005$) (fig. 1B). No difference was observed in patients with vs without dialysis ($p = 0.070$) (fig. 1C), or with vs. without septic shock ($p = 0.707$) (fig. 1D).

Conclusion

Endogenous NO inhibition, as measured by ADMA, increase during the first five days of ICU admission, and is amplified by AKI and endotheliopathy.

References

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2 Koch, A. *et al. J. Crit. Care* 28, 947–53 (2013)

3 Mortensen, K. M. *et al. Shock* 46, 365–372 (2016)

Figure 1: Time course of plasma ADMA concentration in different subgroups during the first five days of ICU admission.