The Malignant Hypertension-Thrombotic Microangiopathy Link

To the Editor:

The article by van den Born et al1 nicely demonstrates the reduction in ADAMTS-13 levels in patients with malignant hypertension. This study is further proof that low levels of this enzyme are more a marker of endothelial dysfunction rather than of thrombotic microangiopathy (TMA). Endothelial dysfunction also causes a reduction of NO, which is an important role player in the pathogenesis of both malignant hypertension and TMA.2,3

Patterson et al2 demonstrated that superoxide anion contributes to the pathogenesis of various forms of hypertension, including malignant hypertension, through a mechanism that is NO dependent. Increased levels of superoxide anion can reduce the bioactivity of NO, which contribute to elevated arterial pressures and renal vascular resistance, leading to the development of malignant hypertension. The administration of the NO synthase inhibitor nitro-L-arginine also inhibited the response to a superoxide dismutase mimetic, indicating the lack of NO in the development of malignant hypertension.

In patients with TMA, the red cell free hemoglobin, present in the plasma during hemolysis, can scavenge NO.3 Hemoglobin, which is outside the red cell has a great affinity for NO compared with when it is compartmentalized inside the red cell. In severe hemolysis, the excess of cell free hemoglobin, depletes NO present in the circulation. Depletion of NO, a platelet antiaggregatory and vasodilatory molecule, can lead to TMA.3

The authors describe that increased levels of von Willebrand factor (VWF) correlate with the low levels of ADAMTS-13. However, it is unlikely that a lower ADAMTS-13 activity would have led to the expression of large VWF multimers. This is confirmed by the absence of ultralarge VWF multimers in these patients. However, the depletion of NO can also cause a release of VWF multimers into the plasma. NO has been shown to exert a negative feedback on VWF secretion mediated by activation of soluble guanylate cyclase and generation of cGMP.4

The close correlation between ADAMTS-13 activity and renal insufficiency in patients with malignant hypertension has also been suggested with a proposal to identify treatment directed at increasing ADAMTS-13 activity and, thus, benefiting patients with renal dysfunction. The correlation between ADAMTS-13 activity and renal insufficiency may actually explain the endothelial dysfunction in malignant hypertension rather than a cause-effect relationship. In the normal renal glomerular physiology, NO is an important molecule.5 In vivo inhibition of NO production can have dramatic effects on renal and glomerular hemodynamics. Endogenous NO is also critical in maintaining normal basal tone in renal (and systemic) circulations. The renal insufficiency in patients with malignant hypertension can be secondary to a lack of NO, among other reasons, and “NO donors” rather than “ADAMTS-13 donors” are likely to be more helpful.

In summary, NO is the common pathophysiological factor that can explain the link between malignant hypertension and TMA. The increased levels of ADAMTS-13, VWF, and indeed the depletion of NO all point to the common endothelial dysfunction, which is well established in both of these conditions.

Disclosures

None.

Jecko Thachil
Department of Haematology
University of Liverpool
Liverpool, United Kingdom

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Jecko Thachil

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