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Review Article

# The endothelium as the common denominator in malignant hypertension and thrombotic microangiopathy

Roy O. Mathew, MD[a,c,*,1], Ali Nayer, MD[b], and Arif Asif, MD[c]

[a]*Division of Nephrology, Department of Medicine, Albany Stratton VA Medical Center, Albany, NY, USA;*
[b]*Division of Nephrology and Hypertension, Department of Medicine, University of Miami, Miami, FL, USA; and*
[c]*Department of Medicine, Jersey Shore University Medical Center, Neptune, NJ, USA*

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## Abstract

The endothelium plays a pivotal role in vascular biology. The endothelium is the primary site of injury in thrombotic microangiopathies including malignant hypertension. Endothelial injury in thrombotic microangiopathies is the result of increased shear stress, toxins, and/or dysregulated complement activation. Endothelial injury can lead to microvascular thrombosis resulting in ischemia and organ dysfunction, the clinical hallmarks of thrombotic microangiopathies. Currently, available therapies target the underlying mechanisms that lead to endothelial injury in these conditions. Ongoing investigations aim at identifying drugs that protect the endothelium. J Am Soc Hypertens 2016;10(4):352–359. Published by Elsevier Inc. on behalf of American Society of Hypertension.

*Keywords:* Malignant hypertension; thrombotic microangiopathy; endothelial dysfunction; hemolytic uremic syndrome.

## Introduction

Hypertension is a common medical problem with significant clinical consequences. The pathophysiology of hypertension involves multiple systems and processes that give rise to an elevation of pressure within the systemic arterial vasculature. The endothelium plays a critical role in blood pressure regulation. Endothelial dysfunction can lead to hypertension and is also frequently encountered in thrombotic microangiopathies (TMAs).[1–4] TMAs are characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and end-organ damage.[5,6] Endothelial dysfunction may represent a link between malignant hypertension and TMAs.

### *Endothelium and Hypertension*

A crosstalk between the endothelial and vascular smooth muscle cells is pivotal in the regulation of vascular tone.[1] The endothelium senses changes in the circulation and regulates vascular tone in a paracrine fashion. The endothelium releases potent vasodilators such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor. Endothelium-derived mediators of vasoconstriction include endothelin-1 and thromboxane A2. Endothelial dysfunction may lead to altered vascular tone and therefore changes in blood pressure.[1] What is clear is that there is no single mechanism, in a singular direction, that links endothelial dysfunction with hypertension. Silva et al demonstrated that endothelial dysfunction is associated with reduced nitric oxide release and increased production of endothelin-1 and reactive oxygen species.[7] Preston et al defined endothelial dysfunction in more mechanical terms.[8] They demonstrated that severe hypertension was associated with increased circulating levels of endothelial and platelet microparticles, which are markers of endothelial and platelet activation, respectively. The authors concluded that severe hypertension causes endothelial and platelet activation. Endothelial dysfunction occurring independent of circulating pressure can also lead to hypertension. The most striking example of this is seen in anti–vascular endothelial growth factor (anti-VEGF) receptor inhibition therapy in oncology.[9] Anti-VEGF directly targets vascular endothelial cells and leads to marked vasoconstriction

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*Corresponding Author: Roy O. Mathew, MD, WJB Dorn VAMC 6439 Garners Ferry Road, Columbia, SC 29209. Tel: (803)776-4000 x4513; Fax: (803)647-5714.

E-mail: roy.mathew@va.gov

[1] Present address: WJB Dorn VA Medical Center, Columbia, SC.

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resulting in hypertension; hypertension is the leading adverse event noted with anti-VEGF therapy. The vasoconstriction is particularly prominent in glomerular arterioles.

### *Endothelium and TMA*

Endothelial injury is the principal mechanism of disease underlying distinct forms of TMAs. In hemolytic uremic syndrome (HUS)- associated with Shiga toxin-producing Escherichia coli (STEC-HUS), endothelial injury is caused by a toxin—Shiga toxin.[2] In atypical HUS (aHUS), endothelial injury is mediated by derangements in the complement system, usually due to some inherited or acquired alteration in its function.[5,10–12] Specifically, activation of the alternative pathway of the complement system, either due to inherited defects in or acquired autoantibodies directed against the regulators of this pathway, has been found to underlie the propagation of endothelial injury (Table and Figure 1). The complement system constitutes an evolutionary conserved part of the immune system and represents the first line of defense against invading pathogens. In addition, the complement system is positioned in the center of an intricate network of biological systems that regulates waste disposal, angiogenesis, regenerative processes, and lipid metabolism. As shown in the Table and Figure 1, the alternative pathway is an intrinsically self-activating component of the complement system. C3 spontaneously breaks down into C3a and C3b. Several soluble and membrane-bound proteins are in place to regulate the activity of complement proteins, and especially C3 proteolysis. Although the complement system exerts various physiological functions, uncontrolled complement activation, again specifically via the alternative pathway, can result in a variety of adverse consequences such as endothelial damage.[13] It turns out that reduced function of complement regulators accounts for unleashed complement activity observed in patients with aHUS.[10] Loss-of-function mutations affecting the genes encoding complement regulators are found in 40%–60% of patients with aHUS.[10] The Table delineates the complement system and regulatory proteins. In thrombotic thrombocytopenic purpura (TTP), endothelial injury has been demonstrated in clinical studies by the finding of endothelial microparticles, considered a marker and mediator of endothelial activation and injury.[14,15]

### *TMA and Hypertension*

The underlying pathophysiology of TMA determines the prevalence and severity of hypertension in this disorder.[16] TTP is a thrombotic microangiopathy secondary to markedly reduced 13th member of a disintegrin and metalloproteinase with thrombospondin type I motif family (ADAMTS13) activity. ADAMTS13 is a protease that cleaves von Willebrand factor (vWF) multimers into smaller fragments thereby controlling vWF-mediated platelet aggregation.[6] TTP, interestingly, is rarely associated with hypertension. Lotta et al reported that cardiovascular disease including hypertension was present in only 4% of individuals with TTP during initial or recurrent presentation.[17] In addition, a review of four case series showed that no patients with acquired TTP and severe ADAMTS13 deficiency demonstrated malignant hypertension.[18] By contrast, HUS is frequently associated with hypertension. Although STEC-HUS may manifest with hypertension, aHUS is more frequently associated with hypertension, likely due to more severe renal disease.[11,12,19]

What are the underlying mechanisms for increased blood pressure in TMA? Renal microvascular thrombosis in TMA reduces glomerular perfusion and leads to activation of the renin-angiotensin system. The pivotal role of the renin-angiotensin system in the regulation of blood pressure is well established.[20] The juxtaglomerular cells of the kidney release renin in response to reduced renal blood flow. Renin converts plasma angiotensinogen to angiotensin I, which is then converted to angiotensin II by the angiotensin-converting enzyme. Angiotensin II causes vasoconstriction as well as increased sodium and water reabsorption in the kidney leading to increased blood pressure. As noted, the various TMA syndromes result in endothelial dysfunction and injury, especially in the renal microvasculature. The contribution of intrarenal endothelial injury and renin-angiotensin system activation, as opposed to generalized endothelial dysfunction, to hypertension is not established. In children presenting with HUS, measured renin activity was only marginally higher in patients with hypertension as compared with those without hypertension, with no statistical differences between patients with and without hypertension.[21,22] This suggests that factors other than increased renin secretion are involved in the hypertension associated with HUS: altered endothelial function after injury and elevated renin-angiotensin axis activation. In addition, renal injury is likely associated with enhanced salt and water retention, which is important in blood pressure elevation in many forms of glomerulonephritis as well as in chronic kidney disease in general.

The reason for less severe hypertension in TTP is not clear. It is clear that renal involvement in TTP tends to be less common than in HUS.[6] A possible mechanism, given that renal microvascular involvement plays a role in the generation of hypertension, is that a lower incidence of renal involvement in TTP, especially acquired TTP, results in less severe elevations in renin-angiotensin system component. In addition, altered salt and water homeostasis seen with hypertension because of impaired renal function, would also not be as pronounced. The role of complement, specifically the alternative pathway, and endothelial dysfunction in the genesis of hypertension is discussed in the following sections.