Endothelial fibrinolytic function in hypertension: the expanding story
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In recent years, impairment of endothelial function has been a major focus of clinical research into cardiovascular disease. Endothelial dysfunction is associated with classical risk factors and there is accumulating evidence that it also independently predicts cardiovascular outcome [1]. This research has almost exclusively focused on endothelium-dependent vasodilatation as a measure of endothelial function. However, although this is important, it may not be representative of other important aspects of endothelial function, such as the regulation of fibrinolysis.

Following the initiation of intravascular thrombus formation, the endothelium acutely releases tissue-type plasminogen activator (t-PA) in response to a range of factors predominantly related to the coagulation cascade, especially factor Xa and thrombin [2]. Once released, t-PA catalyses the conversion of plasminogen to plasmin and thereby facilitates thrombus dissolution through the proteolytic degradation of fibrin to soluble fibrin degradation products. This endogenous fibrinolytic system protects the circulation from intravascular fibrin formation and thrombosis that would otherwise result in vessel occlusion and tissue ischaemia. It follows that impairment of acute t-PA release from the endothelium might be a specific mechanism through which endothelial dysfunction mediates or potentiates thrombotic events.

Jern and colleagues [3] have previously reported that desmopressin-induced endothelial t-PA release is significantly impaired in patients with hypertension and have since explored the mechanism responsible for this observation. Using an \textit{ex vivo} perfusion model in which shear stress was kept constant, increased intraluminal pressure in human umbilical veins decreased t-PA release, as well as gene and protein expression. This suggested that raised intraluminal pressure \textit{per se} may be important in mediating impaired t-PA release in hypertension. The authors have now extended these findings and have specifically investigated the effects of cyclic tensile, rather than compressive, strain on endothelial t-PA production and release. In this issue of the journal, Ulffhamer \textit{et al.} [4] show that cyclically stretching cultured human aortic endothelial cells (HAECs) decreases both t-PA mRNA production and protein secretion but increases the production and secretion of plasminogen activator inhibitor 1, the major natural inhibitor of t-PA \textit{in vivo}. If, as is suggested by this work, raised intraluminal pressure, by increasing circumferential wall strain, impairs the capacity for acute endothelial t-PA release \textit{in vivo}, this would provide a direct mechanistic link between raised blood pressure and atherothrombotic events. It might further be hypothesized that the clinical benefit of blood pressure reduction in reducing these events would, at least in part, be mediated through improvements in endogenous fibrinolysis. Indeed, there is now good evidence that the clinical benefit of antihypertensive therapy is predominantly related to blood pressure reduction \textit{per se} rather than being the result of other drug class-specific effects [5]. Therefore, improvement in endothelial t-PA release might be a common mechanism through which different antihypertensives reduce cardiovascular events.

Of the agonists known to stimulate endothelial t-PA release, bradykinin is one of the most potent. Bradykinin is largely metabolized by angiotensin-converting enzyme (ACE) and ACE inhibitors potentiate bradykinin-induced t-PA release. Indeed, infusion of enalaprilat stimulates t-PA release and this effect is mediated through endogenous bradykinin [6]. Thus, the established clinical benefit of ACE inhibitors in a range of cardiovascular conditions may be partly related to effects on endothelial t-PA release through preservation of endogenous bradykinin. In patients with hypertension, ACE inhibitors are no more effective than other antihypertensive classes in reducing cardiovascular events [7]. This may suggest that any benefit that arises through improved endothelial t-PA release with ACE inhibition is predominantly due to blood pressure reduction rather than specific ACE inhibitor-mediated effects on endogenous bradykinin. Despite this, it is intriguing to speculate that patients with drug-resistant hypertension might benefit specifically from an ACE inhibitor even in the absence of blood pressure reduction.

There are some limitations to the work performed both \textit{ex vivo} and \textit{in vitro} on the effect of mechanical forces on
endothelial t-PA production and release. The effect of strain on HAECs was only investigated at 10% stretch. This is thought to correspond to an intraluminal pressure of 170 mmHg in medium-sized arteries. However, endothelial cells in arteries are exposed to cyclical circumferential strain under normal circumstances and it is possible that, even at this level, t-PA production and release is inhibited. Thus, the difference between the effects of normal physiological strain and the greater strain associated with hypertension may be more relevant. Furthermore, neither model can be expected to reflect accurately the complex pressure-related stresses on the arterial wall that occur in hypertension. Indeed, these stresses will vary both with the vessel size and the subtype of hypertension, whether diastolic, systolic or mixed. In particular, the increased stiffness of large arteries that characterizes isolated systolic hypertension will limit the change in vessel diameter and therefore stretch on the endothelial cell layer. As a result, despite high systolic pressures, endothelial t-PA release might be relatively preserved.

It is now 7 years since Jern et al. [3] first described the important observation that endothelial t-PA release is impaired in patients with hypertension. However, many questions remain. For example, is the relationship between blood pressure and t-PA release linear? What are the effects of the continuous and pulsatile components of blood pressure? Is there a regional or systemic impairment of t-PA release? Does blood pressure reduction improve t-PA release? Are there differences between antihypertensive classes with respect to improving t-PA release? Answering these and other, related, questions may significantly contribute to our understanding of how raised blood pressure leads to atherothrombotic events and why antihypertensive therapy effectively reduces their incidence.

References
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