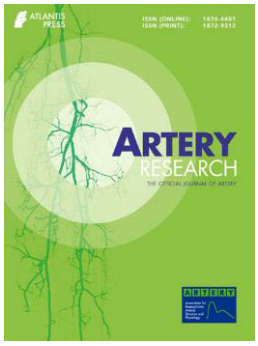

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ABSTRACT OF ARTERY

HOW TO MEASURE ENDOTHELIAL FUNCTION BY PULSE WAVE ANALYSIS

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The vascular endothelium releases a number of biologically active mediators, including nitric oxide (NO), that regulate vessel tone and prevent the development of atheroma. Endothelial dysfunction, characterized by a reduced bioavailability of endothelium-derived NO independently predicts cardiovascular mortality[1,2] and is associated with a range of risk factors for cardiovascular disease, including age, hypertension, obesity, hypercholesterolemia, diabetes and smoking. Moreover, some therapies that improve clinical outcome also improve endothelial function[3]. However, no direct link between improved endothelial function and reduced cardiovascular risk has been made, and the prognostic significance of endothelial dysfunction has not been assessed in a major observational study. Established methods for assessing vasomotor endothelial function centre on measuring the response to an endothelium-dependent, NO-mediated stimulus such as acetylcholine or reactive hyperemia, and a direct (endothelium-independent) nitrovasodilator, like sodium nitroprusside or glyceryl trinitrate (GTN). However, these methods are not suitable for inclusion in large-scale trials. Therefore, new and relatively simple, non-invasive techniques are required to assess the predictive value of endothelial dysfunction.

Arterial stiffness depends, in part, on smooth muscle tone. Indeed, removal of the vascular endothelium alters arterial stiffness in animal models[4], and blocking NO synthesis increases local arterial stiffness[5], suggesting that endothelium-derived nitric oxide contributes to the regulation of large artery stiffness *in vivo*. The shape of the arterial pressure waveform provides a measure of systemic arterial stiffness and wave reflections and can be assessed non-invasively using the technique of pulse wave analysis (PWA). Therefore, PWA might provide a simple method for assessing endothelial vasomotor function. Chowienczyk et al.[6] previously demonstrated that salbutamol, a β_2 agonist, reduces wave reflection, in part, by activation of the L-arginine-NO pathway, and suggested that such methodology might be applied to the assessment of endothelial function. Therefore, in a series of studies, we validated the non-invasive assessment of endothelial function using PWA combined with provocative administration of GTN and salbutamol[7]. Firstly we defined the repeatability of the responses to inhaled salbutamol and sublingual GTN in healthy subjects, by calculating augmentation index (AIx) from derived aortic waveforms on repeated visits. We showed that both salbutamol and GTN significantly reduced AIx and the response to either drug did not differ significantly between visits. Secondly, we sought to determine whether salbutamol acts via the L-arginine-NO pathway, by administering GTN, salbutamol and placebo, separately, during an infusion of L-N^G-monomethyl arginine (LNMMA) or noradrenaline (NA). Only the response to salbutamol was inhibited by LNMMA, consistent with an endothelium-dependent effect. We then tested our novel method of assessing endothelial function in healthy individuals and subjects with hypercholesterolaemia, known to exhibit endothelial dysfunction. Baseline AIx was higher in the hypercholesterolaemic subjects, who exhibited a reduced response to salbutamol but not GTN compared with matched controls. Finally, a comparison between the PWA technique and the 'gold standard' of forearm venous occlusion plethysmography, showed that the responses to salbutamol and acetylcholine were correlated. Therefore, we concluded that this methodology provides a simple, repeatable, non-invasive, means of assessing endothelial function *in vivo*.

We then applied our novel technique to a large population of healthy individuals, spanning a wide age-range, to examine the relationship between endothelial function and arterial stiffness[8]. In order to confirm our findings, we also examined the relationship between arterial stiffness and flow-mediated dilatation, a widely used technique to assess conduit vessel endothelial function, in a separate group of healthy individuals. We observed that endothelial function was significantly, and inversely correlated with aortic pulse wave velocity, augmentation index, and central and peripheral pulse pressure. Moreover, there was a stronger correlation between central, rather than peripheral pulse pressure. After adjusting for potential confounders, endothelial function remained independently and inversely associated with aortic pulse wave velocity and augmentation index. There was also a significant, inverse relationship between conduit artery endothelial function and aortic pulse wave velocity which remained independent after adjusting for confounding factors. Therefore, we observed that in healthy individuals, a decline in endothelial function is associated with increased large artery stiffness, wave reflections and central pulse pressure. Pulse wave analysis coupled with the administration of salbutamol and GTN provides a simple and robust method for the assessment of endothelial function which is applicable to large-scale studies.

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