# MICROVASCULAR FUNCTION PREDICTS CARDIOVASCULAR EVENTS IN PRIMARY PREVENTION: LONG-TERM RESULTS FROM THE FIREFIGHTERS AND THEIR ENDOTHELIUM (FATE) STUDY[1]

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**BACKGROUND:** Biomarkers of atherosclerosis may refine clinical decision making in individuals at risk of cardiovascular disease. The purpose of the study was to determine the prognostic significance of endothelial function and other vascular markers in apparently healthy men.

**METHODS AND RESULTS:** The cohort consisted of 1574 men (age, 49.4 years) free of vascular disease. Measurements included flow-mediated dilation and its microvascular stimulus, hyperemic velocity, carotid intima-media thickness, and C-reactive protein. Cox proportional hazard models evaluated the relationship between vascular markers, Framingham risk score, and time to a first composite cardiovascular end point of vascular death, revascularization, myocardial infarction, angina, and stroke. Subjects had low median Framingham risk score (7.9%). Cardiovascular events occurred in 71 subjects (111 events) over a mean follow-up of 7.2±1.7 years. Flow-mediated dilation was not associated with subsequent cardiovascular events (hazard ratio, 0.92; P=0.54). Both hyperemic velocity (hazard ratio, 0.70; 95% confidence interval, 0.54 to 0.90; P=0.006) and carotid intima-media thickness (hazard ratio, 1.45; confidence interval, 1.15 to 1.83; P=0.002) but not C-reactive protein (P=0.35) were related to events in a multivariable analysis that included Framingham risk score (per unit SD). Furthermore, the addition of hyperemic velocity to Framingham risk score resulted in a net clinical reclassification improvement of 28.7% (P<0.001) after 5 years of follow-up in the intermediate-risk group. Overall net reclassification improvement for hyperemic velocity was 6.9% (P=0.24).

**CONCLUSIONS:** In men, hyperemic velocity, the stimulus for flow-mediated dilation, but not flow-mediated dilation itself was a significant risk marker for adverse cardiovascular outcomes. The prognostic value was additive to traditional risk factors and carotid intima-media thickness. Hyperemic velocity, a newly described marker of microvascular function, is a novel tool that may improve risk stratification of lower-risk healthy men. **[Circulation. 2011;123(2):163-9.]**

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# THE EFFECTS OF PARTICLE SIZE, DENSITY AND SHAPE ON MARGINATION OF NANOPARTICLES IN MICROCIRCULATION[1]

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In the recent past, remarkable advances in nanotechnology have generated nanoparticles of different shapes and sizes, which have been shown to exhibit unique properties suitable for biomedical applications such as cancer therapy and imaging. Obviously, all nanoparticles are not made equal. This becomes evident when we consider their transport behavior under blood flow in microcirculation. In this work, we evaluated the effect of critical physical characteristics such as the particle shape, size and density on a nanoparticle's tendency to marginate towards the vessel walls in microcirculation using an in vitro model. The wall deposition of nanoparticles was tested in a fibronectin-coated microfluidic channel at a physiologically relevant flow rate. Different classes of nanoparticles (liposome, metal particles) of different sizes (60-130 nm), densities (1-19 g ml(-1)) and shapes (sphere, rod) displayed significantly different deposition as a result of different margination rates. The smaller-sized and the oblate-shaped particles displayed a favorable behavior as indicated by their higher margination rates. Notably, the particle density showed an even more essential role, as it was observed that the lighter particles marginated significantly more. Since nanoparticles must escape the flow in order to approach the vascular bed and subsequently extravascular components for meaningful interactions, the design of nanoparticles strongly affects their margination, a key factor for their ultimate in vivo effectiveness**. [Nanotechnology. 2011; 22(11):115101.]**

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# EFFECTS OF DISTURBED FLOW ON VASCULAR ENDOTHELIUM: PATHOPHYSIOLOGICAL BASIS AND CLINICAL PERSPECTIVES[1]

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Vascular endothelial cells (ECs) are exposed to hemodynamic forces, which modulate EC functions and vascular biology/pathobiology in health and disease. The flow patterns and hemodynamic forces are not uniform in the vascular system. In straight parts of the arterial tree, blood flow is generally laminar and wall shear stress is high and directed; in branches and curvatures, blood flow is disturbed with nonuniform and irregular distribution of low wall shear stress. Sustained laminar flow with high shear stress upregulates expressions of EC genes and proteins that are protective against atherosclerosis, whereas disturbed flow with associated reciprocating, low shear stress generally upregulates the EC genes and proteins that promote atherogenesis. These findings have led to the concept that the disturbed flow pattern in branch points and curvatures causes the preferential localization of atherosclerotic lesions. Disturbed flow also results in postsurgical neointimal hyperplasia and contributes to pathophysiology of clinical conditions such as in-stent restenosis, vein bypass graft failure, and transplant vasculopathy, as well as aortic valve calcification. In the venous system, disturbed flow resulting from reflux, outflow obstruction, and/or stasis leads to venous inflammation and thrombosis, and hence the development of chronic venous diseases. Understanding of the effects of disturbed flow on ECs can provide mechanistic insights into the role of complex flow patterns in pathogenesis of vascular diseases and can help to elucidate the phenotypic and functional differences between quiescent (nonatherogenic/nonthrombogenic) and activated (atherogenic/thrombogenic) ECs. This review summarizes the current knowledge on the role of disturbed flow in EC physiology and pathophysiology, as well as its clinical implications. Such information can contribute to our understanding of the etiology of lesion development in vascular niches with disturbed flow and help to generate new approaches for therapeutic interventions**. [Physiol Rev. 2011 Jan; 91(1):327-87.]**

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# A NOVEL APPROACH TO BLOOD PLASMA VISCOSITY MEASUREMENT USING FLUORESCENT MOLECULAR ROTORS[1]

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## ABSTRACT

Molecular rotors, a group of fluorescent molecules with viscosity-dependent quantum yield, were tested for their suitability to act as fluorescence-based plasma viscometers. The viscosity of samples of human plasma was modified by the addition of pentastarch (molecular mass 260 kDa, 10% solution in saline) and measured with a Brookfield viscometer. Plasma viscosity was 1.6 mPa x s, and the mixtures ranged up to 4.5 mPa x s (21 degrees C). The stimulated light emission of the molecular rotors mixed in the plasma samples yielded light intensity that was nonoverlapping and of significantly different intensity for viscosity steps down to 0.3 mPa × s (n = 5, P < 0.0001). The mathematical relationship between intensity (I) and viscosity (eta) was found to be eta = (kappaI)(nu). After calibration and scaling the fluorescence based measurement had an average deviation versus the conventional viscometric measurements that was <1.8%. These results show the suitability of molecular rotors for fast, low-volume biofluid viscosity measurements achieving accuracy and precision comparable to mechanical viscometers [**Am J Physiol Heart Circ Physiol 2002; 282(5):H1609-14**].

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