

High Intraluminal Pressure Increases Vascular Inflammation Contributing to Progression of Vascular Disease



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Despite the widespread availability of blood pressure lowering medications, high blood pressure (high BP; hypertension; HT) remains responsible for more deaths and disease globally than any other biomedical risk. While numerous studies identify HT as a potent contributing factor in the development of coronary artery disease (CAD), the exact mechanism by which this occurs is not known. We have novel evidence that high intraluminal pressure *per se* causes leukocyte to endothelium adhesion, a hallmark of vascular inflammation, and thus forward the hypothesis that high pressure induces inflammation which can result in plaque formation and progression. We show for the first time that high pressure alters caveolae structure and function and suggest that this structural disruption generates increased oxidative stress, upregulates NFκB and increased expression of adhesion molecules and selectins responsible for the adhesion cascade and eventual plaque formation and progression. Furthermore, we show in a novel spontaneously hypertensive diet-induced atherosclerotic mouse model (BPHx*Apoe*^{-/-} mice) that the increase in pressure renders aortic sinus lesions from mice with greater lipid deposition (Oil Red O; $P < 0.05$) and macrophage content (CD68; $P < 0.05$) compared to *Apoe*^{-/-} mice, indicative of reduced plaque stability. We conclude that high intraluminal pressure induces vascular inflammation by promoting caveolae flattening, NADPH oxidase dependent ROS production and NFκB translocation, which all contribute to endothelial activation, adhesion molecule expression and enhanced leukocyte adhesion leading to increased plaque instability.

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Curriculum Vitae

Prof. Jaye Chin-Dusting is an Executive Director of the Baker IDI Heart and Diabetes Institute, Melbourne Australia. She is Domain Leader of the Vascular Division, and Head of the Vascular Pharmacology Lab. Elsewhere she is President of the High Blood Pressure Research Council of Australia and a Monash Uni Faculty of Medicine Adjunct Professor. As well, she is a Visiting Professorial Fellow at the University of New South Wales and a Visiting Professor at UCSI University, Kuala Lumpur Malaysia. She sits on the Research Degrees Committee at Monash University and is on the Advisory Board of ARIN, a Victorian State Government initiative on platform technologies. Her total career publication output numbers over 130 and she has published over 20 invited reviews including in Nature Reviews Drug Discovery. She has trained over 15 PhDs, 20 BSc Hons and 9 Post-doctoral Fellows. Prof Chin-Dusting's research is aimed at developing new approaches for halting the progression of early vascular disorders into coronary artery disease (CAD). Recognising that vascular inflammation is fundamental to the development of these conditions, Prof Chin-Dusting studies the complex and dynamic interaction involving the attachment of monocytes to the endothelium, and their recruitment into blood vessels where they differentiate into macrophages.