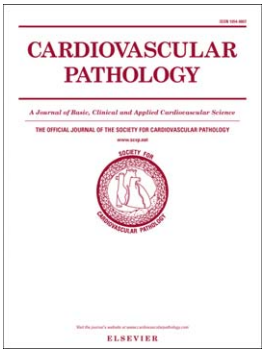

Aortic Calcified Particles Modulate Valvular Endothelial and Interstitial Cells

Nicole C.A. van Engeland, Sergio Bertazzo, Padmini Sarathchandra, Ann McCormack, Carlijn V.C. Bouten, Magdi H Yacoub, Adrian H Chester, Najma Latif

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Running title: Aortic Calcified Particles Modulate Valvular Cells

Nicole C.A. van Engeland[1,2], MSc, Sergio Bertazzo[3], PhD, Padmini Sarathchandra[1], PhD, Ann McCormack[1], BSc, Carlijn V.C. Bouten[2], PhD, Magdi H Yacoub[1], FRCS, Adrian H Chester[1], PhD and Najma Latif[1], PhD

Imperial College London[1], Heart Science Centre, Harefield Hospital, Harefield, Middlesex UB9 6JH, UK, Eindhoven University of Technology[2], Department of Biomedical Engineering and Institute for Complex Molecular Systems, 5600 MB Eindhoven, the Netherlands; University College London[3], Department of Medical Physics & Biomedical Engineering, Malet Place Engineering Building, London WC1E 6BT, UK

Address for correspondence:
N Latif, Imperial College, Heart Science Centre, Harefield Hospital, Harefield, Middx. UB9 6JH
Tel no: 0044 1895 453846
E-mail: n.latif@imperial.ac.uk
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Abstract

Background: Normal and calcified human valve cusps, coronary arteries and aortae harbour spherical calcium phosphate micro-particles of the identical composition and crystallinity and their role remains unknown. Objective: Examining the direct effects of isolated calcified particles on human valvular cells. Method and Results: Calcified particles were isolated from healthy and diseased aortae, characterized, quantitated and applied to valvular endothelial cells (VECs) and interstitial cells (VICs). Cell differentiation, viability and proliferation were analysed. Particles were heterogeneous differing in size and shape and were crystallized as calcium phosphate. Diseased donors had significantly more calcified particles compared to healthy donors ($p<0.05$) but there were no differences between the composition of the particles from healthy and diseased donors. VECs treated with calcified particles showed a significant decrease in CD31, VE-cadherin and an increase in von Willebrand Factor (vWF) expression, $p<0.05$. There was a significant increase in α-SMA and osteopontin in treated VICs ($p<0.05$), significantly decreased VEC and VIC viability ($p<0.05$) and significantly increased number of TUNEL positive VECs ($p<0.05$) indicating apoptosis when treated with the calcified particles. Conclusions: Isolated calcified particles from human aortae are not innocent bystanders but induce a phenotypical and pathological change of VECs and VICs characteristic of activated and pathological cells. Therapy tailored to reduce these calcified particles should be investigated.