Cardiac remodelling contributes to altered ventricular mechanics in hypertensive cardiomyopathy

A.P. Pope, B.H. Smaill and I.J. LeGrice, Department of Physiology/Bioengineering Institute, University of Auckland, Private Bag 92019 Auckland, New Zealand

The complex organisation of cells and extracellular matrix (ECM) contributes to the diastolic properties of the heart. Remodelling of these structures is a significant feature of cardiovascular diseases such as hypertension and heart failure. The change in the content and organisation of ECM collagen is an important aspect of this remodelling because of the role collagen plays in interconnecting cells and limiting cellular movement during passive filling. The objective of this study was to characterise the differences in 3D collagen organisation in normal and diseased hearts and to link these differences to changes in diastolic function.

Ventricular structure and function measurements were made in Spontaneously Hypertensive rats (SHR) and Wistar-Kyoto (WKY) controls at 12 months. Geometry measurements were made using M-mode echocardiography and systolic blood pressure was measured prior to removal of the hearts. The passive left ventricular (LV) pressure-volume (PV) relationship was characterised for each heart by inflating an LV balloon to a pressure of 30 mmHg. Two hearts from each group were perfused with picrosirius red dye via the coronary circulation to stain collagen. Samples from these hearts were resin embedded and imaged using a novel high throughput confocal microscope facility. Imaged blocks were typically 2mm $\times$ 0.5mm $\times$ 0.3mm with 1μm voxel dimension.

In vivo measurements confirmed that the SHRs were both hypertensive (SHR 152.4mmHg ± 7.7mmHg (n=8), WKY 117.6mmHg±3.8mmHg (n=9), P=0.001) and their hearts were hypertrophic (Posterior LV wall thickness: SHR 3.24mm ± 0.24mm (n=6), WKY 2.47mm±0.23mm (n=7), P=0.042). Active ventricular function was reduced in the SHR group with fractional shortening at 74.7%± 4.6% (n=6) compared to 61.1%±4.7 % (n=7) in the WKY group (P=0.07). The mean LV PV curve for the SHR group was shifted leftward with respect to control. LV stiffness ($\Delta P/\Delta V$) was greater in SHR than in WKY at pressures throughout the range 4 to 28mmHg (P&lt0.05:;SHR n=8, WKY n=9).

In WKY blocks, perimysial collagen fibres grouped cells into layers and branched across spaces between the layers whereas the layers in SHR blocks were tightly approximated and there were dense planes of collagen separating them. Furthermore, the epimysial collagen mesh was more obvious in the SHR blocks and both pericellular and perivascular collagen were substantially greater with some regions of cellular necrosis evident.

We believe that these differences in myocardial organisation are responsible for differences in both local and global passive mechanical function. The increased ECM around cells and layers will change cell-to-cell mechanical coupling and limit the ability of myocardial layers to shear relative to each other, likewise increased epimysial collagen will limit ventricular expansion. Additionally, dense collagen around both vessels and individual cells may impair diffusion of oxygen and metabolites and lead to tissue necrosis and scar formation. These changes in local mechanical properties are very likely to be the cause of the reduced ventricular compliance in SHR hearts as compared to WKY and will subsequently result in impaired diastolic function in the diseased hearts.