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Computational modelling of metabolism within the ageing heart

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Age is one of the most significant risk factors for cardiovascular disease. Understanding the biochemical mechanisms underlying ageing, particularly in humans, may facilitate the discovery of new interventions to help us stay healthy as we grow older.

The Sydney Heart Bank is a collection of high-quality human donor heart tissue. Proteomic and metabolomic data of young (≤25 years) and old (≥50 years) hearts have been collected. Informed by this data, we developed a computational model of oxidative phosphorylation within cardiomyocytes to compare the function of old hearts compared to young hearts.

Statistical analyses showed that nicotinamide adenine dinucleotide (NAD) and reduced NAD (NADH) were upregulated in the older cohort relative to the young, whereas creatine was downregulated in the older cohort. Through applying the changes in NAD and NADH abundance, the computational model predicted that in older cardiomyocytes, the phosphocreatine (PCr) to adenosine triphosphate (ATP) ratio could be maintained at higher workloads. However, applying the observed changes in creatine abundance led to a lower PCr/ATP ratio in older cardiomyocytes.

Our results suggest that the increased abundance of NAD and NADH may be protective against heart failure in older people. However, these are offset by the effects of reduced creatine, suggesting that the changes to NAD and NADH could potentially be compensating for the detrimental effects of creatine. While further investigation is needed to confirm these findings, this study is a first step towards using computational and biophysical modelling to make sense of human heart omics data.