Scaffolding domains in cardiac aging: Does caveolin-3 govern age-dependent stress-intolerance?

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The aged heart is more susceptible to stress and refractory to interventions that protect against ischaemic or hypoxic injury in young hearts. We hypothesized that age-dependent dysfunction in myocardial stress-signaling and metabolic flexibility involves repressed 'scaffold' co-ordination of cellular signalling. We specifically examined the contribution of caveolin-3 (Cav-3), an integral scaffolding protein, to cardiac ischaemic tolerance in young to aged mice. We first undertook detailed assessment of age-dependent ischaemic intolerance in male C57BL/6 mice aged 8, 16, 32 and 48 weeks of age. Animals were anaesthetized with Inactin (70mg/kg body weight, i.p.), and on confirmation of a surgical plane of anaesthesia, hearts were removed, the aorta cannulated and hearts perfused in a Langendorff mode with an intraventricular balloon for assessment of contractile function. The hearts were then subjected to 20 minutes of ischaemia followed by 45 minutes of reperfusion. Male mice at 8-weeks of age recovered ~55% of pre-ischaemic function, with significantly elevated diastolic pressure (~19mmHg) and evidence of cell death (~5.4µg/g cardiac Troponin release). While recovery in hearts of males aged 16 weeks was not statistically different hearts from mice aged 32 and 48 weeks displayed significant depression of intrinsic resistance to ischemia-reperfusion injury (recovery of contractile function reduced to ~40% of pre-ischaemic function, diastolic pressure increased to ~38mmHg, and troponin release increased to ~8.8µg/g). RNA extracted from non-ischaemic hearts revealed a decrease in baseline expression of Cav-3 that was evident by 48-weeks of age (relative to 8-week heart 0.35). Proteomic analysis revealed ~50% lower Cav-3 protein at ~2 years of age and near complete loss of caveolar morphology. We also examined Cav-3 dependent protective responses (ischaemic preconditioning, adenosine receptor agonism) in young and aged hearts, and determined that these were negated in older hearts. Hearts from young (3 month) and aged (18 month) mice overexpressing Cav-3 (TG) were found to be more tolerant of ischaemic insult: in young wild-type (WT) littermates, cardiac contractile recovery from ischaemia was 47% of pre-ischaemic function (with diastolic pressure elevated to 35mmHg), while recovery of contractile and diastolic function was impaired in aged WT hearts (21% and 58mmHg, respectively); Cav-3 TG hearts were significantly protected, with diastolic dysfunction reduced to 22mmHg in young TG mice and 32mmHg in aged TG mice, while ventricular pressure development recovered to 60-65% of baseline in young and aged TG hearts. These data reveal a parallel decline in cardiac ischemic tolerance and Cav-3 expression, and indicate that augmenting Cav-3 expression can eliminate age-related ischemic intolerance. Therapies to drive Cav-3 expression in the heart may be a novel means to limit cardiac aging.