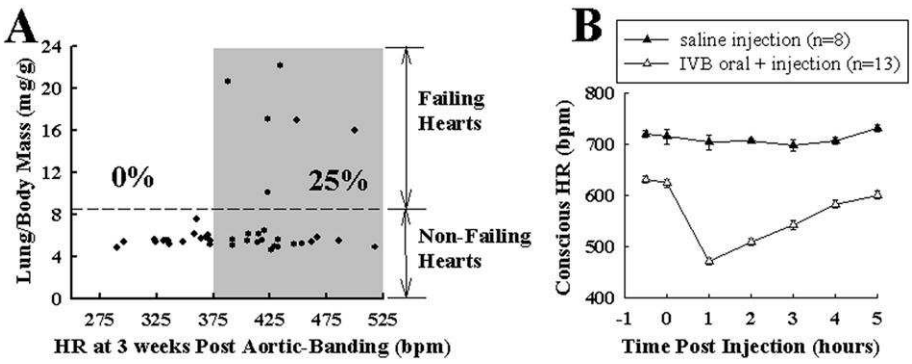
Heart rate is related to the risk of heart failure in pressure-overload mice

H. Kiriazis, X.M. Gao, K. Wang, A.M. Dart, X.J. Du, Baker Heart Research Institute, Melbourne, Vic, Australia

An increased heart rate (HR) at rest has been identified as an independent contributor to the risk of heart failure in persons with hypertension. This points to potential therapeutic benefits of HR reduction in hypertension, however, this has not been directly tested. Using a mouse model of long-term pressure overload, surgically induced by banding the aorta, we firstly examined whether HR plays a role in the development of heart failure in mice which would provide a model to further investigate the potential benefits of HR reduction. Mice were anaesthetised with ketamine/xylazine/atropine (10/2/0.12mg/100g, respectively, i.p.) and a band was placed around the aorta to induced a pressure overload. Animals were followed for 17 weeks post-surgery with HR assessed from periodic echocardiography examinations. At the final time-point, a Millar catheter was used to determine blood pressure in anaesthetised mice (6mg pentobarbitone/0.12mg atropine per 100g, i.p.). Systolic arterial pressure and pulse pressure were elevated in aortic-banded versus sham-operated mice (159±4 vs 116±3 and 88±3 vs 34±2 mmHg, respectively; $p<0.001$ for both). At termination of the catheter experiment, the chest cavity of the anaesthetised animal was opened allowing examination and organ retrieval. Mice with pleural effusion, left atrial thrombus and lung congestion (with increased lung mass) were considered to be in heart failure. Figure A shows a plot of lung/body mass ratio at autopsy and anaesthetised heart rate at 3 weeks (prior to the development of heart failure).



Aortic-banded mice with heart rates greater than 375 bpm had an increased incidence of heart failure, suggesting that lowering heart rate would be beneficial in pressure overload. We are currently investigating the effects of heart rate reduction using Ivabradine (IVB), which selectively reduces heart rate in humans and laboratory animals. Aortic-banded mice on oral IVB (~12mg/kg/day via drinking water) and daily supplemental s.c. injections of IVB (10mg/kg) have ~15-20% lower HR compared to untreated aortic-banded mice (Figure B). An improved prognosis in the IVB treatment group would add support towards incorporating a reduction in heart rate as an important part of a treatment regime for hypertensive patients.

Work funded, in part, from The Alfred Research Trusts