**INTRODUCTION AND AIM**
Cardiovascular complications are the leading cause of diabetes-related morbidity and mortality characterized by structural and functional abnormalities of the myocardium. However, there is a lack of translational and robust animal models of diabetic cardiomyopathy that can aid elucidation of mechanisms of action, and support the development of improved therapeutic agents. Here, we hypothesized that surgically induced diabetes (pancreatectomy) and pharmacological (isoprenaline) driven cardiac stress could accentuate cardiac remodelling and dysfunction resulting in a useful rat model for pre-clinical investigations.

**STUDY DESIGN AND GROUPS**

![Graph](image)

**RESULTS**

**Figure 2** | Daily body weight (left panel) and weekly blood glucose (right panel). Px rats were considered diabetic and included in study if non-fasted blood glucose was ≥14 mmol/L, within 14 days after surgery (one rat was excluded). Data are mean ± SEM. n=12-18.

**Figure 3** | Absolute total length (left panel) and left ventricular weight relative to body weight (right panel). Data are mean ± SEM. Two-way ANOVA (p>0.05 vs sham) with Sidak’s post hoc test; **p<0.001 vs sham-vehicle; #p<0.05 vs sham-iso. n=8-18.

**Figure 4** | R-R interval measured immediately before and after first isoprenaline dose (left panel). Measurement of R-R interval (right panel). Data are mean ± SEM. Two-way ANOVA with Sidak’s post hoc test; **p<0.001, ***p<0.001 vs Sham-vehicle; #p<0.05, ##p<0.001 vs Sham-iso. n=7-8.

**Figure 5** | Cardiac function was examined with a Philips IE33 ultrasonograph and a 12.4-MHz sector transducer. Two-dimensionally guided M-mode of the left ventricle (LV) was taken at the papillary muscle level (A, B). Two-dimensionally guided early LV filling was measured by transmitted pulsatile wave Doppler (C, D).

**Gene expression levels indicate pancreatectomy-driven hypertrophy and decreased contractility**

**Figure 6** | Relative left ventricular (LV) end-diastolic and -isovolumetric diameter (EDD, ESD) (upper panel). Ejection fraction (EF) and early LV filling in diastole (E) (lower panel). Two-way ANOVA with Sidak’s post hoc analysis; **p<0.001 vs sham-vehicle, #p<0.01, ##p<0.001 vs sham-iso, #p<0.05, ###p<0.001 vs Pax-vehicle. n=12-18.

**Figure 7** | Left ventricular gene expression levels of alpha- and beta-myosin heavy chains (MHC) (left panel) and glucose transporter type 4 (GLUT-4, right panel). Data are mean ± SEM. Two-way ANOVA with Sidak’s post hoc analysis; **p<0.001 vs sham-vehicle, ***p<0.001 vs sham-iso.

**Figure 8** | Left ventricular collagen stained by picro-sirius red (upper panel) with quantification of collagen area fraction (lower panel). Data are expressed as mean ± SEM. Two-way ANOVA with Sidak’s post hoc analysis; **p<0.001 vs sham-vehicle, ###p<0.001 vs sham-vehicle, *p<0.05 vs sham-vehicle, #p<0.01 vs px-vehicle. n=8-11.

**Mitochondrial function was decreased by pancreatectomy and isoprenaline treatment**

**Figure 9** | Mitochondrial function (oxygen consumption) measured using high-resolution respirometry. Saponin-permeabilized muscle fiber bundles of the left ventricle were prepared and respiration was measured using substrate-uncoupler-inhibitor titrations. Data are expressed as mean ± SEM. Two-way ANOVA with Sidak’s post hoc analysis; **p<0.05, ***p<0.001, ###p<0.001 vs sham-vehicle, p<0.05 vs sham-iso, p<0.01 vs sham-vehicle, #p<0.05 vs sham-iso, ##p<0.01 vs px-vehicle, $p<0.05 vs px-vehicle. n=6-8.

**CONCLUSION**
The combination of pancreatectomy with isoprenaline treatment exhibited several clinical hallmarks of diabetic cardiomyopathy, including:

- Pronounced hyperglycaemia
- Endomyocardial fibrosis
- Decreased left ventricular contractility and ejection fraction
- Mitochondrial dysfunction (pancreatectomy at isoprenaline)
- Regulation of genes indicative of heart failure and hypertrophy

This model may be useful in the evaluation of cardiovascular effects of novel compounds in the pre-clinical phase of drug development.