Investigating the Effects of Advanced-Stage Pancreatic Ductal Adenocarcinoma on Cardiovascular Function and Cardiac Structure in Patient-Derived Xenograft Mice

Amelia R. Malicki[1], Leslie M. Ogilvie[1], Aditya Brahmbhatt[2], Alexa N. King[1], Bridget Coyle-Asbil[1], Patrick Sanosa[1], Jana Michaud[1], Praveen Bhoopathi[3], Vignesh Vudatha[4], Jose G. Trevino[4], Christopher G. R. Perry[2], Keith R. Brunt[5] and Jeremy A. Simpson[1]

[1]Department of Human Health and Nutritional Sciences, College of Biological Science, University of Guelph. [2]School of Kinesiology & Health Science, Muscle Health Research Centre, York University. [3]Department of Human and Molecular Genetics, Virginia Commonwealth University. [4]Department of Surgery, Virginia Commonwealth University. [5]Department of Pharmacology, Faculty of Medicine, Dalhousie University.

Introduction

While chemotherapy is a known contributor to cardiotoxicity, the direct effects of advanced pancreatic cancer on cardiovascular function remain unclear. Previous studies in ovarian cancer models show that tumours impair cardiac function and induce hypotension. Furthermore, previous studies on cancer-related effects in skeletal muscle show that muscle weakness precedes atrophy, suggesting that functional impairments may arise independently of muscle mass loss.

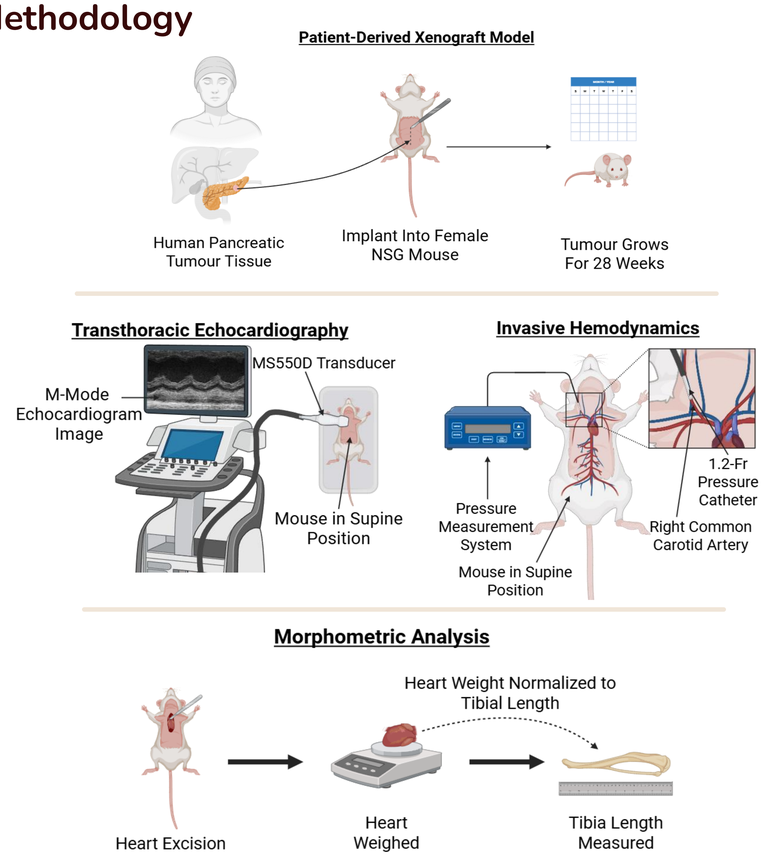
Objective

To determine whether advanced-stage pancreatic ductal adenocarcinoma (PDAC) induces cardiovascular dysfunction independent of cardiac atrophy.

Hypothesis

Mice bearing advanced-stage PDAC tumours would exhibit impaired cardiac function and systemic hypotension, without reduced heart weights.

Methodology



Decreased Cardiac Dimensions Reflect Geometric and Volumetric Remodeling

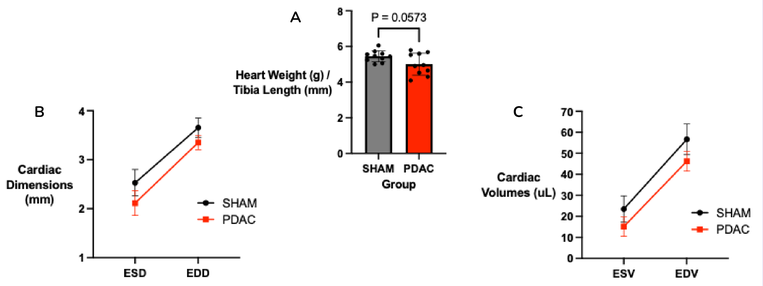


Figure 1. Advanced-stage PDAC induces geometric and volumetric remodeling without gross cardiac atrophy. (A) Heart weight was maintained in PDAC mice compared to sham, indicating no cardiac atrophy. (B) End-systolic (ESD) and end-diastolic dimensions (EDD) were significantly reduced in PDAC mice, reflecting geometric remodeling. (C) End-systolic (ESV) and end-diastolic volumes (EDV) were significantly decreased, consistent with volumetric remodeling and smaller ventricular chamber size. Data are presented as mean ± SD. Statistical analysis was performed using an unpaired t-test.

Preserved Ejection Fraction and Cardiac Output

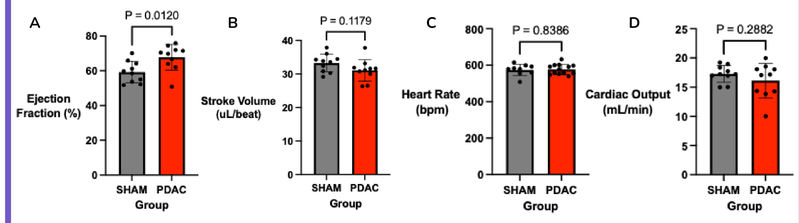


Figure 2. Preserved ejection fraction and cardiac output in advanced-stage PDAC mice. (A) Ejection fraction did not decrease in PDAC mice, further suggesting compensatory left ventricular remodeling during late-stage disease. (B) Stroke volume, (C) heart rate, and (D) cardiac output were maintained, demonstrating preserved circulatory output despite evidence of intrinsic contractile dysfunction (see Figure 3). Data are presented as mean ± SD. Statistical analysis was performed using an unpaired t-test.

Decreased Contractility Despite Preserved Cardiac Output

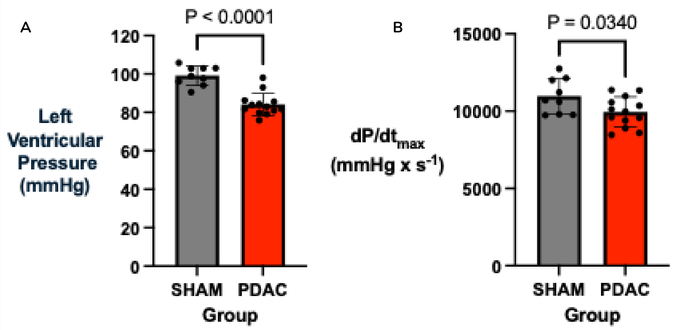


Figure 3. Intrinsic myocardial contractile dysfunction in advanced-stage PDAC mice. (A) Left ventricular pressure was significantly reduced in PDAC mice compared to sham. (B) Maximal rate of pressure development (dP/dt max) was also significantly decreased, indicating impaired intrinsic myocardial contractility. These findings reveal subclinical cardiac dysfunction despite preserved circulatory output (see Figure 2). Data are presented as mean ± SD. Statistical analysis was performed using an unpaired t-test.

Decreased Systemic Blood Pressure

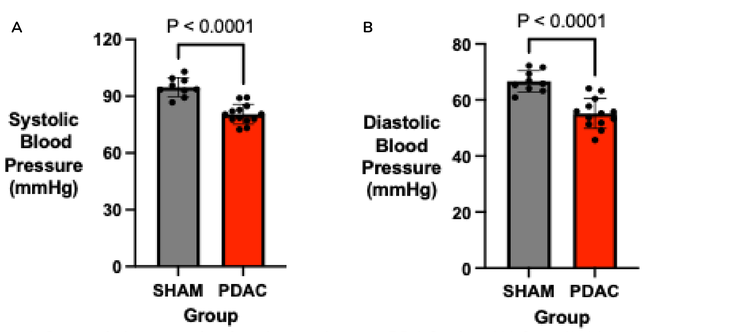


Figure 4. Systemic hypotension in advanced-stage PDAC mice. (A) Systolic blood pressure and (B) diastolic blood pressure were decreased in PDAC mice compared to sham. These findings suggest systemic hemodynamic alterations during late-stage disease. Data are presented as mean ± SD. Statistical analysis was performed using an unpaired t-test.

Conclusion

- Advanced-stage PDAC in mice induces compensatory geometric and volumetric remodeling of the left ventricle, characterized by reduced end-systolic and end-diastolic dimensions and volumes, without cardiac atrophy. Despite intrinsic myocardial contractile impairment, as shown by reduced left ventricular pressure and dP/dt max, systolic output was preserved, with maintained stroke volume, heart rate, and cardiac output. Ejection fraction was maintained, further suggesting a compensatory response.
- Furthermore, both systolic and diastolic blood pressures were reduced, indicating systemic hypotension.
- Therefore, pancreatic tumors alone — independent of chemotherapy — negatively affect cardiovascular function.
- This highlights the importance of monitoring heart health in cancer patients, investigating long-term cardiovascular risks post cancer, and exploring the underlying mechanisms in future studies.