The C-26 tumour-bearing mouse model of cancer cachexia exhibits cardiac atrophy, systolic and diastolic dysfunction

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Cancer cachexia describes the progressive loss of muscle mass and function that affects ~80% of all cancer patients (Bruera, 1997). Up to one-third of all cancer related deaths are the result of cachexia, with most deaths being attributable to cardiac or respiratory failure (Tan & Fearon, 2008). The cardiac wasting and dysfunction associated with many cancers is referred to as 'cardiac cachexia', and there is currently no effective treatment. Pre-clinical models of cardiac cachexia have not been characterised extensively. We tested the hypothesis that the Colon-26 (C-26) tumour-bearing mouse model of cancer cachexia exhibits cardiac atrophy and dysfunction that makes it a suitable preclinical model of cardiac cachexia.

All experiments were approved by the Animal Ethics Committee of The University of Melbourne and conducted in accordance with the Australian code of practice for the care and use of animals for scientific purposes (NHMRC). Male CD2F1 mice were anaesthetized (ketamine, 100 mg/kg; xylazine, 10 mg/kg, *i.p.*) and given either a subcutaneous injection of phosphate buffered saline (PBS; control) or C-26 cancer cells in their right flank. Mice injected with C-26 cells developed tumours by 7 days. After 3, 7, 14 or 21 days, mice underwent transthoracic 2-dimensional B- and M-mode echocardiography (GE Vivid 9; 15 mHz i13L linear array transducer) to assess heart structure and function. Cardiac geometry was assessed (interventricular septal width, IVS, left ventricular posterior wall thickness, LVPW and left ventricular internal diameter, LVID), along with systolic (fractional shortening, FS and ejection fraction, EF) and diastolic parameters (E/A ratio, E/E' ratio). Following echocardiography mice were anaesthetized deeply with sodium pentobarbitone (Nembutal, 60 mg/kg, *i.p.*) and killed by cardiac excision. The excised hearts were trimmed, weighed and then snap frozen for biochemical analyses (n=6) or fixed in 10% phosphate buffered formalin for staining with Masson's Trichrome (n=6) to assess fibrosis.

Injection of C-26 cells caused tumours that were associated with anorexia and a progressive loss in body, skeletal muscle and fat mass ($P < 0.05$). Heart mass decreased significantly 7 days post C-26 cell injection, and was decreased by 16% after 21 days ($P < 0.05$). Fibrosis within transverse ventricular sections was evident only in tumour-bearing mice at 21 days ($P < 0.05$). Echocardiography revealed significant thinning of ventricular walls with both septal wall thickness (31% decrease) and posterior wall thickness (32% decrease) reduced by day 21 ($P < 0.05$). In addition, a 19% increase in chamber diameter was observed at 21 days ($P < 0.05$) indicating a dilated phenotype in the C-26 tumour-bearing mice. Impairment in systolic function was also evident in C-26 tumour-bearing mice with a 41% decrease in fractional shortening and a progressive decrease in ejection fraction from 14 days, by 35% at day 21 ($P < 0.05$). Diastolic dysfunction was apparent with a 20% increase in E/E' by 21 days ($P < 0.05$).

Our findings reveal the C-26 tumour-bearing mouse exhibits progressive cardiac atrophy, fibrosis and systolic and diastolic dysfunction making it an appropriate preclinical model of cardiac cachexia.

Bruera E. (1997) *BMJ* **315**: 1219-22.
Tan BH & Fearon KC. (2008) *Current Opinion in Clinical Nutrition & Metabolic Care* **11:** 400-7.

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