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Limited regenerative potential of the neonatal porcine heart after myocardial infarction

Authors:
K Malliaras¹, E Polychronopoulou¹, P Poulakida¹, D Sagris¹, K Makaritsis¹, University of Thessaly, School of Medicine - Larissa - Greece,

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Background: Neonatal murine hearts possess, for a brief period after birth, a robust capacity for spontaneous myocardial regeneration following cardiac injury. Whether hearts of neonatal large mammals possess similar regenerative potential is a matter of active investigation. Recently, two studies reported that 1-day-old and 2-day-old neonatal pigs exhibit a significant cardiac regenerative response post-myocardial infarction (MI), characterized by minimal cardiac fibrosis and spontaneous recovery of left ventricular (LV) function; this regenerative capacity is purportedly lost after the first two days of life.

Purpose: We sought to evaluate the regenerative potential of neonatal porcine hearts after MI.

Methods: Twenty-one neonatal farm pigs were randomly assigned to undergo MI by permanent ligation of the left anterior descending artery on postnatal day 1 (P1) or postnatal day 3 (P3). Infarcted P1 and P3 pigs were euthanized either at 1 week or at 7 weeks post-MI. Hearts explanted at 1 week post-MI underwent fluorescent immunohistochemistry for Ki67 and alpha-sarcomeric actinin to quantify myocyte cell cycle re-entry. Transthoracic echocardiography was performed at 7 weeks post-MI to quantify fractional shortening and systolic thickening of the anterior (infarcted) LV wall and the posterior (non-infarcted) LV wall. Hearts explanted at 7 weeks post-MI underwent staining with triphenyl-tetrazolium chloride and Masson’s Trichrome to quantify infarct size, infarct circumference and infarct transmurality.

Results: Fourteen animals successfully completed the protocol. Infarct size (P1: 9.5±2.2% vs P3: 8.9±3.6% of LV, p=0.797), infarct circumference (P1: 33.8±7.1% vs P3: 29.8±10.6% of LV, p=0.566) and infarct transmurality (P1: 38.1±4.3% vs P3: 40.4±13.7% of anterior wall, p=0.764) were comparable in P1 and P3 animals at 7 weeks post-MI. LV fractional shortening (an index of global LV systolic function) was similar in P1 and P3 animals at 7 weeks post-MI (P1: 25.5±2.9% vs P3: 23.7±4.5%, p=0.662). Furthermore, systolic thickening in the anterior (infarcted) LV wall was depressed to a similar degree in P1 and P3 animals (P1: 31.8±5.3% vs P3: 32.3±8.5%, p=0.914) compared to systolic thickening in the posterior (non-infarcted) wall (P1: 72.5±9.0% vs P3: 69.0±11.4%, p=0.666) at 7 weeks post-MI. Myocyte cell cycle re-entry in the infarct border zone was increased in P1 animals compared to P3 animals (P1: 4.5±1.3 vs P3: 2.3±0.6 per field of view, p=0.045) at 1 week post-MI.

Conclusions: In contrast to recently-published reports, we did not observe a robust cardiac regenerative response in neonatal porcine hearts post-MI. Hearts of both 1-day-old and 3-day-old neonatal pigs exhibited substantial scarring and significant hypokinesia of the infarcted myocardium post-MI. Additional research is warranted to assess the cardiac regenerative potential of neonatal large mammals.