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**Lack of macroscopically-evident cardiac regeneration or spontaneous functional recovery in infarcted neonatal pigs**

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**Background:** Neonatal mice possess an impressive - albeit transient - capacity for spontaneous cardiac regeneration following myocardial injury. Whether such robust cardiac regenerative potential is also present in neonatal large mammals has been under-investigated. Recently, two studies reported that 1-day-old and 2-day-old neonatal pigs exhibit a significant spontaneous cardiac regenerative response post-myocardial infarction (MI), characterized by minimal scarring and recovery of left ventricular (LV) function. According to the aforementioned studies, this regenerative capacity is purportedly lost after the first two days of life.

**Purpose:** We sought to investigate the regenerative capacity of neonatal porcine hearts post-MI.

**Methods:** Neonatal farm pigs (n=21) were randomized 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 sacrificed either at 1 week or at 7 weeks post-MI. Hearts explanted at 1 week post-MI underwent 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 was comparable in P1 and P3 animals at 7 weeks post-MI (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 similar in P1 and P3 animals at 7 weeks post-MI. LV function (as assessed by fractional shortening) was comparable 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. P1 animals exhibited significantly increased myocyte cell cycle re-entry compared to P3 animals in the infarct border zone (P1: 4.5±1.3 vs P3: 2.3±0.6 per field of view, p=0.045) at 1 week post-MI.

**Conclusions:** Contrary to recently-published reports, we did not observe robust cardiac regeneration or spontaneous functional recovery in neonatal infarcted pigs. Both 1-day-old and 3-day-old neonatal pigs exhibited substantial cardiac scarring and significant hypokinesia of the infarcted myocardium post-MI. Additional research is warranted to investigate the cardiac regenerative potential of neonatal large mammals.