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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 transmuralty.

Results: Fourteen animals successfully completed the protocol. Infarct size (P1: $9.5 \pm 2.2\%$ vs P3: $8.9 \pm 3.6\%$ of LV, $p=0.797$), infarct circumference (P1: $33.8 \pm 7.1\%$ vs P3: $29.8 \pm 10.6\%$ of LV, $p=0.566$) and infarct transmuralty (P1: $38.1 \pm 4.3\%$ vs P3: $40.4 \pm 13.7\%$ 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: $25.5 \pm 2.9\%$ vs P3: $23.7 \pm 4.5\%$, $p=0.662$). Furthermore, systolic thickening in the anterior (infarcted) LV wall was depressed to a similar degree in P1 and P3 animals (P1: $31.8 \pm 5.3\%$ vs P3: $32.3 \pm 8.5\%$, $p=0.914$) compared to systolic thickening in the posterior (non-infarcted) wall (P1: $72.5 \pm 9.0\%$ vs P3: $69.0 \pm 11.4\%$, $p=0.666$) 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.