PHILADELPHIA ACADEMY OF SURGERY
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Autologous CD117+ Mesenchymal Stem Cell Injections Provide Superior Therapeutic Benefit as compared to CD117+ Cardiac-Derived Stem Cells in a Feline Model of Isoproterenol Induced Cardiomyopathy.

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Intro: Stem cells injected during cardiac surgery or catheterization improves cardiac function after myocardial injury. While most clinical trials have focused on cardiac- (CSC) and mesenchymal-derived (MSC) stem cells, derived from bone marrow, the optimal source of progenitor cells has yet to be determined. This study is the first to compare autologous CD117+ CSC and CD117+ MSC treatment after myocardial injury in a large animal model.

Methods: MSC and CSC were isolated after bone marrow aspiration or thoracotomy and right atrial biopsy of adult felines (day 0). After recovery (day 28), cardiomyopathy was induced by infusion of L-isoproterenol (1100 ug/kg/hr) from Alzet minipumps for 10 days. Bromodeoxyuridine (BrdU) was infused during the injury phase (starting day 31) via minipumps (50 mg/ml) for pulse-chase labeling of proliferative cells. Following injury (day 38), 1 x 10^6 autologous CSC (n=7) or MSC (n=4) were delivered by intracoronary injection and aortic root occlusion for 10 seconds via balloon catheter inserted by carotid cut down. These animals were compared to those receiving atrial surgery (n=5) or bone marrow aspiration (n=6) followed by sham injections of saline. Echo was done at baseline, after injury, and at sacrifice. Animals were euthanized after invasive hemodynamics at day 66. Collagen deposition and BrdU+ cells were quantified by immunohistochemistry.

Results: Fractional shortening improved for both CSC (26.9±1.1% vs. 16.1±0.2%, p=0.01) and MSC (25.1±0.2% vs. 12.1±0.5%, p=0.01) as compared to shams. MSC were superior to CSC in improving left ventricle end-diastolic (LVED) volume (37.7±3.1% vs. 19.9±9.4%, p=0.03) and ejection fraction (27.7±0.1% vs. 19.9±0.4%, p=0.02). MSC therapy resulted in greater improvement in peak positive change in pressure over time (dp/dt) (figure). LVED pressure was lower in the MSC group (6.3±1.3 mm HG) as compared to CSC (9.3±0.7 mm HG) or sham (13.3±0.7); p=0.01. MSC treated animals had less LV

hypertrophy than CSC as measured by heart weight/tibia length ratio (1.36±0.12 vs. 1.71±0.23, p=0.02). More BrdU+ LV myocytes were observed in MSC animals (0.17±0.03%) than in CSC (0.09±0.01%) or sham (0.06±01%); p<0.001. In addition, percent collagen was lower in MSC (13.1±1.4%) than in CSC (20.1±1.7%) or sham (29.4±2.4%); p<0.001.

Conclusion: Both CD117+ CSC and MSC therapy improve cardiac function and attenuate pathological remodeling. MSC therapy demonstrated greater functional improvement relative to CSC with reduced LV replacement fibrosis. In addition, MSC treatment was associated with a higher percentage of BrdU+ myocytes, suggesting a greater degree of new myocyte formation.