Quantifying Therapeutic Agent Retention in The Heart: A Review of Three Delivery Modalities for Three Cell Types

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Background

Pharmacokinetics of locally delivered biologic therapies is characterized by local tissue distribution over time and is likely to vary as a function of delivery methodology, target tissue, and agent physiochemical properties. Our group developed the Helix™ Transendocardial Delivery System to provide for safe and routine interstitial intramyocardial delivery in the beating heart transendocardially. Quantifying delivery efficiency by measuring retention is deemed to be critical to understanding the effective dosages delivered with different delivery platforms. Here, we present retention and biodistribution of Bone Marrow Mononuclear Cells[1] (BM MNC) and Bone Marrow Derived Mesenchymal Cells[2] (BM MSC) with ^{18}F-FDG PET imaging techniques and similarly, retention and biodistribution of Adipose Derived Regenerative Cells[3] (ADRCs) using BioPAL neutron activation assays for isotope-labeled microspheres.

Experiments

Three sets of experiments were performed, each with one cell type and specific methodologies:

- Healthy swine were used
- Analysis was performed an hour after the last injection
- ***Cell Types:***
  1) Bone Marrow Derived Mesenchymal Cells (BM MSC),
  2) Bone Marrow Mononuclear Cells (BM MNC) and
  3) Adipose Derived Regenerative Cells (ADRCs)
- ***Delivery Modalities:***

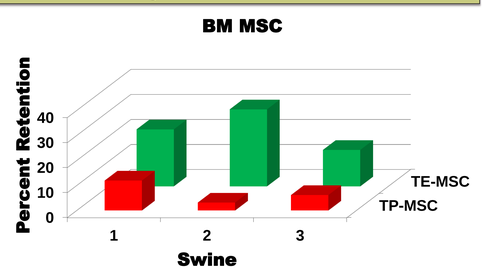
  A) Intracoronary infusion (IC) using an over-the-wire angioplasty balloon catheter,

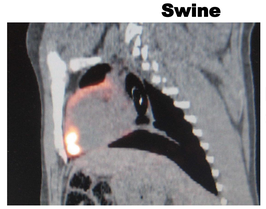
  B) Straight needle transepicardial delivery (TP) using an angled 27G needle and syringe,

  C) Transendocardial intramyocardial delivery (TE) using the Helix Transendocardial Delivery System.

Bone Marrow Mesenchymal Cells

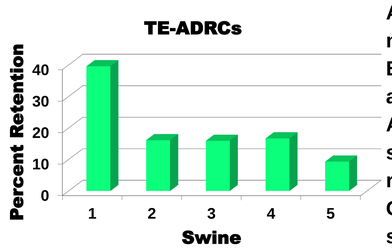
BM MSC were cultured, labeled with ^{18}F-FDG and injected in the animals using TE or TP. Just after the last injection, the animals underwent PET-CT scans and acquisition proceeded at one, four and six hours. Data at one hour are presented here.
Each acquisition produced images for both PET scan and CT scan. Both images are overlaid to ensure correct localization of the injections. Signals were pooled (heart versus rest of the body) to yield the retention rate.





Example of PET-CT overlay

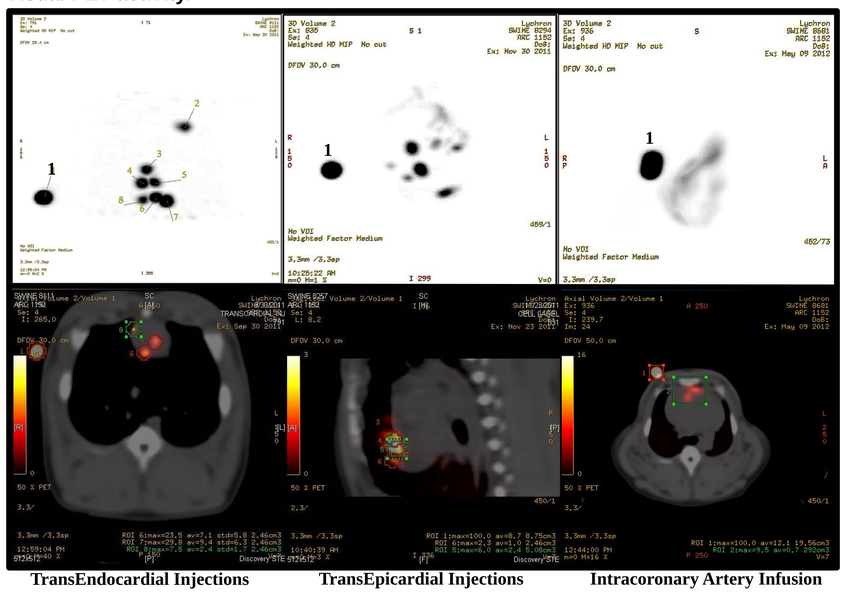
Adipose Derived Regenerative Cells



ADRCs were prepared, labeled with neutron activated particles according to Biopal procedures, and injected into the animals.
After the last injection, the animals were sacrificed and various organs were removed for sampling.
Organs were dissected, placed in vials and sent for neutron activation analysis.

Bone Marrow Mononuclear Cells

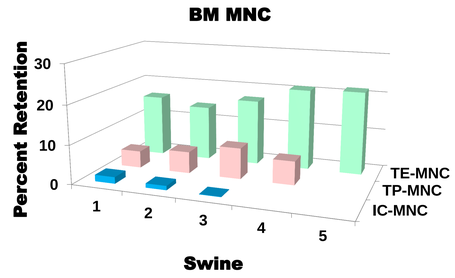
BM MNC were purified using Ficoll density gradient centrifugation, labeled with ^{18}F-FDG and injected via IC, TP or TE. After the last injection, PET-CT scans were acquired and processed using GE Advanced Windows Workstation (AW) Software, Version 4.4. A 3D Maximum Intensity Projection (MIP), PET, CT, and fused PET/CT images were viewed and volumetric regions of interest (ROI's) were placed over injection sites and over the control to obtain maximum and average percentage of counts. The threshold intensity was set to include the full injection volume, including any injection demonstrating the smallest visual activity, but not extended beyond the visual PET activity.



TransEndocardial Injections | TransEpicardial Injections | Intracoronary Artery Infusion

Top row: 1: Control (100µL of ^{18}F-FDG labeled BMMNCs in a microcentrifuge tube taped on the right side of the chest of the swine), 2: cardiac lymphatic node, 3-8: injections in the myocardium of the left ventricle. The PET-CT signals for the injections were calculated relative to the control marked as 100% to account for the decay of the radioisotope and the cell volume retention was thus calculated.
Bottom row: Cardiac PET-CT signals after TE, TP and IC in swine. The signals as they appear after the PET-CT scans are shown. Each injection site is identified and the region of interest (ROI) is drawn around each site. The percent max, average and the volume of the ROI are recorded and the percent retention is calculated relative to a positive control on the left of the image which is equivalent to 100%.

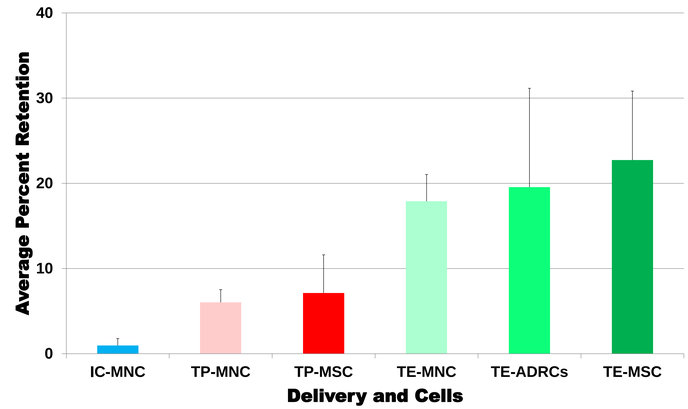
Bone Marrow Mononuclear Cells



In healthy swine, approximately 3 times more cells were retained after transendocardial intramyocardial injections (~18%) compared to transepicardial intramyocardial injections (~6%).

Intracoronary artery infusion led to retention rates of ~1%, lower than both transendocardial and transepicardial intramyocardial delivery.

Combined Results



Average combined percent retention + s.d. of all IC, TP, and TE per swine

- Helix TE delivery resulted in 23%, 20%, and 18% retention in the beating heart of swine for BM MSC, ADRCs and BM MNC, respectively. TP delivery resulted in 7% retention for BM MSC and 6% retention for BM MNC, while IC artery infusion resulted in 1% retention for BM MNC.

Conclusions

It is hypothesized that the reason for improved retention with Helix TE delivery versus TP delivery is due to the stability of the Helix in the beating heart, the longer helical pathway into the tissue, and the potential for this helical pathway to be self-sealing during systole. These are believed to significantly reduce or even eliminate back leak which has been repeatedly reported in TP deliveries and TE deliveries with straight needle systems. This hypothesis of improved efficiency is supported by the common differences shown for larger cells. Strong conclusions are limited by the lack of randomization and the use of different experimental techniques. Other studies have reported similar efficiency differences between TP and IC delivery.

References

1 Wong Po Foo C, International Conference on Cell Therapy for Cardiovascular Disease, NYC, January 2013, 18F-FDG labeled cells.
2 Cardio3 Biosciences, Report R-C3BS-PC-07-1c Version 1.0, dated December 3, 2007, 18F-FDG labeled cells.
3 Perin E, 10th International Symposium on Cell Therapy and Cardiovascular Innovations, Madrid, Spain, June 2013, Madrid 2013. Biopal labeled cells