PET of cardiac transgene expression: comparison of 2 approaches based on herpesviral thymidine kinase reporter gene.

Abstract:

PET of reporter gene expression holds promise for noninvasive monitoring of gene therapy. Previously, 2 approaches based on the herpes simplex virus type 1 thymidine kinase gene (HSV1-tk) have been successfully applied to the heart. Wild-type HSV1-tk was imaged with (124)I-labeled 2’-fluoro-2’-deoxy-5-iodo-1-beta-D-arabinofuranosyl-5-iodouracil (FIAU), and a mutant HSV1-tk (HSV1-sr39tk) was imaged with (18)F-labeled 9-[4-fluoro-3-(hydroxymethyl)butyl]guanine (FHBG). The aim of this study was to compare these 2 combinations with regard to specificity, imaging contrast, and reporter probe kinetics using dynamic PET in small and large animals. METHODS: Similar titers of adenovirus-expressing wild-type HSV1-tk (Ad(tk)), mutant HSV1-sr39tk (Ad(sr39tk)), or control genes were directly injected into the myocardium of 24 rats and 8 pigs. Two days later, dynamic PET was performed with a clinical scanner during the 120 min after injection of (124)I-FIAU (Ad(tk) animals and controls) or (18)F-FHBG (Ad(sr39tk) animals and controls). Imaging with (13)N-ammonia was performed to identify cardiac regions of interest. RESULTS: In rats, significant cardiac (124)I-FIAU accumulation occurred in images obtained early (10-30 min) after Ad(tk) injection. Because of
tracer washout, however, no difference between Ad(tk)-injected animals and controls was seen in the images obtained later. For (18)F-FHBG, specific myocardial accumulation greater than background levels was detected in Ad(sr39tk)-injected animals at early imaging and, in contrast to (124)I-FIAU accumulation, increased over time until the latest imaging (105-120 min). At maximum, cardiac (18)F-FHBG concentration showed a 4.15 +/- 1.65-fold increase compared with controls (105-120 min), and cardiac (124)I-FIAU concentration reached a maximal increase of 1.34 +/- 0.38-fold compared with controls (10-30 min, P = 0.0014). Global cardiac reporter probe kinetics in rats were confirmed by regional myocardial analysis in pig hearts. Transgene expression was specifically visualized by both approaches. The highest target-to-background ratio of (124)I-FIAU in Ad(tk)-infected pig myocardium was 1.50 +/- 0.20, versus 2.64 +/- 0.49 for (18)F-FHBG in Ad(sr39tk)-infected areas (P = 0.01). In vivo results were confirmed by ex vivo counting and autoradiography. CONCLUSION: Both reporter gene/probe combinations were feasible for noninvasive imaging of cardiac transgene expression in different species. Specific probe kinetics suggest different myocardial handling of pyrimidine (FIAU) and acycloguanosine (FHBG) derivatives. The results favor (18)F-FHBG with mutant HSV1-sr39tk because of continuous accumulation over time and higher imaging contrast.