

ERROR IN PARAMETER ESTIMATES OBTAINED FROM ^{82}Rb /PET STUDIES OF BLOOD-BRAIN BARRIER PERMEABILITY

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Blood-to-brain and blood-to-tumor transport rate constants (K_1) for ^{82}Rb (half-life 76 sec) and plasma water volume per unit mass of brain/tumor tissue (V_p) have been estimated in vivo using dynamic positron emission tomography (PET). The accuracy of these parameter estimates depends upon the accuracy of PET measurements of regional brain/tumor radioactivity and the accuracy of scintillation well detector measurements of whole-blood radioactivity. We have studied the error in parameter estimates through computer simulations and have demonstrated the feasibility of obtaining clinically useful values of K_1 and V_p using ^{82}Rb /PET. A two-compartment model (blood vs brain) for the passive exchange of Rb across the blood-brain barrier (BBB) was employed for parameter estimation, yielding the operational equation:

$$A_m = \int_{T_1}^{T_2} A_m(t) dt = K_1 \int_{T_1}^{T_2} e^{-k_2 t} \int_0^t C_p(u) e^{k_2 u} du dt + \int_{T_1}^{T_2} V_p C_p(t) dt \quad (1)$$

where A_m is brain tissue ^{82}Rb activity ($\mu\text{Ci-min/g}$) measured by PET (i.e., including intravascular label), $C_p(t)$ is instantaneous plasma ^{82}Rb activity ($\mu\text{Ci/ml}$), K_1 is the influx rate constant (ml/min/g), k_2 is the efflux rate constant ($1/\text{min}$) and V_p is plasma water volume (ml/g). T_1 and T_2 are scan beginning and end times. ^{82}Rb , eluted with physiological saline from a $^{82}\text{Sr}/^{82}\text{Rb}$ generator, was administered as a "slow" intravenous bolus or constant intravenous infusion. Serial 30 sec PET scans were acquired over a 7 min period, and radial arterial blood samples were collected every 9 sec using a high-speed peristaltic pump. Blood and brain data were fit to Equation 1 and K_1 , k_2 and V_p estimated using a non-linear regression routine. Preliminary results suggested the range of parameters to be used for subsequent error analysis.

For our error analysis, simulated blood curves were generated for both bolus and constant infusion (CI) protocols for equal injected radioactivity. Theoretical values for A_m were generated for several data sets covering the range of parameters of interest. Noise was added to the brain activity and the model equation solved for K_1 , k_2 and V_p . Percent error was calculated for each parameter, p , as $100 \cdot (\hat{p} - p/p)$, where \hat{p} is the parameter estimate.

For the bolus infusion protocol and a 5% error in A_m , the error in K_1 ranged from -3.4% to 1.3% for $0.01 < K_1 < 0.1$ and from 13% to -3.4% for $0.001 < K_1 < 0.01$. Errors in V_p ranged from -4% to 8% for $0.03 < V_p < 0.08$. Errors in k_2 were extremely large ($> 100\%$) for $k_2 < 0.1$ but were acceptable ($< 15\%$) for $k_2 > 0.1$. The results for a CI protocol were similar to those for the bolus case. Our preliminary data and error analysis demonstrate the feasibility of obtaining influx rate constants and plasma water volumes for both tumor and brain tissue using ^{82}Rb /PET.