194c Transport of Amitriptyline across Capillary Walls in Isolated Rat Hearts

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Measurement of the permeability of capillary walls for a variety of solutes is becoming increasingly important due to rapid advances in the drug delivery area. Here we present an approach to determine the permeability of the capillaries in the heart tissue by using isolated heart experiments. The isolated heart is subjected to a flow of a solution containing amitriptyline, which is a sodium channel blocker. As the drug flows through the heart's vascular system, a part of it traverses the capillary wall and enters the heart tissue space. The drug then crosses the cell wall of the tissue cells and binds to the sodium channels from the cytoplasm side. The blocking of the sodium channels by the drug leaves an imprint in the electrocardiogram. Specifically, the QRS interval, which is a parameter of the electrocardiogram, increases on sodium channel blockage. Thus, the extent of changes in the QRS signal can be used to monitor the drug concentration in the tissue space. Experiments are performed to measure the changes in the QRS interval after exposure to three different concentrations of the drug. Additionally, a mathematical model is developed for the mass transfer in the isolated heart. Two models are developed to describe drug transport in the capillaries: (1) a well-mixed model that assumes the drug concentration in the capillary is not spatially dependent and (2) a dispersion model that assumes the time scale for convection is smaller than the time scale for dispersion. In both of the models, the resistance offered by the capillary is considered to be rate limiting, and the resistance that may be encountered from the cell walls of the cells present in the heart tissue is neglected. This assumption is validated by performing single cell patch-clamp experiments. The experimental data for the dynamic QRS after drug exposure is fit to the mass transfer models to determine the capillary permeability. The results of both the well-mixed and dispersion models suggest a capillary permeability for the heart tissue is about 10^{-8} m/s for amitriptyline.