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Myosin VI as a transporter and an anchor: A model for kinetics of the motor under load PEIYING CHUAN, JAMES SPUDICH, Dept. of Biochemistry, Stanford University, ALEXANDER DUNN, Dept. of Chemical Engineering, Stanford University — Myosin VI is an actin-based motor that is thought to function both as a transporter and an anchor *in vivo*. In an earlier study (Altman et al, *Cell* 2004), inhibition of myosin VI stepping kinetics by load applied using an optical trap was observed at saturating ATP and low ADP concentrations (< 2.5 μM). A simple mechanism whereby the rate of ADP binding increases exponentially with load was proposed. This model predicts that myosin VI functions primarily as an anchor at loads greater than $\sim$0.5 pN under physiological nucleotide conditions, which is potentially inconsistent with its roles *in vivo*. Here we present myosin VI stepping data taken at a variety of applied loads and ADP concentrations, and show that the Altman model only holds at low ADP concentrations. At higher, physiologically relevant ADP concentrations under load we observe dwell times that are an order of magnitude smaller than predicted by the Altman model. We present a modified model in which applied load alters the equilibrium between two myosin VI states with different nucleotide affinities. This new kinetic scheme accurately describes myosin VI behavior at various nucleotide conditions under a large range of loads, and explains how the motor is able to carry out its roles *in vivo*, both as a force-generating transporter and as an anchor.

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