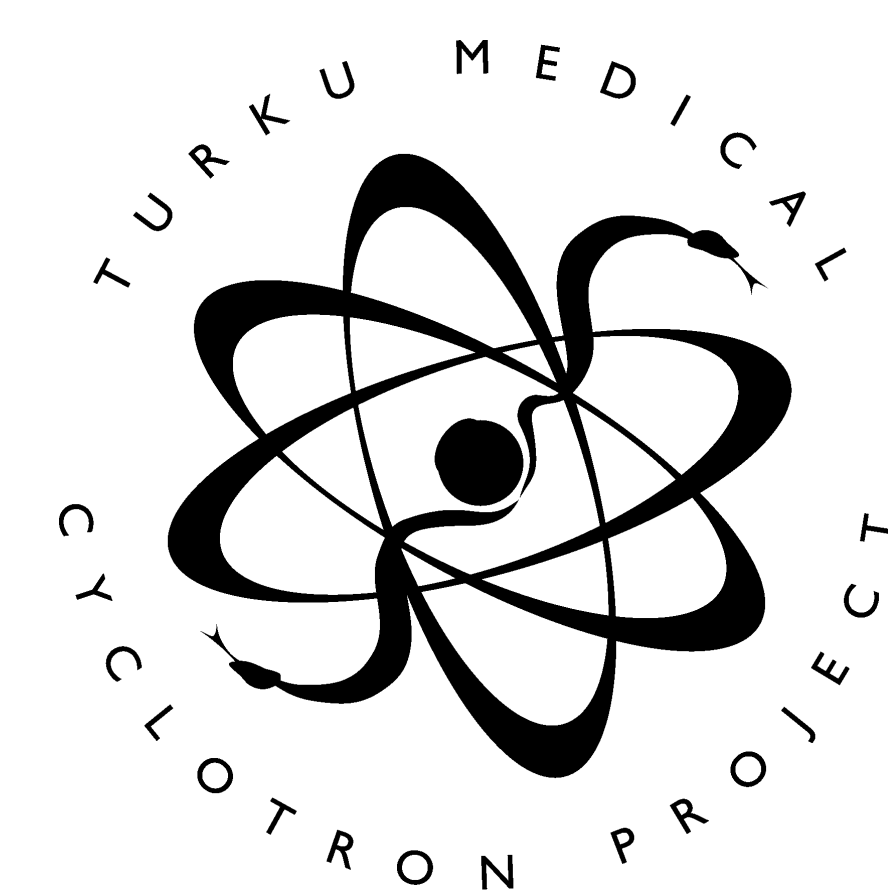


# GLUCOSE UPTAKE IS PERFUSION-INDEPENDENT IN RESTING SKELETAL MUSCLE

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## Aim

It has been proposed that insulin-mediated vasodilation in skeletal muscle could be an important component of glucose disposal, and that an impairment of this mechanism would contribute to the development of insulin resistance. The relations between perfusion and glucose uptake in resting skeletal muscle were studied using positron emission tomography (PET) and [<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG).

## Methods

**PET studies.** Ten healthy men (age 26±1) were studied with FDG PET, five in fasting state and five during an euglycemic hyperinsulinemic clamp (1 mU·(kg body weight)<sup>-1</sup>min<sup>-1</sup>). All subjects fasted overnight prior to the PET studies. FDG (0.15-0.33 GBq) was injected intravenously over 2 min and femoral regions were scanned for 90 min (insulin studies) or 120 min (fasting studies). During hyperinsulinemia, normoglycemia was maintained using variable rate of glucose infusion. An ECAT 931/08 whole-body PET scanner was used for image acquisition. Arterial blood samples were withdrawn during scan time. PET data were analyzed using a four-compartmental model with five rate constants  $k_1$ - $k_5$  and vascular volume fraction  $V_A$  (Bertoldo A *et al. Am J Physiol Endocrinol Metab* 2001;281:E524-E536). The net FDG uptake constant  $K$  was calculated using the estimated model parameters as  $K=k_1k_3k_5/(k_2k_4+k_2k_5+k_3k_5)$ .

**Lumped constant.** The differences between FDG and glucose uptake (lumped constant,  $LC$ ) and the extracellular glucose concentrations were estimated by applying the method and values for difference between FDG and glucose transport and phosphorylation by Bøtker HE *et al. (J Nucl Med* 1999;40: 1186-1196) from the model parameters estimated in the present study.

**Simulations.** The model parameters  $k_1$  and  $k_2$  are both dependent on perfusion ( $f$ ) and the permeability-surface area ( $PS$ ) of capillary endothelium, as  $k_1=f*(1-e^{-PS/f})$ . Because vasodilatation affects perfusion and  $PS$ ,  $k_1$  and  $k_2$  were assumed to be in direct relation to perfusion. The impact of insulin-stimulated perfusion on  $K$  and on the concentration of glucose in extracellular volume was simulated by decreasing or increasing  $k_1$  and  $k_2$ .

## Results

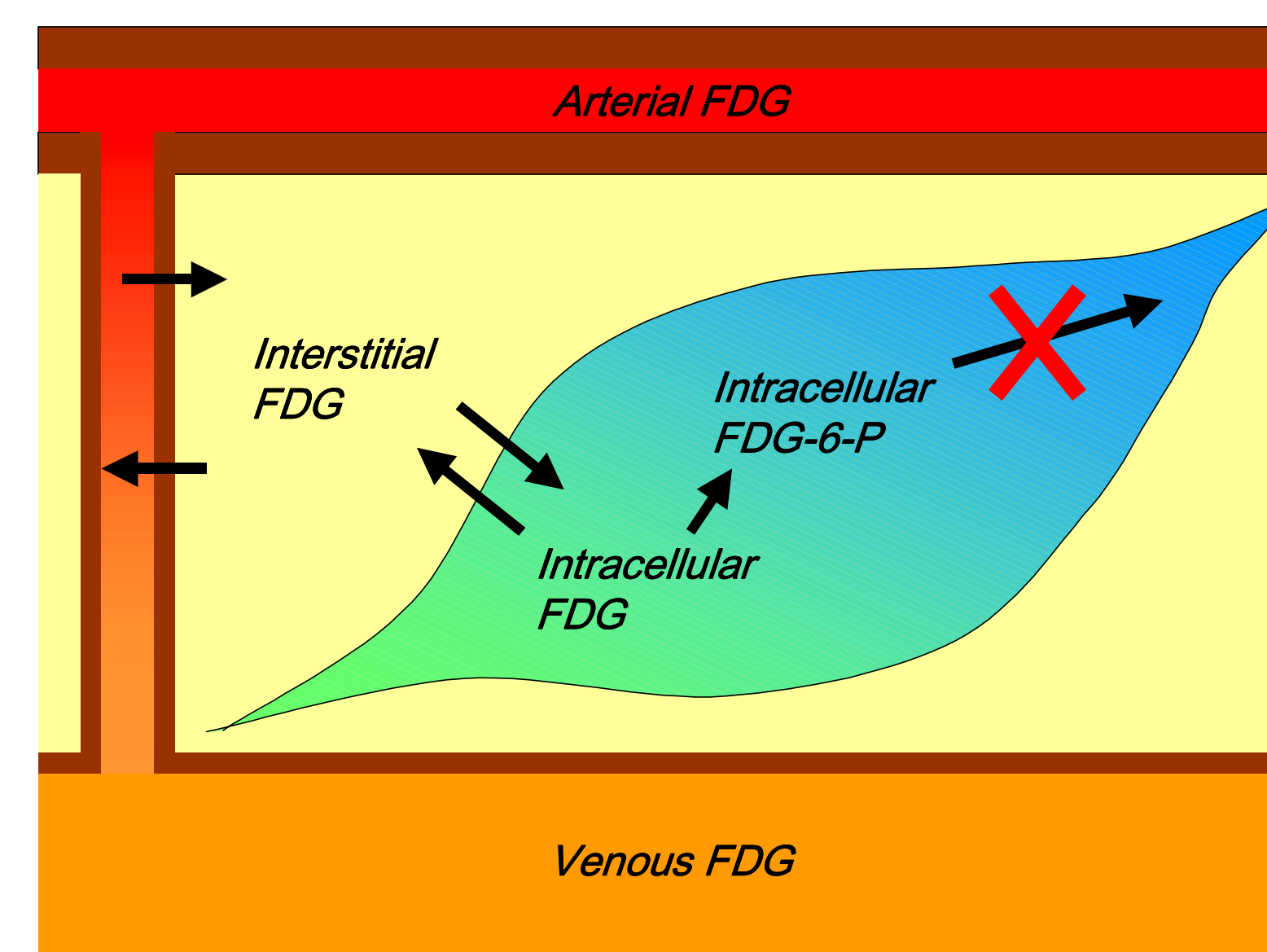
Hyperinsulinemia induced a three-fold increase in FDG transport rate  $k_3$  ( $p=0.010$ ; Table 1) and a six-fold increase in FDG uptake  $K$  ( $p=0.015$ ), but the increase in  $k_1$ , representing mainly change in perfusion, was only 27 % ( $p=0.23$ ). Simulation shows that even if the increase in  $k_1$  observed in insulin studies were totally abolished from  $k_1$  and  $k_2$ , the two perfusion-dependent parameters, the insulin-mediated increase in FDG uptake would still persist (Figure 1).

The effects on FDG and glucose uptake are the same, since in these conditions the estimated  $LC$  was not changed ( $1.08±0.11$  in the fasting state and  $1.10±0.49$  during hyperinsulinemia;  $p=0.95$ ). These  $LC$  values are similar to those found in three recent studies applying different methods (about 1.2).

In Figure 2 the low dependence of glucose uptake on perfusion is further demonstrated by the relatively small difference between arterial and extracellular glucose concentrations even during hyperinsulinemia, and the small impact of abolishing the insulin-mediated perfusion increase.

FDG uptake is less dependent on  $k_1$  and  $k_2$  in the fasting state than during hyperinsulinemia (Figure 3). Therefore, we can expect that in insulin-resistant subjects glucose uptake would be even less dependent on insulin-mediated perfusion increase than in these healthy subjects.

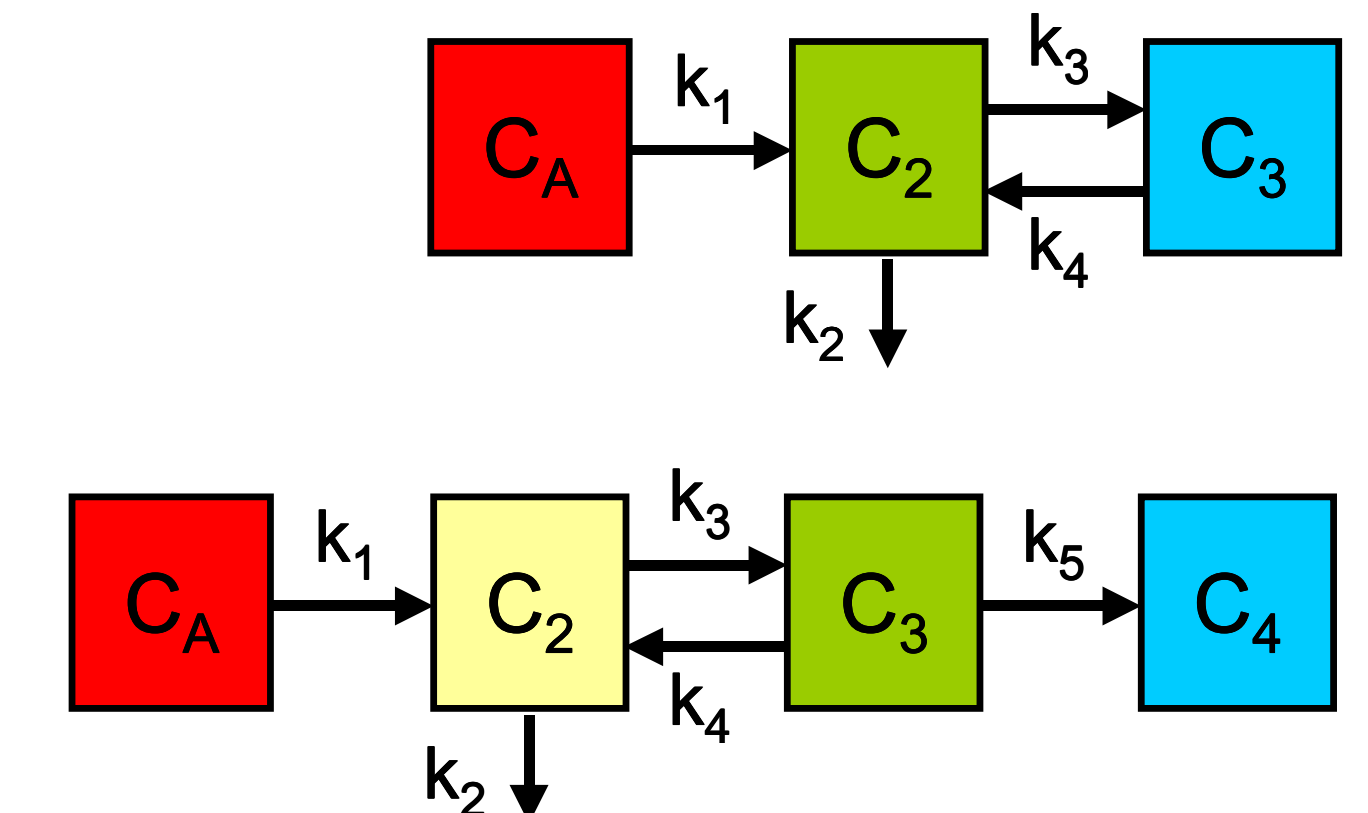
## Compartmental model for FDG



FDG is a glucose analog, which is transported into muscle and phosphorylated. Since FDG phosphate is not a suitable substrate for glucose-6-phosphatase and the level of glucose-6-phosphatase is low, FDG phosphate accumulates in muscles.

Glucose transport has been generally considered as the predominant step controlling muscle glucose uptake. Impaired insulin-stimulated glucose transport has been shown to cause the reduced rate of glucose uptake in subjects with type 2 diabetes. The analysis of previous clinical FDG PET studies of muscle was based on a three-compartmental model with three or four rate constants ( $k_1$ - $k_3$  or  $k_1$ - $k_4$ ) developed for the brain studies. In the brain, capillary endothelium forms a tight blood-brain barrier and is the rate-limiting step for glucose transport. Due to high perfusion and low extraction, the uptake of FDG is nearly independent of perfusion in the brain.

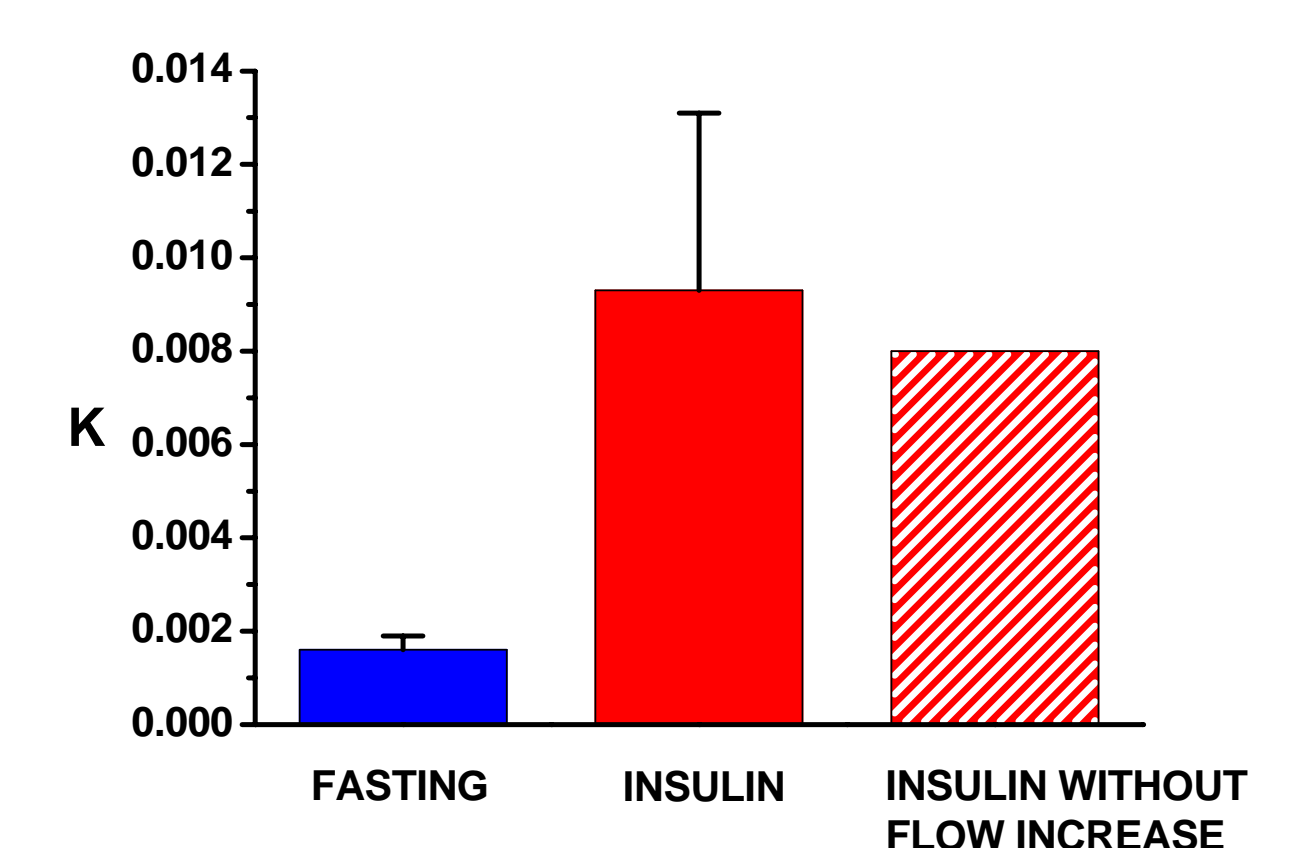
The parameters  $k_1$  and  $k_2$  represent the transport, and  $k_3$  the phosphorylation rate of FDG. However, in skeletal muscle perfusion is low and endothelium allows almost free diffusion of glucose and FDG. Because resistance to glucose and FDG flux is composed of perfusion and sarcolemma, the model for skeletal muscle must include an extracellular compartment between arterial input and intracellular spaces. The traditional "brain model" misinterpreted the meanings of  $k_1$  and  $k_3$  in muscle, leading to underestimation of the impact of insulin on glucose transport, and in diabetic subjects to false location of the defect.



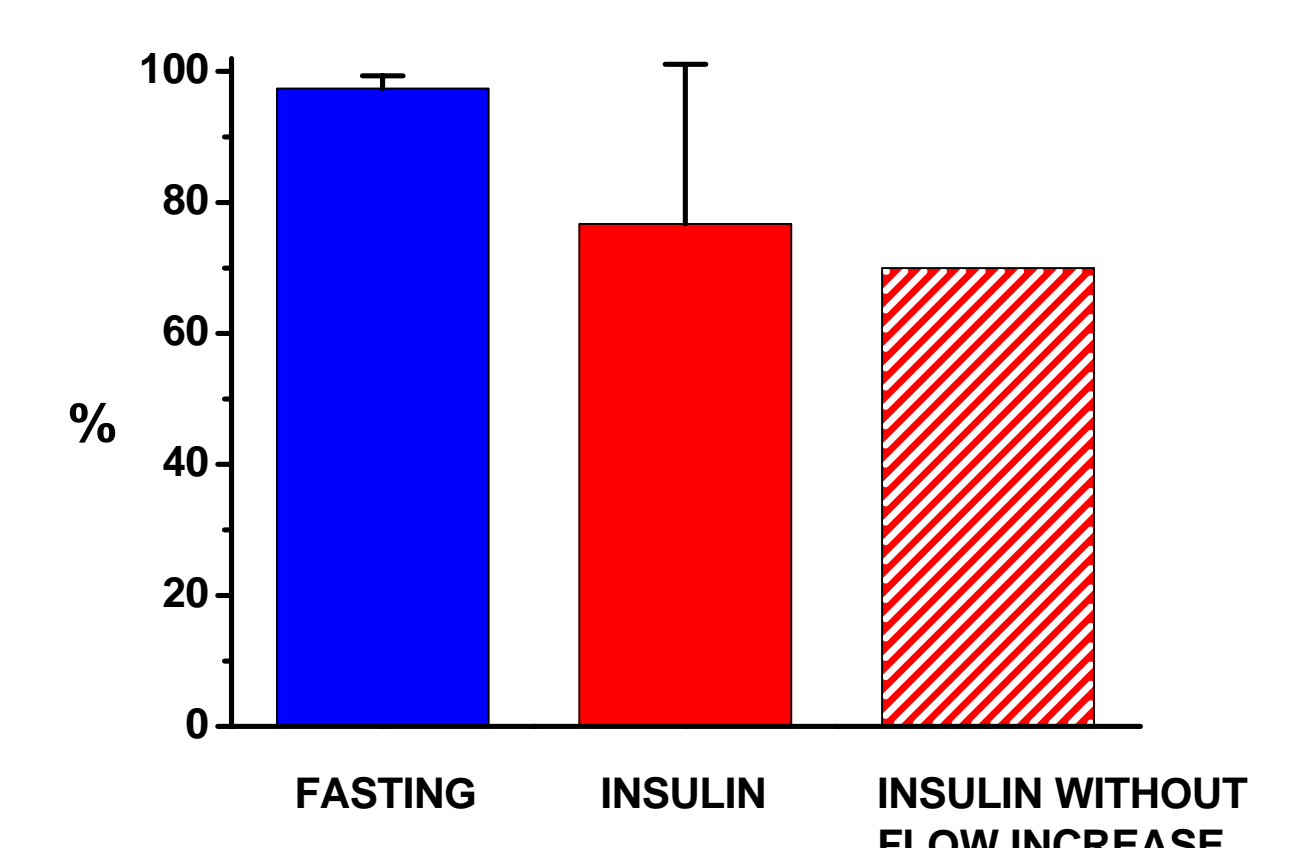
The tissue compartments in the present four-compartmental model for muscle are the concentrations of FDG in the extracellular space ( $C_2$ ) and in the intracellular space ( $C_3$ ), and the intracellular concentration of phosphorylated FDG ( $C_4$ ). The rate constants  $k_1$  and  $k_2$  represent perfusion and endothelial permeability and surface area,  $k_3$  and  $k_4$  represent the FDG transport rate across the sarcolemma (dependent on the concentration of glucose transporters in the sarcolemma), and  $k_5$  is the phosphorylation rate (dependent on the intracellular activity of hexokinases). This model results in physiologically realistic extracellular ( $k_1/k_2$ ) and intracellular ( $k_3/k_4$ ) distribution volumes for FDG.

**Table 1.** The results of FDG PET studies in the fasting state and during hyperinsulinemia.

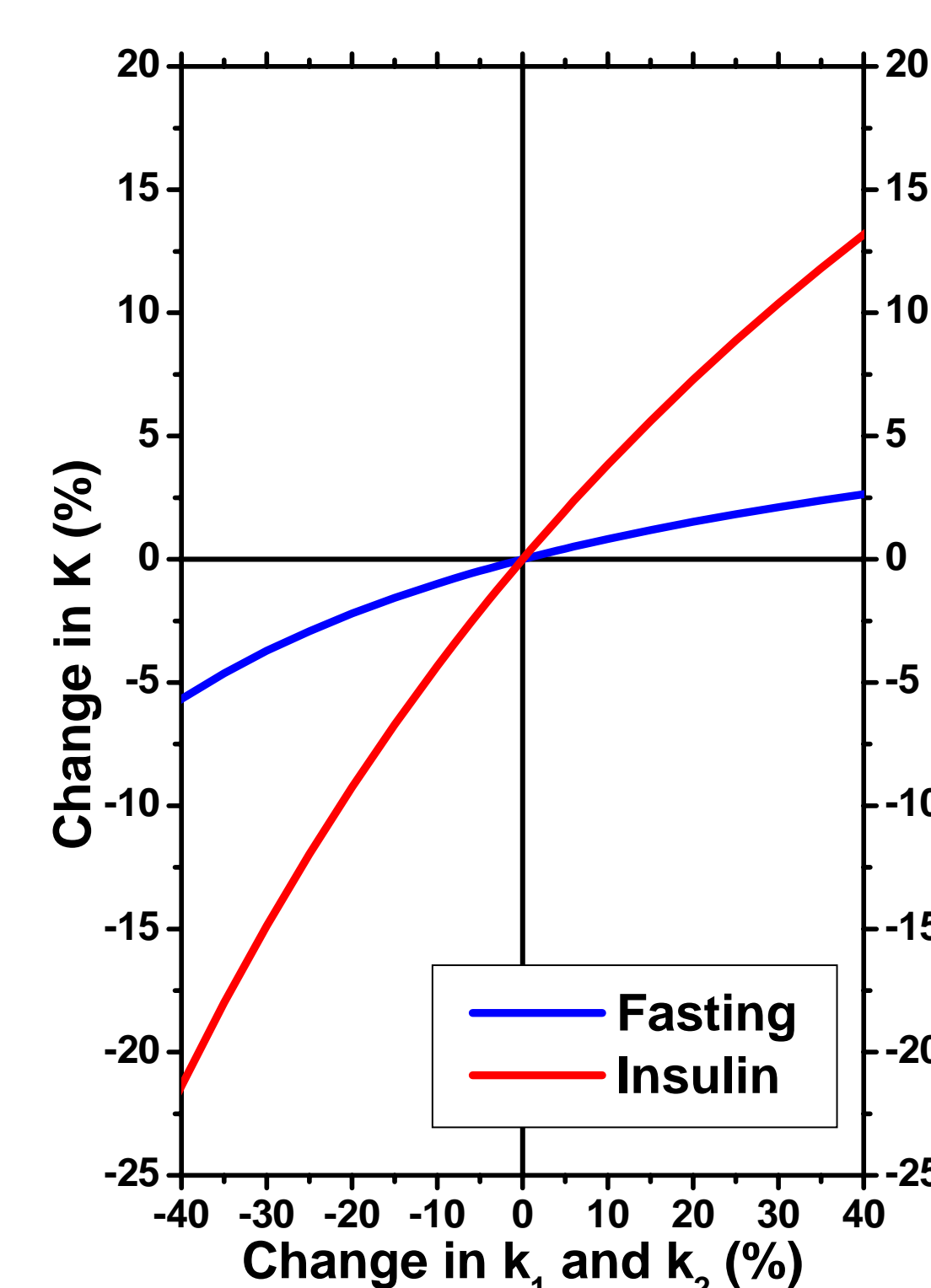
	Fasting (N=5)	Insulin (N=5)
$k_1$	0.017±0.001	0.022±0.007
$k_2$	0.224±0.023	0.178±0.136
$k_3$	0.039±0.014	0.123±0.039
$k_4$	0.019±0.012	0.003±0.004
$k_5$	0.025±0.008	0.72±0.83
$V_A$	0.018±0.010	0.015±0.009
$K$	0.0016±0.0003	0.0093±0.0004



**Figure 1.** FDG uptake ( $K$ ) in fasting state and during hyperinsulinemia.



**Figure 2.** Estimated extracellular glucose concentration as a percentage of the arterial concentration.



**Figure 3.** Simulated effect of decreased or increased perfusion on FDG uptake.

## Conclusion

The effect of insulin on perfusion to muscle is minimal when compared to its impact on glucose transport. Increased perfusion is not expected to markedly enhance glucose uptake in resting skeletal muscle in healthy and especially not in insulin-resistant subjects.