

Overall research theme:

**Interactions of the sympathetic nervous system and the nitric oxide system in the control of blood pressure and flow during rest and exercise. Integrative pharmacological and neurophysiological studies.**

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Characteristics of the research group:

Integrative physiological studies of cardiovascular control are combined with molecular biology to determine gene expression in skeletal muscle during rest and exercise. A specific characteristic is the direct measurement of sympathetic nervous activity by microneurography. The studies are generally invasive using arterial and venous catheters as well as microdialysis of skeletal muscle and muscle biopsies. Muscle metabolism and specifically nitric oxide production is studied by the use of stable isotope techniques. Both human volunteers as well as patient groups are studied, and pharmacological interventions are used. Mechanistically the interplay between nitric oxide and the sympathetic nervous system is a focal point.

Running projects: Titles and abstracts:

**Nitric oxide deficient hypertension. Is there a sympathetic neural component?**

It has long been hypothesized that nitric oxide deficiency could contribute to the development of human hypertension. The first proof of concept was provided when the nitric oxide inhibitor L-NAME increased blood pressure in normotensive volunteers to levels that would be considered hypertension stage I or II (Sander et al. 1999). In the same study the use of the alpha-adrenergic inhibitor phentolamine provided strong support that a sympathetic neural component contributes to the late phase of L-NAME-induced hypertension. This has later been strengthened by direct microneurographic measurements during L-NAME-administration in humans, as presented recently in abstract form. Whether primary or secondary forms of human hypertension are characterized by nitric oxide deficiency is now a future focus using stable isotope techniques. In addition, a recent collaboration has provided the first data on skeletal muscle nitric oxide synthase expression in humans genetically predisposed to hypertension compared to humans with no predisposition.

**Exercise-induced skeletal muscle nitric oxide production. Effects on control of blood flow and metabolism.**

Skeletal muscle has abundant expression of nitric oxide synthase both as the endothelial isoform in the vascular wall and as the neuronal isoform in myocytes. It is believed that exercise increases nitric oxide production from the myocytes, and such production could have strong local vasodilatory effects. Evidence that skeletal muscle derived nitric oxide is important for the metabolic inhibition of sympathetic vasoconstriction has been demonstrated in animal models (Thomas et al. 1998), as well as in Duchenne muscular dystrophy patients, who lack nitric oxide synthase in skeletal muscle (Sander et al. 2000) and more recently also in L-NAME treated healthy volunteers (Chavoshan et al. 2002). On the other hand, it has been more difficult to provide evidence using pharmacological inhibitors of nitric oxide synthase that nitric oxide is important for exercise-induced hyperemia in situations without sympathetic activation. Even within the last year the evidence has been conflicting in this area. Skeletal muscle exercise-induced nitric oxide production by stable isotopes will be determined in the near future. In collaboration with a group in Århus the interaction between nitric oxide and the sympathetic nervous system in the heart has been studied (Buus et al. 2001).

### **Hypoxia-induced sympathetic activation. Underlying mechanisms.**

Chronic hypoxemia in healthy volunteers produce a dramatic sympathetic activation, and the underlying mechanisms are unclear. The first direct measurements of sympathetic traffic after weeks of acclimatization has been provided in collaboration with Dr. Jim Hansen, and the follow-up study to identify underlying mechanisms has been completed and is undergoing analysis. Whether nitric oxide deficiency plays a role in this model of sympathetic overactivity is unclear, but the model may provide new insights into the underlying mechanisms for sympathetic overactivity in chronic pulmonary and heart diseases, which are both characterized by chronic hypoxemia and sympathetic overactivity. In collaborations the control of heart rate during hypoxemia is also studied. In other collaborations the control of sympathetic activity during carbon monoxide poisoning is studied.

### **Muscle metaboreflex. Underlying mechanisms.**

During fatiguing exercise metabolic products activate afferent nerve endings within skeletal muscle that gives rise to the muscle metaboreflex characterized by increases in sympathetic traffic and blood pressure. The underlying metabolic products and signal transduction pathways are unknown. In collaborations the role of hydrogen ions and potassium is studied by microdialysis (Vissing et al. 2001).

### *Recent publications related to the projects described above:*

- Sander M**, Hansen PG, Victor RG: Sympathetically mediated hypertension caused by chronic inhibition of nitric oxide. *Hypertension* 1995;26:691-695.
- Sander M**, Hansen J, Victor RG: The sympathetic nervous system is involved in the maintenance but not the initiation of L-NAME-induced hypertension. *Hypertension* 1997; 30(1):64-70.
- Thomas GD, **Sander M**, Lau KS, Huang PL, Stull JT, Victor RG. Impaired metabolic modulation of alpha-adrenergic vasoconstriction in dystrophin-deficient skeletal muscle. *Proc Natl Acad Sci U S A* 1998;95:15090-95. [See editorial for this article].
- Sander M**, Chavoshan B, Victor RG: A large blood pressure-raising effect of nitric oxide synthase inhibition in humans. *Hypertension* 1999;33:937-42.
- Hansen J, **Sander M**, Hald CF, Victor RG, Thomas GD. Metabolic modulation of sympathetic vasoconstriction in human skeletal muscle: Role of tissue hypoxia. *J Physiol* 2000;527(Pt 2):387-396.
- Sander M**, Chavoshan B, Harris SA, Iannaccone ST, Stull JT, Thomas GD, Victor RG. Functional muscle ischemia in neuronal NOS-deficient skeletal muscle of children with Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A* 2000;97(25):13818-13823. [See "news & views" commentary on this article in *Nature Medicine*, January 2001].
- Frandsen U, Bangsbo J, **Sander M**, Höffner L, Betak A, Saltin B, Hellsten Y. Exercise-induced hyperaemia and leg oxygen uptake are not altered during effective inhibition of nitric oxide synthase with N(G)-nitro-L-arginine methyl ester in humans. *J Physiol*. 2001;531(Pt 1):257-64.
- Buus NH, Bottcher M, Hermansen F, **Sander M**, Nielsen TT, Mulvany MJ. Influence of nitric oxide synthase and adrenergic inhibition on adenosine-induced myocardial hyperemia. *Circulation* 2001;104(19):2305-2310.
- Vissing J, MacLean DA, Vissing SF, **Sander M**, Saltin B, Haller RG. The exercise metaboreflex is maintained in the absence of muscle acidosis: insights from muscle microdialysis in humans with McArdle's disease. *J Physiol* 2001;537(Pt 2):641-649.
- Chavoshan B, **Sander M**, Sybert TE, Hansen J, Victor RG, Thomas GD. Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle. *J Physiol* 2002;540(Pt 1):377-386
- Bouschel R, Langberg H, Gemmer C, Olesen J, Cramer R, Scheede C, **Sander M**, Kjær M. Combined inhibition of nitric oxide and prostaglandin reduces skeletal muscle blood flow during exercise. *J Physiol* 2002 (accepted for publication)