

Overall research theme:

Integated basic and clinical studies of the resistance vasculature in hypertension and erectile dysfunction. Therapeutic approaches.

Latest update:

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Characteristics of the research group:

Basic pharmacological and clinical therapeutic studies are conducted to develop a rational drug therapy for arterial hypertension, pulmonary hypertension, and erectile dysfunction.

Running projects: Titles and abstracts:

Analysis of the causes of altered peripheral resistance in essential hypertension

Using in vitro techniques the characteristics of resistance vessels in essential hypertension are characterized, where in particular it is found that they have an abnormal structure (remodelling). The determinants of the abnormalities are investigated using animal models. Particular interest focuses on the renal afferent arterioles. Therapeutic approaches to correction of the abnormalities are made both experimentally and clinically. In particular the beneficial effects of vasodilator therapy are being investigated.

Cellular and molecular mechanisms of resistance vessel remodelling.

Using an organ culture arrangement, where small arteries are held under known conditions of pressure, flow and hormonal environment for several days, the signalling pathways for the remodelling process are investigated using protein analysis and real-time PCR. Particular attention is paid to the role of growth receptors and extracellular signal regulated kinase.

Pulmonary hypertension

The mechanisms underlying acute pulmonary vasoconstriction are investigated by in vitro techniques. The effect of vasodilator therapy for treatment of chronic pulmonary hypertension is addressed by hemodynamic measurements in rats and evaluation of function and morphology of pulmonary small arteries from rat and man. Currently the efforts are concentrated on new NO donors and endothelin receptor antagonists.

Endothelial mediated vasorelaxation

The signal transduction pathways underlying endothelium-dependent vasodilatation evoked by agonists and flow are investigated by in vitro measurements of vasorelaxation, intracellular calcium, nitric oxide concentration, and membrane potential in arteries. The perspective is to develop specific treatments for endothelial cell dysfunction associated with cardiovascular risk factors such as hypertension.

Erectile dysfunction

The impact of hypertension and treatment of hypertension on penile vasculature and erectile function is addressed by in vivo and in vitro investigations. The mechanisms underlying contractility of penile arteries are investigated with particular attention to the vasodilator pathways.

Recent publications related to the projects described above:

Buus CL, Pourageaud F, Fazzi GE, Janssen G, Mulvany MJ, De Mey JGR. Smooth muscle cell changes during flow-related remodeling of rat mesenteric resistance arteries. *Circ Res* 2001; 89: 180-186

Buus NH, Bøtcher 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: 2305-2310.

Buus NHB, Simonsen U, Pilegaard HK, Mulvany MJ: Nitric oxide, prostanoid and non-NO, non-prostanoid involvement in acetylcholine relaxation of isolated human small arteries. *Br J Pharmacol* 2000, 129, 184-192

Chlopicki S, Nilsson H, Mulvany MJ. The initial and sustained myogenic response of rat mesenteric small arteries: effect of cytochrome P450 blockers. *Am J Physiol* 2001; 281: H2176-H2183.

Christensen KL, Mulvany MJ. Location of resistance arteries. *J Vasc Res* 2001; 38: 1-12.

Christensen KL, Mulvany MJ. Vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension: a literature survey. *J Hypertens* 2001; 19: 1001-1006

Kvist S, Mulvany MJ. Reduced medication and normalization of vascular structure, but continued hypertension in renovascular patients after revascularization. *Cardiovasc Res* 2001; 52: 136-142.

Matchkov VV, Tarasova OS, Mulvany MJ, Nilsson H. Myogenic response of rat femoral small arteries in relation to wall structure and Ca^{2+} . *Am J Physiol* 2002; 283: H118-1125.

Matrougui K, Eskildsen-Helmond YEG, Fiebeler F, Henrion D, Levy BI, Tedgui A, Mulvany MJ. Angiotensin II stimulates Extracellular Signal-Regulated Kinases activity in intact pressurized rat mesenteric resistance arteries. *Hypertension* 2000; 36: 617-621.

Prieto D, Buus CL, Mulvany MJ, Nilsson H. Neuropeptide Y regulates intracellular calcium through different signalling pathways linked to a Y_1 -receptor in rat mesenteric small arteries. *Br J Pharmacol* 2000; 129: 1689-1699.

Rizzoni D, Porteri E, Guelfi D, Piccoli A, Castellano M, Pasini G, Muiesan ML, Mulvany MJ, Agabiti Rosei E. Cellular hypertrophy in subcutaneous small arteries of patients with renovascular hypertension. *Hypertension* 2000; 35: 931-935.

Simonsen U., García-Sacristán A., Prieto D. Penile arteries and erection. *Journal of Vascular Research* 2002;39, 283-304.

Simonsen, U. Interactions between drugs for erectile dysfunction and drugs for cardiovascular disease. *Int. J. Impot. Res.* 2002; 14, 1-11.

Simonsen, U., Contreras, J., García-Sacristán, A., Martínez, C. Effect of sildenafil on non-adrenergic non-cholinergic neurotransmission in bovine penile small arteries. *European Journal of Pharmacology* 2001;412, 155-169.

Simonsen, U., Wadsworth, R.M., Buus, N.H., Mulvany, M.J. In vitro simultaneous measurements of relaxation and nitric oxide concentration in rat superior mesenteric artery. *J. Physiol.* 1999; 516.1:271-282.

Stankevicius E, Martinez AC, Mulvany MJ, Simonsen U. Blunted acetylcholine relaxation and nitric oxide release in arteries from renal hypertensive rats. *J. Hyperten.* 2002;20, 1-9.

Tankó, L.B., Mikkelsen, E.O., Simonsen, U. A new experimental approach in endothelium-dependent pharmacological investigations on isolated porcine coronary arteries mounted for impedance planimetry. *Br. J. Pharmacol.* 1999;128, 165-173.

Vecchione C, Fratta L, Rizzoni D, Notte A, Poulet R, Porteri E, Frati G, Guelfi D, Trimarco V, Mulvany MJ, Agabiti-Rosei E, Trimarco B, Cotecchia S, Lembo G. Cardiovascular influences of alpha1b-adrenergic receptor defect in mice. *Circulation* 2002; 105: 1700-1707.