

Overall research theme:

Cardiovascular pharmacology and pathophysiology: Experimental and human investigations with focus on nitric oxide, heart failure and heart transplantation.

Latest update:

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Characteristics of the research group:

The research focuses on two main areas. 1) Cardiovascular pharmacology related to vascular biology and endothelial function in both experimental and human settings and 2) Pathophysiology and treatment strategies in patients with acute/chronic heart failure and heart transplantation.

Running projects: Titles and abstracts:

Cardiovascular pharmacology related to vascular biology and endothelial function in both experimental and human settings

NO donor agents like nitroglycerin are important in the treatment of patients with heart disease. At present, a rapid declining effect of continuous nitroglycerin administration ("nitroglycerin tolerance") comprises a clinical problem. Recent findings suggest that the cause of tolerance development probably is related to increased inactivation of nitroglycerin-derived NO. In recent years, we have investigated the multifaceted physiological importance of NO by various methods. This has been done in isolated vessels, in vivo animal models, healthy volunteers and patients with cardiovascular disease. The experiments include investigations of

- NO production: Functional evaluation using NO modulating agents (e.g. NO-donor agents like nitroglycerin, endogenous agonists like acetylcholine and NO synthase inhibitors like L-NAME) in vivo and in vitro.
- NO production: Quantitative NO measurements using in vivo NO trapping and subsequent in vitro electron spin resonance
- NO producing enzymes: Measurements using PCR and western analyses of iNOS and cNOS RNA and protein combined with immunohistochemical methods for tissue localisation of NO synthases.
- NO producing enzymes: direct enzyme activity measurements using endothelial NO synthase activity (citrulline assay)
- "New" biochemical pathways for NO-mediated vasorelaxation: Potassium channel-mediated effects of NO
- NO inactivating mechanisms: Using qualitative and quantitative measurements of superoxide anion production and membrane bound oxidases.

Pathophysiology and treatment strategies in patients with acute/chronic heart failure and heart transplantation

Acute heart failure: Within this area the dominating group of patients are those with AMI complicated by cardiogenic shock. These patients have a short-term mortality exceeding 70%. We have recently shown that the timing of shock development (early vs late after AMI) and early revascularisation are strong predictors of outcome in these patients. At present ongoing research is focusing on the prognostic impact of age, diabetes and other likely risk factors. In addition a number of bio-markers are evaluated in order to predict outcome. Virtually nothing is known about the biological effects of mechanical unloading of the failing heart in this situation and this is currently studied with respect to vascular peptides.

Chronic heart failure: In a consecutive group of several thousand patients more than a 100 clinical variables are registered in each patient and corresponding blood samples are available. In this group the diagnostic and prognostic value of ANP, BNP and other peptides are evaluated. The use of these peptides as guidance to treatment is also investigated.

At present patients with life-threatening heart failure receive a total artificial mechanical left ventricular assist device and in these patients the biological impact of total unloading of the failing heart is evaluated regarding hemodynamic and neurohormonal changes and myocardial structure.

Patients with severe heart failure have significantly decreased cerebral blood flow and mental changes. The importance of cerebral autoregulation and the impact of pharmacological interventions are evaluated.

Human heart transplantation: Changes in vascular biology and vascular peptides are looked at before and after heart transplantation. The influence of changes in the NO system (eNOS and iNOS) is evaluated in sequential myocardial biopsies with special focus on graft vasculopathy and acute rejection episodes.

Publications related to the projects described above:

Endogenous and pharmacological NO

- Boesgaard S, Aldershvile J, Enghusen Poulsen H. Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992;85:143-49
- Boesgaard S, Enghusen Poulsen H, Aldershvile J, Anderson M, Meister A. Acute effects of nitroglycerin depend on both plasma and intracellular sulfhydryl compound levels in vivo. Effect of agents with different sulfhydryl modulating properties. *Circulation* 1993;87:547-553
- Boesgaard S, Aldershvile J, Enghusen Poulsen H, Christensen S, Dige-Petersen H, Giese J. N-acetylcysteine inhibits angiotensin converting enzyme in vivo. *Journal of Pharmacology and Experimental Therapeutics* 1993;256:1239-1244
- Boesgaard S, Aldershvile J, Poulsen HE, Loft S, Anderson M, Meister A. Nitrate tolerance in vivo is not associated with depletion of arterial or venous cysteine and glutathione levels. *Circulation Research* 1994;74:115-120
- Boesgaard S, Iversen H, Poulsen H, Wroblewski H, Frandsen H, Kastrop J, Aldershvile J. Altered peripheral vasodilatory profile of nitroglycerin during long-term infusion of N-acetylcysteine. *J Am Coll Cardiol* 1994;23:163-169
- Laursen JB, Boesgaard S, Poulsen HE, Aldershvile J. Nitrate tolerance impairs nitric oxide-mediated vasodilation in vivo. *Cardiovascular Research* 1996;31:814-819
- Laursen JB, Mülsch A, Boesgaard S, Mordvintcev P, Trautner S, Gruhn N, Nielsen-Kudsk JE, Busse R, Aldershvile J. In vivo nitrate tolerance is not associated with reduced bioconversion of nitroglycerin to nitric oxide. *Circulation* 1996;94:2241-2247
- Boesgaard S, Nielsen-Kudsk JE, Laursen JB, Aldershvile J. Thiols and nitrates: Re-evaluation of the thiol depletion theory of nitrate tolerance. *American Journal of Cardiology*, 1998;81:21A-29A
- Gruhn N, Aldershvile J, Boesgaard S. Tetrahydrobiopterin improves endothelium-dependent vasodilation in nitroglycerin-tolerant rats. *European Journal of Pharmacology* 2001;416:245-249
- Laursen JB, Boesgaard S, Trautner S, Rubin I, Poulsen HE, Aldershvile J. Endothelium-dependent vasorelaxation is inhibited by in vivo depletion of vascular thiol levels. Role of endothelial cNOS. *Free Radical Research*, 2001;35:387-394.
- Gruhn N, Søren Boesgaard, Claus B Andersen and Jan Aldershvile. Nitroglycerin tolerance: Different mechanisms in vascular segments with or without intact endothelial function. *Journal of Cardiovascular Pharmacology*. In press 2002

Potassium channels and interactions with NO

- Nielsen-Kudsk JE, Boesgaard S, Aldershvile J. K⁺ channel opening: a new drug principle in cardiovascular medicine. *Heart* 1996;76:109-116
- Bang L, Nielsen-Kudsk JE, Gruhn N, Olesen SP, Trautner S, Theilgaard S, Boesgaard S, Aldershvile J. Hydralazine-induced vasodilation involves opening of high conductance Ca⁺⁺-activated K⁺ channels. *Eur J Pharmacol* 1998;361:43-49
- Bang L, Nielsen-Kudsk JE, Gruhn N, Theilgaard S, Olesen SP, Boesgaard S, Aldershvile J. Vascular smooth muscle contraction is an independent regulator of endothelial nitric oxide production. *Scand Cardiovasc J*, 1999;33:71-78
- Bang L, Boesgaard S, Nielsen-Kudsk JE, Vejstrup NG, Aldershvile J. Nitroglycerin-mediated vasorelaxation is modulated by endothelial calcium-activated potassium channels. *Cardiovasc Res*, 1999;43:772-78
- Gruhn N, Boesgaard S, Eiberg J, Bang L, Thiis J, Schroeder T, Aldershvile J. Large conductance calcium-activated potassium channels modulate nitroglycerin-mediated vasorelaxation without affecting venous tolerance development in humans. *European Journal of Pharmacology*, in press 2002

Human heart transplantation and heart failure

- Krogsgaard K, Boesgaard S, Aldershvile J, Arendrup H, Mortensen SA, Petterson G. Cytomegalovirus infection rate among heart transplant patients in relation to potency of anti-thymocyte immunoglobuline induction therapy. *Scand J Infect Dis* 1994;26:239-247
- Boesgaard S, Nielsen Kudsk JE, Aldershvile J. NO and the Heart. Aspects of nitric oxide in the cardiovascular system. In: Coronary microcirculation during ischaemia and reperfusion, *Munksgaard* 1997;132-140
- Bundgaard H, Boesgaard S, Mortensen SA, Arendrup H, Aldershvile J. Effect of nitroglycerin in patients with increased pulmonary vascular resistance undergoing cardiac transplantation. *Scand Cardiovasc J* 1997;31:275-281
- Vejstrup N, Bouloumie A, Andersen CB, Boesgaard S, Mortensen SA, Harrison DG, Busse R, Aldershvile J. Inducible nitric oxide synthase (iNOS) in the human heart. Expression and localization in congestive heart failure. *J Mol Cell Cardiol*, 1998;30:1215-1223
- Boesgaard S, Gruhn N, Wanscher M, Sander K, Mortensen SA, Aldershvile J. Treatment strategies in cardiogenic shock complicating acute myocardial infarction. *HeartDrug* 2001;1:176-181
- Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001;32:2530-2533
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- Vejstrup NG, Andersen CB, Boesgaard S, Mortensen SA, Aldershvile J. Temporal changes in myocardial endothelial nitric oxide synthase (NOS3) expression during the first 3 years following Human Heart transplantation. *J Heart Lung Transplant* 2002;21:211-216
- Bay M, Kirk V, Parner J, Hassager C, Nielsen H, Krogsgaard K, Trawinski J, Boesgaard S, Aldershvile J. NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. *Heart*, In press 2002
- MG Lindholm, J Aldershvile, C Sundgreen, Erik Jørgensen, Kari Saunamäki, S Boesgaard. Effect of early revascularisation in cardiogenic shock complicating acute myocardial infarction. *European Journal of Heart Failure*, In press 2002
- Mathias G Lindholm, Lars Køber, Søren Boesgaard, Christian Torp-Pedersen, Jan Aldershvile. Cardiogenic shock complicating acute myocardial infarction: Prognostic impact of early and late shock development. *European Heart Journal*, in press 2002