

Overall research theme:

Experimental and clinical studies of potassium and genes in cardiovascular disease focusing on diagnostic and therapeutic implications.

Latest update:

July 1, 2003.

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Characteristics of the research group:

The research group combines competence in physiological and genetic research as well as in and clinical medicine. A unique feature is the combination of clinical research in patients with methods in physiology and patophysiology, cellular and molecular biology as well as in molecular genetics. The present research group has established a research laboratory for human and experimental ion research applying state of the art methods for heart and muscle Na,K-ATPase studies as well as an outpatient clinic focusing on genetic cardiology. The present main focus for the research is implication of potassium-homeostasis dysfunction and gene defects for the development of heart arrhythmia.

Running projects: Titles and abstracts:

Regulation of heart and muscle Na,K-ATPase in heart disease

It has become well established that myocardial Na,K-ATPase is of importance for extracellular potassium regulation in the myocardium. It has also become well established that skeletal muscle Na,K-ATPase in addition to being of importance for extracellular potassium regulation in skeletal muscles also is of major importance for the ongoing short term (seconds-minutes) plasma-potassium regulation. We have documented that myocardial and skeletal muscle Na,K-ATPase undergoes regulation in physiological as well as patophysiological conditions in animals as well as in human subjects. Dysregulation resulting in muscular weakness and abnormal plasma-potassium shifts. On this basis the present project aims at elucidating such dysregulations and their implications as well as possibilities for prevention and treatment in patients with heart disease.

Clinical genetic cardiology

Clinical genetic cardiology is a rising subspeciality within cardiology for patients with mutations in cardiac genes and their families. We have recently in a number of papers described the relationship between phenotype and genotype in hypertrophic cardiomyopathy and established an outpatient clinic with a program for clinical handling of such patients and relatives. On this basis the present project aims at extending this work also to patients with other heart diseases where mutations could be in play. This will include sudden, unexpected, heart death in young age; sudden, unexplained syncope; ideopathic ventricular tachycardia and fibrillation; pharmacologically induced long-QT-syndrome; arrhythmogenic right ventricular syndrome; atrial fibrillation and flutter; dilated cardiomyopathy; amyloidosis, Fabrys disease etc. These studies will be performed in collaboration with Michael Christiansen, Statens Seruminstitut.

Provocation of arrhythmia in mutations by potassium-homeostasis dysfunction

Much genetic research has hitherto been mostly descriptive. A major problem being why a mutation that has been existing since birth suddenly after many years without symptoms causes arrhythmia and death. Our hypothesis is that mutations bring about vulnerability to potassium shifts whether normal but extreme or abnormal. Extreme shifts in potassium can occur during extreme exercise being the immediate factor eliciting sudden, unexpected death. Abnormal shifts in potassium may occur in patients with heart disease due to the disease per se or due to the treatment. Disturbances in potassium-homeostasis are a well known eliciting factor for arrhythmia in e.g. long-QT-syndrome with mutation induced dysfunction of myocardial potassium-channels. Moreover, we have documented Na,K-ATPase dysregulation in the human myocardium and muscle in e.g. heart failure and due to diuretic treatment. On this basis the present project aims at evaluating potassium shifts during exercise tests and Na,K-ATPase in muscle and heart biopsies in patients with cardiac gene mutations at risk of arrhythmia. These studies will be performed in collaboration with Niels H. Secher, Rigshospitalet.

Recent publications related to the projects described above:

Na,K-ATPase:

- A. Ziegelhoffer, K. Kjeldsen, H. Bundgaard, A. Breier, A. Vrbjar & A. Dzurba. Na,K-ATPase in the myocardium: Molecular principles, functional and clinical aspects. *Gen. Physiol. Biophys.*, 2000, 19, 9-47.
- K. Kjeldsen. Human myocardial Na,K-ATPase in remodeling. In: *The hypertrophied heart*. Eds.: N. Takeda, M. Nagano, N.S. Dhalla. Kluwer Academic Publishers, Boston 2000, 393-398.
- A.S. Mahailidou, H. Bundgaard, M. Mardini, P.S. Hansen, K. Kjeldsen & H.H. Rasmussen. Hyperaldosteronemia in rabbits inhibits the cardiac sarcolemmal Na⁺-K⁺ pump. *Circulation Res.*, 2000, 86, 37-42.
- D.F. Gray, H. Bundgaard, P.S. Hansen, K.A. Buhagiar, A.S. Mihailidou, K. Kjeldsen & H.H. Rasmussen. HMG CoA reductase inhibition reduces sarcolemmal Na⁺-K⁺ pump density. *Cardiovasc. Res.*, 2000, 47, 329-335.
- H. Bundgaard & K. Kjeldsen. Regulation of myocardial K and Na,K-ATPase during high K intake. In: *Na,K-ATPases and related ATPases*. Eds.: K. Taniguchi, S. Kaya. Excerpta Medica. International Congress Series 1207. Elsevier, The Netherlands, 2000, 551-554.
- H. Bundgaard, T.A. Schmidt & K. Kjeldsen. Human myocardial Na,K-ATPase in structural cardiac disease. In: *Na,K-ATPases and related ATPases*. Eds.: K. Taniguchi, S. Kaya. Excerpta Medica. International Congress Series 1207. Elsevier, The Netherlands, 2000, 705-708.
- T.A. Schmidt, H. Bundgaard & K. Kjeldsen. Digoxin treatment related to human myocardial and skeletal muscular Na,K-ATPase. In: *Na,K-ATPases and related ATPases*. Eds.: K. Taniguchi, S. Kaya. Excerpta Medica. International Congress Series 1207. Elsevier, The Netherlands, 2000, 743-746.
- T.A. Schmidt, H. Bundgaard & K. Kjeldsen. Receptor occupancy with digoxin vs. receptor occupancy with a putative endogenous diglitalislike factor. *Hypertension Res.* 2000, 23, S39-S43.
- H. Bundgaard & K. Kjeldsen. Regulation of myocardial and skeletal muscle Na,K-ATPase in diabetes mellitus in humans and animals. In: *Diabetes and cardiovascular disease. Etiology, treatments and outcomes*. Eds.: A. Angel, N. Dhalla, G. Pierce, P. Singal. *Advances in experimental medicine and biology* volume 498, Kluwer Academic/Plenum Publishers, New York, 2001, 319-322.
- K. Kjeldsen, A. Nørgaard & M. Gheorghide. Myocardial Na,K-ATPase: the molecular basis for the hemodynamic effect of digoxin therapy in congestive heart failure. *Cardiovasc. Res.* 2002, 55, 710-713.
- S.F. Fraser, J.L. Li, M.F. Carey, X.N. Wang, T. Sangkabutra, S. Sostaric, S.E. Selig, K. Kjeldsen & M.J. McKenna. Fatigue depresses mammalian in vitro skeletal muscle Na,K-ATPase activity in untrained and trained individuals. *J. Appl. Physiol.*, 2002, 93, 1650-1659.
- H. Bundgaard & K. Kjeldsen. Potassium depletion increases potassium clearance capacity in skeletal muscles in vivo during acute repletion. *Am. J. Physiol.*, 2002, 283, 1163-1170.
- H. Bundgaard, K. Kjeldsen, K.S. Krabbe, G. van Hall, L. Simonsen, J. Qvist, C.M. Hansen, K. Møller, L. Fonsmark, P.L. Madsen, B.K. Pedersen. Endotoxemia stimulates skeletal muscle Na,K-ATPase and increases blood lactate level under aerobic conditions in humans. *Am. J. Physiol.*, 2003, 284, H1028-H1034.
- T.A. Schmidt & K. Kjeldsen. Regulation of digitalis glycoside receptors in digoxin treatment. In: *Cardiac remodeling and failure*. Eds.: P.K. Singal, I.M.C. Dixon, L.A. Kirshenbaum, N.S. Dhalla. Kluwer Academic Publishers, New York, 2003, 501-510.
- H. Bundgaard & K. Kjeldsen. Muscular K-clearance capacity in vivo must be evaluated on the basis of K and Na,K-ATPase concentrations. In: *Na,K-ATPase and related cation pumps*. Eds.: P.L. Jørgensen, S.J. Karlish, A.B. Maunsbach. *Annals of the New York Academy of Sciences*, 2003, 986, 623-624.
- K. Kjeldsen & H. Bundgaard. Myocardial Na,K-ATPase and digoxin therapy in human heart failure. In: *Na,K-ATPase and related cation pumps*. Eds.: P.L. Jørgensen, S.J. Karlish, A.B. Maunsbach. *Annals of the New York Academy of Sciences*, 2003, 986, 702-707.
- R.H.G. Schwinger, H. Bundgaard, J. Müller-Ehmse & K. Kjeldsen. Role of Na,K-ATPase in the failing human heart. *Cardiovasc. Res.*, in press.
- A. Ziegelhoffer, H. Bundgaard, T. Ravingerova, N. Tribulova, M.T. Enevoldsen & K. Kjeldsen. Diabetes- and semi-starvation-induced changes in metabolism and regulation of Na,K-ATPase in rat heart. *Diabetes, Nutrition & Metabolism*. In press.

M.J. McKenna, S.F. Fraser, J.L. Li, X.N. Wang, M.F. Carey, E.A. Side, J. Morton, G.I. Snell, K. Kjeldsen & T.J. Williams: Impaired muscle Ca and K regulation contribute to poor exercise performance post-lung transplantation. *J. Appl. Physiol.*, in press.
H. Lajer, H. Bundgaard, N.H. Secher, H.H. Hansen, K. Kjeldsen & G. Daugaard: Severe magnesium and potassium depletion in patients treated with cisplatin. Submitted.

Clinical genetic:

H. Bundgaard, O. Havndrup, P.S. Andersen, L.A. Larsen, N.J. Brandt, J. Vuust, K. Kjeldsen & M. Christiansen. Familial hypertrophic cardiomyopathy associated with a novel missense mutation affecting the ATP-binding region of the cardiac beta-myosin heavy chain. *J. Mol. Cell. Cardiol.*, 1999, 31, 745-750.

P.S. Andersen, O. Havndrup, H. Bundgaard, L.A. Larsen, J. Vuust, K. Kjeldsen & M. Christiansen. Adult onset familial hypertrophic cardiomyopathy caused by a novel mutation, R694C, in the MYH7 gene. *Clinical Genet.*, 1999, 56, 244-246.

O. Havndrup, H. Bundgaard, P.S. Andersen, L.A. Larsen, J. Vuust, K. Kjeldsen & M. Christiansen. A novel mutation, Leu390Val, in the cardiac beta-myosin heavy chain associated with pronounced septal hypertrophy in two families with hypertrophic cardiomyopathy. *Scand Cardiovasc. J.*, 2000, 34, 558-5563.

O. Havndrup, H. Bundgaard, P.S. Larsen, J. Vuust, K. Kjeldsen & M. Christiansen. The val(606)met mutation in the cardiac beta-myosin heavy chain gene in patients with familial hypertrophic cardiomyopathy is associated with a high risk of sudden death at young age. *Am. J. Cardiol* 2001, 87, 1315-1317.

P.S. Andersen, O. Havndrup, H. Bundgaard, J.C. Moolman-Smook, L.A. Larsen, J. Mogensen, P.A. Brink, A.D. Børglum, V.A. Corfield, K. Kjeldsen, J. Vuust & M. Christiansen. Myosin light chain mutations in familial hypertrophic cardiomyopathy: phenotypic presentation and frequency in Danish and south African populations. *J. Med. Genet.* 2001, 38, (e43) 1-6.

O. Havndrup, H. Bundgaard, P.S. Andersen, L.A. Larsen, J. Vuust, K. Kjeldsen & M. Christiansen. Outcome of clinical versus genetic family screening in hypertrophic cardiomyopathy with focus on cardiac beta-myosin gene mutations. *Cardiovasc. Res.*, 2003, 57, 298-301.

P.S. Andersen, O. Havndrup, H. Bundgaard, L.A. Larsen, J. Mogensen, A.D. Børglum, K. Kjeldsen, J. Vuust & M. Christiansen. Myosin light chain mutations in familial hypertrophic cardiomyopathy and their phenotypic presentation. *Heart*, in press.

P.S. Andersen, O. Havndrup, H. Bundgaard, L.A. Larsen, J. Vuust, A.K. Pedersen, K. Kjeldsen & M. Christiansen. Genetic and phenotypic characterization of mutations and polymorphisms in myosin binding protein C in familial hypertrophic cardiomyopathy: Total or partial haploinsufficiency. *J. Moll. Cell. Cardiol.*, in press.

M. Christiansen, N. Tønder, L.A. Larsen, P.S. Andersen, H. Simosen, N. Øyen, J.K. Kanters, J.R. Jacobsen, I. Fosdal, G. Wettrell, K. Kjeldsen. Mutations in the HERG ion channel: A novel link between long QT-syndrome and sudden infant death syndrome. Submitted.

M. Christiansen, K. Kjeldsen, G. Wettrell, L.A. Larsen, L. Lundkvist, P.S. Andersen, J.K. Kanters & J. Vuust. Potassium and genotypic-specific treatment should be considered in long QT-syndrom. Submitted.