

Spotlight: Øyvind Ellingsen, MD, PhD



Photograph courtesy of Lasse Berre.

Ninety-Five-Percent Confident That Interval Training Can Improve Heart Function in Chronic Heart Failure

Øyvind Ellingsen, professor of cellular cardiology, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, and consultant physician, Department of Cardiology, St. Olavs Hospital, Trondheim, Norway, talks to Jennifer Taylor, BSc, MSc, MPhil.

Proving that interval training (intermittent high-intensity exercise) reverses the adverse effects of heart failure by reducing heart size represents the current goal for Øyvind Ellingsen, MD, PhD, professor of cellular cardiology in the Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, and consultant physician in the Department of Cardiology, St. Olavs Hospital, Trondheim, Norway. He has just embarked (March 2009) on the SMARTEX-HF (Study of Myocardial recovery AfTer EXercise Training in Heart Failure) study, which is randomising 200 patients with chronic heart failure into 1 of 3 exercise regimens. “What we expect to see is a nice reversal of the adverse effect of heart failure on the heart,” says Professor Ellingsen. The 7 centres collaborating on the study—Antwerp, Copenhagen, Leipzig, Munich, Stavanger, Trondheim, and Utrecht—made their connections through the European Association of Cardiovascular Prevention and Rehabilitation, which operates under the auspices of the European Society of Cardiology, and Professor Ellingsen serves as head of its Section for Basic and Translational Research.

Ellingsen’s scientific life began during his childhood in a rural district near Sandefjord, a small city in Southern Norway, where his mother and grandparents raised him. His grandfather, who taught all subjects to students between the ages of 7 and 14 years, allowed him to have a science laboratory in the basement. He recalls, “I created quite a few firework items in that lab, but also some pH measurements.”

Between 1971 and 1973, Ellingsen studied physics at the Norwegian University of Science and Technology. During that time, he took a part-time job with a researcher working on ultrasound. And when a doctor came into the laboratory to carry out some investigations on a patient, Ellingsen says, “I knew then that I wanted to deal with patients.” He gained acceptance into the University of Oslo, Oslo, Norway, and became an MD in 1980.

Even before his PhD studies, Ellingsen had carried out his first scientific study, which led to his first article—a small clinical trial comparing different medications in angina. He found inspiration in his supervisor, cardiologist John Kjekshus, MD. Professor Ellingsen considers him “a very good example of a person who starts out doing some basic research and takes what he learns from basic research back to the patients.” They remain in touch—Professor Kjekshus sits on the end-point committee of the SMARTEX study.

“You Bring Something Home That You Didn’t Know You Were Looking For”

For his PhD at the University of Oslo, which he received in 1989, Ellingsen studied myocardial potassium balance during adrenergic stimulation. He describes his supervisor, Arnfinn Ilebekk, MD, PhD, as a mentor who “taught me to make high-quality physiological measurements and the tedious work of doing technically good science.”

Ellingsen shared his office with David Rutlen, MD, FACP, FACC, a professor visiting from Yale, who convinced him that he should go to the United States for a postdoc—specifically to the laboratory of Thomas W. Smith, MD, at Brigham and Women’s Hospital, Cardiovascular Division, Harvard University, Boston, Mass. Professor Smith had a reputation as a very good mentor, and he was doing groundbreaking work. “He was probably one of the first people who brought cellular cardiology and molecular medicine into contact with cardiology, which I think had been for many years mostly occupied with haemodynamics and the biochemical aspects of the heart,” says Professor Ellingsen.

Having an excellent place to go helped Ellingsen win a Fogarty international research fellowship for 2 years, from 1990 to 1992. His application benefited from the fact that he had already had some good publications, and his interests made a good match for the laboratory at Harvard. For 5 years, he had been working on potassium balance in the intact heart in experimental pig models, and Professor Smith’s laboratory conducted cellular experiments on the sodium potassium pump and the effect in isolated myocytes. Professor Ellingsen says, “I think it was probably obvious from the project I had proposed that Harvard would take me from the level of the whole organ to the cellular level within the field that I was interested in.”

But Ellingsen ended up doing something completely different. He recalls, “I had imagined that I would continue the work on the sodium potassium pump that I had been doing for my PhD thesis in Norway, and to work on sodium, potassium, and maybe calcium regulation in the heart. But, at that time, these ideas were a little bit old for the lab. It was working on mechanisms of hypertrophy and molecular biology which was quite new in basic cardiology research at that time. So, it was an introduction to a new way of looking at the heart and heart disease.” He became trained in isolating cardiac myocytes, and in carrying out cell culture

and contractility measurements, which proved highly beneficial because, as he says, “You bring something home that you didn’t know you were looking for.”

“In Heart Failure the Heart Tends to Grow. With Exercise Training We Were Able to Reverse Those Changes”

On returning to Norway, Ellingsen felt energised, but he found the transition moving on from his postdoctoral post disappointing. He could not find any available positions, so he opted out of research and took up a post in clinical cardiology. Eventually, in 1995, he took up his current position of professor of cellular cardiology. He describes his specialty as a kind of translational cardiology, looking at cell physiology but with a clinical perspective.

Professor Ellingsen’s first task involved establishing a laboratory of cellular cardiology, which he found very rewarding. He says, “I was, for the first time, able to try out some of the ideas I had gotten from Harvard—that the cellular aspects of heart function would lead us to new discoveries and new therapies.”

He considers himself fortunate that he had a couple of very bright, talented, and inspiring PhD students there from the start—in particular Ulrik Wisløff, PhD, a sports scientist who now runs his own group as a tenured professor in the same department. Together, they found that in the rat model of heart failure, interval training (exercise with a high intensity) had a very powerful beneficial effect on heart muscle function.¹ Interval training increased the function of the heart and also reversed some of the adverse effects of heart failure on the heart morphologically. Professor Ellingsen explains, “In heart failure, the heart tends to grow. With exercise training, we were able to reverse those changes, at least to the same extent as the most powerful medical therapy.”

“One of the Hottest Labs in Molecular Cardiology”

The discovery that interval training both increased the function of the heart and also reversed some of the adverse effects of heart failure on the heart morphologically produced a desire for tools to figure out the molecular mechanisms behind it, and partly for this reason Professor Ellingsen spent his first sabbatical, from 2003 to 2004, as a visiting scholar in the laboratory of Kenneth R. Chien, MD, PhD, in the Institute of Molecular Medicine, University of

California, San Diego. The location had a reputation as “one of the hottest labs in molecular cardiology” with a lot of transgenic mice models to work on.

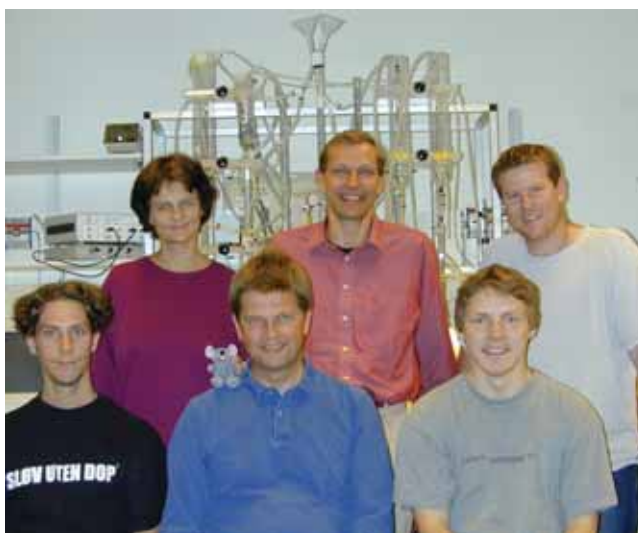
Professor Ellingsen came away from his sabbatical with the tools he needed, but not in the way he had expected. “I had thought that I would learn the details of doing molecular biology, and what I ended up doing was establishing contacts I could collaborate with,” he says. It provided the start of a collaboration with Gianluigi Condorelli, MD, a professor at the Parco Scientifico San Raffaele in Rome, Italy. Professor Ellingsen’s laboratory continues to do exercise training, at the level of experimental models in mice and rats, and also in people, and then gets help with molecular analyses from Professor Condorelli and other skilled scientists.

Professor Ellingsen had hoped to learn more than he accomplished in his sabbatical year, but he realised when he returned to Norway that a small laboratory like his should, perhaps, specialise on a few aspects and not try to cover

everything. He says, “I think one of the lessons I learned from that experience is that science is really about people, and one of the most important aspects is establishing good collaborations and having good communication.”

When asked whether he thinks laboratories spread themselves too thin by trying to do too much Professor Ellingsen says, “It depends on the resources—if you are a large lab, as in those that I’ve visited and spent some time in, in the United States, you can probably cover most of what you need. But I also think that if you look at some of the best articles, many of them are collaborative, meaning 2 or 3 excellent groups who work together. You cannot be at the cutting edge of all the areas that you need.”

Realising the benefits of collaboration has helped Professor Ellingsen deal with the frequent frustration of having an idea but not having the resources to pursue it. For several years he felt that he could not properly explore the molecular mechanisms behind the beneficial effects of exercise on the heart. But now, through the collaboration with Professor Condorelli, he believes they will untangle some of those mechanisms. So far, the mechanism seems different from those behind medical therapy, which means that uncovering the pathway could unearth targets for new heart failure drugs and, perhaps, also for high performance in sports medicine.



The Norwegian University of Science and Technology Research Group in Cellular Cardiology in 2001. Back row, left to right: Ingerid Arbo, MSc, technician, now PhD student; Jan Pål Loennechen, MD, PhD, student, now associate professor of cardiology; Ulrik Wisløff, MSc, PhD student, now professor of cardiovascular physiology. Front row, left to right: Vidar Beisvåg, MSc, PhD student, now postdoc; Øyvind Ellingsen, MD, PhD, professor of cellular cardiology; Ole Johan Kemi, MSc, PhD student, now lecturer in biomedical sciences, University of Glasgow, Glasgow, Scotland. Photograph courtesy of Professor Ellingsen.

“If You Do Higher-Intensity Training, Like Interval Training, Then You Have More Than Twice the Beneficial Effect”

After returning from San Diego in 2004, Professor Ellingsen contributed to an article in *Circulation* showing a very close relation between fitness (as measured by performance on a treadmill) and myocardial function.² Professor Ellingsen and his colleagues trained rats, then stopped training them, and found that the beneficial effects went away.

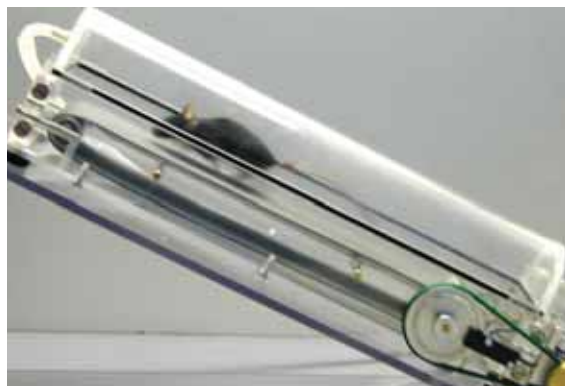
The same idea also came through in a *Science* paper in 2005,³ which a new collaboration had made possible. Professor Steven Britton, Medical College of Ohio, Toledo, Ohio, had seen an article about the work in Professor Ellingsen's laboratory and sent him an e-mail, asking whether he could test some of his animals, to prove that they had a higher level of fitness and a higher oxygen uptake. The laboratory in Toledo had been selectively breeding, for 10 generations, the best and the worst performers on the treadmill.

Through the collaboration they reinforced the concept that improved level of fitness has a correlation with the muscle function of the heart. They also showed that, at least in skeletal muscle, that correlation had to do with energy metabolism and metabolism related to mitochondria.

The importance of intensity in exercise provided the next big finding.⁴ Professor Ellingsen explains, “If you exercise at moderate intensity, you certainly have a nice effect on the arteries and also on the heart. But, if you do higher-intensity, training, like interval training, then you have more than twice the beneficial effect.”

Professor Ellingsen's contribution to research in exercise training and cardiology gained recognition in 2005 with the Ole Storstein Award for excellence in cardiovascular science from the Norwegian Society of Cardiology. Professor Ellingsen says, “Ole Storstein was an early Norwegian cardiologist and scientist, and though it's not a huge amount of money, the honour and the recognition was quite nice.”

The basic research was becoming practical, because if the same proved true in people, then patients with heart



Professor Ellingsen says, “For the past 10 years Professor Wisløff has been the most influential researcher that I've been in contact with because he introduced me to the exercise training perspectives. He was very keen on training rats and mice and insisted that we should get treadmills. And he was right.” Photograph courtesy of Professor Ellingsen.

failure could gain a greater effect from exercise training after a myocardial infarction if they exercised more intensely. So, a clinical study came next. In a relatively small number of heart failure patients, the group directly compared moderate-intensity exercise with interval training, and also with the recommended level of exercise given by general physicians. Their finding that high-intensity exercise had a much larger effect, particularly on the heart, appeared in *Circulation* in 2007.⁵ It generated so much interest that they received an invitation to present the results in a session of groundbreaking research from *Circulation* at the American Heart Association meeting in New Orleans, La, in November 2008.

Their findings have had a mixed response. People feel excited about the large effect, but also think it seems too good to be true. And some have concerns about safety. So, SMART-EX-HF represents the next step, which will test

exercise training on a larger cohort of patients and look for side effects, to see whether more or fewer complications appear. Professor Ellingsen says, “I think when we have completed that study with a year of follow-up we should be able to either convince ourselves that this was not a good idea or convince the world that this is a good idea and that it's also safe to try and do this.” At this stage, Professor Ellingsen feels 95% confident in characterising it as a good idea, because of the evidence that improving heart function improves prognosis and the fact that doing this type of exercise improves cardiac function.

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Jennifer Taylor is a freelance medical journalist.

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