

New treatments for heart failure

Protection for weak hearts





When the pumping action of the heart weakens, there is a lot more behind it than just a minor fault with the machine: heart failure is the most rapidly increasing cardiovascular disease in the world. Bayer HealthCare researchers are looking at different ways to help the weakened heart.

Palpitations and shortness of breath now and again: many people still believe that a "weak heart" is a natural sign of wear and tear. But behind it can lurk a deadly threat: in the industrialized countries alone, up to 50 percent of those affected die of heart failure within five years. If the disease is already advanced, only half of all patients live for another year. "Heart failure is not only extremely complex, but just as serious as cancer," says Dr. Peter Kolkhof, project manager in cardiological research in the Global Drug Discovery department of Bayer HealthCare in Wuppertal. "What is tragic is that many people don't even know that the chances of survival of many patients with heart failure are much worse than those of people with breast, prostate or bowel cancer, for example," says Kolkhof. And like many cancers, at present we can only slow down the development of heart failure, not cure it completely. Moreover, the condition is not a rare disease: it is estimated that globally over 20 million people suffer from heart failure, with another two million added to this every year – and rising.

"But the heart doesn't simply become worn out because it is weakened by age," says Dr. Johannes-Peter Stasch, who also works in cardiological research at Global Drug Discovery. Rather, the body's own reactions contribute significantly to the dangerous downwards spiral. "As soon as the heart is overloaded, the body tries to compensate for the decrease in performance by activating the sympathetic nervous system and other hormonal messenger substances, and by means of structural adaptations," says physician Dr. Silvia Lentini who, as project manager in clinical pharmacology at Bayer HealthCare, is responsible for the first vital clinical trials with the

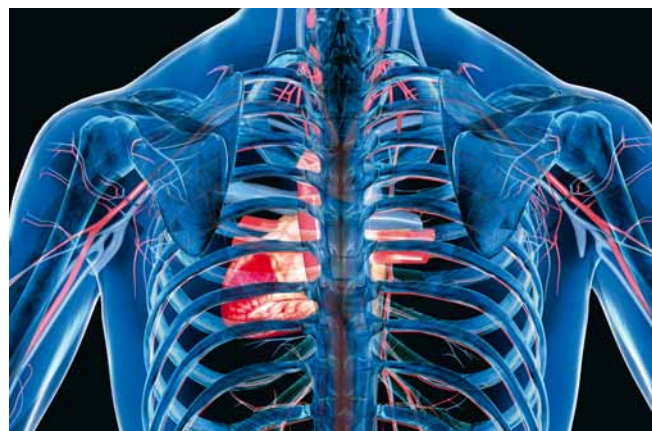
innovative substances coming out of Kolkhof and Stasch's laboratories. "We now know that the human body reacts with countermeasures to even the first signs that the force of contractions is becoming weaker."

Poor circulation resulting from a weak heart muscle and insufficient pumping strength

High blood pressure, smoking, diabetes and arteriosclerosis are nearly always the start of the problem. All of them pave the way for a heart attack. And in two-thirds of all cases this is the cause of subsequent heart failure. The one risk factor that is most dangerous, however, is high blood pressure over a prolonged period, as it constantly requires the heart to increase its pumping workload. In rarer cases, heart valve failure or viral infections can also be the cause of the condition. The result is the same in the end: the heart muscle is so weakened that it no longer has the strength to pump the blood through the body when its chambers are filled normally. The shortness of breath results essentially from a reflux of blood upstream of the left chamber of the heart in the pulmonary circulation. This reflux causes an increase in pressure in the pulmonary circulation, which the patient experiences as shortness of breath.

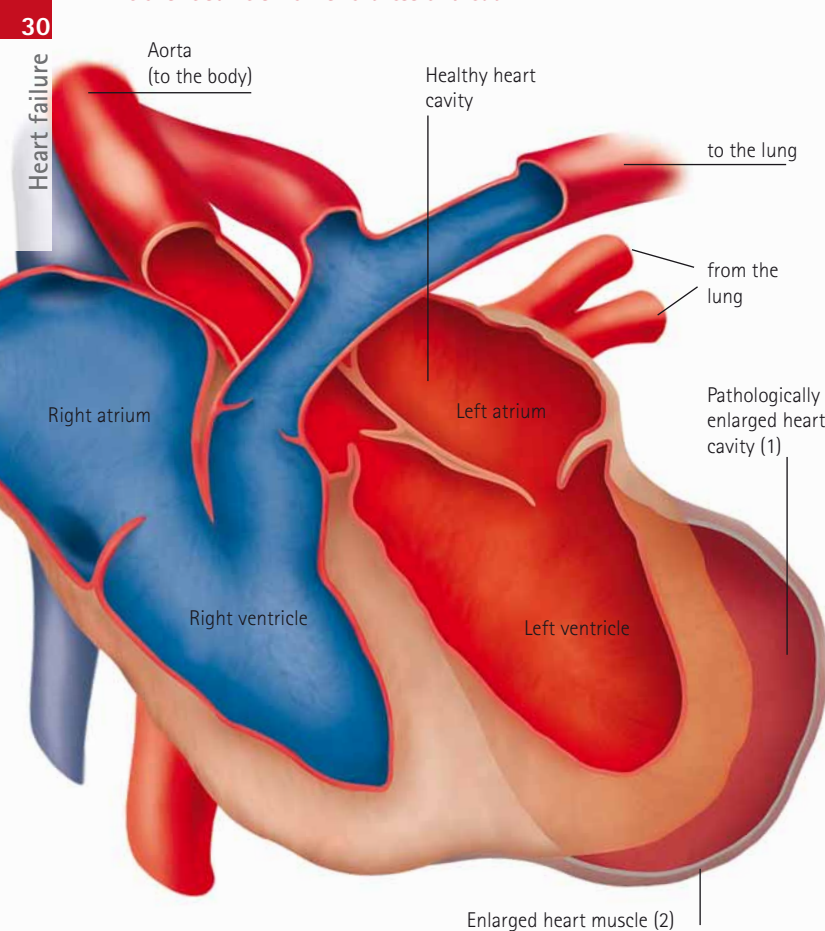
But the mechanisms which the heart uses to compensate for short-term overload lead to disaster if they are in constant use. For example, the body tries to stimulate the heart to work harder in order to maintain blood pressure. To do this, it activates what is called the renin-angiotensin-aldosterone system.

Heart specialist with an eye for detail: Dr. Peter Kolkhof (photo left), project manager in cardiological research, checks a slide before examining it under the microscope in the Bayer Schering Pharma laboratory in Wuppertal. The scientists are investigating heart disease and the processes in the body's blood vessels (photo right) so that new treatments can be found.



Weak blood pump

Heart failure weakens the cardiac muscle. The cause is usually a myocardial infarction or sustained high blood pressure. This represents an extreme burden to the heart. The consequences are pathologically changed muscle mass or excessively enlarged heart cavities (1). The diseased muscle then becomes larger (2) but weaker. It is no longer able to pump blood adequately through the vascular system. The body and organs are at risk of oxygen and nutrient deficiency. The patient's physical performance drops, he or she suffers from shortness of breath.



If the left half of the heart is weakened, blood accumulates in the lung. This makes breathing difficult. If the right half of the heart is weakened, the blood pools back into the stomach, the liver and even the legs. Fluid accumulates (edema). In many cases, both sides of the heart are affected. Heart failure is more frequent in elderly people, but it can also affect younger patients. In the past thirty years alone, the number of patients with heart disease worldwide has tripled.

"A whole chain of reactions leads first of all to the production of the protein molecule angiotensin II," explains Kolkhof. This ensures that the muscles in the walls of the blood vessels contract, but also means that the blood has to be pumped through the vessels against increased pressure. "In a healthy body, this reaction is an extremely effective way of stabilizing blood pressure which is too low," he says. However, as the motor of the blood circuit, the heart now has to battle against greater resistance – which further weakens it. In addition, the narrowed arteries reduce the amount of vital oxygen which is carried to the heart.

A cocktail of hormones, a stiffer heart muscle and fluid accumulation in the legs

At the same time, the nervous system also pushes up the pulse rate – which in turn further weakens the heart. The adrenal cortex then also produces increased amounts of the hormone aldosterone. This messenger substance causes the body to secrete less sodium and hence less water. If the heart is no longer working at full strength, however, it is unable to get rid of the additional fluid from the body. The result: fluid accumulates in the tissues, causing edema. The swollen legs which are the result of this are a typical sign of heart failure.

Aldosterone, however, has yet another, more damaging effect. "It causes the heart to produce increased amounts of connective tissue, especially after a heart attack. The result of this is that the walls of the heart become thicker, the vol-

Laboratory work: Linda Sarah Hoffmann and Sandra Geschka (left to right) prepare test series for trials with a new active ingredient. The substance is designed to prevent pathogenic restructuring of the cardiac muscle.





ume of the chambers decreases, and the entire heart muscle becomes stiffer,” says Kolkhof. In the end, instead of six liters of blood per minute, the heart is only able to push two liters through the body. Organs and tissues get too little oxygen and too few nutrients. Many of the people affected not only run out of breath when going for a walk or climbing the stairs; at some point even going to the bathroom or the kitchen becomes a major effort.

The drug products which are currently available and used as standard treatment intervene in some of these harmful mechanisms. In the case of chronic heart failure, doctors give drugs called beta-blockers, which protect the heart against the adverse effects of increased stress hormones and allow it to beat more slowly and efficiently, and ACE inhibitors which interrupt the chain of reactions leading to the formation of angiotensin II, dilate the blood vessels and hence control the escalating blood pressure. The third element of treatment are drug products which promote urinary output, known as diuretics. These ensure that fluid is flushed out of the body and so help to prevent edema and shortness of breath. When all the possibilities, including drug treatment, have been exhausted, the only options left for patients with a severely impaired heart pumping function are a heart transplant or the surgical implantation of pacemakers as the final alternative.

Although ACE inhibitors, beta-blockers and aldosterone antagonists have brought about a marked decrease in the high mortality rate in patients with heart failure since the late 1980s, overall mortality is still very high. Doctors have long

been dissatisfied with this. “Current treatments are far from ideal,” comments the internationally renowned heart failure expert Professor Mihai Gheorghiade from the Feinberg School of Medicine at Northwestern University in Chicago, USA. The reasons for this are, on the one hand, that the drugs are not effective in all patients and, on the other, that they can have serious side effects.

Optimized therapeutic approach undergoing clinical testing

“The subject of heart failure has therefore become an important new focus in Cardiology at Bayer HealthCare,” says Kolkhof. He and his colleagues have certainly responded to the challenge. At present, they are working simultaneously on three promising approaches to treatment that selectively intervene in the disease process and are very effective. But what is much more important is that in the research phase they were optimized so that they work very specifically, and none of the side effects associated with the current treatments for heart failure are expected to occur.

Stasch's team came across one of the top drug candidates in the late 1990s (see *research* 17, page 82: “For an easy heart”). At the time, the trained chemist and pharmacist was studying an enzyme whose medical potential was believed to be exhausted: soluble guanylate cyclase (sGC). In the human body, it is activated by the body's own nitrogen oxide (NO) and goes on to form an important endogenous messenger



The four stages of heart failure

Heart failure is now classified internationally according to four levels of severity based on the recommendations of the New York Heart Association (NYHA) (NYHA stages I-IV).

Stage	Symptoms
I	Physical capacity is normal. Only diagnostic examinations such as echocardiography – an ultrasound examination of the heart – show impairment.
II	Shortness of breath and exhaustion occur with severe exertion. Walks of up to five kilometers are still possible.
III	Patients struggle for breath even with slight physical exertion such as going upstairs, but have no symptoms when lying down or sitting.
IV	Any physical activity becomes a great effort. Pronounced muscle weakness is even noticeable at absolute rest: Those affected are tired, but can hardly sleep, sometimes have problems concentrating and are severely restricted in their everyday activities

Interview



“We need several elements of treatment”

Dr. Bertram Pitt is Professor of Cardiovascular Medicine at the University of Michigan in Ann Arbor. *research spoke* to him about heart failure.

Why are so many people still dying a few weeks after they are admitted to hospital with acute heart failure?

No one can say for sure. Why the heart fails in many cases despite intensive treatment is hotly debated by experts. One theory is that although the drugs which are currently used in acute treatment are very effective in the short term, in the longer term they appear to make the condition worse.

How can that be?

Studies suggest that these drugs not only increase the risk of arrhythmias, but they also appear to affect the salt and water balance in the blood which is controlled via nerve pathways and messenger substances in the blood.

What sort of drug products would help?

The condition is much too complex for us to be able to control it with a single drug product. Our study at the end of the 1990s showed, however, that the inhibition of aldosterone – in addition to other approaches – can be an important element in the treatment of heart failure.

What are the other elements?

We need both active substances which improve the contractility of the heart and others which prevent the pathological transformation of the heart. Another important aspect of treatment will certainly be drugs which dilate the severely constricted blood vessels of heart failure patients. Although it is too early to say whether the drug candidate cinaciguat will prove itself in the long term, the early data look very promising.

substance, cyclic guanosine monophosphate (cGMP), which dilates and protects blood vessels. The administration of drug products which are converted to this nitrogen monoxide in the body has long been a key element in the treatment of cardiovascular disease. Not all patients respond to it, however. In addition, the effect of these substances also clearly diminishes when they are used over a prolonged period.

Stasch's aim was therefore to find drug products which work independently of NO. In the course of screening 200,000 substances, he and his team found one that increases the formation of cGMP in the body enormously. All the subsequent studies were so successful that the active substance, which the researchers christened "cinaciguat," is now in Phase IIb clinical trials.

"We now know why NO stops working in patients with cardiovascular disease: a large proportion of the guanilate cyclase molecules in their bodies are defective," says Stasch. The reason for the enzyme defect is found in oxidative stress. This means that the free radicals which occur in the human body can no longer be adequately captured by the body's own antioxidants and destroy the beneficial sGC molecules, so that NO can no longer bind to this enzyme and activate it. "The great advantage of cinaciguat is that it works particularly well on the defective enzyme," says Stasch.

The second therapeutic approach being pursued by the Wuppertal researchers also draws on the experience of earlier generations: a major clinical study in the late 1990s showed that an aldosterone antagonist called spironolactone reduced

Heart check: internal medicine specialist Dr. Silvia Lentini, project manager in Clinical Pharmacology at Bayer Schering Pharma, examines the cardiovascular function of a trial subject.





mortality in patients with heart failure by 30 percent. It had been used for the first time in the 1960s for the treatment of edema, but after the introduction of the first ACE inhibitors it had almost fallen into disuse. This was because it also had unpleasant side effects: because spironolactone also binds to receptors of sex hormones such as testosterone and progesterone, it leads to very painful breast growth in men, for example. Many patients discontinued the treatment for this reason.

The kidneys induce increased fluid excretion

Kolkhof and his team have now found a novel active substance which very selectively and effectively blocks the aldosterone receptor. We also now know: "The earlier we give the aldosterone antagonist, for example after a heart attack, the more effectively we can prevent the pathological transformation of heart muscle which leads to the infiltration of connective tissue and the stiffening of the pumping organ," emphasizes Lentini.

The heart experts at Bayer HealthCare are also pursuing yet another treatment strategy: they want to help the kidneys excrete more water – but without the loss of electrolytes and without impairing renal function. Their newly developed substances inhibit the effect of the hormone vasopressin which, although it has important functions in the body in maintaining blood pressure, also causes reuptake of water via the kid-

neys and the constriction of blood vessels. This increases the pumping load on the the weakened heart, and leads to greater edema formation and shortness of breath. With their new drug candidates, the Wuppertal scientists want to prevent this in the long term – with few side effects.

"All three new therapeutic approaches taken together could fundamentally change the treatment of heart failure in the near future," says Kolkhof.

The individual approaches are already being tested. Not only is cinaciguat already going through the clinical trial process, but the promising aldosterone receptor antagonist has also overcome the first important hurdle: Bayer HealthCare management recently gave the go-ahead for the clinical phase. The vasopressin antagonist will soon follow – and if all goes well, the new treatments should be helping heart patients within a few years.



www.heartfailurematters.org

The website of the European Society of Cardiology contains further details about the heart, ranging from tips for a healthy diet to information about warning signs.

Finding targets: the scientists at Bayer Schering Pharma are looking for new therapeutic approaches to heart disease. Virtual representations of molecules help them to find the ideal binding point for a potential active ingredient.

