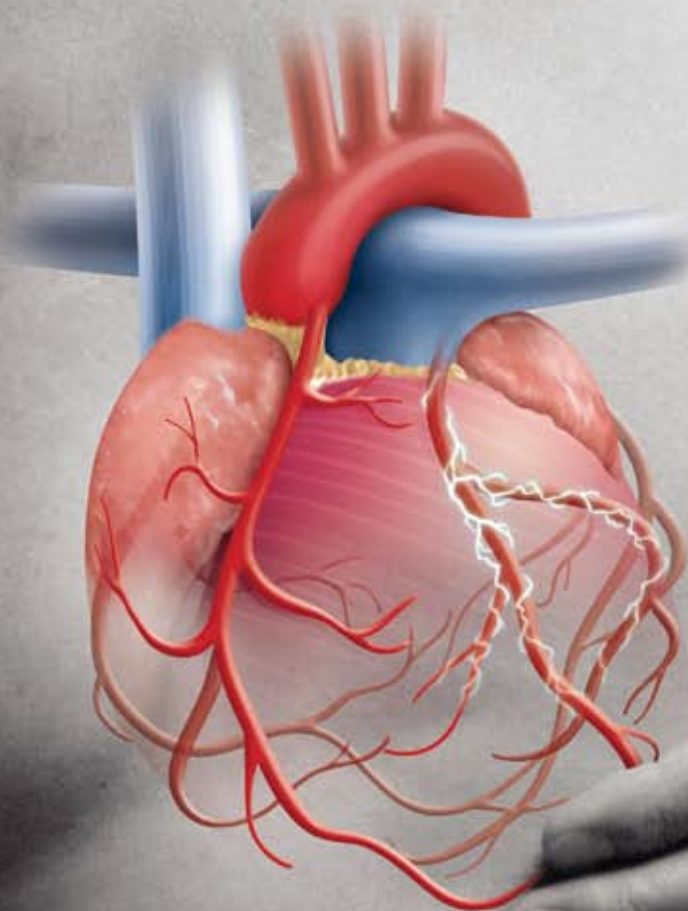


Discovery of a new active substance which controls raised heart rates

Be calm, my beating heart



Every year, a total of 15 million individuals around the world die as a result of the consequences of cardiovascular disease such as thrombosis, stroke and heart failure. The reason for this is not merely an unhealthy lifestyle. Another contributory factor is our body's inbuilt overreaction to stress, which causes sick hearts to race and sometimes even to lose their rhythm. Scientists at Bayer HealthCare have now found a substance which should prevent the heart from causing damage to itself by overreacting in this way.



Heartache: during angina pectoris attacks, regulation of the heart beat runs out of control (left). Michael Schulz enriches sample substances by means of centrifugation for molecular testing (above right).

If an engineer had ever built such a powerful engine, he would have guaranteed himself a place in the Guinness Book of Records: a hundred thousand times a day, more than 36 million times a year, our heart pumps the blood round the approximately 100,000-kilometer-long network of arteries, veins and tiny capillaries. This powerful hollow muscle provides every organ in the body with a regular supply of oxygen and energy.

However, the effect of years of high blood pressure, high cholesterol or blood sugar levels, nicotine and other poisons on the internal walls of the blood vessels can cause premature damage to this engine. Over time, more and more deposits from the blood accumulate there, causing the arteries to become narrower and less flexible. When there is a need for increased oxygen, for example for climbing the stairs or exercising, they are then no longer able to dilate adequately. It is this narrowing of the vessels which can later lead to a fatal myocardial infarction or stroke.

There are of course many drug products available to doctors today which can successfully lower blood pressure and cholesterol and blood sugar levels. "In many people's minds, the problem of cardiovascular disease is as good as solved," says Dr. Martin Bechem, Head of the Bayer HealthCare Cardiovascular Research Institute in

Wuppertal, Germany. Yet this impression is misleading, because the pathological transformation of blood vessels is still very much an ongoing concern. A classic sign of this is angina pectoris. This is the name given by doctors to sudden severe chest pains accompanied by tightness in the chest and difficult breathing which often make sufferers fear they are about to die.

Many heart conditions remain basically untreatable

The reason for an attack such as this is a sudden inadequate supply of oxygen and nutrients to the heart muscle which occurs with increased physical or psychological stress. As the disease progresses, attacks can happen out of the blue - even when the sufferer is relaxing in an armchair.

This is not all - there is a gradual increase in the risk of thrombosis, heart failure and cardiac arrhythmia, as well as the risk of suffering a myocardial infarction. "At this point," says Bechem "there is a shortage of optimal therapies." There is still no way of repairing myocardial tissue damage caused by heart attacks and, according to Bechem, with certain arrhythmias where the heart loses its rhythm and starts to race, "Doctors still have no idea how to treat these patients."

He hopes, however, that this will soon change, thanks to a new active

Cardiovascular test: Dr. Thomas Krahn investigates how the new adenosine substitute affects the physical performance of a mouse suffering from heart failure.

substance from Bayer HealthCare. With the aid of Bayer's own compound library, which has been consistently built up since the 1990s and today contains about 1.7 million compounds, the team behind biologist Dr. Thomas Krahn and chemist Dr. Thomas Krämer has developed a substance which prevents a pathological increase in the heart rate of angina pectoris patients. And there is evidence to suggest that the substance is not only better tolerated than the substances which have previously been available, stresses Bechem. "It also seems to target the actual causes of death amongst cardiovascular patients, such as heart attack, arrhythmias and heart failure."

This is because from the start, the dysregulation of the heart rate plays an

important part in the pathogenesis of cardiac complications. As doctors now know, a sudden loss of control of the regulation of the heart beat in angina pectoris patients can happen even with minor exertion. What happens before the attack is in fact quite rational: whenever increased demands are placed on the body, the muscles and organs need more oxygen than usual. The heart meets this demand by promptly beating faster and more strongly. As a result, per unit of time, more oxygen-rich blood reaches the cells throughout the body.

Normally, an increase in the pumping rate does not represent a problem for the heart, because as soon as it starts to beat more strongly, the coronary vessels which supply the pump



muscle with oxygen-rich blood dilate to compensate.

It is more difficult, however, when the coronary vessels have become too narrow and have lost their elasticity – as in the case of advanced arteriosclerosis. Even a small amount of additional effort means that the heart has to pump harder, in order to bring sufficient oxygen to its own cells. The fact that it is beating faster, however, means that it needs a good deal more oxygen than otherwise.

Vicious circle leads to angina pectoris attacks

In addition, with a rapid pulse, the heart has less time per beat to be perfused with fresh blood than with a resting pulse. This is because the heart is only sufficiently perfused in the phase in which it relaxes and dilates. Since, however, the vessels of a heart with arteriosclerotic changes are barely able to dilate, only a little oxygen reaches the cells. The body perceives the deficiency as an acute threat and releases large quantities of the stress hormones epinephrine and norepinephrine as a result.

From a certain point onwards, the process in angina pectoris patients becomes so uncontrolled that an attack occurs. "The heart virtually maneuvers itself under stress into a condition of acute oxygen deficiency," says Krahn in explanation.

Precisely how an attack develops remains unclear. What is clear, however,

according to the experience of Erland Erdmann, Professor of Cardiology at the Cologne University Hospital, "is that the pain is often so excruciating that patients believe that their end has come." And what is more, "Every angina pectoris attack also leads to further damage and even to the loss of myocardial cells."

A few years ago, Thomas Krahn had an idea: he set about looking for a substance which could prevent the disastrous increase in heart rate in angina pectoris patients in an almost natural way, thereby clearly distinguishing itself in its effect from other established treatments.

The body's own protective mechanism has been known for many years: as long ago as 1929, researchers discovered the substance adenosine which, amongst other things, lowers the heart rate when specific receptors in the heart are activated. Nowadays, doctors also know how it works: in the

conduction system of the myocardium in particular, with what are known as sinus and atrioventricular nodes, there are large numbers of adenosine type I binding sites which react specifically to the molecule adenosine. As soon as the messenger substance is released and "docks" onto these type 1 receptors, the heart rate is damped down.

Extremely unstable endogenous substance

For decades, therefore, scientists have been trying to make adenosine useable for the treatment of heart disease. But it is not quite so straightforward. Adenosine is not only extremely short-lived – after only a few seconds, the majority of the molecules are broken down in the body. It is also unsuitable for administration in the form of a pill. This is because as soon as adenosine reaches the stomach, it is destroyed. This is why pharmaceutical companies have

Automatic helper: a pipetting robot is an essential tool in the search for potential substances to treat angina pectoris.

The relaxation molecule

The tiny molecule adenosine is a real all-rounder. Not only is it part of the universal source of energy in cells, adenosine triphosphate (ATP), but it is also involved in the regulation of almost every cell in the human body. In addition, the human body has four different types of receptor which are stimulated by adenosine. The messenger substance therefore mediates different reactions according to the type of cell and the type of receptor.

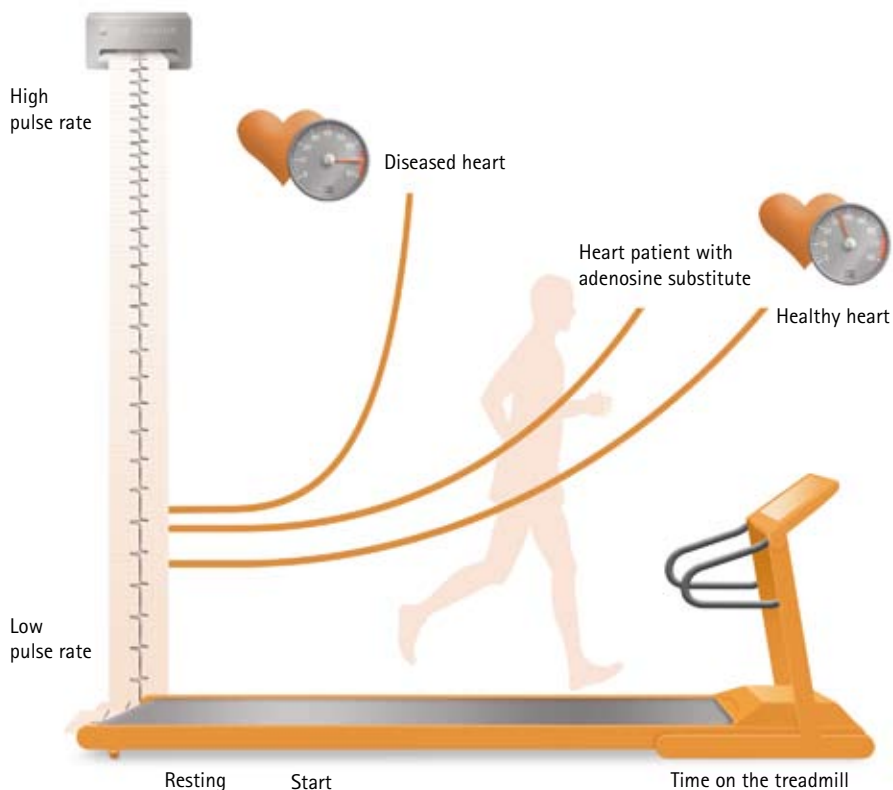
You can easily try out one of these for yourself: all you have to do is to drink coffee, cola or tea. This is because the caffeine contained in these drinks has the same receptors as adenosine. If these binding sites are blocked after you have drunk a strong cup of coffee, the body's own sedative is unable to exert its effect. This is why espresso, cappuccino, etc. liven you up and keep you alert and awake.

There are also well-known household remedies for the opposite effect. As scientists at the University of Bonn discovered in experiments with rats, valerian extract contains substances which bind to adenosine receptors in the brain. Unlike caffeine, however, these substances imitate the effect of the real messenger substance: they alter the brain waves by reducing those waves which are more pronounced in the case of nervousness. The body becomes calmer and more relaxed.

Of course, as with coffee, Homo sapiens came across this information long before the development of modern measuring techniques and pharmacology: even Hippocrates knew that valerian had a calming effect. And the self-test with coffee – most of us do that one every morning.

Efficacy on demand

The new adenosine substitute curbs the fatal increase in heart rate that causes the pulse of angina pectoris patients to race under even minimal exertion. The substance acts like a kind of speed regulator: it prevents the heart beat from increasing to unhealthy rates and thus protects the patient during exercise. The findings to date suggest that the substance has no effect on the normal, resting heart rate.



Synthesis: Dr. Nicole Diedrichs and Dr. Thomas Krämer have synthesized the adenosine substitute for experiments in the laboratory.

still not succeeded in bringing adenosine preparations to the market. Nor is there any specific preparation which, when administered in tablet form, activates the adenosine type 1 receptors. All preparations found so far have to be injected intravenously and are only suitable for short-term use.

Cardiovascular active substance discovered in record time

A few years ago, however, with the aid of the molecular screening technology developed by Bayer, the research team discovered a new substance class which imitates the effect of adenosine on the heart rate almost perfectly: it binds highly specifically only to those receptors which affect the heart rate, works at very low concentrations and has a half-life of only a few minutes. Best of all, however, the scientists had stumbled across the first type 1-specific adenosine substitute which is not structurally related to adenosine and can be administered orally.

Krahn is still enthusing about the fact that the search for the basic framework of the new medicinal product was successful after only a few weeks: "It was an amazing stroke of luck – like getting six numbers right in the lottery." Only two months after the discovery of the lead structure, the Bayer scientists were able to start their first strategic project. By way of com-



Cell tests: Dr. Barbara Albrecht checks cultivated cells to see whether the new adenosine substitute has exerted the desired effects.

parison: in other cases, scientists have trawled through their compound libraries for months or even years before finding a suitable candidate - if indeed they found one at all.

Of course, the chemists in the research team have now further "refined" their candidate. By making several small changes to the molecular structure, they have been able to extend its life in the human body from a few minutes to several hours. In addition, many experiments in the laboratory have shown the efficacy of the new substance.

Active substance shows its potential on the exercise bike

A few months ago, therefore, after the necessary safety and tolerability studies in healthy volunteers, the first clinical trials were started in patients. In each one, several angina pectoris patients were given a specific dose of the drug and then underwent to a normal exercise test: the patients had to sit on a bicycle ergometer and pedal until signs of angina occurred. The researchers then compared the heart rates of the trial subjects with and without the drug and the time for which they had managed to continue with their exercising.

Lo and behold: the results from these first trials suggest that patients who took the adenosine substitute with

the development name BAY 68-4986 had lower heart rates and were able to keep going for longer. As expected, the patients who did not take the drug were only able to pedal for a short time until the first symptoms of angina appeared, but after just one single dose of the new product they were able to achieve more.

Initial tests in patients went extremely well

Project leader Dr. Maria-Luisa Rodriguez of Bayer HealthCare is especially pleased with the clear result. "Normally with this type of test, if patients can pedal for even 30 seconds longer, it is considered to be clear proof of efficacy. The fact that we have achieved this effect with the lowest dose and with just one single dose naturally makes us very optimistic."

Unlike beta blockers, which up to now have been frequently used to control angina pectoris, the new Bayer drug appears to neither tire the patient nor to reduce the heart rate generally. Rather, the new active substance only inhibits the increase in heart rate which comes with stress or exertion, and the higher the initial rate the greater the inhibition. The resting pulse, on the other hand, remains unchanged.

Other studies are now needed to show whether the new Bayer substance will prove its worth in large-scale clinical

trials. If it manages to overcome the next hurdle successfully, there is unlikely to be a lack of demand. For one thing, many of the drug products which have been used up to now for the treatment of angina pectoris lose their effect after a while. "Every new drug product that we have is therefore valuable," says cardiologist Erland Erdmann from Cologne.



www.americanheart.org

The American Heart Association website provides information on cardiovascular disease.

Causes of death in Europe

The statistics show that cardiovascular disease is currently the leading cause of death in both the European Union and the United States. A low rate of child mortality and the successful suppression of infectious diseases have meant that people live longer. As a result, cancer and, above all, cardiovascular diseases are becoming increasingly significant, in many cases favored by cigarette smoking and poor dietary habits.

