

Riociguat: new active ingredient to combat difficult breathing

Lungs under too much **pressure**

Arterial hypertension in the lungs is often diagnosed very late, with fatal consequences. When diagnosed early on, however, modern drug products can at least relieve patients' suffering. Bayer researchers are now developing entirely new active ingredients that tackle the problem at its source. These substances are designed to significantly lengthen patients' lives as well as improve their quality of life.

It begins with palpitations, tiredness, difficult breathing or fainting – symptoms that are similar to heart failure or a lung disease. For this reason, this life-threatening disease is frequently not diagnosed in time. Yet high lung pressure, known as pulmonary hypertension in medical terminology, is not uncommon. It is estimated that up to 17 million people worldwide are affected by some form of this disease, although the gray figure may be higher.

Pulmonary hypertension can have different causes. It can be triggered by drugs and can also develop from diseases of the connective tissue or liver or as a result of heart or lung disease. Because there is no immediately noticeable damage to organs and the blood pressure in the systemic circulation is within the normal range, patients often traipse from doctor to doctor looking for a diagnosis. "A reading of 130 over 85 is only half of the blood-pressure story," warns internist Dr. Gerrit Weimann of Bayer HealthCare in Wuppertal-Elberfeld. Many people are still unaware that high blood pressure can also occur in the pulmonary circulation – ultimately with fatal consequences.

Because the pulmonary circulation is located deep inside the chest cavity, the world of medicine long paid little attention to it. "You can't just measure the blood pressure there from the outside with a cuff and stethoscope," explains Weimann. Precise diagnosis is only possible with a right-heart catheter – a surgical procedure in which a probe is inserted into the veins of the groin or the neck area and guided into the blood vessels of the lungs in order to measure the blood pressure there. If this pressure is significantly elevated, the diagnosis is pulmonary hypertension.

Five different causes for the disease

In humans, the right ventricle of the heart pumps oxygen-depleted blood into the lungs, where it picks up inhaled oxygen via the pulmonary alveoli. The re-oxygenated blood then flows back into the left ventricle of the heart. The pulmonary circulation system has only approximately one-seventh of the veins of the systemic circulation, yet has to transport the same amount of blood. Evolution has therefore ensured that the vessels in this system are especially elastic. If this elasticity is compromised, the consequences are fatal.

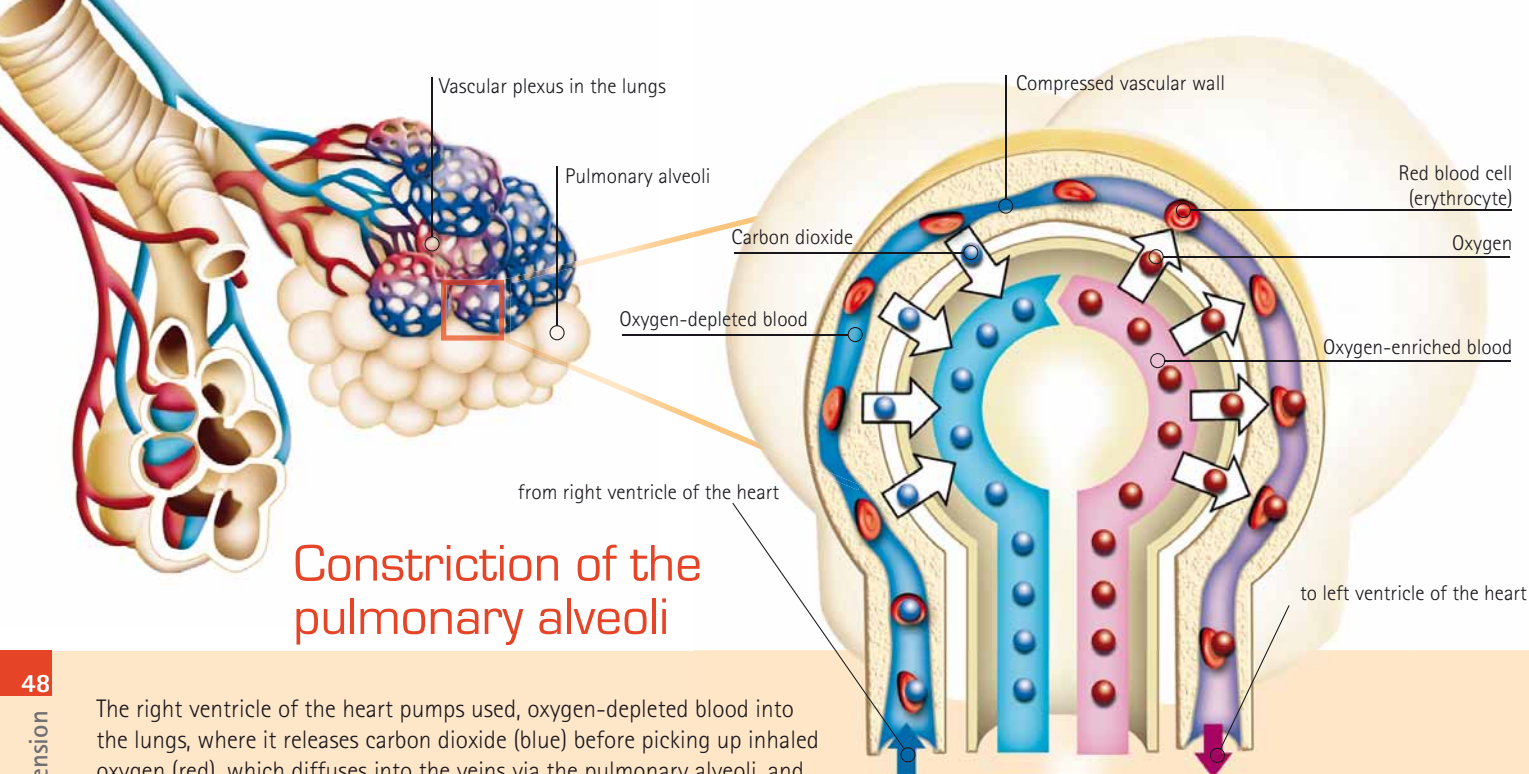
There are many potential causes: pulmonary hypertension can result from five different groups of primary diseases. Pulmonary arterial hypertension (PAH) is caused by still mostly unknown genetic factors or as a result of other illnesses such as rheumatic diseases, HIV infection or cirrhosis of the

liver. Pulmonary hypertension can also be triggered by left heart failure, chronic obstructive pulmonary disease (COPD) or chronic thrombosis and embolism. "All of these factors impair the arteries of the pulmonary circulation system," explains Weimann. They constrict, and the prolonged restructuring causes massive damage – the layer of smooth muscle cells alone grows several times thicker. The delicate vascular tube thus turns into "a car tire caked in cement," as Professor Friedrich Grimminger, a specialist from Giessen University Hospital (see also "Interview"), puts it.

In patients suffering from pulmonary hypertension, the walls of the vessels in the lungs are too thick or hard, constricting the passageway for the blood. As a result, too little oxygen is diffused. The heart must pump harder to push the insufficiently re-oxygenated blood back into the circulatory system. The pressure steadily increases. In the end, the overstrained heart is unable to keep pumping against the extreme pressure and fails.

Medications for this disease have only been available for approximately ten years. One important milestone in the development of active ingredients to combat pulmonary hypertension was prostacyclin (epoprostanol) and its synthetic derivative iloprost, which have since become an established therapeutic option for drug treatment of pulmonary hypertension. Iloprost and other substances can at least delay the ultimate consequences of right ventricular failure. They dilate the constricted pulmonary vessels, reducing breathing

Complex fresh air system: the colored X-ray of the heart and lungs shows how fine and delicately branched the vascular system that provides the human body with oxygen actually is.



Constriction of the pulmonary alveoli

The right ventricle of the heart pumps used, oxygen-depleted blood into the lungs, where it releases carbon dioxide (blue) before picking up inhaled oxygen (red), which diffuses into the veins via the pulmonary alveoli, and flowing back to the left heart. The blood vessels in the pulmonary alveoli are normally very flexible to allow them to adapt to the varying stress-related blood throughput requirements. In patients with pulmonary hypertension, as high blood pressure in the lungs is known, the vascular walls in the lungs are too thick or hardened and can no longer dilate sufficiently. This leads to less blood being supplied with fresh oxygen. This in turn stimulates the heart to pump harder and the pressure steadily increases until, ultimately, the heart can no longer manage to overcome the extreme pressure and fails.

difficulty and increasing physical endurance. As these effective forms of therapy can only be administered by catheter or inhaler, drugs such as bosentan, ambrisentan and sildenafil have also been developed in tablet form.

Despite all this success, however, there is still a need for research to further improve treatment for patients. Preferably, this is to be accomplished by clever use of other metabolic pathways that affect the elasticity of the pulmonary vessels. A group of Bayer research scientists headed by pharmacologist Dr. Johannes-Peter Stasch is therefore working on an alternative method. "The starting point for us was the discovery that the body's nitric oxide (NO) system is insufficiently active in patients with pulmonary hypertension," explains Stasch.

The gas nitric oxide (NO) is already familiar to the world of medicine (see *research* 17, "For an easy heart"). In 1998, the U.S. scientists Ferid Murad, Robert Furchgott and Louis J. Ignarro were awarded the Nobel Prize in Medi-

cine and Physiology for discovering how nitric oxide functions in the body. NO signals to the vessels to relax, and thus to dilate. NO is not suitable for long-term therapy, however: it is broken down within seconds and the body becomes accustomed to it, reducing the effect. There is a good reason that NO is so short-lived: it is only formed in the pulmonary vessels when they are mechanically dilated, permitting perfect adaptation to breathing. "The vessels in the lungs always expand when the pulmonary alveoli are filled by an intake of breath," explains Weimann. This is the body's way of ensuring that ample blood flows only to areas where gas exchange can occur.

PDE inhibitors block important signal substances

The fact that NO is so short-lived poses an obstacle to its clinical use, however. "NO inhalation in cases of pulmonary hypertension remains a form of emergency therapy only, for example in

neonates suffering from this disease or during heart operations," explains Weimann. The Bayer researchers wanted to attain more stable therapeutic effects. They realized that they would have to manipulate the processes which come into play after nitric oxide takes effect.

NO is formed in endothelial cells, the inner layer of cells in arteries, but rapidly diffuses to deeper-lying smooth muscle cells where it first activates the enzyme soluble guanylate cyclase (sGC). This in turn produces the messenger substance cyclical guanosine monophosphate (cGMP), which acts as the actual signal substance for relaxation of the smooth muscle cells. The logical result is that more cGMP leads to more elasticity in the vessels, thus reducing blood pressure sooner. The entire pathway is less active in patients with pulmonary hypertension – they have too little cGMP. One way of counteracting this problem is to slow the breakdown of cGMP. Phosphodiesterase (PDE) inhibitors can do just that. This method is ineffective



Combating pulmonary hypertension together: Bayer researchers (left to right) Dr. Gerrit Weimann, Dr. Maria-Luisa Rodriguez and Dr. Johannes-Peter Stasch are devoted to substantially extending the life expectancy of patients and hope that one day, their efforts will have helped to make this serious, frequently undiagnosed condition as easy to treat as high blood pressure.


for one in every four patients, however, perhaps because these patients produce so little cGMP that slowing its breakdown doesn't help. The Bayer researchers therefore set their sights on another goal: "We wanted to influence the guanylate cyclase as directly as possible – to selectively stimulate it with active ingredients," says Stasch in explaining the approach.

Promising substance already in several clinical trials

Beginning in 1994, a group of researchers in Elberfeld worked on the identification, synthesis and testing of substances which directly affect the enzyme – the guanylate cyclase (GC) stimulators. The many years of persistence finally paid off: in 2002, Stasch's group was able to present an entirely novel substance. This sGC stimulator unexpectedly displays two positive effects: it stimulates the enzyme directly via a different binding site than NO and laboratory tests also proved that these GC stimulators and the NO gas in fact mutually reinforce each other's effects.

"We have discovered a real pharmacological innovation to treat a disease for which new drugs are desperately being sought," says Dr. Maria-Luisa Rodriguez, manager of the global project team in Wuppertal working on bringing the new active substance to market. Clinical studies are already under way.

In several hospitals in Germany, patients with pulmonary hypertension were given tablets with the active ingredient riociguat in an initial Phase II study. The patients not only had to have their cardiopulmonary functions examined regularly; every 14 days, they also had to spend six minutes walking up and down the hospital hallways, going as far as they could. For many people with pulmonary hypertension, this six-minute test ends after 200 or 300 meters. "An additional 50 or 100 meters would be a great improvement," says Weimann. The trial is currently being evaluated and if it was successful, Phase III trials will start in numerous hospitals in Europe, North and South America, South Africa, Australia and Asia. The hope is that the new drug products will make the condition as easy to treat as high blood pressure.

 www.nhlbi.nih.gov/health/dci/Diseases/pah/pah_what.html
This site shows more information about pulmonary arterial hypertension.

Interview



"On suspicion of pulmonary hypertension, consult a specialist!"

Professor Friedrich Grimminger is the Director of Medizinische Klinik IV and V at Universitätsklinikum Giessen Marburg GmbH – the world's premiere center for treatment of pulmonary hypertension. The new Bayer active substance is being tested there as well.

Pulmonary hypertension is often diagnosed too late. What can patients who think they may be affected do?

General practitioners should always refer patients with non-specific breathing difficulties to a specialist, as we now finally have drug products that can reduce or even normalize pulmonary hypertension if treatment is started early. And we know that blood pressure in the systemic circulation hardly shortens life expectancy at all when the right drugs are prescribed early on. Why shouldn't the same hold true of pulmonary hypertension? In addition, we are hoping for further advances in pharmaceutical research.

Ideally, where should development go from here?

We need more drugs that don't dilate all of the constricted vessels in the lungs but only those which are supposed to transport blood. In patients whose lungs may have been partially destroyed by previous illnesses, it only makes sense to open those vessels which lead to areas of the lungs that are still aerated.

What results has your clinical Phase II trial with riociguat yielded thus far?

A Phase III program is scheduled to begin before the end of 2008 on the basis of these results. The new substances definitely represent a big step towards causal therapy. We believe that we can tackle the disease at its roots through the NO system.