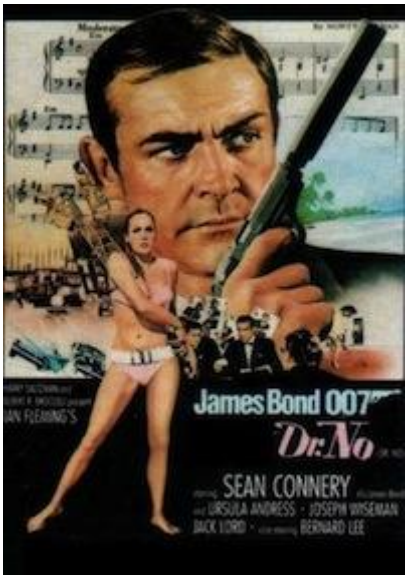
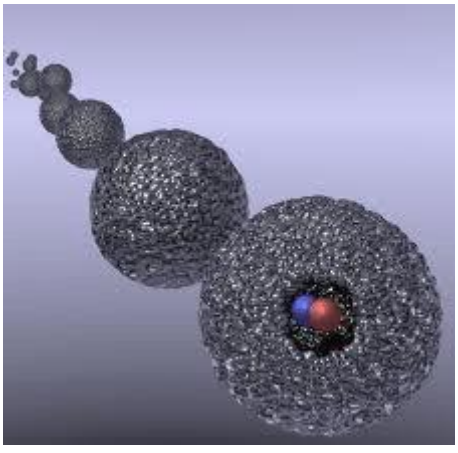
What is the connection between oxidative stress and heart attacks?

At this point I must acquaint you with **“NO”.** What is your first association? Maybe you remember “Dr. No” from the first James Bond film; the villain who was finally hunted down and caught by Sean Connery.



However, in this case NO is a chemical substance: nitric oxide. **“NO” is a small, highly active molecule that is produced in the blood vessel wall.** Every pulse, every expansion of the vessel wall caused by rhythmically pulsing blood stimulates the production of nitric oxide. NO passes easily through the cell membrane. It expands the blood vessels and passes into the heart muscle, where the production of “cGMP” is activated.



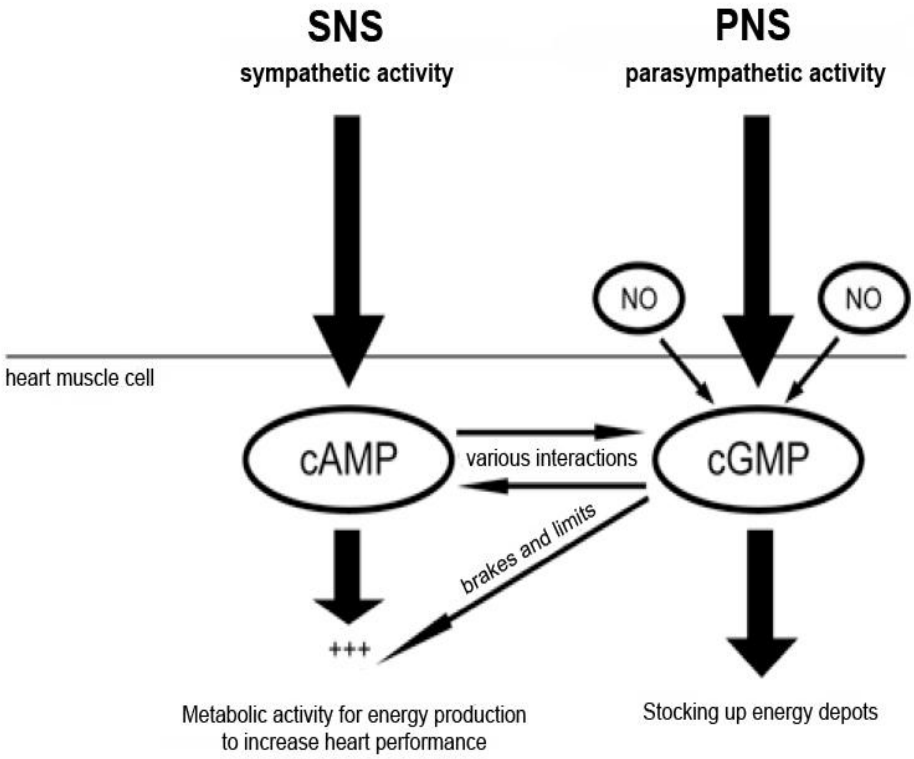
NO molecule in a nano droplet

For the curious among you

For those who want to go into more detail, I would like to first introduce the two rapid messengers “cGMP” and its antagonist “cAMP”. This is unavoidable if one is to

understand the relationship between oxidative stress and heart attacks. cGMP (cyclic guanonsine monophosphate) transmits the messages of the PNS in the cells of the heart muscles, as it does in other cells in the body; cAMP (cyclic adenosine monophosphate) transmits the messages of the SNS. SNS activity increases the content of cAMP, PNS increases cGMP in the cells. An increase in cAMP activates numerous reactions in the cell; likewise, a cGMP increase sets off other processes that often counteract one another.

These messengers transmit the commands of the PNS and the SNS control centers in the brain. The commands of the SNS stimulate activity, performance and energy consumption, whereas the PNS commands relaxation, regeneration, economy, cell protection and "homeostasis". In its concern for "homeostasis", the PNS ensures that the functioning of the cells remains balanced and does not get out of control.



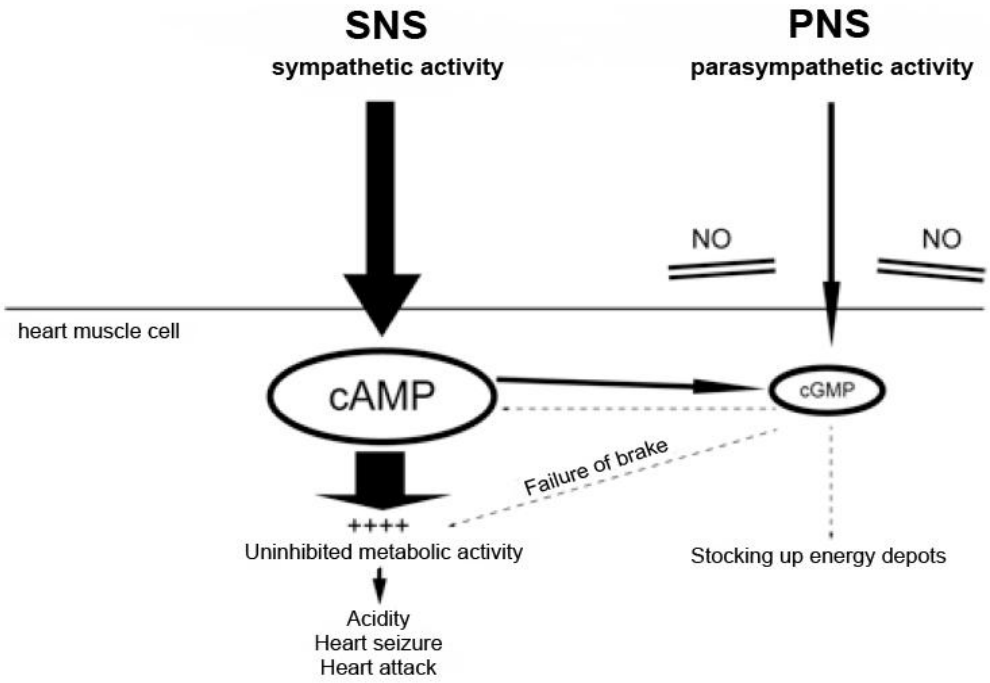
Balanced cAMP and cGMP

cAMP and cGMP influence each other in a variety of ways. One very important effect is that a large increase in one substance automatically activates the counter-pole. A large increase in cAMP causes an automatic rise in the level of cGMP. Due to this protective action, even if the stress is "at danger level", the heart muscle is not damaged. Serious increases in cAMP are limited by the activation of cGMP. (See above diagram.)

Getting back to "NO". The PNS increases cGMP content in the cell; NO also increases cGMP. A blockade of the PNS reduces the cGMP content in the cell. However, this is not critical, as long as sufficient NO is available. The crucial conditions are a blockade of the PNS and of NO at the same time. The resulting lack of cGMP leads to a failure of the metabolic brake. Under these conditions an uninhibited increase in metabolic activity will

result. Therein lies the danger of developing acidity ("acidosis") with heart seizure and heart attack. (See diagram below).

Free radicals impair the availability of NO; superoxide radicals react with NO and destroy it. **Oxidative stress destroys NO and robs the body of the numerous protective effects of NO on the heart and circulation. A lack of NO provokes a tendency to angina pectoris and heart attack**.



Disturbed balance caused by blockade of the "PNS" and "NO"

If NO is lacking, the arteries have a tendency to injury. NO expands the vessels. NO produced in the vessel wall with every wave of the pulse, allows the vessel wall to adapt to the blood flow; the stronger the blood flow, the greater the production of NO and the more the vessel wall dilates. NO thereby minimizes the "stress" caused by the blood flow on the vessel walls. If NO is lacking, the arteries lose their flexibility and have a tendency to injury. A lack of NO further increases the coagulability of the blood. A lack of NO as a result of oxidative stress is one of the most important factors in the development of arteriosclerosis.

The focus of research: "cGMP"

A defect in PNS heart control, together with the disappearance of "NO" due to oxidative stress leads to a chronic lack of "cGMP" in the heart muscle cells. If the situation becomes acute, acidity develops and there is danger of a heart seizure. Lack of "cGMP" appears to play a key role in this process.

Research into the "NO-cGMP" complex is currently in full swing. In an experimental setting, if cells of the heart muscle are subjected to simulated "ischemia" (bloodlessness), as occurs during a heart seizure, then these cells will die sooner or later. If, beforehand, one increases the cGMP content in the cells, then the cells are much more stable and resistant in such a situation (49,50).

It has been shown that cGMP is able to seal the mitochondria via a complex signaling pathway (51). The mitochondria are the "power plants" in the cell, in which energy-rich phosphates, the energy sources of the body, are produced via cell respiration. Sealed mitochondria are better protected against acidity ("acidosis") and all the other processes that play a role in the development of heart attacks. **cGMP plays a central role in the complex processes that ensure the survival of cells during a heart seizure or a threatening heart attack.**

cGMP prevents cAMP getting out of hand. cGMP inhibits the activity of metabolic processes that lead to acidosis during a heart attack (52). **cGMP protects the heart**. In future, cGMP will surely play an important pharmacological role in heart attack prevention. **However, the causal procedures to remove the lack of cGMP are, of course, more important: to strengthen the PNS and to reduce oxidative stress.**

The following illustration (53) shows a group of hormones that protects the heart and helps the heart muscle cells to survive. During recent years, more and more of these substances have been discovered. I have included this illustration just to give you an impression of the focus of current research in the "NO-cGMP axis".