INSIGHTS INTO SHOCK

By: Landry, Donald W., Oliver, Juan A. (*Sci. Am.*, February 2004, Vol. 290, Issue 2)

Doctors know what causes shock: very low blood pressure that results in dangerously reduced delivery of blood to tissues. And they know that it kills when the lack of oxygen irreparably damages the brain and other vital organs. They also have a few tools for reversing shock before it goes too far, at least in some people. But too often treatment is ineffective, especially when a runaway' infection is the trigger.

Because shock is so devastating, many investigators are aggressively trying to develop better treatments. Several seemingly helpful drug candidates have failed in recent years, but a chance discovery we made not long ago has led to a successful therapy. This agent does not cure the conditions that caused the shock, but it is already helping to treat thousands of shock victims. In addition, during the course of our research into this compound, we learned new information about the underlying mechanisms of shock.

Under Pressure

To understand shock, it helps to know a bit about the circulatory system, in which blood carries molecules over long distances. For most organisms, the heart provides the driving force for this flow, which, in turn, delivers crucial gases and nutrients to every part of the body.

Oxygen-rich blood makes contact with tissues through lots of branching vessels that culminate in small, highly permeable vessels called capillaries. Arteries carry the blood from the heart to the narrowest arteries, or arterioles, which then lead into the capillaries. For blood to circulate, the heart must generate enough force to overcome the resistance it meets as the passageways become smaller and smaller. Blood pressure is a measurement of the force applied to blood as it is pumped.

In humans, the heart pumps five liters or so of blood through 10 miles of blood vessels about 1,000 times a day. A mere six second cessation in blood flow can render an individual unconscious. Even a modest drop in blood pressure can deprive the brain of oxygen and leave a patient limp and dazed. In minutes other organs can become impaired. Shock has set in. If it persists and organs are irreversibly damaged, shock will lead to death.

Shock can be triggered in several ways and is often classified by its triggers. One of the most common causes, leading to what is called hypovolemic shock, is a rapid decrease in the volume of blood--as can occur when a trauma or a stomach ulcer causes extensive bleeding or when severe diarrhea drains fluid from the body. The heart pumps too little blood with each beat, and although it tries to compensate by increasing its pumping rate; it cannot do enough: blood pressure falls, and nourishment does not reach the tissues. In cases of hypovolemic shock, of which there are thousands every year, physicians try to stanch bleeding or other fluid loss and administer blood or saltwater, or do both, to replenish what was lost. And researchers are investigating new ways to stop bleeding--applying a paste to enhance coagulation, for example--as well as using substitutes for blood in cases where enough is not available.

Another form of shock, termed cardiogenic, arises when the heart stops pumping properly. If, say, a blood clot were blocking a coronary artery, preventing oxygen from reaching the heart muscle fed by that artery, a heart attack would occur: part of the muscle would become starved for oxygen and die, often leaving the heart unable to function normally. Alternatively, arrhythmia--too fast, too slow or nonsynchronized beating--or the failure of a heart valve to seal can also lead to cardiogenic shock. When cardiogenic shock occurs, physicians often try to perform one of various interventions. They administer medicines to increase the heart muscle's ability to contract, they undertake valve replacements (using a mechanical or a pig valve), or they implant a defibrillator, a device that delivers an electrical charge to the heart, keeping the heart muscle pumping at the right rate. If all else fails, they then try to find a heart for transplant.

The third and most common type of shock--the vasodilatory form--can result from cardiogenic or hypovolemic shock that has lasted for several days. In such cases, the heart may have been repaired or blood transfused, yet shock has persisted. But vasodilatory shock most frequently results from

sepsis, a severe infection in which bacteria or fungi run rampant in the blood, setting in motion an inflammatory response. White blood cells and other immune system agents disrupt the function of tissues throughout the body in a deranged attempt to fight infection. In this condition, the heart is blameless: the organ is pumping a high flow of blood, and the patient's skin feels warm to the touch. Instead the problem lies far away in the arterioles.

Researchers have long suspected that an understanding of what goes wrong in the arterioles could lead to improved therapy for vasodilatory shock. The story of why the arterioles behave abnormally begins well before shock sets in. The body's first reaction to falling blood pressure is compensatory--an effort to forestall shock-and this response centers in the arterioles. These hollow tubes are ringed by muscle cells that contract or relax, varying the width of the tube. The normal orchestration of the arterioles is highly complex and entails the input of myriad compounds--including norepinephrine, vasopressin, angiotensin II, dopamine and nitric oxide. As blood pressure falls, some of these actors become involved. Both norepinephrine and angiotensin II, which constrict the arteriole muscles, are secreted into the bloodstream; at the same time, the body halts the secretion of atrial natriuretic peptide, a protein that causes arteriole muscles to relax and the arterioles to dilate. If successful, these maneuvers cause the arterioles in places such as the skin and certain nonessential muscles to constrict, increasing their resistance to the incoming blood; meeting this resistance allows the blood to flow to critical organs such as the brain. To visualize this, imagine a garden hose that branches in two; if one branch constricts, the pressure in and flow through the other branch increases. It is the same with arterioles.

Failing Resistance

But if something goes wrong and certain arterioles fail to constrict, the blood does not encounter the resistance necessary to direct it on toward vital regions. Strangely, patients experiencing vasodilatory shock have high blood levels of both norepinephrine and angiotensin II. This fact suggests that the absence of constricting signals is not the problem. Clinical experience also supports this observation: when shock patients are given these two compounds, relatively little happens. Because of this puzzling result, many experts came to the conclusion long ago that something in the muscle cells of the arterioles was not functioning: the cells were not responding to their normal cues.

In the mid-1980s, however, researchers discovered that one root of the problem was not an error on the part of arteriole muscle cells; it was instead the action of a dilating agent. The body's most prominent dilator is nitric oxide, a simple molecule with wide-ranging effects. It became clear that the very infections that cause sepsis--such as pneumonia or meningitis-cause cells to increase their synthesis of nitric oxide.

A clinical trial designed to test a nitric oxide inhibitor--the idea being that once the dilator was taken off the scene, the constrictors (norepinephrine and angiotensin II) would succeed at their jobs, tragically caused higher than expected rates of death and complications. Nitric oxide has so many diverse and poorly understood roles in the human body that inhibiting it led to serious and unanticipated problems.

In 1992, we discovered an alternative way to constrict the arterioles during vasodilatory shock. It has long been known that every cell membrane has an electrical potential across it--in other words, the inside and the outside are differently charged. This happens for the most part because positively charged potassium ions reside inside cells, along with all kinds of negatively charged entities, but they also tend to leak outside, causing the outer part of the membrane to be sometimes slightly more positively charged than the inside.

In the case of arteriole muscle cells, this electrical potential is used to regulate the influx of calcium ions through calcium channels, which play a role in constriction. If the membrane's polarization is slightly more negatively charged on the outside, calcium channels open in response to norepinephrine or angiotension II, and calcium rushes into the cell. The cell then constricts. If the outer membrane becomes more positively charged, the calcium channels close, despite the urgings of the vasoconstricting hormones, and as calcium levels inside the cell fall, the muscle cell dilates.

Thus, the electrical potential determines the responsiveness of calcium channels to the hormones that brings about constriction. Simply put, the behavior of the arteriole muscles is orchestrated by calcium channels. But the passage of calcium ions depends on potassium-carrying channels to control membrane polarization properly. The channels are, in turn, regulated by a variety of compounds, including adenosine triphosphate (ATP), a form of cellular energy created by the oxygen-based metabolism of nutrients. When ATP levels drop, certain potassium channels open, allowing potassium to flood out of the cell, which causes the outer membrane to become more positively charged than normal, the calcium channels to close and the cell to relax.

We wondered whether the low-oxygen conditions of shock could reduce levels of ATP, leading to the relaxation of the muscle cells and a consequent decline in blood pressure. So we administered a compound called glibenclamide, which blocked the activity of ATP-sensitive potassium channels. And, indeed, the move boosted blood pressure. This mechanism explains why doctors giving norepinephrine or angiotensin II had little success increasing constriction: those compounds do not work well when the potassium channels are open.

Yet, as with the nitric oxide inhibitor described earlier, there were problems with the drug. Its effect was short-lived, and it led to low blood sugar when given in the high levels needed to reverse shock. (At lower levels, glibenclamide works to increase the pancreas's release of insulin and is used to treat diabetes.) It was a frustrating time. We knew that potassium channels regulated by ATP were important, and we knew that nitric oxide was important. But we could not figure out how to regulate them without causing harm elsewhere.

A New Approach

In 1997, an accidental observation changed the entire direction of our work. We had a patient who was bleeding in the esophagus and who later developed a serious infection. On admission, he had been placed on a hormone that would constrict his esophageal blood vessels and stop the bleeding there. This hormone, called vasopressin, was well known for its role in constricting arterioles--it acted throughout the body when released by the pituitary gland in response to low blood pressure. But previous clinical studies showed that when administered as therapy, it worked its magic solely on esophageal vessels. So we were not expecting to see any effect on our patient's blood pressure. To our surprise, we found that his blood pressure dropped when we stopped giving him the vasopressin. When we started administering it again, his blood pressure rebounded. Perhaps, we thought, the infection had somehow made our patient more sensitive to the hormone.

We had to determine whether this was a fluke. We needed to find a patient with septic shock, and we had to be very careful about the dosage and adhere to the heartfelt dictum of physicians, primum non nocere ("first do not harm"). So we gave a shock patient one tenth of the amount we had given the patient with esophageal bleeding, expecting to see no effect until we slowly increased it. To our amazement, his blood pressure rose dramatically. Further studies revealed that vasopressin levels in this and other septic shock patients were very low, even though logic dictated that the body would produce vasopressin to try to get blood pressure up.

We began to wonder why vasopressin deficiency developed in patients with vasodilatory shock. Our subsequent studies showed that at the outset of shock no matter its origin--levels of vasopressin are exceedingly high. But after a few hours, vasopressin declines. The body's stores are released when shock starts, the compound then degrades in the bloodstream, and replacement vasopressin takes a long time to synthesize. We subsequently found two reports (neglected because everyone had concluded that vasopressin did not raise blood pressure) that vasopressin reduces nitric oxide's dilating effects on arterioles and blocks ATP-sensitive potassium channels, allowing the calcium channels to open and the cell to contract.

Since these early discoveries, vasopressin has been examined in 10 small studies around the world, and it has been found to reliably restore blood pressure--with no significant side effects. An extensive multicenter trial is under way in sepsis patients to determine more definitively whether restoring blood pressure will reduce shock-related symptoms and deaths.