INSIGHTS INTO SHOCK

Still a last step before death for thousands of people, shock is shedding some of its medical mystery and becoming more treatable

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Whatever the cause--a heart attack, a car accident, a serious bacterial infection--**the glassy-eyed catatonia of a person in shock** often portends death. Every year in the U.S. alone, about 500,000 people go into sudden shock, and half die from it. For millions more, it is the final stage of terminal illness. Doctors know a good deal about what causes the condition: **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 all 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. **Yet** despite **their** initial promise, **several seemingly helpful drug candidates** have failed in recent years. To our great satisfaction, **though**, 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**. With luck, our insights and those of others may lead to further advances in treatment.

Under Pressure

TO UNDERSTAND SHOCK and its recondite nature, **it** helps to know a bit about the circulatory system. Early life in the earth's ancient seas used **a simple principle to obtain oxygen and nutrients and to dispose of carbon dioxide and waste**: diffusion. In **this process**, molecules move naturally from areas of high concentration to those of low concentration. **But** such life-sustaining diffusion proved efficient across only millimeters. Bigger creatures needed a more robust **mechanism**. Nature's solution was 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 **intimate arcades 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. In the roughly 280,000 cases of cardiogenic shock that occur annually in the U.S., 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. Sepsis affects 500,000 people in the U.S. every year; about half of **them** develop septic shock, and 125,000 die from **it**. 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. **Indeed**, efforts to tease out the source of arteriole malfunction led **us** to our unexpected discovery six years ago.

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** [see "Biological Roles of Nitric Oxide," by Solomon H. Snyder and David S. Bredt; ***SCIENTIFIC AMERICAN***, May 1992]. It became clear that the very infections that cause sepsis--such as pneumonia or meningitis-cause cells to increase their synthesis of nitric oxide. This news was

greeted with excitement, and investigators designed a clinical trial 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, the new treatment 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.

Then, in 1992, we discovered **an alternative way to constrict the arterioles during vasodilatory shock**. Our insight came from **brainstorming about how cell membranes work**. 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 [see "Patch Clamp Technique," by Erwin Neher and Bert Sakmann; ***SCIENTIFIC AMERICAN***, March 1992].

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 (rather than merely leak) 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 A SERENDIPITOUS 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. Anecdotally as well, we hear from doctor after doctor about **cases of restored blood pressure saving patients from the scythe of shock**, and many large medical centers around the world are now using it. **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**. Luckily, vasopressin is not patented, which means it can be produced without high cost.

The ongoing work on vasopressin is not the only front researchers and clinicians are investigating to thwart shock. In recent years, for example, scientists have pinpointed **elements of the inflammatory cascade triggered by sepsis**, which ultimately leads to shock. They are attempting to design antibodies--such as INNO 202--and other compounds that interfere with **certain of the actors in the inflammatory response**. They are also looking at the role steroids play in curbing the inflammatory response in some patients. It is hoped that these lines of research will result in **a set of lifesaving therapies for sepsis and shock**.

It has been very exciting for us to see **the different threads of knowledge about the cellular and molecular mechanisms of constriction, dilation and shock** come together through a chance observation. To have it translate so quickly into clinical practice in so many places has been most gratifying of all.

MORE TO EXPLORE

- Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock. Donald W. Landry et al. in Circulation, Vol. 95, No. 5, pages 1122-1125; March 4, 1997.
- The Pathogenesis of Vasodilatory Shock. Donald W. Landry and Juan A. Oliver in New England Journal of Medicine, Vol. 345, No. 8, pages 588-595; August 23,2001.

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