Decoding Scientific Literature

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Tiny desert rodents have found a way to take the sting out of scorpion venom.

A protein in the nerves of southern grasshopper mice hijacks the venom’s toxins, silencing pain signals that usually race to the brain when scorpions strike. The protein and venom together can even numb the animals to other types of agony, researchers report in the Oct. 25 Science.

“In these mice, the venom actually works like a painkiller,” says neuroscientist Frank Bosmans of Johns Hopkins University, who was not involved with the work.

The Arizona bark scorpion, *Centruroides sculpturatus*, wields particularly nasty venom. “It’s pretty painful,” says study coauthor Ashlee Rowe, an evolutionary neurobiologist at Michigan State University in East Lansing. “People say it feels like being branded, or burned with a cigarette, and then driving a nail in.” A hefty dose of bark scorpion venom can kill infants and small children.

Because the venom is so toxic to mammals, Rowe thought that bark scorpions must use it to defend themselves from mammalian predators. She decided to take a look at southern grasshopper mice, *Onychomys torridus*, carnivorous rodents known to chow down on scorpion species less toxic than bark scorpions. Other researchers had guessed that grasshopper mice might shun bark scorpions, or somehow dodge their stings.

About a decade ago, Rowe collected wild scorpions and mice in Arizona and placed the animals in a terrarium. The mice devoured the pests and didn’t seem to mind getting stung.

To investigate the animals’ high pain tolerance, Rowe and her team injected a drop of venom into the hind paws of house mice and grasshopper mice, and then timed how long the animals tended their wounds. House mice licked their injured paws for about four minutes, while grasshopper mice licked for just a few seconds. In the grasshopper mice, the venom injection even blocked pain from a follow-up injection of formalin, a chemical that provokes a burning sensation.

The researchers suspected that bark scorpion venom might somehow halt pain messages’ journey to the brain. In humans and house mice, venom toxins switch on a pain signal via proteins embedded in nerve cells in the skin. These proteins, called sodium channels, operate tiny gates to control the flow of sodium into the cell.

Venom cues the gates to open, letting sodium flood in and triggering neighbor-ing gates to open. The domino effect lets a pain signal race to the brain.

But when the researchers dissected pain-sensing nerves from grasshopper mice and added venom, one type of sodium channel behaved differently and stopped the usual flow of sodium.

If sodium can’t flow in, the pain signal peters out, says neuroscientist Thomas Park of the University of Illinois at Chicago. When scorpions sting the mice, he says, “the nerves say, ‘no, I’m not going to send that signal up.’” And when venom is around, the nerves can block pain signals from other sources too.

The mice’s pain-avoiding strategy is similar to that used by naked mole rats in Africa, Park says. Those animals resist pain from acidic environments by shutting down a different type of sodium channel. Park thinks other animals may also deal with pain in similar ways.

The findings will probably interest people designing pain-relieving drugs, says molecular neurobiologist Gary Lewin of the Max Delbrück Center for Molecular Medicine in Berlin. “Drug companies have been trying for at least the last 15 years to make specific molecules that block these channels,” he says.

“What’s nice about this story is that here comes evolution and actually shows how it can be done.”
With the score tied and 30 seconds left in overtime, Wes Leonard, a 16-year-old point guard for the Fennville Blackhawks, sank the winning layup that carried his team to a 57-55 victory on March 3, 2011. It was a Hollywood triumph for the final game of an undefeated season. Leonard’s teammates from his Michigan high school hoisted their star player skyward. Seconds later, to the horror of the packed stadium, the boy collapsed. Doctors at a nearby hospital soon pronounced Leonard dead of cardiac arrest.

By one often-used estimate, about 1 out of every 200,000 U.S. high school athletes dies suddenly each year, quite often in full view of shocked teammates and fans, sometimes on live television. Almost every one would have seen a doctor who used a medical history and physical to look for silent heart problems.

Under the specter of tragedies like Wes Leonard’s, however, some advocates want more rigorous tests. Their solution: Add an electrocardiogram (referred to as an EKG), which measures the electrical signature of the heart.

"Your gut instinct is to do everything you can to save a kid’s life," says N.A. Mark Estes, director of the New England Cardiac Arrhythmia Center at Tufts Medical Center in Boston. It seems to make sense: Identify players at risk of dying and bench them for their own safety. Already in Israel and Italy, competitive athletes ages 12 to 35 must have an EKG before they can step onto a court or playing field.

The problem is, for every life saved, the test
could mistakenly flag many more who aren’t in danger. Estes tells the story of a talented young athlete who came to his office after being recruited to one of New England’s legendary pro teams (to protect the patient’s privacy, Estes won’t publicly reveal which one). The young man’s electrocardiogram appeared to indicate massive cardiomyopathy, a dangerous enlargement of heart muscle that can trigger sudden death. Three previous doctors — “three very good doctors,” Estes is quick to say — had made the same diagnosis. Without ever seeing a minute of game time, a gifted prospect was in danger of being cut. Estes ordered more tests. “His MRI was stone-cold normal,” Estes says. The young man’s heart was nearly perfect. His risk of dropping dead was very slim, but by the time this became clear, the team had already let him go.

Heart of an athlete
The main problem is that, on the etchings of an EKG, the heart of a conditioned athlete might look too much like a heart with hypertrophic cardiomyopathy, the most common cause of sudden death in young athletes. With this inherited condition, the muscle cells that make up the heart are not stacked into tidy rows as they should be, and the heart walls grow thick and rigid. As a result, the waves of electricity that sweep across the heart to orchestrate rhythmic contractions can become disorderly. Under physical exertion, the heart can be seized by cardiac arrest and stop pumping blood — which is fatal within minutes unless the heart is restarted with a defibrillator.

An EKG can pick up signs of hypertrophic cardiomyopathy by detecting an abnormally high voltage when the heart’s ventricles contract. Yet often even to skilled eyes, the interpretation is not straightforward. The same telltale elevated voltage can occur in the muscled heart of an athlete as a result of conditioning, not disease, Estes says.

To add to the complexity, reading an EKG is not like measuring blood pressure, with distinct demarcations that anyone with medical training can understand. In a study published in the Journal of Pediatrics in 2011, 53 pediatric cardiologists read 18 EKGS from both healthy and ill hearts. They misread the results about 30 percent of the time. In addition, they ordered 380 follow-up tests that were deemed unnecessary and failed to order 340 further tests that were considered necessary for correct diagnosis. In 26 percent of the cases where the doctors would have recommended restriction from sports, the hearts actually were fine.

Opponents of universal EKG screening say that the risk of disqualifying healthy athletes — and of falsely clearing those truly in danger — far outweighs the test’s benefits. A misdiagnosis can be more than an inconvenience. It can saddle a young life with a diagnosis that may be hard to take back.

One ambiguous or misread EKG could write the next Michael Jordan or Wayne Gretzky out of sports history.

Estes recalls another patient who walked into his office on the brink of surgery to receive an

Silent risk
Years of training can reconstruct the heart of an athlete (middle) in response to a greater demand for fuel. An electrocardiogram can sometimes misdiagnose a healthy athlete as someone with a heart problem (right), but may also help identify those who are at risk.

**Heart wall cells**

**Normal** Cells in the heart wall are stacked like bricks, allowing an electrical signal to smoothly sweep across the muscle and regulate beats.

**Athlete normal** Heart chambers may enlarge and the heart wall thicken, but cells retain normal structure. EKGS may flag as abnormal.

**Hypertrophic cardiomyopathy** The heart wall is enlarged and its cells chaotically arranged, putting a person at risk for sudden death.
Implantable defibrillator. Estes determined that the teenager was, in fact, healthy. “There will be many people with the sword of Damocles over their head who believe they have the condition, when they don’t,” Estes says. “They could live their whole life with this diagnosis.”

He and others want to keep using the standard history and physical for student athletes.

“The problem is that the history and physical doesn’t work,” says Jonathan Drezner, a sports medicine specialist at the University of Washington in Seattle. He says 80 percent of young athletes who die do not have symptoms that a doctor can detect through routine methods. That means when he starts an exam, “I’m going to walk into the evaluation knowing I’m going to miss four out of five.”

And despite the uproar over false-positive rates of EKGs, he believes false-positive rates for history and physical can be even higher, with diagnoses that are made but often left unconfirmed.

The latest opinion of the issue is expected to come out this spring, when the American Heart Association releases an updated scientific statement on the screening of young athletes for heart disease. Up to now, the country’s premier voice on medical matters of the heart has not supported routine EKG screening for asymptomatic athletes. Whatever the new statement says, few in the field believe the matter will be settled.

### Counting headlines

Though heartbreaking when they happen, deaths from cardiac arrest are extremely uncommon among young athletes. In the United States, about 8 million high school and college students play sports, yet only about 100 die from cardiac arrest each year. That’s good news for athletes, but a burden for scientific study. Cases arise so infrequently that large randomized trials (considered the gold standard in medical research) are lacking. To capture the few athletes who might die or show symptoms of heart problems, studies would need to be so large as to make them logistically and financially challenging. That means scientists must cobble together research that relies on indirect measures to weigh the value of EKGs.

Central to the controversy is the true number of athletes at risk. “If you really think the incidence is 1 in 200,000 [per year], it’s hard to justify EKG screening,” Drezner says. “At one point, that was the best data we had.” That figure appears in a 1998 analysis of Minnesota high school athletes published in the Journal of the American College of Cardiology.

He contends the number is much higher. Estimates tend to rely on counting media reports, he says, since most, like the case of Wes Leonard, generate news stories. They don’t all, however, and he says even death certifications can be unreliable. In 2011 in Circulation, Drezner and his colleagues published a study that scoured not only the media, but insurance databases and records at
the National Collegiate Athletic Association from 2004 to 2008. He found 45 deaths from cardiovascular disease among athletes during that time, which, given the number of college athletes, would put the death rate from sudden cardiac death far above previous estimates, at about 1 in 44,000 per year among NCAA athletes. For reasons not understood, male basketball appeared to have the highest death rate, at 1 in 7000 players — far from the often-cited 1 in 200,000 number.

The incidence of cardiomyopathy in nonathletes is even harder to measure than in athletes, since the student who doesn’t die in a sports arena is unlikely to generate widespread media coverage. Among the young, more nonathletes die of cardiac arrest simply because they outnumber their athlete peers, says cardiologist Barry Maron, director of the Hypertrophic Cardiomyopathy Center at the Minneapolis Heart Institute Foundation. Maron is chairman of the heart association committee that is writing the new athlete screening statement. If it turns out that athletes are not at higher risk, policy makers have an ethical dilemma: Is it right to require screening only for sports participation if a member of the chess team has the same odds of sudden death?

Drezner is trying to calculate comparisons with nonathletes. Last year at the annual meeting of the American Medical Society for Sports Medicine, he presented data on the risk of sudden cardiac death in the general high school population. After studying the occurrence of cardiac arrest at more than 2,000 U.S. high schools, he determined that student athletes have a risk of cardiac arrest nearly four times higher than their peers.

**The Italian model**

The closest thing to a comprehensive look at the benefits of EKGs — the research often cited as a cornerstone in arguments for widespread screening — comes from a study headed by Domenico Corrado, a cardiologist at the University of Padua Medical School in Italy, whose study appeared in the *Journal of the American Medical Association* in 2006. He and his colleagues tracked more than 42,000 athletes between 1979 and 2004. Beginning in 1982, Italy launched a nationwide EKG screening program for athletes. Compared with the years before the screening program began, sudden death, mostly from cardiomyopathy, dropped by 44 percent in the first 10 years, and 79 percent between 1993 and 2004.

Overall, 55 deaths occurred in EKG-screened athletes, and 265 in nonscreened. Nearly 4,000 athletes had initial positive findings during the years of the study, but after further tests, only 879 were ultimately disqualified from playing. "All these findings suggest that screening athletes for

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**Shock to the heart**

The benefit of routine EKGs may be in question, but one proven means of saving young athletes in cardiac arrest is available today and under-used. Requiring automated defibrillator devices, or AEDs, at all schools and sports venues and making coaches and players keenly aware of the signs of sudden cardiac arrest can dramatically cut the mortality rate of players who go into cardiac arrest during practice or competition.

In case studies collected by Jonathan Drezner of the University of Washington, 16 of 18 athletes who suffered cardiac arrest during practice or games survived when their campuses were equipped with AEDs. "The defibrillator piece is so important," says Drezner, who published the research in 2013 in the *British Journal of Sports Medicine*.

Inspired by Drezner’s work and similar studies, the Wes Leonard Heart Foundation’s goal is to ensure that all schools have working defibrillators in easy-to-find locations around campus and people trained to use them. When Leonard collapsed, the crowd around him initially thought he was dehydrated or overheated; the recognition that he was in cardiac arrest came too late. When rescuers finally did locate an AED at Leonard’s school — they had to dig it out of a storage room — the battery was dead. While it’s not known whether an EKG could have protected his heart from stopping, a working defibrillator might have gotten it pumping again. — Laura Bell
Healthy or not? These lines on an EKG represent one heart's electrical activity. Interpreting this readout is not straightforward, even for skilled eyes. Cardiomyopathies is a lifesaving strategy, the authors wrote in the journal.

The Italian research profoundly affected the debate, says Maron, creating "a cottage industry of EKG screening." But he remains unconvinced. If anything, he says, the study affirmed the rarity of sudden death in athletes, with just 315 occurring during the 25 years. And it did not demonstrate that screening caused the drop in deaths, only that the two occurred simultaneously.

There is also the problem of equating the screening experience in the United States with that in Italy, says Estes. Italy has a sophisticated system for screening, he says, with referral centers that specialize in the interpretation of athlete EKGs. Drezner, who is also a team physician for the Seattle Seahawks, says that the false-positive risk is the critical point of discussion in this EKG debate. If it is 20 percent, it's not worth it. Yet it is high from a lack of skill "maybe what we want to focus on is training physicians to read an EKG in an athlete." In other words, if the root of the problem is that the U.S. medical system doesn't have enough expertise in athlete EKGs, the solution is to better train cardiologists, not abandon the idea altogether.

America's diverse population makes importing the Italian model even more challenging. For reasons that are unexplained, studies have found that the hearts of black athletes are more likely to undergo changes that could be mistaken for cardiomyopathy. Take one study, published last spring from researchers at St. George's University of London in the journal Circulation. Using EKGs and other methods, the researchers examined the hearts of 675 high-level athletes, including 300 black athletes. In addition to the enlargement of the left ventricle that is known to occur in highly trained athletes, black athletes were 10 times more likely than white athletes to have enlargement of the right ventricle combined with EKG abnormalities that could lead to a disqualification from sports because it mimics disease.

Considering the greater proportion of black players in the United States, the lack of infrastructure and the dearth of experience in reading EKGs of athletes, Maron believes, "in the United States, the percentage of false positives is going to be much greater." So are false negatives, he says, "which hurts the very population you're trying to help."

But Sanjay Sharma of St. George's, one of the researchers in the Circulation study of black athletes and a proponent of wider screening, says a takeaway like that misses the point. If the problem is that EKGs are likely to be misread, the solution is to make sure that they are performed by skilled cardiologists who can either take into account the normal remodeling of an athlete's heart, or order follow-up tests that will confirm a diagnosis. "In our clinical practice, our false-positive rate is only 2 percent," he says.

Any full assessment of the issue must consider not just the cost of needlessly derailing student aspirations, but also the financial burden of widespread EKG screening and the follow-up tests to verify a diagnosis. Those cost estimates are remarkably inconsistent. One study from researchers in Israel, published in the Journal of the American College of Cardiology in 2012, put the price of one life saved at more than $10 million.

"The idea that you could have a national mandatory screening program that cost $10 million because it might save one life is not something most scientists could relate to," says Maron. In total, U.S. costs could reach into the billions.

That said, another study presented at the European Society of Cardiology in 2012, this one of Swiss athletes, came up with a screening cost of $157 per athlete. And in March 2010, researchers from Stanford University published a study in the Annals of Internal Medicine also suggesting that screening, when compared with the years of life saved, could be cost effective.

As the debate continues, the stakes get higher. Participation in high school sports is growing, and with skyrocketing college costs, many student athletes push hard to win scholarships to fund their educational goals. On the sidelines, scientists and policy makers are left to figure out whether EKGs will be lifesaving diagnostic tools or wasteful impediments to promising athletic careers.

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