Black bear: medical marvel

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While a research team including Paul Iaizzo, Ph.D., gathers clues from hibernating bears about improving human health, the bears benefit, too. At left, biologist Dave Garshelis, Ph.D., assesses one bear's health status before checking on her cubs' growth. (Photo: Ann Arbor Miller)

U researcher heads to the woods to learn more about the human heart

BY DAN HAUGEN

In the mid-1990s, Paul Iaizzo, Ph.D., was studying muscle loss in intensive care unit patients when he received an intriguing phone call.

“How would you like to study a population of individuals who do not get weak even though they’re immobilized for four to six months?” the caller asked.

Iaizzo responded, “Well, that would be amazing.”

The caller was University of Wyoming wildlife biologist Henry “Hank” Harlow, Ph.D., and the population he was referring to was hibernating black bears.

Some patients who spend two to three weeks in an intensive care unit can lose up to 50 percent of their muscle mass, which slows recovery and can lead to ventilator dependence. Bears, on the other hand, can go four to six months without eating or activity and wake up ready to run.

How do they do it, and what if their secret could be translated to hospital patients?

Such questions have led Iaizzo from his lab in Minneapolis to bear dens in Colorado, Wyoming, and northern Minnesota.

Paul Iaizzo, Ph.D. (Photo: Brady Willette)

A unique population

Sitting in his windowless office in the basement of the University's Mayo Memorial Building, Iaizzo sips tea from a kitschy black bear coffee mug, the kind you can find for sale in any north woods gift shop. Wildlife scenes decorate the walls, and a pair of toy stuffed bears flanks a collection of physiology textbooks. The lanky surgery professor is dressed in a polo shirt, a pair of jeans, and well-worn tennis shoes that match his laid-back demeanor.

Iaizzo has spent most of his life in Minnesota. He grew up in the St. Paul suburb of White Bear Lake. He studied biology and chemistry at the University of Minnesota, Duluth, where running track and cross-country sparked his interest in applied physiology. He stayed in Duluth for his master's degree and then earned a Ph.D. in physiology at the Twin Cities campus.

When Harlow first called him more than 15 years ago, Iaizzo was establishing the University's Visible Heart Laboratory, where he was experimenting with reanimating swine hearts using a clear liquid that lets cameras capture what is happening inside the heart — groundbreaking work that he now performs on a smaller number of donated human hearts.

Harlow had been studying bears in Colorado and Wyoming and hypothesized that the animals lost very little muscle mass during hibernation, despite months of fasting and inactivity. But he needed a way to quantify his hunch. He found an answer in one of Iaizzo's articles describing a study that used a leg brace-type device to assess force and quantify muscle loss in hospitalized patients. Harlow asked Iaizzo if he'd be interested in collaborating.

"I'm from Minnesota," says Iaizzo. "I love the outdoors. I go to the Boundary Waters regularly. So I jumped at the opportunity."

Teamwork made it easier to weigh this 164-pound female black bear (Photo: Ann Arbor Miller)

Into the den

Iaizzo and his longtime collaborator Tim Laske, Ph.D., vice president for research and development at Medtronic, Inc., joined the team, and the following winter they headed to Colorado to visit their first bear dens. They brought along a modified version of the leg brace as well as tools for performing muscle biopsies on the bears. Their findings, which were published in the journal *Nature*, showed that hibernating bears do lose some strength — a mere 20 percent in certain muscles. But other muscle groups showed no loss at all.

The project has since expanded into an annual collaboration that includes work in northern Minnesota with University alumnus and adjunct professor Dave Garshelis, Ph.D., a world-renowned bear researcher with the Minnesota Department of Natural Resources. Each of the past eight winters, Iaizzo and Laske have joined Garshelis on visits to about a dozen bear dens around Minnesota, where Garshelis carefully tranquilizes the animals before the team takes measurements of the bears' morphology and physiology.

One thing they've found: hibernating bears' physiology favors muscles involved in their fight-or-flight response, including the heart and skeletal muscles, meaning a hibernating bear can still respond quickly if disturbed over winter.

A unique collaboration

The bear research is a unique, cross-disciplinary collaboration among biologists, an applied physiologist, and a biomedical device engineer.

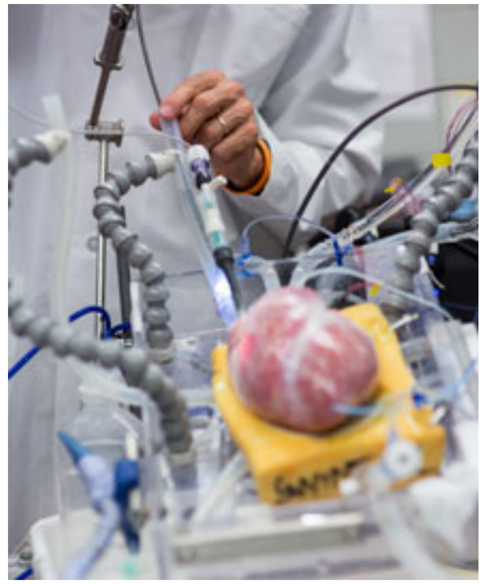
"You've got these different backgrounds coming together to talk through the data and think through what it all means," says Iaizzo. "It's really fun."

Laske, who studied wildlife biology in college before going into medical device engineering, worked with Medtronic to design implantable data loggers for monitoring bears' heart and respiratory activities. These data, along with the biopsies and Harlow's small mammal studies, are beginning to give a clearer picture of what happens inside hibernating bears.

"These bears, they're just a walking marvel," says Harlow.

A person who goes five seconds without a heartbeat will pass out, but Medtronic monitors show that hibernating bears go 10 to 15 seconds between heartbeats, with as few as five beats per minute. The bears have an extreme arrhythmia in which their heartbeat nearly stops between breaths and then speeds up to 60 or 70 beats a minute when they inhale. The energy-conserving condition means the heart doesn't have to work as hard during hibernation.

Iaizzo believes mimicking the bears' arrhythmia could someday be an alternative to inducing comas in intensive care patients. Controlling respiratory rates and pacing the patients' hearts, along with possibly injecting drugs that mimic bear proteins or acids, could allow doctors to induce hibernation instead of comas.



After hearts are reanimated in the Visible Heart Lab, they are scanned and stored in the lab's "heart library." The scans are used to produce detailed models and digital images. (Photo: Brady Willette)

University graduate student Mark Ditmer holds a black bear cub in northwest Minnesota. (Photo: Ann Arbor Miller)

From the woods to the ICU

Scientists have long been fascinated by the possibility that hibernating bears could hold the keys to advances in human medicine. "There's always been kind of this intrigue about bears because they are so special and so different from other animals," Garshelis says. In the 1980s, he collected bear blood and urine samples for a researcher who was searching for a miracle weight-loss treatment, a pill that would let people stop eating and burn only excess fat instead of muscle. Like other attempts, the project never unlocked the bears' secret.

Garshelis is more optimistic about his research with Iaizzo and Laske.

“I really think that because of the specific people I’m collaborating with, there’s a much higher chance of this actually making it into human medicine,” he says.

As part of that quest, Iaizzo and his students are experimenting in University laboratories with bile acids found in bear plasma and a hibernation-induction trigger — a delta opioid agonist — that appears to help tissue survive and recover from lack of oxygen. Could putting a patient into a hibernation-like state before, during, or after a shock — such as surgery or a heart attack — help the body withstand the experience and recover better? That’s a concept they’re considering.

The hunt for a secret agent

Ph.D. candidate Stephen Howard is investigating whether injecting bile acids and hibernation triggers from bears might help oxygen-deprived tissue prepare for the reintroduction of blood, which can sometimes cause additional shock and tissue damage, prolonging recovery time. He hopes to find an agent that could be injected before surgery or after a heart attack to help minimize damage. Knee replacement surgery, for example, often involves cutting off circulation to the leg with a tourniquet for 60 to 90 minutes. What if there were a way to first put that leg into hibernation?

The team is also looking for a mix of injections that would prolong the window of time surgeons have to perform heart transplants, which could save thousands of lives annually by extending the geographic range between donors and recipients. Today, from the time a donor dies, physicians have only four to six hours to recover the organ, transport it to the recipient’s hospital, and complete the surgery.

Iaizzo and his collaborators have been injecting bile acids and hibernation-induction triggers from bears into swine hearts before they are reanimated, observing some improvements in function. If this research progresses, they hope to find a way to treat both heart donors and recipients that would increase the number of possible transplants, improve outcomes — or both.

The paths to explore are many, and Iaizzo is just fine with that.

“I have one of the coolest jobs on the planet,” he says. “I get to do everything from bear research to collaborating with Medtronic on cutting-edge technologies to reanimating human hearts. I never get sick of doing this.”

Dan Haugen is a Minneapolis-based freelance journalist who writes about science, energy, and business.

To support work under way in the Visible Heart Laboratory, contact Amanda Storm Schuster at 612-626-2475 or a.schuster@mmf.umn.edu, or visit www.mmf.umn.edu/giveto/vhlab.

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