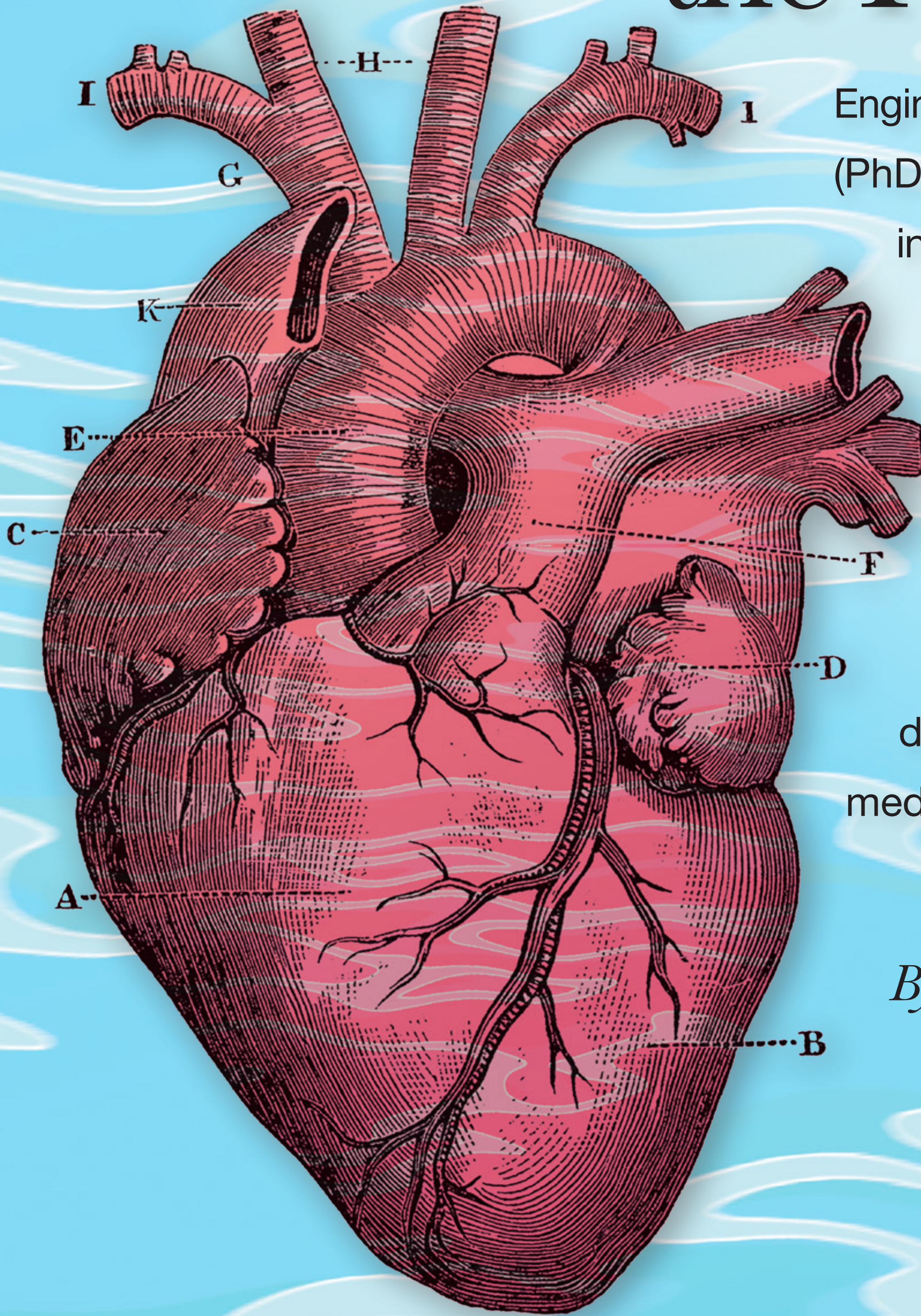
Ripples from the Heart



Engineer **Mory Gharib** (PhD ’83) delves into the mechanics of the body’s most critical biological pump to reveal its secrets and develop lifesaving medical devices.

By Katie Neith

The heart is an enigma that has mesmerized philosophers, physicians, and scientists for centuries. At its most basic level, it is a muscle that pumps blood throughout the body and delivers oxygen and nutrients to cells while removing waste. But if you look closer, the heart is much more than that, says engineer Mory Gharib (PhD ’83), who has not only been intrigued by the organ’s mechanics but has spent decades trying to understand how it functions at its most fundamental levels.

“It’s a fascinating physiological machine,” Gharib said in his 2023 Watson Lecture, “Enigma of the Heart,” noting the organ’s remarkably intricate structure of four chambers and four valves represents a wonder of evolutionary engineering. “It is also a sensory organ that can detect changes in environment and respond to them in complex ways. It beats up to 2 billion times over our lifetime. We can’t find any mechanical machine that lasts that long. It is one of the most impressive autonomous systems in nature—as long as it is taken care of.”

The pursuit of enhanced cardiological care has been bolstered in recent years thanks to Gharib’s expertise in fluid dynamics and aerodynamics. While the study of how aircraft fly and how the heart pumps blood may seem like unrelated fields, phenomena such as vortex dynamics and turbulence affect planes and the human body alike. “All it requires is somebody to be curious and try to connect the two,” Gharib says. He and his team apply their knowledge to the development of more sustainable and efficient medical devices and technologies that can both harness information hidden within pulse waves emitted by the heart and lengthen the organ’s lifespan.

Over his career, much of which has been spent at Caltech, Gharib has welcomed the challenge of finding creative solutions to a wide range of problems, especially those involving the fluid dynamics of biological machines. He traces this trait back to his childhood in Tehran, where his brother, a pediatric surgeon, came to him with an intriguing idea. “I was in high school, and he challenged me to design a shunt for hydrocephalus, which occurs when the pressure in the brain goes up due to a buildup of cerebrospinal fluid,” Gharib says.

Gharib finally completed the design 30 years later after investigating how liquid flows and pulses in and around the brain. He and his brother now hold a patent for a pump that is small enough to be implanted without interfering with the brain’s functions.

Listening to His Heart

Gharib remembers the day his cardiac curiosity was first sparked. After receiving a PhD from Caltech in 1983, he worked for two years as a senior scientist at JPL, which Caltech manages for NASA, before joining UC San Diego as a professor. “We were working on an experiment trying to see the drag reduction around submerged bodies, like underwater vehicles,” Gharib says. “The room is dark, the laser is going, and the head of pediatric cardiology just walks in and says, ‘Can you tell me why your engineers aren’t working to design a better heart valve?’”

Current mechanical replacements for valves—the parts of the heart that open and close to regulate the flow of blood through the organ—are rigid and damage blood cells. Plus, they are loud; the metal “doors” make an audible noise when they click back and forth. The alternative—biological valves from pig hearts—typically last 10 to 15 years. And they are expensive, both in the cost to prepare them for transplantation and in the lives of the pigs themselves. Gharib knew there had to be a better solution.

He returned to the Institute as a faculty member in 1992, and with the help of lab members and other Caltech faculty, Gharib spent years exploring the mechanics of animals. Jellyfish propulsion, the vascular systems of embryonic zebrafish, and the respiratory systems of dragonfly larvae taught him more about how nature builds valves, which proved valuable to his concurrent research in how blood flows, pulses, and pushes through the human heart. After analyzing how the fluid dynamics they observed might be affected by different materials used to create artificial valves, Gharib and some of his students teamed up with the late Caltech chemist and Nobel laureate Bob Grubbs, who lent his polymer synthesis and characterization expertise to help Gharib’s team design a biocompatible, polymer-based mitral valve. The device has no pig or other animal parts and can be manufactured by programmable robots, reducing the cost of each valve by thousands of dollars.

The mitral valve, one of the heart’s four valves, regulates the flow of blood from the upper left chamber (the left atrium) to the lower left (the left ventricle), which is the heart’s main pumping chamber. When the mitral valve weakens or is damaged, the amount of blood being pumped from the ventricle and into the body is reduced; this can lead to fatigue, dizziness, irregular heartbeats, and even heart failure if left untreated.

The TRIA polymer heart valve.

Gharib co-founded Foldax, a Caltech-funded company committed to delivering polymer heart valves to patients in urgent need. In 2019, doctors implanted the valve, called TRIA, into a patient for the first time as part of an FDA clinical trial. The Foldax team, together with the patient, recently celebrated the fifth anniversary of the successful procedure.

Foldax is currently sponsoring clinical trials of the TRIA mitral valve in India for young female patients who have had rheumatic fever, an inflammatory disease more common in developing countries that can cause severe mitral valve damage. Currently, women of childbearing age have only two options if their mitral valve begins to disintegrate: a mechanical valve that requires the patient to take blood-thinning medication for the rest of their life and can lead to pregnancy risks, or an animal-tissue valve that might degenerate and thus require multiple replacements through open heart surgery.

"The TRIA polymeric mitral valve represents an opportunity for these patients to obtain a better quality of life with a valve that can last their lifetime," says Ken Charhut, executive chair of Foldax and a co-founder, adding that Caltech's backing played a crucial role in the device's development. "It's not only Mory who's unbelievable. Caltech is unique in the way it supports technology and is committed to supporting the road to success over immediate financial gain." Charhut worked as a biotech executive for more than 40 years and has teamed up with Gharib on numerous projects over the past 30 years.

The trials in India represent the largest clinical evaluation to date of a polymer heart valve in humans. The data will be submitted for commercial approval of the valve upon the trial's completion; early results have been positive. "We're saving lives and at a low cost," Gharib says. "Millions can potentially benefit from this device in a way that I hope helps to make it more affordable."

A Wave of Discoveries

One of the heart's mysteries that has piqued Gharib's curiosity is the idea that our pulse might encode information about our health beyond simple heart-rate readings. So, Gharib challenged the students and staff in his lab to help him figure it out. Through that collaborative process, he and his students were the first to calculate that for every heartbeat that generates a pulse, an ensuing wave returns to the heart, bringing with it information in much the same way that sonar bounces back to a submarine.

"When the heart contracts, it generates a pressure wave," explains Alessio Tamborini (PhD '23), who studied with Gharib as a graduate student and is now a postdoctoral research associate in Caltech's Andrew and Peggy Cherng Department of Medical Engineering. "As this pressure wave propagates through the vascular system and eventually returns to the heart, its morphology changes in a patient-specific way. By capturing and analyzing this waveform, we can gather information noninvasively about an individual's cardiovascular health."

But Gharib's team first needed to figure out how to extract that information for use in diagnostics. They decided to combine two common devices—a blood pressure cuff and an electrocardiogram patch—with a machine-learning algorithm to detect pulse characteristics associated with heart failure. More specifically, they developed a noninvasive way to measure the pressure that builds in the left ventricle immediately before the aortic valve opens to let blood flow out into the body's arteries. Left ventricular end-diastolic pressure (LVEDP) is greatly elevated in patients with heart failure.

"We collected pulse data from patients with various stages of heart failure," Gharib explains. "This information allowed us to then develop software to detect high LVEDP, a sign of heart failure, which affects millions of people worldwide and is hard to catch in the early stages."

This work led to Vivio, the first and only device to enable noninvasive clinical diagnosis of heart failure. Current diagnostics often require cardiac catheterization—a process in which a tube is inserted into a major artery and maneuvered through the body to the heart—to accurately diagnose, and sometimes treat, the condition.

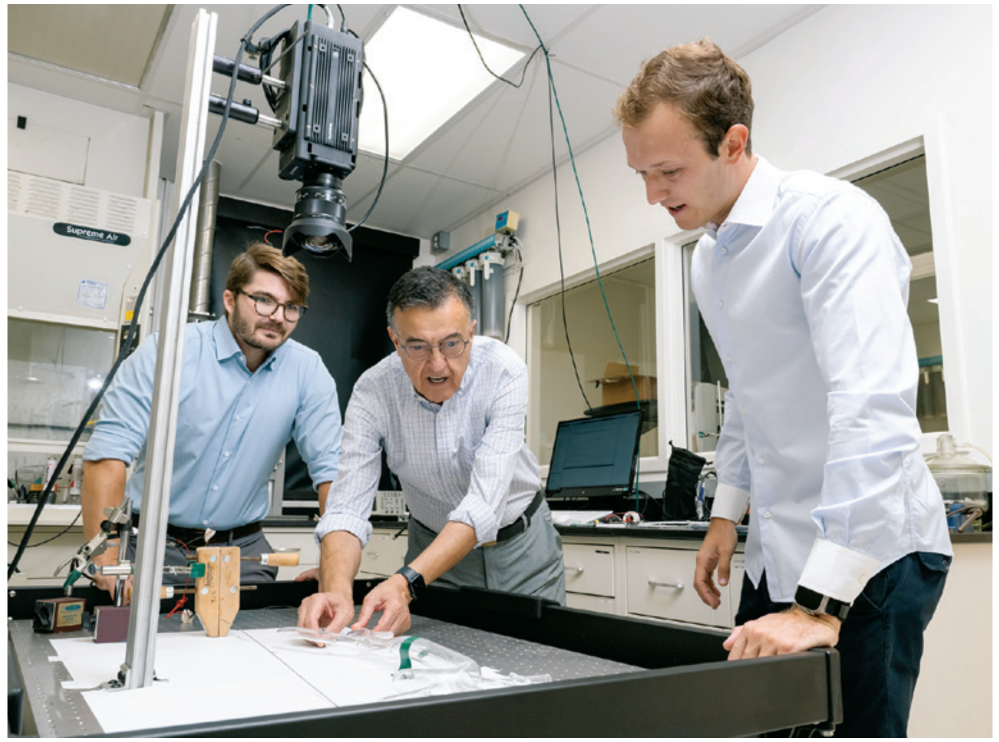
Vivio, on the other hand, does not require a trained specialist to operate it. A health care provider simply needs to place a cuff on a patient's arm and push a button. The information is then collected on a tablet computer that connects to the cloud, where the data can be reviewed by physicians. This means it can be used in patients' homes, in nursing homes, and in rural communities that might not have easy access to a range of diagnostic tests. "Four or five years ago, this work began as just a box of wires, but now, after multiple iterations, it is being used in clinics by physicians as a cardiovascular diagnostic tool," Tamborini says. "I love being able to develop medical device prototypes in the lab and seeing them evolve to potentially impact human health."

Using the noninvasive Vivio for diagnostic tests also lowers exposure to radiation for both patients and their cardiologists during catheterization because the new device does not require using X-ray technology, while a fluoroscope uses live X-rays to guide the catheter as it moves through an artery to the heart. "We hope to shift the way in which heart failure and other cardiovascular diseases are diagnosed," says Sean Brady, CEO of Ventric Health, a company he co-founded with Gharib and Caltech alumni Niema Pahlevan (PhD '13) and Derek Rinderknecht (PhD '08) to bring Vivio to market. "Earlier diagnosis allows for earlier intervention, improved outcomes, and an overall better quality of life for patients," Brady says.

Right: The Vivio device, which noninvasively measures pressure buildup in the left ventricle, enabling clinical diagnosis of heart failure.

Ventric Health received FDA clearance for Vivio in 2023 and launched commercially in 2024. The device has been used on more than 2,000 patients since its launch as the rollout continues, Brady says.

Tamborini and Gharib are also working to expand Vivio's capabilities. They believe the device could be used not only to diagnose heart failure but to predict onset of the condition by monitoring pressure measurements both in high-risk situations and over time. Combined with advanced data analysis and machine learning, the product could be used, for example, during surgery or in an emergency room to get real-time readings of a patient's heart health. "Often, the cardiac pulse signal is used in combination with other clinical measurements to give detailed diagnostics of the heart," Tamborini says. "Our objective is to build a comprehensive device to assess pressure throughout the cardiovascular system, enabling physicians to noninvasively understand how the heart is functioning and where it might be failing. This could provide physicians with more accessible information to support more informed clinical decisions."



Alexandros Rosakis (PhD '23), left, **Mory Gharib** (PhD '83), center, and **Alessio Tamborini** (PhD '23) working on their new heart catheter system in the lab.

The Shape of Catheters to Come

Although Vivio could reduce the need for catheters in some diagnostic tests, those catheters are still needed to perform heart biopsies, repair heart defects, and implant stents and replacement valves. That is why Gharib is also working with Alexandros Rosakis (PhD '23), an aerospace research scientist at Caltech who performed heart valve research in Gharib's lab as part of his graduate and postdoctoral work, to design a new shape-sensing cardiac catheter.

To eliminate the radiation risks that come with visualizing the steering of a catheter through blood vessels to the heart for these intricate procedures, Rosakis and Gharib, along with aerospace graduate student Ioannis Mandralis (MS '22) and others at Caltech's Center for Autonomous Systems and Technologies (CAST) have developed an inexpensive catheter guide wire equipped with sensors that can be located using ultrasound instead of X-ray technology. "For our catheter, information from the sensors is combined with a preexisting MRI scan of the patient, which allows surgeons to 'see' the catheter as it travels through the body without the need for direct imaging of the body," says Rosakis, who also works at Foldax. "The data is then fed into an algorithm so that AI can help inform the catheter how to move based on the shape of the artery it is traveling through."

The team soon plans to test the new catheter system in a tabletop model of the vascular system, which will gauge how accurately the device can be navigated from outside the body using a combination of human and AI input. "It's very exciting," Gharib says.

Even after decades of success and multiple spin-off companies that are advancing health care, Gharib is not done delving into the enigmas of the heart. There are, after all, still questions to ask about this complex organ and its individual components, and Gharib sees the Institute as the place where he and his colleagues will be able to find their answers.

"At Caltech, we don't educate technicians, we educate visionaries," Gharib says. "I'm proud that, together with my students, I've been able to come up with unique solutions that not only improve health but do so inexpensively, ensuring that large populations can access them in a more democratized system of care."

Mory Gharib is the Hans W. Liepmann Professor of Aeronautics and Medical Engineering, director and Booth-Kresa Leadership Chair of Caltech's Center for Autonomous Systems and Technologies (CAST), and director of the Graduate Aerospace Laboratories of the California Institute of Technology (GALCIT).

Watch Mory Gharib's Watson Lecture