NEW UNDERSTANDING OF WHEN WE'RE AT RISK FOR VENTRICULAR FIBRILLATION

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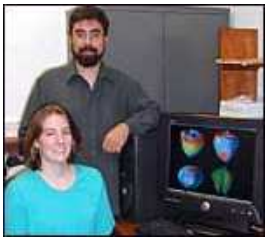
Ventricular fibrillation —two big words that mean a frenzied, irregular heartbeat that kills. In the United States alone, this condition claims hundreds of thousands of lives each year.

Cardiac arrhythmia is a generic phrase that covers many kinds of heartbeat irregularities —from the occasional skipped beat, which happens to many of us, to various flutters and throbs. Ventricular fibrillation is a cardiac arrhythmia, but in a class by itself for rapid fatal consequences. The heart's built-in synchronization, which keeps millions of muscle cells firing in coordinated wave-like rhythm, goes awry. Instead of a muscular blood pump that sustains life, the heart suddenly becomes a wriggling lump of fibrous tissue. Unless normal heartbeat is restored, blood pressure goes to zero in minutes.



Flavio Fenton and Elizabeth Cherry

What happens? "After decades of research," says Flavio Fenton, director of electrophysiology at the Heart Institute, Beth Israel Medical Center, New York City, "we still have only an incomplete understanding of how ventricular fibrillation initiates and evolves."

To bring a systematic approach to understanding these problems, Fenton leads a research program that combines clinical, experimental and theoretical work with an emphasis on computer simulation. Using LeMieux, Pittsburgh Supercomputing Center's terascale system, Fenton and his colleagues have incorporated the effects of arrhythmia-inducing drugs into whole-tissue models, the first time this has been done, obtaining excellent agreement with experimental results. And in other recent work, they show that a popular hypothesis for predicting the likelihood of fibrillation is incomplete.

"Despite the seriousness of the problem," says Fenton, who also works with the Center for Arrhythmia Research at Hofstra University, "treatment for some arrhythmias at this time is in general unsatisfactory." Implantable defibrillators help many patients, once they're diagnosed as at risk, but many deaths from fibrillation occur in people with no prior symptoms. Anti-arrhythmic drugs work with varying success, although how they work isn't clearly understood, and some research has shown that the same drugs that suppress fibrillation can, in other circumstances, trigger it.

Fenton and his colleagues have developed models that combine cellular details of electrical transmission with realistic heart anatomies. In this, their work is at the forefront

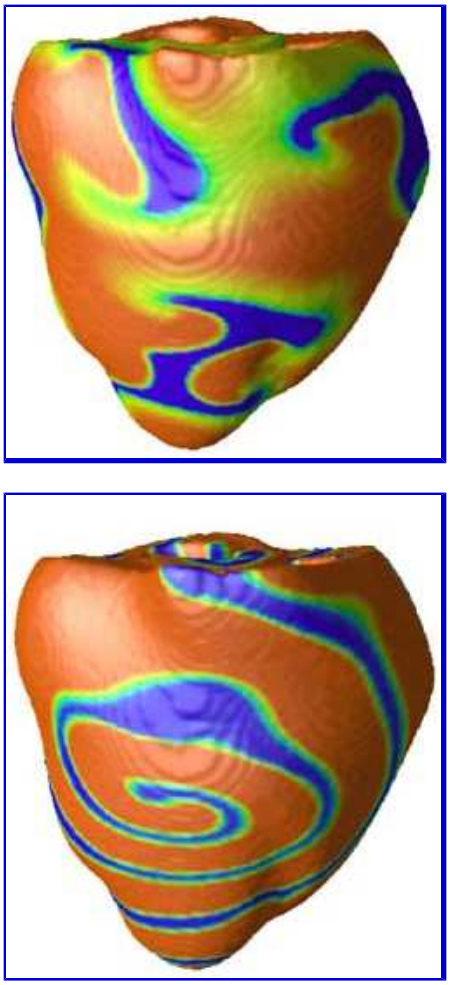
of computational cardiac electrophysiology. "The heart is complicated," says Fenton, "because there are so many variables. Computational modeling is an invaluable tool as a complement to traditional experiments because it allows us to ask and answer questions that we otherwise can't investigate."

Waves of Bioelectricity

The steady lub-dub we call the heartbeat is regulated by a built-in pacemaker —the sinus node, a small piece of tissue at the top of the right atrium, which sends out electrical pulses about once a second. These pulses stimulate channels in nearby cardiac cells to open. In this "excited state," the cell allows ions to flow in and out, which in turn excites nearby cells, generating a cell-to-cell electrical wave that flashes in milliseconds from the atria to the ventricles and becomes the concerted muscular contraction that pumps blood.

Research shows that many dangerous arrhythmias occur due to "reentrant waves" —in effect, a mistimed electrical pulse that interferes with the normal pattern and loops through the heart-muscle fibers at high frequency. These rapid arrhythmic pulses tend to circle back on themselves, like a dog chasing its tail, and form spiral waves. With a single spiral wave, the resulting fast heartbeat is known as tachycardia. When a single spiral wave becomes unstable and breaks down into many smaller waves, tachycardia transforms into potentially lethal fibrillation.

What's known about these reentrant pulses represents a bare outline, from which Fenton's team works to fill-in the blanks. "The complicated structure of cardiac tissue, as well as the complex ionic currents in the cell," says Fenton, "has made it extremely difficult to pinpoint the detailed dynamics of these life-threatening, reentrant arrhythmias."



Click Image to Enlarge

Cell-to-Cell Coupling in a 3D Rabbit Ventricle
These images show cell-to-cell coupling effects in a 3D computational model of rabbit ventricles. Colors represent electrical potential, showing excited tissue (orange) distinct from quiescent tissue (dark blue) and intermediate voltages (yellow & green). In one model (top), spiral waves break into multiple waves. In the other model (above), with identical restitution properties, cell-to-cell effects suppress alternans and prevent breakup of the spiral wave.

"COMPUTATIONAL MODELING ALLOWS US TO ASK AND ANSWER QUESTIONS WE OTHERWISE CAN'T INVESTIGATE."

Over the past several years, they have developed a set of computational models that allow them to do basic research on how arrhythmias get started and evolve, both as a function of the electrical properties of heart cells and larger-scale heart anatomy. "To represent anatomical complexity," says Fenton, "the cells must be formed into realistic geometrical structures, including several distinct cell types that influence arrhythmia dynamics."

The models draw on the branch of mathematical physics called nonlinear dynamics, which analyzes the evolution in time of systems whose components compete and interact in ways that make the whole more complex than simple cause-and-effect relations among its parts. Because of the great range of scales involved in realistic heart anatomy —both spatially (single cell to full-size heart) and over time (microseconds to minutes) —this kind of modeling demands terascale-level systems such as LeMieux.

Alternans and the Restitution Hypothesis

In one recent project, Fenton's team followed up on experiments carried out at the University of Alabama, Birmingham, using two drugs, each of which produced a different arrhythmia —tachycardia or fibrillation —in rabbit ventricles. From the experimental data for each drug, they built separate mathematical models of cellular electrical activity, and they integrated the cellular models into an anatomical model of rabbit ventricles (developed at the University of California, San Diego).

With LeMieux, using up to 500 processors, they simulated the effects of each drug. "We found that two different arrhythmias were induced," says Fenton, "that matched the experimental results not only qualitatively but also quantitatively, with excellent agreement in the dominant frequencies of each arrhythmia."

In another study, Fenton and his colleague Elizabeth Cherry addressed a phenomenon called "alternans," the term for an every-other-heartbeat variation that shows up on electrocardiograms, and which is a well recognized warning sign for ventricular fibrillation. Research with single cells has shown that alternans occurs when, as heart rate quickens, the length of time a cell stays in the excited state becomes shorter more quickly than time in the unexcited state.

Click Image to Enlarge

Simulation of Spiral Waves
A spiral wave was simulated in 2D sheets of tissue with two different models, differing only in cell-to-cell coupling current due to differences in cell repolarization. In the first model (left), alternans develops and the wave breaks up. In the larger-current model (right), alternans is suppressed, and the induced spiral wave remains stable. Excited tissue (white and light gray) is differentiated from quiescent tissue (black).

Using LeMieux, Fenton and Cherry constructed a series of models to test this relationship —called the "restitution hypothesis" —in the more realistic situation in which cells are in 2D sheets of tissue and also in a realistic 3D heart anatomy, where other physiological effects come into play. In both these situations, they show that accurate predictions of alternans depend not only on the restitution hypothesis, but also on the effects of cell-to-cell coupling and a property called short-term memory, which describes how cells adapt to rate changes.

These results help to explain experimental findings that don't fit the restitution hypothesis, and they are a step forward in understanding the complex processes involved in ventricular fibrillation. "With computational modeling," says Fenton, "we have shown for the first time in whole tissue how arrhythmias may not occur, even when the restitution hypothesis predicts that they will. Our results support the idea that designing antiarrhythmic drugs targeting restitution may not be appropriate because restitution alone is not under all conditions an appropriate predictor of alternans and arrhythmia."

Researchers:
Flavio Fenton & Elizabeth Cherry, Beth Israel Medical Center, New York City.

Hardware:
Terascale Computing System.

Software:
User-developed code.

Related Material on the Web:
Center for Arrhythmia Research, Hofstra University.

References:
F.H. Fenton, E. M. Cherry, H. M. Hastings, S. J. Evans, "Computers and arrhythmias: computational approaches to understanding cardiac electrical dynamics," *Computational Fluid and Solid Mechanics*.

E. M. Cherry, F. H. Fenton, "Suppression of Alternans and Conduction Block Despite Steep APD Restitution: Electrotonic, Memory and Conduction Velocity Restitution Effects,"

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