December 2024
Vol. 26, No. 2

HeartLine

News from the Division of Cardiology at the University of California, San Francisco

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About the UCSF Cardiology Council

Established in 1997, the UCSF Cardiology Council is made up of a group of dedicated friends who support the research, clinical and educational programs of the UCSF Division of Cardiology.

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The UCSF Center for Biosignal Research uses advanced tools to study continuous, measurable physiologic signals to better diagnose, treat and prevent heart disease. From left, Dr. Geoff Tison, co-director; Dr. Fabio Badilini, director; and Dr. David Mortara, founder, standing in the server room where patient electrocardiogram recordings are electronically stored.

Center for Biosignal Research

Decoding Music of the Heart

Imagine that the heart is like an opera singer, producing an exquisite song throughout its lifespan – a song that might stumble or fall out of tune due to heart disease. Currently, we only study this music by recording brief snatches of the heart's activity. But we can now capture days or even weeks of that song, and are starting to use sophisticated tools to detect subtle changes that reveal clues about what ails that heart, and how we might restore it to health.

That's one way to understand the mission of the UCSF Division of Cardiology's Center for Biosignal Research (formerly known as the Center for Physiologic Research). "If your heart is always the same, it's a boring song," said Fabio Badilini, PhD, the center's director. "Just like music can have crescendos or speed up, the heart has to vary, but in a regular, harmonic way. When the rhythm becomes chaotic and 'irregularly irregular,' that's when you know something is broken."

"A 'biosignal' is any continuously measurable signal representative of human physiology," said the center's co-director, Geoff Tison, MD, MPH. Many biosignals emanate from the heart, such as electrocardiograms (ECGs), which record cardiac electrical signals and can detect heart attack and abnormal heart rhythms known as cardiac arrhythmias. Others include blood pressure, respiratory rate, and blood oxygen level.

Most of these biosignals are used to monitor hospitalized patients' vital signs, but are purged from hospital servers due to limited storage capacity – similar to

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The Center for Biosignal Research was founded in 2017 through a generous endowment from David Mortara, PhD, a preeminent electrocardiogram expert.

security camera footage from stores which is deleted after a few weeks. Since its founding, the center has collected some of this wealth of data, and its expert team has begun analyzing this untapped resource to learn more about cardiac physiology and improve patient care.

Trailblazer in ECG Technology

The center was founded in 2017 through a generous endowment from David Mortara, PhD, a preeminent ECG expert. After earning his doctorate in physics and teaching at the University of Illinois, in 1973 he became an engineer at Telemed, a Chicago ECG software company. He had no previous experience with ECGs, but collaborated with cardiologists who reviewed a computer's initial ECG interpretation. "Besides learning how to read ECGs myself, I also learned where the computers made mistakes," he said.

Dr. Mortara then joined Marquette Electronics in Milwaukee, creating hardware and software for stress testing systems and ECGs. In 1982 he founded his own company, Mortara Instrument. They developed and licensed ECG software and hardware to other companies, and eventually earned enough recognition to sell products under their own name.

He is best known for creating standalone ECG machines which both record and interpret ECGs at the bedside – now the worldwide standard. Previously, ECG machines printed out paper tracings of a patient's heart rhythm that were handed to a cardiologist, who reviewed them and handwrote his or her interpretation on the printouts. Eventually ECG machines transmitted ECGs electronically to a central computer, but cardiologists still needed to print and review them.

The 1979 release of the Motorola 68000 32-bit microprocessor chip was a gamechanger. "This chip allowed us to design a circuit board with the horsepower to do everything," said Dr. Mortara, who invented the hardware and software for the new interpretive ECG device. "It no longer had to be connected to an outside computer, and the interpretation was rendered immediately [by the machine], right at the bedside. We introduced that capability for the same cost as the prior technology, which was central to my whole entrée into the field. Who would buy a non-interpretive ECG, when you could buy an interpretive one for the same price?"

Mortara Instrument's focus on refining and extending the utility of ECGs set them apart. In the 1990s, after several weight loss drugs were linked to potentially fatal heart conditions, the U.S. Food and Drug Administration (FDA) began requiring all new pharmacological compounds to be tested for cardiac safety. "That led us to becoming a major success with the pharmaceutical industry, because they are an *enormous* consumer of devices for testing," said Dr. Mortara.

Dr. Mortara also developed a collaboration with Barbara Drew, PhD, RN, FAAN, now professor emerita in the UCSF School of Nursing. She led research on alarm fatigue in the Intensive Care Unit (ICU) – the constant beeping and overwhelming number of false alarms on patient monitoring devices such as ECG machines, which makes it difficult to detect true emergencies.

Establishing a New Center

In 2016, Dr. Mortara received a cancer diagnosis. "That made me think about what I was going to do with the time I had left," he said. "I love extracurricular activities like bocce, but I'm not a retiring type of person. I'm extremely lucky because I still love my work. It's the most satisfying part of my life, because there are fresh, new things all the time."

His fruitful research collaboration with Dr. Drew, as well as his passion for wine, drew him to the Bay Area. In 2016, Dr. Mortara sold his company, bought vineyard land in Sonoma County, and made a generous gift that established the Center for Physiologic Research in the UCSF School of Nursing.

Dr. Mortara recruited Dr. Badilini as the center's director. After earning doctorates in electrical engineering from the Polytechnic University of

Milan in Italy and the University of Rochester, Dr. Badilini founded AMPS, a software company which develops and licenses state-of-the-art ECG software, particularly for safety testing of new drugs. He and Dr. Mortara were longtime collaborators in their work with the FDA.

Dr. Badilini played a key role in digitizing study data that the FDA used to evaluate cardiac safety of new drugs. Until the early 2000s, pharmaceutical companies dispatched Federal Express trucks loaded with boxes of data from drug studies. "The FDA wanted to make this process digital, and as an engineer and ECG expert, I was part of a small group that defined that standard," he said. In recognition of his efforts, he received a special citation from the FDA commissioner in 2003.

He also developed a method to store the original, complete high-resolution source data from ECGs, rather than just a PDF of the paper tracings, which only captures some aspects of the heart's electrical activity. ECGs are such a rich source of information that storing the original recordings allows future investigators to plumb their depths when new research questions arise – now aided with novel tools such as AI. "We wanted a way to store all the information we originally acquired, with thousands of values per second, without losing anything – unlike a standard paper tracing, which just shows you a line," said Dr. Badilini.

Addressing Alarm Fatigue

The center's first project was tackling alarm fatigue, particularly the huge number of false alarms for potentially life-threatening cardiac arrhythmias like ventricular tachycardia. Dr. Badilini and Dr. Mortara collaborated with Michele Pelter, PhD, RN, FAHA, and other nursing faculty colleagues at the center. Their initial studies showed that 90 percent of arrhythmia alerts were false alarms.

While hospitalization is already difficult for patients and their families, the frequent loud beeps can increase their stress level and prevent patients from getting much-needed rest. When so many of these alarms are false, they create extra work for nurses and physicians and can contribute to burnout. They also increase the risk that actual emergencies go unrecognized, which can have serious health consequences and even contribute to preventable deaths. To address these problems, the center's team wanted to find a way to design more accurate systems that are better at identifying when patients are actually experiencing dangerous cardiac arrhythmias.

A fundamental problem was that every algorithm created by medical device manufacturers to detect cardiac arrhythmias was developed based on several databases developed more than 30 years ago for different purposes. Those databases included a small number of ECG recordings from a few dozen patients and used just two ECG leads. (By contrast, modern hospital-based ECG monitoring utilizes information from seven ECG leads: leads I, II, III, aVR, aVL, aVF and a precordial "V" lead.) Even worse, those legacy ECG databases tended to record a few minutes to three hours of data, and included relatively few critical arrhythmia events. "They have zero predictivity when used in real situations, because those databases are far, far too small," said Dr. Mortara.

The center set out to create a new gold standard. They compiled 20 months of ICU data from a total of more than 6,000 UCSF patients, including all seven ECG leads commonly used in bedside ECG monitoring, as well as other biosignals such as blood oxygen level. Compared with the most commonly used prior database, which had a total of about 24 hours of ECG recordings, the new UCSF database has about 75 years' worth of recordings.

To analyze this treasure trove of data, Dr. Pelter led a team of five nurse-scientists, all with PhDs and decades of bedside experience caring for heart patients. Each alarm was randomly assigned to three team members for review. Researchers evaluated

"You don't want to be admitted to an ICU where the machine that is monitoring you keeps beeping for no reason – and when it should beep, it doesn't." – Dr. Fabio Badilini

whether it was a true or false alarm for a potentially fatal cardiac arrhythmia such as ventricular tachycardia, ventricular fibrillation or asystole. If all three reviewers agreed on whether the alarm was true or false, it was coded accordingly; in case of disagreements, another nurse-scientist or Drs. Mortara and Badilini weighed in.

For ventricular tachycardia, they found that about half the alarms were true positives and nearly one-third were false positives. They also discovered that a small handful of patients with underlying electrophysiologic disorders generated the majority of ventricular tachycardia alarms, including many which were difficult to interpret, even by these highly trained experts. "There's a lot of variability in the data, which makes it rich but also hard [to analyze]," said Dr. Tison. "There's a lot of noise, but there's also a lot of signal."

By painstakingly analyzing all the data, hand-labeling true positive and false positive alarms and also screening for false negatives, the center created a new benchmark. In March 2024, the FDA designated the UCSF Lethal Arrhythmia Database as a Medical

“The center aims to become a leader in the deployment, validation, refinement and implementation of novel algorithms.” – Dr. Geoff Tison

Device Development Tool. “Our database can now be used by industry as a new reference standard to assess quality and accuracy of existing and new lethal arrhythmia alarm algorithms,” said Dr. Badilini. “Ultimately, the ones who will gain will be patients. You don’t want to be admitted to an ICU where the machine that is monitoring you keeps beeping for no reason – and when it should beep, it doesn’t.”

“Companies are well aware of this development, and I think it will drive industry standards and rationalize their efforts to improve their products,” said Dr. Mortara. “Although we will charge for access to the database, because of the center’s endowment we were able to make a long-term commitment to maintaining it. It was important to the FDA that this resource not depend on grants or disappear due to lack of funding.”

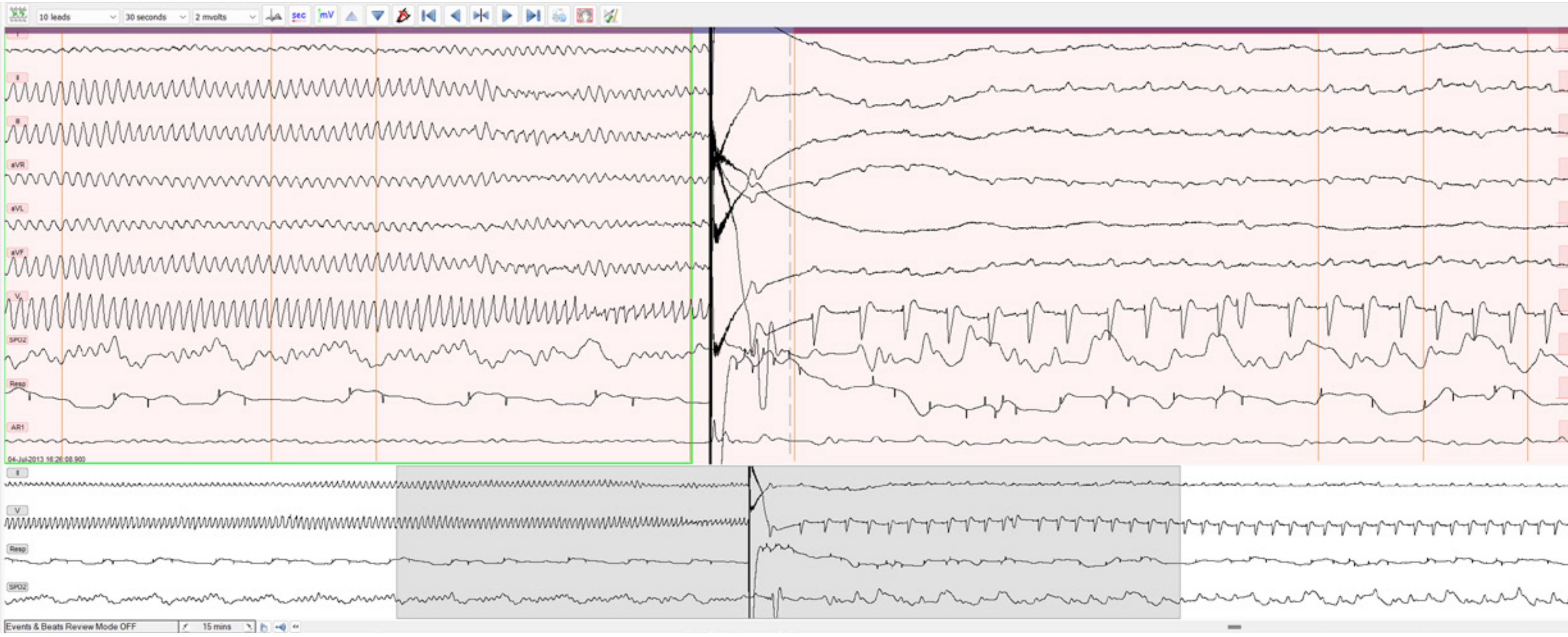
Creating New Synergies

Gaining FDA approval was a major milestone. “As we were nearing the end of our first project, we wanted to spread our wings,” said Dr. Mortara. He and Dr. Badilini had been talking with Jeffrey Olgin, MD, chief of the UCSF Division of Cardiology and Ernest Gallo-Kanu Chatterjee Distinguished Professor in Clinical Cardiology. With the division’s exceptional strengths in cardiac electrophysiology, digital cardiology, AI, and other areas, there were natural synergies.

In March 2024, the center relocated to the UCSF Division of Cardiology. “What we do fits with quite a few people in the Division of Cardiology, and we’ve had the terrific support of Jeff Olgin,” said Dr. Mortara. “That empowers the whole machinery and is strategically important to our center.” This spring, the center held a retreat with its new advisory board, redefined its mission, and changed its name to the Center for Biosignal Research to reflect its new scope.

“The Center for Biosignal Research is a place where an extremely intelligent variety of scientific minds live together happily under one roof,” said Dr. Badilini. “It’s rare that engineers and cardiologists work together in the same room. But now, if UCSF cardiologists have biomedical engineering questions, they don’t have to go to UC Berkeley – we’re right here. And if we engineers have an idea, we can easily bounce it off cardiologists. I already knew all the [faculty] names from the literature, and now they are colleagues. These are the top people in cardiology, and yet they’re humble.”

Dr. Tison had been affiliated with the center for several years, and was recently appointed as its new co-director. He is a cardiologist who also leads his own research lab that employs machine learning, AI and technology-leveraged clinical research methods to identify and prevent cardiovascular disease.



The Center for Biosignal Research is finding new ways to analyze continuous physiologic signals, such as electrocardiograms like the one above.

"I'm excited by the ways the mission of the center aligns with my own work, and energized by opportunities to translate our findings to clinical settings," he said.

Dr. Tison and his colleagues want to use biosignals to better understand biology and physiology.

For example, the center has just started to scratch the surface of what continuous ECGs could reveal about hospitalized patients. "We are capturing massive amounts of data that we have the potential to explore in ways that weren't possible just 10 years ago," said Dr. Mortara. Some items on the center's wish list including developing ways to better measure respiratory rates in the hospital, as well as predicting in-hospital cardiac arrest hours before it actually happens.

They also hope to find ways to use ECG to predict hypertrophic cardiomyopathy (HCM) – a rare but potentially deadly heart condition. "Finding conditions like HCM is like looking for a needle in a haystack," said Dr. Mortara. "It's good to detect it, but you don't want to make too many false calls, or burden a whole health care system with lots of testing. ECG is a nice technology, because it can be recorded inexpensively, with relatively little training." By using existing data in new ways, these innovations could help diagnose or predict other health conditions, potentially improving population health and global health equity.

Translating Discovery and Training New Leaders

The center is committed to not only developing new algorithms, but implementing and testing them in clinical settings like the ICU or telemetry wards. "Unless we prove that a new algorithm is better than the status quo for diagnosing patients or decreasing cardiac events, we aren't going to convince doctors to use it, or convince vendors to incorporate it into their worldwide infrastructure," said Dr. Tison. "The center aims to develop such evidence and become a leader in the deployment, validation, refinement and implementation of novel algorithms. My lab and others have developed algorithms over the years, but many fewer have tested them in real-world settings because deployment is hard. It's a huge need for the field."

They hope to recruit experts in implementation science, and to leverage the Division of Cardiology's existing relationships with stakeholders throughout UCSF and UCSF Health. "It will take high-level support and boldness to change clinical workflows to deploy and test these new models," said Dr. Tison. "If, for example, we conduct a randomized trial of a new algorithm in the ICU, we'll need evidence to show it works, as well as support from ICU directors and others to deploy it more widely. This entire process can be challenging, and will require multi-disciplinary expertise which the center aims to attract."

The center includes experts in both AI as well as signal processing, a subfield of electrical engineering which uses more traditional method of analyzing biosignals. For example, the UCSF Lethal Arrhythmia Database relied on humans to review and label each alarm as true or false, rather than developing an AI algorithm.

"We want labels to be as accurate as possible, rather than training an algorithm on labels with error," said Dr. Tison. "Manual review can have error, too, but the whole process is documented. When there is disagreement in interpretation, we can investigate the underlying reasons. AI is amazingly good for some things, but it can be fabulously wrong, and it doesn't necessarily give us the 'why' as to the reason it was wrong. Part of the vision of the center is to encourage all methods of data analysis, not only AI. That requires first understanding the problem, then next picking the right tool for the job."

One of the center's pillars is training the next generation of experts and authorities in biosignal processing. "Part of our mission is to teach and transmit the legacy," said Dr. Badilini. "I feel a big responsibility to be a good mentor to the younger generation."

Dr. Tison is a leading expert in the use of machine learning and AI to predict and diagnose forms of heart disease. He also has tremendous respect for Dr. Mortara's decades of expertise in signal processing. "David understands the ECG and automated ECG analysis in an incredibly deep way, at a level matched by few people in the world," said Dr. Tison. "In addition to developing experts in AI, we also want to find people who are interested in working with biosignals and can help reclaim the prior art of signal processing that is being lost amid the AI hype."

"Dr. Mortara is a 'ghost' giant in the field of electrocardiography," said Dr. Olgin. "He is the brains behind automated interpretation algorithms used on most ECG machines worldwide, but only ECG nerds know of him. He has driven significant research in ECGs and patient monitoring for decades. I've known of David for a long time, and have been fortunate to work closely with him on several research projects over the last five years. I am thrilled that the Center for Biosignal Research is part of the Division of Cardiology, and that together we can move the science forward."

The center's leaders are excited about the possibilities for transforming patient care. "Our endowment allows us to do bold, nontraditional things," said Dr. Tison. "We hope to garner additional funds through philanthropy as well as traditional grant sources to expand our scope, go faster, and be even bolder…. Instead of being constrained by habit, we've challenged ourselves to reimagine what we'd want to measure if, for example, we redesigned the ICU and patient monitoring from the ground up. Both in the hospital and outside of it, there are now so many more possibilities to sense and hear the 'music' of the heart more frequently than a 10-second snapshot every few years. We want to develop new uses for existing biosignals, and innovate for novel signals to improve patient care and outcomes." ■