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HeartFlow: Disrupting The Diagnostic Paradigm In Cardiology

Most current cardiac diagnostic imaging tests are highly inexact, relying heavily on clinicians' observations. HeartFlow is adapting advanced computer modeling to cardiology to produce a precise, predictive, noninvasive diagnostic that doubles as a treatment planning tool. The test could eliminate unnecessary procedures for patients and save the system money, but is that what interventionalists want?

BY STEPHEN LEVIN

- Noninvasive cardiac diagnostic testing has proven to be a challenging market, with current tests lacking the desired certitude.
- FFR is an invasive test that can provide increased accuracy, but adoption has been low due primarily to reimbursement issues.
- HeartFlow has developed a noninvasive technology for determining FFR based on data from CT scans.
- This technology may reduce the number of diagnostic and therapeutic interventions, while improving outcomes, making it attractive to patients and payors.
- But this may mean fewer procedures for physicians at a time when cath lab procedures are already declining, raising the question of whether interventionalists will buy it.

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Innovation is often described as an idea that is ahead of its time. Sometimes that refers to a unique idea that no one else has yet come up with, but once conceived, can then be implemented. In other cases, the idea truly is ahead of its time because the capabilities do not yet exist to bring that innovation to fruition. The latter describes cardiovascular diagnostic start-up **HeartFlow Inc.**

Formed only in 2010 and already on the verge of receiving CE mark approval, with the hope of US commercialization next year, the company appears to be something of an overnight success in developing a noninvasive technology to measure fractional flow reserve (FFR) using data from CT scans. But in fact, this is a technology that truly has been a long time coming, based on an idea conceived well before the infrastructure existed to turn it into reality.

HeartFlow is the story of the confluence of disparate technologies, brought together by three leading figures in different fields to form a hybrid start-up that is part medical device, part IT software company. Nearly two decades ago, Charles Taylor, PhD, a pioneer in applying computational fluid dynamics to human biology, began working with Christopher K. Zarins, MD, PhD, then chief of vascular surgery at **Stanford Medical Center**, to begin modeling blood flow using hemodynamic engineering techniques widely used in other fields. At the time, however, neither the computing power nor diagnostic imaging capability was readily available to make their idea practicable. Recent advances, however, in both of those technologies have made this innovation commercially viable, and Zarins and Taylor joined with experienced surgeon/entrepreneur John Stevens, MD, to turn their idea into a company that may significantly alter the diagnostic paradigm in cardiology.

Current cardiovascular diagnostic tests lack precision, leaving a great deal of room for physician interpretation, which results in a significant number of unnecessary tests and treatment. HeartFlow's FFR_{CT} technology appears to enable physicians to more accurately assess which lesions pose significant risk to patients, thereby requiring interventional or surgical treatment, and which do not require intervention. This could mean that using this noninvasive approach will eliminate many invasive diagnostic and therapeutic procedures. Not only does this technology therefore have the ability to improve patient outcomes by eliminating unnecessary procedures, but it also can produce considerable savings for the health care system as a whole. The latter may be an example of good timing for HeartFlow, given the current climate of health care reform and comparative effectiveness.

At the same time, however, fewer interventional cardiology procedures are being performed today. In this respect, HeartFlow could be the victim of bad timing as interventionalists may not be as eager to adopt a technology that further reduces their current caseload. The company believes it can demonstrate that FFR_{CT} will actually help clinicians by enabling them to more accurately identify patients who can benefit from interventional treatment, thereby spending their time in the cath lab more efficiently, making this technology a winner for physicians, patients and payors.

BEGINNING OF A LONG ROAD

For John Stevens, the pathway to becoming president and chairman of HeartFlow evolved from pure happenstance. A cardiac surgeon and experienced device entrepreneur, Stevens was not even working in the device industry at the time he learned of the company's technology, having taken a hiatus to focus on an energy start-up.

Stevens' introduction to HeartFlow came out of connections made during his time at the **Stanford University Medical School**, where he was a medical student, resident and fellow, before joining the faculty in the department of cardiac surgery. There he worked with Christopher Zarins, who was chief of vascular surgery. The two remained friends after Stevens gave up his surgical practice to become a full-time entrepreneur, and Zarins was the one who introduced Stevens to HeartFlow.

Not an entrepreneur by nature, Stevens credits Wesley D. Sterman, MD, a medical school classmate who also got an MBA while at Stanford, with awakening his interest in starting companies. Stevens and Sterman have been friends since starting medical school together. The two took divergent career paths, with Stevens going into surgery, while Sterman became a venture capitalist, joining Menlo Ventures after Stanford. There, Sterman came across a business plan for what he thought was an interesting company called EndoVascular Technologies Inc. (EVT), founded by Harrison Lazarus, MD, a vascular surgeon in Stevens' hometown of Salt Lake City, UT. Sterman called Stevens to see if he knew Lazarus, which he did, and to ask Stevens to do some clinical consulting on the project, a minimally invasive approach to treating abdominal aortic aneurysms (AAAs) with stent grafts. (EVT was later acquired by Guidant Corp.) According to Stevens, "Working on EVT was my first glimpse into the world of the device industry and that got me interested in becoming an entrepreneur."

This was the early 1990s, which marked the beginning of the growth of minimally invasive surgery (MIS) procedures, starting with laparoscopic cholecystectomy ("lap choly"). "Towards the end of my training in general surgery, I remember a faculty member coming back from a training course talking about being able to remove gall bladders with newly-developed scopes," Stevens recalls. "That got me thinking, 'If they could do lap cholys, what minimally invasive procedures could be done in heart surgery?'"

That realization, combined with Stevens' newfound entrepreneurial spirit, sparked the then-32-year-old to recruit Wes Sterman away from EVT and, in 1992, the pair launched **Heartport Inc.**, one of the companies that pioneered minimally invasive cardiac surgery. (*See "Heartport's Quiet Exit,"* IN VIVO, *February 2001, "Heartport: Still Beating,"* IN VIVO, *February 2000, "Re-Starting Heartport,"* IN VIVO, *July 1998, "Whither Heartport?"* IN VIVO, *May 1998, "Be Still My Beating Heart: Can Heartport Deliver?"* IN VIVO, *February 1997.*) Initially, Stevens tried to balance his cardiac surgery practice with his duties as the company's chief technology officer. "I wrote Heartport's early patents based on work I did at home using pig hearts from the local butcher," he recalls. But Stevens soon realized that "you can't be a part-time heart surgeon," and, in 1997, he decided to give up his surgical career to become a full-time device executive and entrepreneur.

Despite boasting one of the decade's most successful IPOs when the company went public in April 1996, raising nearly $97 million with a market cap approaching $500 million (unheard of at the time for a device company, particularly one without products yet on the market), Heartport's MIS business, *per se*, was not successful, and the company was acquired by **Johnson & Johnson** in 2001 for $81 million with J&J also assuming roughly $80

million in debt. Indeed, the company's lasting legacy is not its products – largely MIS cardiac surgery instruments – but rather its incredible wealth of IP, which resulted in subsequent major cardiovascular device breakthroughs, as well as the number of talented executives involved with the company, many of whom went on to successful careers at other product companies (e.g., interventional cardiologist Frederick St. Goar, MD, a leading clinician and co-founder of percutaneous mitral valve pioneer **Evalve Inc.**; Hanson Gifford, one of the founders of The Foundry, a leading device incubator; and Richard Brewer, who became president and CEO of **Scios Inc.**, a biopharma company acquired by J&J in 2003 for nearly $2.7 billion). "Heartport had more than 100 issued patents by the time J&J bought us and clearly they made much more money from that IP than they did from our actual products," Stevens acknowledges.

> **"Nobody had ever built a computer model from medical imaging data at that time. I had the idea that if I could extract the geometry from imaging data, then I could produce the first 3-D patient-specific model simulating blood flow."**
> **– Charles Taylor, PhD**

Heartport was best known for developing instruments to enable surgeons to endoscopically perform CABG procedures. Yet, as John Stevens notes, "That was probably the fourth or fifth idea the company had; it was just the fastest to go to market."

What is likely to turn out to be Heartport's most notable legacy product is John Stevens' first device idea, which was catheter-based valve replacement. He initially developed aortic valve approaches, the IP for which was eventually acquired from J&J by **Edwards Lifesciences Corp.** and which has helped that company become the leader in what looks to be the next blockbuster device market: TAVI (transcatheter aortic valve implantation).

Heartport also developed atrial fibrillation (AF) ablation technology that was spun out into **Epicor Medical Inc.**, which was acquired by **St. Jude Medical Inc.** In addition, Heartport collaborated with robotics leader **Intuitive Surgical Inc.** on endoscopic surgical technology. In retrospect, Heartport's success as an IP generator may not be as widely known as the company's disappointing business performance, but is likely to ultimately prove more valuable to the device industry.

Stevens points to several lessons he learned from Heartport that have carried over to his other companies. Most important, he says, is "it's about having great people, letting them go to work, and they'll figure out how to solve hard problems." Indeed, Stevens remains close with several of his Heartport colleagues, including Fred St. Goar, who is also involved with HeartFlow (both as an investor with an observer board seat and working with the company's clinical advisory board).

Heartport also was ahead of its time in placing great emphasis on developing clinical data to support new technology, another lesson Stevens has brought to HeartFlow. This was right at the early stages of the growth of evidence-based medicine. Most device companies back then did not rely heavily on clinical data to drive new product adoption, with that trend just beginning to take hold particularly in interventional cardiology, where it ultimately would thrive. "I strongly believe that if you focus first on the patient, and then the supporting clinical data, the commercial results will follow," Stevens says.

He acknowledges, however, that this was one of the areas in which Heartport ran into problems. The company initially thought that its MIS CABG system would be approved under a lengthy PMA process and planned accordingly, only to be surprised when the FDA advised them that the product would qualify for, and ultimately received, faster 510(k) clearance. "We thought we'd have a couple of years to conduct clinical trials, but all of a sudden we were cleared to sell in the US and that triggered a certain schizophrenia: just because we were cleared to sell, did that mean we should start selling?," Stevens recalls. "From my perspective, we let our sales efforts get ahead of our clinical data and we learned a lot from that experience."

Another factor generally attributed to Heartport's failure to drive widespread adoption is that the company's MIS system was extremely complex, which limited adoption to only the most technically adept surgeons. "Heartport's procedure was incredibly hard to perform; you needed to be a very skilled surgeon to be able to do it successfully," he says.

After selling Heartport to J&J in 2001, Stevens sought to take advantage of the dot-com boom by getting involved with MediBuy, one of several e-commerce hospital supply companies that had sprung up at the time. MediBuy had raised around $100 million, but along with the other independent e-commerce medical supply firms, it was essentially short-circuited when most of the large device companies joined together to form a consolidated purchasing consortium called the **Global Healthcare Exchange LLC**, which ended up acquiring MediBuy in 2003 for about ninety-five cents on the dollar. "We sold for a small loss, but our investors were relieved because MediBuy was losing money at the time and the e-commerce market had imploded in about three months," he explains.

Stevens admits to being burned out after MediBuy, and he took a break from health care to launch a geothermal energy company called Amp Resources and a few years later another called Sundrop Fuels. But he continued to stay in touch with former Heartport colleagues, and in 2007, Matt Vaska, who was responsible for developing the AF ablation technology at Heartport that became Epicor, contacted him about a new sleep apnea start-up called **ApniCure Inc.** that he had launched based on technology he'd invented. Stevens was so enthused about the project he agreed to invest and serve as an active director of the company. (ApniCure is in late-stage clinical trials, and its venture investors include USVP and Capricorn Ventures, who are also investors in HeartFlow, along with Kleiner Perkins.) It was through a similar kind of referral that Stevens was introduced to HeartFlow.

A PHD STUDENT WALKED INTO A SYMPOSIUM...

In 2010, John Stevens was contacted by a friend who had an idea for a vascular closure device for the kind of large punctures required for TAVI procedures. Stevens

wasn't interested in getting involved with the device himself, but agreed to run the idea past his former Stanford surgical colleague, Christopher K. Zarins. Stevens recalls, "Chris immediately gave me several reasons why the vascular closure idea wouldn't work, and then he said, 'But if you want to see something interesting, let me show you what I've been working on with Charley Taylor [another Stanford faculty member].'"

In addition to his work as a leading vascular surgeon, particularly well-known for his work in AAAs, and as chief of vascular surgery at Stanford, Zarins has also done extensive research throughout his career on atherosclerosis and the underlying causes of coronary artery disease. This dates back to his time as a surgeon and assistant professor at the **University of Chicago Medical Center**, where in 1976, he started working with the late Seymour Glagov, MD, a noted pathologist and expert on vascular disease. At the time, Chicago was one of five specialized research centers in the country focusing specifically on atherosclerosis. Then, the main message of medical therapy for treating coronary disease was lowering cholesterol and lipids through the use of statins and adjusting risk factors, particularly diet.

"Glagov, as a pathologist, noticed the same thing that I was seeing as a vascular surgeon," Chris Zarins points out, "which was that atherosclerosis or plaque is not a generalized phenomenon, but a very localized phenomenon. It occurs in one spot in your carotid or coronaries that can kill you, but it doesn't occur throughout your coronary vessels. And we arrived at the same question: if plaque is caused by cholesterol and diet, why doesn't it occur more systemically?"

Glagov also invented the gel electrode used in EKGs and was involved in heart rate monitoring research. Zarins (an undergraduate engineering major) and Glagov were drawn to an issue raised as early as 1959 in a medical journal article: whether hemodynamic factors related to blood flow play a role in explaining why plaques form in localized areas within the vasculature. For 17 years, Zarins and Glagov at Chicago, working with Don Giddens, PhD, a leading biomedical engineer at Georgia Tech, conducted extensive research on how hemodynamic influences, including heart rate, localize atherosclerosis and the arterial response to that plaque.

The results proved to be surprising. For example, Zarins points out, "Everyone thought that plaque narrows the artery, but in fact, what happens is that the artery actually enlarges to compensate for the presence of the plaque." Funded over the years with a total of $15 million in NIH and NSF grants, Zarins', Glagov's and Giddens' research concluded that "arteries know how big they are supposed to be, either embryologically or through adaptive signals later on in life as a response to disease," and this fundamental finding served as the basis, years later, for the development of HeartFlow.

In 1993, Zarins was recruited to Stanford to be chief of vascular surgery and build up the surgical program. There, he continued the research he'd begun at Chicago; indeed, shortly after arriving at Stanford, Zarins scheduled a symposium on hemodynamics and atherosclerosis that featured Glagov, Giddens and other leaders in the field. In the audience that day was Charles Taylor, a Stanford engineering PhD student. Taylor was so impressed by what he heard that after the symposium he approached Zarins and asked if he had any projects that Taylor could work on, as he was looking for a PhD project. "I said, sure, why don't you solve the three-dimensional pulsatile flow field for the abdominal aorta," Zarins recalls, noting, "That wasn't a simple project. I'd been working on it for ten years with Don Giddens at Georgia Tech and we hadn't gotten very far. But Charley Taylor did in one year what no one else had been able to do."

Zarins was so impressed with Taylor that, within 24 hours of their first meeting, he hired him as a graduate student to work in his lab, and Zarins became Taylor's co-advisor, along with Thomas J.R. Hughes, PhD, who is known as the leading scientist in the field of computational mechanics. Stanford was the early mecca for this area of study, which is what brought Taylor there and contributed significantly to the development of HeartFlow's technology.

Before coming to Stanford, Taylor had worked at General Electric, which was among the first companies to use computer simulation tools to help design a variety of products, from basic materials research to building refrigerators and jet engines. "The tremendous advantage of this approach was that it enabled companies to build better, more effective products at a lower cost by avoiding expensive and less accurate prototyping," Taylor explains.

Taylor's early work at Stanford was largely in aerodynamics research, focusing on computer modeling of airflow. At the same time, Zarins was conducting similar research but on fluid dynamics – modeling blood flow through the vasculature. Zarins' symposium brought the two eventual co-founders of HeartFlow together.

UNVEILING THE TECHNOLOGY

Charles Taylor continued working in Chris Zarins' medical school lab until he received his PhD in 1996. At the time, Stanford didn't have a bioengineering program and, like many leading universities, rarely hired its own newly-minted doctoral students, so Zarins convinced the medical school to hire Taylor as an assistant professor – he was the only engineer on the medical school faculty. It wasn't until three years later that the engineering department offered Taylor a full-time faculty position.

From the beginning of their collaboration, Zarins and Taylor were working on the technology that would become HeartFlow, but not with the expectation of starting a company. Their work was confined to research projects, largely because the level of computing power necessary to perform this type of vascular modeling was only available at large research institutions. Indeed, Taylor was only able to solve the initial abdominal aortic project by convincing computer giant Silicon Graphics to allow him to use its supercomputer.

In addition to being a leader in computational mechanics, Stanford was also in the forefront of the rapid evolution then occurring in medical imaging technology, and Taylor was looking to combine the two. He worked closely with Geoffrey Rubin, MD, then a Stanford professor doing early work involving CT imaging. "Nobody had ever built a computer model

from medical imaging data at that time," Taylor explains. "I had the idea that if I could extract the geometry from imaging data, then I could produce the first 3-D patient-specific model simulating blood flow," which he did in 1995.

Taylor recognized that this patient-specific model would provide clinicians with a realistic picture of an individual's blood flow, rather than a theoretical model. He then thought about taking this one step further by using this model to develop patient-specific therapies. According to Taylor, "Currently a physician sees a patient and has certain diagnostic data that describes the patient's current condition. What the physician really needs is a tool that can predict what will happen if they treat a patient a certain way, or what will happen if the patient is in a situation different from that at the time the medical imaging data was obtained."

Taylor's idea was to model blood flow during dynamic exercise conditions, which is where many patients run into physiologic problems, as opposed to when they are at rest, which is when CT scans and other images are taken. In other words, he was looking to recreate the kind of physical activity that often causes chest pain in a computer model that could then be used to predict the outcomes of conditions that weren't previously measured, like exercise, or even different interventional therapies, such as implanting a stent. Taylor calls this research area image-based modeling and also refers to it as predictive medicine.

Zarins and Taylor first unveiled this patient treatment planning tool in 1999 at the Society for Vascular Surgery (SVS) meeting. Again with computing help from Silicon Graphics, the two created models, including outcomes analyses, of various peripheral vascular surgical procedures. "We had four past presidents of the SVS up on stage and we used our system to solve patient problems using this computer analysis. Everyone was floored by the display," recalls Zarins, who was then himself president-elect of the SVS.

This demonstration marked the first display of what ultimately became HeartFlow's technology. Zarins and Taylor were able to take patient-specific CT scan imaging data, do flow analysis using computational models, and use that to solve blood flow problems in the peripheral vascular system. Although the idea looked promising, the problem in 1999 was that the capabilities didn't exist to scale this model to any kind of widespread basis; specifically, neither the computing power nor the imaging capabilities yet existed to make this any more than an academic research exercise.

Nevertheless, Taylor and Zarins continued to work on this project. Taylor points out that "It took a long time to really develop the models so that they were accurate representations of blood flow and pressure in the circulatory system." The research benefitted from the continuing improvements in both computing power and medical imaging capabilities, particularly the eventual development and widespread availability of 64-slice CT scanners. But perhaps the most important advance that ultimately made it possible to think about commercializing this technology was the development of a diagnostic procedure called fractional flow reserve (FFR) in 1996.

VALIDATION THROUGH FFR

Taylor's and Zarins' technology was aimed at helping interventional cardiologists resolve one of the most vexing problems they currently face, namely how to determine which patients with some level of intermediate arterial stenosis to treat with PCI (percutaneous coronary intervention) and which should only receive medical therapy. Current guidelines are relatively clear in recommending that symptomatic patients (those who are suffering most commonly from angina) with severely occluded arteries – blockages of at least 70% - are generally candidates for PCI, and accordingly, patients with minor chest pain and minimal obstructions are generally better off treated only with medical therapy. It is that large group of patients who fall somewhere in between that present interventionalists with their most difficult diagnostic challenges, and that is the group that Taylor and Zarins were targeting with the technology that ultimately became HeartFlow.

Prior to the availability of FFR, there were two types of diagnostic tools available to cardiologists: tests conducted prior to the patient coming to the cardiac cath lab and those conducted while the patient was in the cath lab. Of the former group, SPECT (single photon emission computed tomography) nuclear scans are the most widely used, followed by stress echocardiograms (either using treadmills or stationary bicycles) and cardiac CT tests. In the cath lab, cardiologists rely on traditional fluoroscopy, IVUS (intravascular ultrasound) and OCT (optical coherence tomography). "All of these noninvasive tests have their pros and cons," says John Stevens, "but consistent among all of them is that none are highly accurate. And none of them are very precise in answering the fundamental questions facing that patient and physician: what's causing the chest pain and how do we best treat it?" He suggests that HeartFlow's technology can answer both of those questions, while also being able to determine in advance which patients need to go to the cath lab and which ones don't.

SPECT and stress echo tests provide purely functional, not anatomical, results, and the specificity of those tests is not high. Thus, relying on those tests can result in normal results for people who actually have functionally significant disease, as well as the converse when results indicate the presence of coronary disease where none really exists.

The problem with the other CV diagnostic tests - CT, angiography, IVUS and OCT - is that they only provide an anatomical or structural – as opposed to functional – view of any blockages in the patient's vessels. These tests frequently require the clinician to make a subjective, largely visual assessment of the degree to which a specific vessel is occluded, often referred to as the oculostenotic reflex. According to John Stevens, "We know that visual inspection is highly inaccurate." A recent article in *The New England Journal of Medicine* cited a study in which two-thirds of stable angina patients who were sent to the cath lab to undergo angiograms were actually found not to have significant lesions that needed treatment, and the other third had significant lesions, at least according to visual inspection. "That means those two-thirds went to the cath lab unnecessarily, and a good portion of the remaining group of patients were probably treated unnecessarily due to the inaccuracy of visual inspection," Stevens argues. In his view, clinical data suggests that up to half of all elective PCIs may be unnecessary because most of those procedures are the result of the significant ambiguity that results from noninvasive diagnostic testing and then relying on visual information from angiography.

While the idea of revascularizing an occluded vessel to increase blood flow sounds intuitively like it will improve the

patient's condition, clinical studies have demonstrated that not all obstructions impede cardiac function; indeed, with certain lesions, a patient's outcome is better if the obstruction is left untreated than if stented. In addition, the outcome of most of these tests – with the exception of stress tests – is also skewed because they are conducted while the patient is at rest, which is often not when they most commonly suffer symptoms of coronary disease such as chest pain.

The idea behind FFR was to come up with a diagnostic test that could provide a functional measurement of a patient's coronary arteries in order to determine which patients needed to undergo PCI or surgery to treat certain obstructions in order to improve cardiac function, and which patients' lesions did not affect cardiac function, no matter how large the apparent blockage, thereby obviating the need for any revascularization procedure. FFR is based on the principle that measuring blood pressure and flow through a specific section of an artery can determine if the plaque occluding that vessel will restrict cardiac function sufficiently to require treatment.

This notion of measuring blood flow across an occluded segment is actually not new in cardiology. Andreas Gruentzig, MD, the inventor of angioplasty, had a separate lumen built into the early balloon catheters he designed to measure pressures at the proximal and distal ends; the greater the gap between the two pressures, the greater the blockage. At the end of a procedure, Gruentzig would inflate the balloon repeatedly to ensure the blockage was removed. The requirement of an extra lumen, however, meant these balloon catheters were too big to maneuver into smaller vessels and interest declined among many cardiologists in measuring pressure, resulting in companies discontinuing these products.

The challenge of identifying which patients could best be treated by PCI remained, so research continued on ways to measure vascular pressure. In the early 1990s, Bernard de Bruyne, MD, PhD, of the Cardiovascular Center in Aalst, Belgium, and Nico Pijls, MD, PhD, of Catharina Hospital, Eindhoven, the Netherlands, developed the concept of fractional flow reserve. They published the first article on FFR in *Circulation* in 1993, followed by several validation studies, including one major human study published in *The New England Journal of Medicine* in 1996 demonstrating that FFR usage could have a potentially major impact in the treatment of patients with coronary artery disease. That article gave rise to the increased availability and adoption of the technology worldwide.

FFR is typically performed in the cath lab as part of a diagnostic angiogram. What distinguishes FFR from most other cardiac diagnostic tests is that the patient is injected with adenosine, a common compound that will vasodilate the microvasculature – the small vessels that typically dilate during exercise, causing what is called maximal hyperemia. "The adenosine causes blood flow to quickly increase to maximum levels, as if the patient was doing strenuous exercise on the table," Bernard de Bruyne explains.

"FFR enables us to assess the true severity of coronary narrowings that we see on the angiogram, which otherwise are very difficult for us to assess angiographically through visual analysis or by noninvasive testing."
– Bernard de Bruyne, MD, PhD

A specially designed, very thin pressure-monitoring guidewire is inserted across the lesion and measures blood flow and pressure both distal and proximal to the lesion, resulting in a pressure gradient. The FFR is basically the ratio of the distal pressure divided by the proximal pressure. According to de Bruyne, "If this measurement is above 0.8, this lesion cannot induce myocardial ischemia and does not require PCI, and if the ratio is below this threshold, the lesion can be associated with myocardial ischemia and PCI should be considered."

De Bruyne estimates that it takes an experienced operator just two-to-three minutes to perform an FFR measurement on most lesions, and the procedure can be repeated on multiple lesion sites during the course of an angiogram. "By the end of the procedure, this test gives the clinician a real combination of anatomic or structural information from the basic angiogram and functional information from the FFR," he explains.

The effectiveness of FFR in identifying patients whose stenosis is likely to lead to ischemia and the need for PCI, while screening out those whose lesions are not likely to prove problematic and can therefore avoid PCI has been demonstrated in two major clinical studies. Indeed, clinical outcomes with FFR are so positive that the data are considered Level 1 evidence, making it the standard of care. First, the DEFER trial in 2007 showed that up to 55% of patients who would have been treated with stents based on angiography had non-significant stenosis according to FFR. (Data shows that treating these non-significant lesions with stents does not improve patient outcomes over five years.) FFR patients in DEFER who did not undergo PCI also did not experience any increase in adverse outcomes.

Then, in 2009, the FAME trial demonstrated that FFR-guided therapy could reduce the risk of death or major adverse cardiac events by 33% in patients who underwent PCI, compared with angiography-guided PCI alone, with better patient outcomes and lower costs. According to John Stevens, these studies also demonstrated that "anatomy alone, whether from a scanner or an angiogram, doesn't correlate with functional significance, indicating we need both types of data."

In de Bruyne's view, providing functional information to go along with the anatomical information from the angiogram can dramatically improve the level of patient care. "FFR enables us to assess the true severity of coronary narrowings that we see on the angiogram, which otherwise are very difficult for us to assess angiographically through visual analysis or by noninvasive testing," he notes.

Despite the benefits FFR provides, adoption by interventionalists remains low. De Bruyne estimates that the procedure is most widely used in Belgium, the Netherlands, the UK and Spain, where the adoption rate is still only around 15%. In the US, the rate is even lower, an estimated 5%-8%, despite there being a CPT code for measuring FFR in the cath

lab. De Bruyne attributes the low adoption figures largely to reimbursement issues. "The main resistance to fractional flow reserve comes from the fact that it is poorly reimbursed. If the wire was reimbursable and there was a fee for the physician, the adoption rate would be 90%," he argues.

Another important factor contributing to low adoption rates, at least among certain interventionalists, is that FFR is likely to reduce the number of PCIs those physicians perform. Coming at a time when cardiologists are already seeing fewer cath lab procedures, this additional blow to clinicians' incomes won't be well received among certain physicians. De Bruyne acknowledges that the financial factor is playing a role in limiting the use of FFR. "I have had colleagues tell me that 'We don't do FFR because we know it will reduce our business,'" he says.

For De Bruyne, the value of FFR is clear. As a result, he admits to being skeptical when he first heard HeartFlow was developing a noninvasive means of determining FFR. According to de Bruyne, "When I found out the company was trying to noninvasively calculate fractional flow reserve from CT, I thought that was absolutely impossible. Then when I got a good explanation, I was almost convinced, and now that I've seen the early results they can produce, I have to say that they are really impressive."

MOVING OFF CAMPUS

With the development and clinical confirmation of the value of FFR, along with the continuing increase of available computing power and the enhancement of medical imaging quality, Taylor and Zarins began to think about turning this from an academic research project into a commercial entity. In July of 2007, they started **Cardiovascular Simulation Inc.**, which was the precursor to HeartFlow.

"We didn't envision starting a company when we first began this work," Charles Taylor points out. Indeed, during the dot-com craze of the late 1990s, his research in computational fluid dynamics (CFD) started attracting a lot of attention and enthusiasm in the media. But after a while, Taylor recalls, the increased attention led to the question: this technology may be amazing but what is it going to be used for and what will its clinical impact be? "It would have been easy for us to go out and raise money then to start a company, but the timing wasn't right because the technology wasn't ready," Taylor explains. "We just didn't know enough about how to model the circulation to properly execute this idea."

Whereas the version of the system that they first unveiled at SVS focused on the peripheral vasculature, Taylor and Zarins agreed that the ultimate success of this project would be achieved by making it applicable to the entire vascular system. They also needed to focus their efforts more tightly on a particular vascular area – at the time they were working on five different computational models, each for a different area (carotids, lower extremities, aortic aneurysms, pulmonary vessels, and coronaries). In order to make sure they had what Zarins called "a viable clinical application," they decided to focus initially on applying this technology to the coronary arteries. "The reason we focused first on coronaries is not only because it's the biggest clinical problem," Zarins notes, "but also because it's the only vascular bed where we could truly validate that the system worked because there are no drugs that can do for the other circulatory beds what adenosine does in the coronaries. We had to prove that the system was accurate in humans, and the best place that we could do that was in the coronaries by comparing it with FFR."

"This is going to make some physicians uncomfortable, but it is possible that there are going to be gatekeepers, such as insurance companies, who may require the use of this technology to determine who does or doesn't go to the cath lab."
– Fred St. Goar, MD

Essentially, Taylor's and Zarins' system was a noninvasive means of replicating the results of FFR by applying modeling software to a coronary CT angiography (CCTA) scan. They eventually came up with the acronym FFR_{CT} for the new technology. In addition to the increased diagnostic accuracy, FFR_{CT} has the added advantage of enabling interventionalists to access this data prior to the patient coming to the cath lab, providing an effective treatment planning tool. This allows physicians to identify in advance those patients who need not be treated in the cath lab, while also helping interventionalists better understand and prepare for those patients who need to undergo PCI.

For the first two years, Taylor and Zarins worked at CV Simulation in their spare time, while both also maintained full-time faculty positions at Stanford. In July of 2009, the company hired its first employee and began to set up a prospective clinical trial at Stanford.

As CV Simulation started to make the transition from academic research project to start-up company, they also needed to move beyond their Stanford labs. Noted surgeon/entrepreneur Thomas Fogarty, MD, had recently launched the Fogarty Institute for Innovation at El Camino Hospital in Mountain View, CA. (*See "The Fogarty Institute For Innovation: A Device Incubator For Difficult Times," this issue.*) Fogarty, himself, was familiar with the bureaucratic challenges of launching a start-up within the confines of an academic medical center, having had his own battles with Stanford before ultimately deciding to de-camp for El Camino.

CV Simulation ran into similar issues, a common theme echoed increasingly by start-ups that are initially launched within academic centers. The pace of development and the ability to obtain rights to intellectual property can often be a lengthy process, hindering a start-up's initial momentum. While Taylor and Zarins had successfully negotiated a licensing agreement with Stanford for the elements of CV Simulation's technology developed at the university, the process of developing the company there, particularly launching an early clinical trial, was slowing their progress.

El Camino Hospital offered Taylor and Zarins the best of both worlds. Because of its location in the heart of Silicon Valley, the community hospital is home to leading clinicians, such as interventionalists Fred St. Goar and Jim Joye, MD, who are experienced working with start-ups and value device innovation. And the level of bureaucracy is much less than that of a major academic medical center like Stanford. As Tom Fogarty notes, "The nurses

and staff at Stanford are jaded and often view the paperwork and other procedures associated with conducting clinical trials to be a pain in the neck, whereas at El Camino, the staff is much more interested in participating in these studies."

Fogarty, however, was not immediately receptive to CV Simulation's technology. Indeed, when Chris Zarins first approached him with the idea of moving the company to the Fogarty Institute, "Tom was skeptical about what we were doing, and he expressed that skepticism in his typical colorful way," Charles Taylor recalls. Fogarty agrees, noting that he wasn't truly convinced until he saw some data. "Until then, I thought they were completely full of themselves and would never get it done," he says.

In Fred St. Goar's view, the company's move to the Fogarty Institute rapidly accelerated its development because El Camino is so much better suited to serve start-up companies. According to St. Goar, "Early stage companies require flexibility because they need to be nimble. The space and the access to people at El Camino provide that opportunity. Could the company have developed at Stanford? Maybe, but certainly things happened much quicker after it moved."

The delays that CV Simulation encountered trying to start its first clinical trial at Stanford also caused the company to look elsewhere to launch this first study. Chris Zarins was born in Latvia, escaping with his family to the US as a young boy just prior to the invasion of Latvia by the then-Soviet Union. He has maintained strong ties to his homeland, including helping launch the first cardiac cath lab there, the Latvian Heart Center in the capital of Riga.

In 2009, CV Simulation had completed only one coronary patient analysis and Zarins and Taylor were frustrated by the slow pace of trying to get the trial started at Stanford. In September, at that year's TCT meeting in San Francisco, Zarins approached his friend Andrejs Erglis, MD, an interventional cardiologist who heads the Latvian Heart Center, and explained CV Simulation's technology. "He understood immediately what we were doing and asked if they could do some cases in Latvia comparing our technology with FFR," Zarins says.

One month later, Zarins and Taylor flew to Latvia to begin the first-in-man application of CV Simulation's system. By the end of the year, Erglis had successfully completed 12 cases, a pace that could never have been achieved in the US. The data from those cases served as the basis for a paper that was accepted for presentation at the 2010 European Society of Cardiology meeting, and by the time of that presentation in August in Stockholm, Erglis had successful data on 20 patients.

CREATING A REAL COMPANY

The progress that CV Simulation had made through early 2010 was achieved without raising any outside funding. All of the financing to that point came from Zarins and Taylor and one other small investor. With the success of the first-in-man work in Latvia, however, the co-founders realized that this company was rapidly reaching the point where it needed to grow beyond their ability to fund it.

This now brings the story back full circle to the meeting at the Fogarty Institute in March of 2010 where John Stevens approached Chris Zarins about his friend's vascular closure technology. After dismissing the potential of that device, Zarins told Stevens, "But if you're looking to invest some money in medical technology, take a look at what Charles Taylor and I are working on."

After showing Stevens the CV Simulation technology, Zarins says, "Just like Erglis, he got it immediately." That initial meeting took place on a Friday and on Monday, Stevens called Zarins and said he wanted to both invest and get personally involved with the company. Stevens recalls instantly having one of those "Ah, ha" moments. "I recognized that this had the potential to change cardiovascular medicine," he says.

The other factor that convinced Stevens to actively return to running a health care company was the quality of the people involved with CV Simulation. Drawing on his Heartport experience of always trying to work with the best people available, Stevens points out that only rarely are there opportunities to work with world class clinicians and scientists like Chris Zarins and Charles Taylor. "These are A+ guys who have done A+ science over the years, and that convinced me to drop everything else I was working on and come in with my own money and my own time," he says.

Initially, Stevens was going to come on board only as chairman, in addition to investing in the company, but Taylor and Zarins convinced him to also become the company's CEO. When he agreed to run the company, both co-founders decided to give up their tenured faculty positions at Stanford and also join the company full-time.

Stevens stepped in at a key inflection point in the company's development. CV Simulation's original business model was to develop software and sell it to device companies to use to improve product designs. After the first couple of years of focusing on that goal, Taylor and Zarins realized that wasn't the direction in which they wanted to take the company. According to Taylor, "We saw that it was the wrong direction because the market for selling medical device design software is so small, and, more importantly, it wasn't what we wanted to focus on. We wanted to develop something that was clinically-driven."

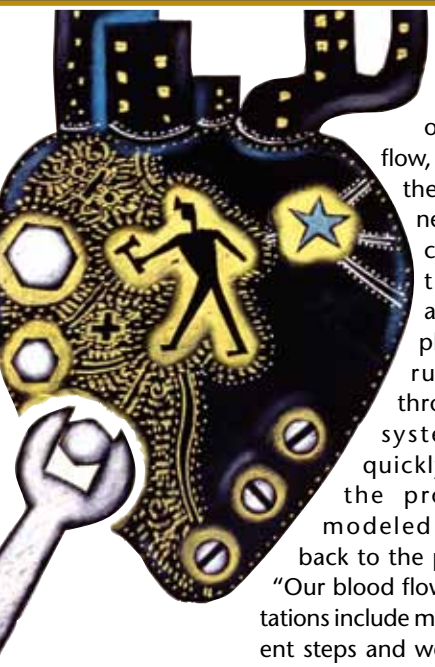
In July of 2009, they essentially "rebooted the company," Taylor says. This primarily meant taking a new approach to the software they were developing. "We began to focus on extracting the geometry from the imaging data more efficiently and accurately, which helped us improve the quality of our computer modeling capability," he explains.

By the time Stevens came on board, the company was well along in this new direction. "Our new approach to the software turned out to be a good decision," Taylor notes, "because the timing was right."

Indeed, the timing could not have been better on several fronts. As noted, the success of CV Simulation's technology depended on the capabilities and availability of two technologies very much beyond the company's control: sophisticated medical imaging scanners and enhanced computing power. By 2009, both of these technologies had reached the point where it was becoming feasible to turn Taylor's and Zarins' research projects into viable commercial applications.

In terms of imaging, by 2005, advanced multi-slice CT scanners were becoming increasingly available throughout the world and now they are easily accessible. Patients no longer needed to go to an academic medical center for a 64-slice CT scan, which is necessary for HeartFlow's FFR_{CT} technology.

CV Simulation also benefitted from the Moore's Law effect of continuing increases in available computing power. The company's model depends on computer capabilities in two ways: first is the ability to run the complex algorithms to perform the



necessary modeling of blood flow, and then there is the need to receive patient images from physicians, run them through the system and quickly return the processed, modeled images back to the physician. "Our blood flow computations include many different steps and we need to be able to complete the flow simulation in 20 minutes or so to return to the physician in order to have the turn-around time we need for our service model," Taylor explains. "What we used to need a $4 million supercomputer to do, we can now do with machines that cost only a couple hundred thousand dollars."

But the company's fortuitous timing had to do with more than just better imaging systems and more powerful computing. In 2009, the results of the FAME trial were published in *The New England Journal of Medicine*. "FAME really proved the efficacy of invasive FFR," John Stevens notes. And because CV Simulation was able to calculate all of the components of FFR – blood flow, pressure and velocity – and derive the same calculation noninvasively, Taylor and Zarins realized that the FAME trial essentially also provided the scientific basis underlying the clinical efficacy of noninvasive FFR as well. The FAME results effectively served as a surrogate enabling the company to demonstrate proof of concept even though they had yet to use the technology on any patients. Of course, the FAME data did not obviate the need for the company to conduct its own clinical trials, but it certainly provided significant support to the potential value of the technology.

For CV Simulation, the propitious timing of these events coming together marked the company's true emergence as a commercial entity. In John Stevens' view, "We couldn't do what we are doing today ten years ago, we couldn't even have done it five years ago, and frankly we couldn't have done it before FAME just two years ago."

ENTER HEARTFLOW

Stevens capitalized on this massive confluence of positive events by changing the company's name to HeartFlow, beginning to build up infrastructure and hire employees, and embarking on the company's first external round of financing. He had personally funded most of HeartFlow's $2 million Series A round in April of 2010, along with Summit Life Sciences and a small group of individual investors, including Tom Fogarty and Fred St. Goar. The company quickly out-grew its space at the Fogarty Institute and last spring moved into expansive offices in Redwood City, just down the block from Dreamworks.

In Stevens' view, HeartFlow's new neighbor reflect the true nature of the company's technology. "Our business model and team composition are unique in being closer to those of a software company than a traditional medical device company," he posits. Among the skillsets of HeartFlow's 50 employees are those of traditional device areas such as clinical, regulatory and biomedical engineering experience, as well as people with high-performance scientific computing and software backgrounds. "In some ways we're competing with Google and Dreamworks to get good talent, and the level of talent is in parallel," Stevens explains. "There is a subset of those really bright people who don't want to just do the next gaming company; they want to work on something more meaningful."

HeartFlow's Series B round followed right on the heels of its Series A financing. This was one example of the company's timing being less than ideal, as the funding climate for device start-ups was still recovering from the 2008 economic collapse and HeartFlow was hardly a typical device start-up. Yet, the company was able to quickly bring together a small syndicate of investors who saw the promise of FFR_{CT}. "We hand-chose a small, select group of investors that we know and trust, and fortunately they were excited, so it wasn't a six month process for us on Sand Hill Road," John Stevens says. He tapped another former Heartport colleague, Casey Tansey, who along with his partner Phil Young was among the device VCs at US Venture Partners. Young actually has a background in computational fluid dynamics and was immediately intrigued by HeartFlow's technology.

One of the company's challenges in telling its story to investors was that the technology depended upon a complex and unproven approach that had only been tried on a handful of patients and for which there was no noninvasive predicate. Whereas company officials argued that HeartFlow had the capability to be transformative, critics labeled it a science project, which often is the kiss of death among VCs, who are generally reluctant to take on the wide range of risk inherent in such early-stage deals.

Indeed, USVP's Phil Young acknowledges that was precisely the concern his partners had raised during discussions of whether the firm would back HeartFlow. According to Young, "When we were considering making our initial commitment to the company, there was big risk at the front end; could they really do it?"

The more due diligence he did on HeartFlow, the more Young says he became convinced that USVP should invest. Like Stevens, one of the most persuasive elements of the company's story for Young was its people. In Young's view, "Having Zarins, Taylor and Stevens, leaders in their fields, working together made HeartFlow the epitome of the integrated, cross-functional type of company that Stanford has been trying to produce for years, looking to combine expertise in medicine and engineering. I became convinced that these guys knew how to make this work."

In July of 2010, USVP led the Series B round along with Capricorn Investment Group, the investment fund of eBay's first president, Jeff Skoll. The financing totaled $20 million in equity, delivered in two tranches based on clinical milestones, along with an $8 million debt facility.

Armed with this fresh infusion of capital, HeartFlow's pace of development began to grow exponentially. The company completed its first-in-man Discover Flow clinical study, the results of which were presented in May at the EuroPCR meeting in Paris (triggering the second Series B financing tranche). There, HeartFlow also received the conference's annual Innovation Award.

The Discover Flow study was conducted at five hospitals (three outside the US) and enrolled 103 patients with a total of 159 lesions that were at least 50% occluded. All of the patients underwent CCTA, the results of which were mapped with HeartFlow's noninvasive FFR_{CT} technology, as well as invasive angiography with FFR. When the HeartFlow data were compared with traditional FFR, the results were nearly identical.

While comparable with FFR, the HeartFlow data proved superior to CCTA. The CCTA scans scored well for sensitivity and negative predictive value, but much lower

for specificity, positive predictive value, and overall accuracy. These differences in data were not unexpected as they reflect typical limitations of CCTA. By comparison, however, the FFRCT results showed sensitivity and negative predictive value numbers similar to those of CCTA, but produced much higher specificity and positive predictive value scores, while increasing overall accuracy by 25%. *(See Exhibit 1.)*

HeartFlow is in the process of enrolling patients for a larger study, DEFACTO. According to Stevens, this will be a 20 center, 240 patient trial in the US, Europe and Asia comparing FFR_{CT} with CCTA. He expects enrollment will be completed by October, with the study completed by the end of this year, and results submitted for publication early in 2012. This kind of study is made easier and quicker by not having to follow patients to determine outcomes; the study data are purely a matter of gathering and synthesizing the information.

THE HEARTFLOW MODEL

While the Discover Flow study validated HeartFlow's clinical model, the company's ultimate success will depend on clinicians validating the company's business model, which will be quite different than what they are used to. According to John Stevens, "HeartFlow's goal is to shift the diagnostic paradigm in cardiology so that cardiac CT becomes the gatekeeper." *(See Exhibit 2.)*

The process works like this: a cardiologist refers a patient for a standard cardiac CT angiogram. The physician then uploads that scan to a HeartFlow clinical analyst through a secure website where it is analyzed on the company's system using its proprietary software to create a three-dimensional model of the heart and the coronary tree. The geometry of every person's heart is unique. The software extracts a broad range of data from the CT on both the target vessels and the myocardium, such as size and thickness, and combines that with physiologic conditions, such as blood pressure and flow (which is estimated from the patient's myocardial mass). All of those data points are fed into a supercomputer, which generates a simulated flow and pressure model. The HeartFlow process includes a quality assurance review of the data, which is included in a case report that is e-mailed back to the physician. *(See Exhibit 3.)*

Currently it takes around five hours for HeartFlow to analyze a case and send it back to the physician. "We've taken that time down from 20 hours to five over the last year, and we hope by the end of this year that we can get it down to two hours," Stevens says.

The cardiologist is then able to click on any segment of the model – any specific artery or segment thereof – and the analysis will provide a precise FFR value. Similarly, the physician is able to use the model as a treatment planning tool and generate data indicating what the FFR would be if a certain size stent was placed at a particular lesion site, including data on how that specific implant would affect blood flow and pressure in other branches of the coronary tree, and what the FFR will be after the stent is deployed.

"Where the CT indicates the presence of coronary disease, our analysis delineates with precision which disease is significant and which isn't, so physicians can determine with great confidence which patients need to be treated in the cath lab and which ones don't," Stevens explains. "That's really where the paradigm shift is; we accomplish this with no additional risk to the patient and not even any additional radiation. We just analyze the data in a different way."

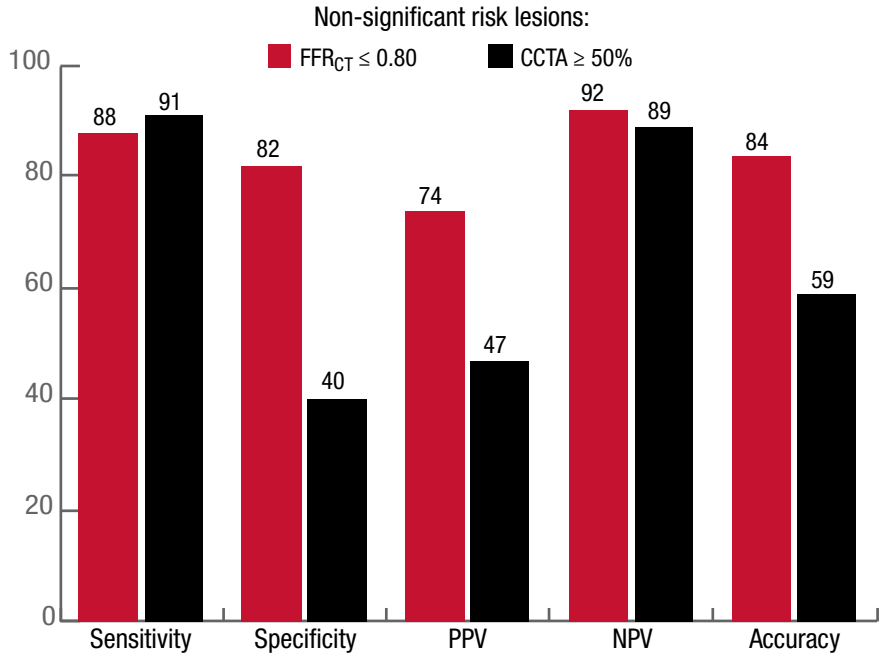
HeartFlow's secret sauce that enables the company to conduct this unique non-invasive data analysis goes back to Charles Taylor's and Chris Zarins' pioneering work in applying computational fluid dynamics to human anatomy, specifically to blood flow. "The single most important message concerning our technology is that anatomy alone cannot predict coronary events," John Stevens states. "You have to understand the hemodynamic significance of the lesion in question. That is the key issue." (For that reason, HeartFlow's technology may also prove useful in better understanding vulnerable plaque, possibly demonstrating that the hemodynamic forces are the primary cause of plaque rupture, as opposed to the plaque's biological composition, e.g., thin capped atheromas with lipid cores.)

To further illustrate the importance of hemodynamics, Stevens points to a recent study that compared quantitative coronary angiography (QCA), which is the gold standard in the cath lab for assessing coronary anatomy, with FFR. The study found that 65% of intermediate lesions – those with stenosis of 50%-70%, HeartFlow's primary targets – were not functionally significant. In lesions with 70%-90% stenosis, 20% were not significant, and even a small number of lesions with stenosis of 90%+ proved to be not significant. Stevens' points to this study as yet another example "that anatomy cannot predict functional significance, no matter how good a doctor thinks his or her eyeballs are."

Although Stevens believes that FFR_{CT} will result in the dramatic decline of certain diagnostic tests, most notably SPECT and stress echo, he is quick to point out that

EXHIBIT 1

Discover-Flow Data: FFR_{CT} Superior To CCTA

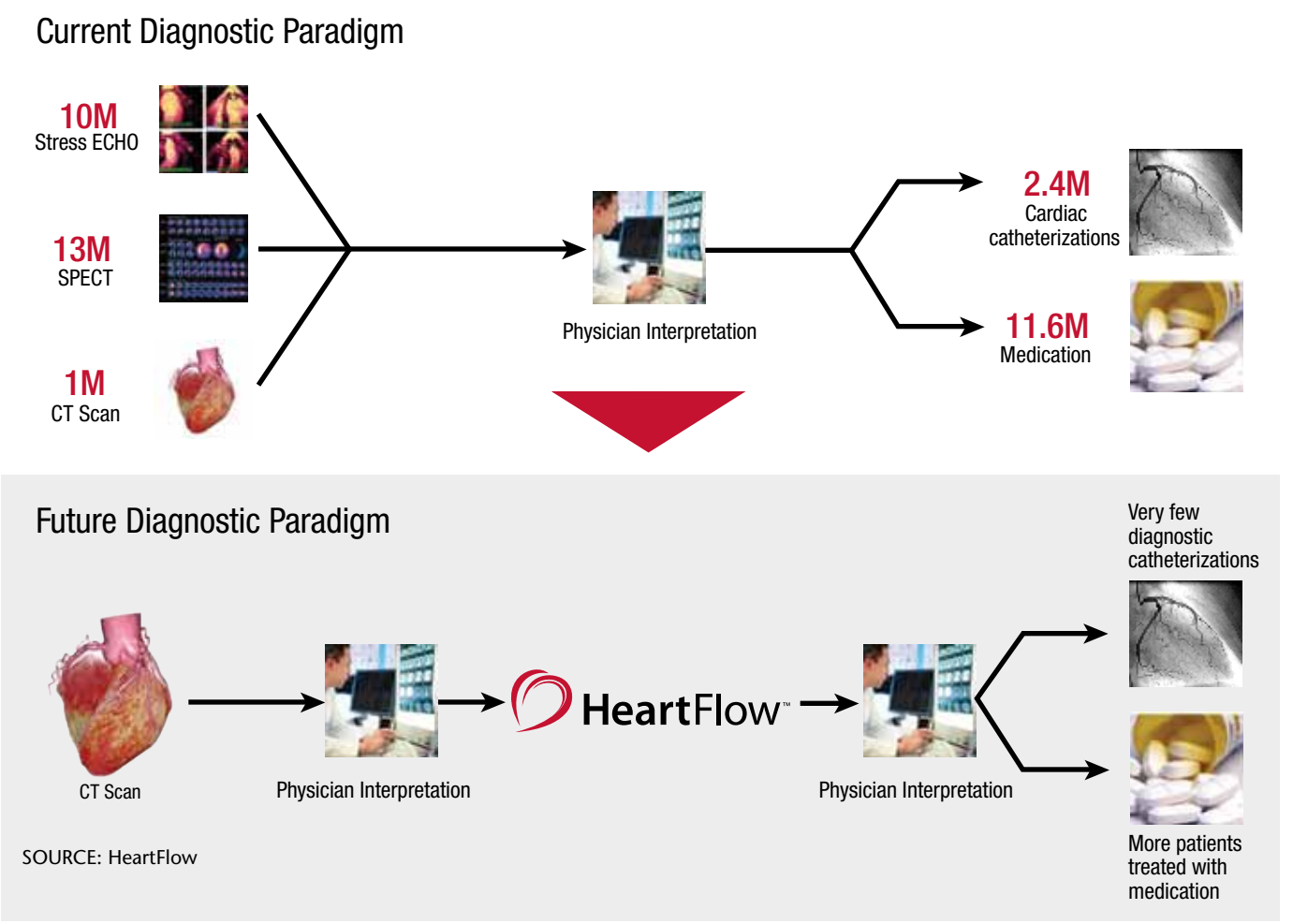


PPV=positive predictive value; NPV=negative predictive value

SOURCE: HeartFlow

EXHIBIT 2

How HeartFlow Can Change The Diagnostic Model In Cardiology



there will still be a place in the cath lab for technologies like IVUS and OCT. "The purpose of FFR_{CT} is to determine which lesions to treat. The utilization of IVUS and OCT is to confirm that you treat the lesions properly by placing and deploying the stent correctly. FFR won't tell you that, so these technologies fit together perfectly," he explains.

By using cardiac CT together with FFR_{CT} as the primary cardiac diagnostic tool, Stevens believes that appropriate use of PCI will improve and the number of unnecessary cath lab procedures will decline. Today, it is likely that less than 50% of patients treated with PCI actually have clinically significant lesions, he says, but with the use of FFR_{CT}, that number could improve to 90%.

BUT WILL CARDIOLOGISTS BUY IT?

In attempting to lay the foundation for cardiologists to adopt this new diagnostic paradigm of CCTA and FFR_{CT}, HeartFlow is drawing on John Stevens' Heartport experience in relying heavily on clinical data to convince cardiologists of the benefits of this approach. In the nearly 20 years since Heartport was founded, evidence-based medicine has taken a firm hold, particularly in interventional cardiology. Some of HeartFlow's work has already been done for it, as studies such as FAME and DEFER appear to have established the clinical benefits of FFR. HeartFlow must now establish that FFR_{CT} meets that same clinical standard, and the initial data looks promising.

But clinical data notwithstanding, worldwide adoption of FFR remains quite low. And John Stevens, again drawing on his Heartport experience and the slow adoption of MIS cardiac surgery approaches acknowledges that when it comes to physicians, "Old habits die hard," even among interventionalists, who are probably the most eager adopters of new technology.

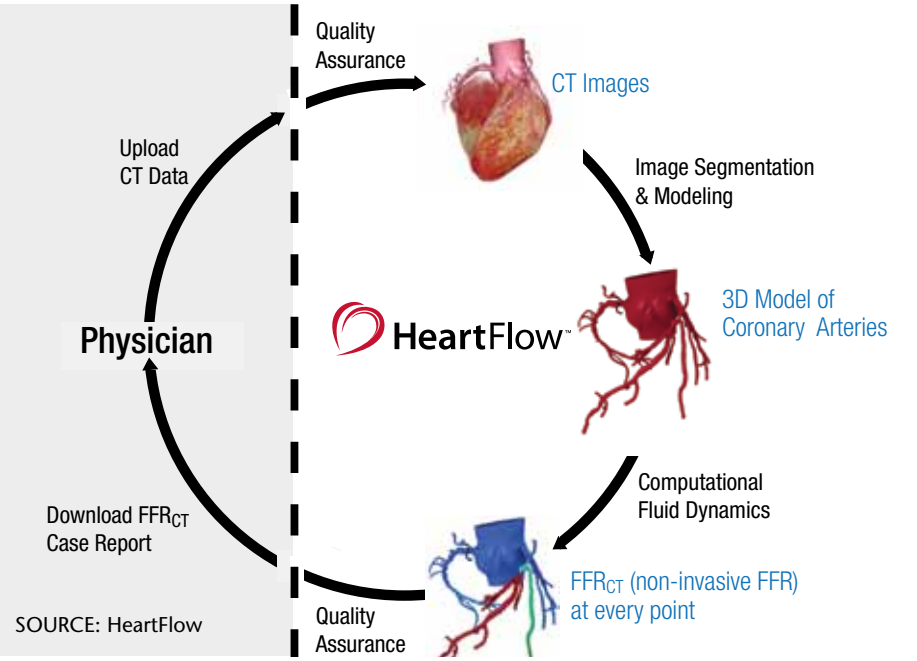
Stevens believes, however, that we are reaching a tipping point in cardiology when it comes to the adoption of FFR. In his view, this was clearly evident at this year's EuroPCR meeting. "I can't think of a single live case where the moderator wasn't asking about the FFR," he says. "The mindset is changing and I expect that we'll begin to see the overwhelming body of inertia moving towards using FFR to guide therapy."

In the early days of the technology's development, Charles Taylor recalls being pleasantly surprised at physicians' attitudes when he and Chris Zarins presented data from their early cases. According to Taylor, "I was prepared for the worst and, just in case, I had done slides with analogies about the skepticism surrounding the invention of the microscope. But we really didn't encounter much resistance; the physicians were overwhelmingly enthusiastic to the point that it made me a little nervous because, as an engineer, I knew we still had a long way to go to really prove that it works."

One important difference between now

EXHIBIT 3

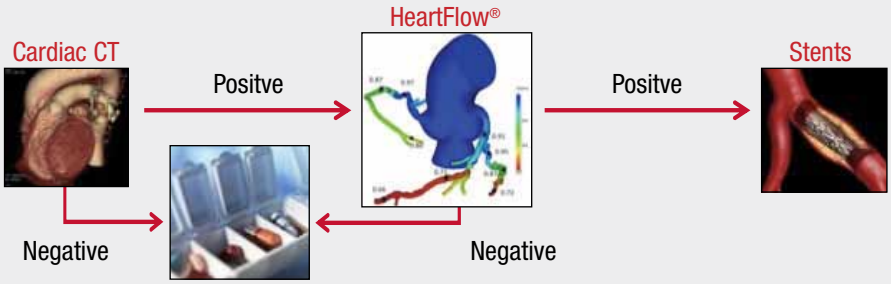
HeartFlow's Business Model



SOURCE: HeartFlow

EXHIBIT 4

HeartFlow's Treatment Planning Model



Simple & Comfortable

- No additional testing required - patients undergo a familiar 5 min Cardiac CT scan
- Test results available in a simple and intuitive visual form

Non-invasive & Safe

- Non-invasive FFR measurement prevents unnecessary invasive procedures
- Radiation dosage from prospectively gated CT scans is 1/20th that of nuclear studies such as SPECT1

Effective & Accurate

- Easy to integrate into existing clinical practices
- Results suggest very high diagnostic accuracy in preliminary trials

SOURCE: HeartFlow

and then is that cath lab procedures and interventionalists' incomes then were booming. Now, procedures are declining and many clinicians are looking to add to their diminishing caseload, not reduce it as could happen with FFR_{CT}.

Phil Young acknowledges that this is a potentially significant challenge for HeartFlow. In his view, "There is a non-trivial risk in integrating this new information into current physician practice patterns, depending on reimbursement rates associated with it, because on a micro-economic level, it is going to be potentially disruptive to the revenues of some interventional cardiology practices. And we've learned over the years that financial incentives to clinicians and reimbursement are enormous drivers behind all of the new technologies that have been introduced into medicine." Young adds that FFR_{CT} also has the potential to produce "multi-billion dollar savings to the health care system, with better patient care," but notes that still may not be enough to convince individual physicians to adopt the technology.

As a practicing interventional cardiologist, Fred St. Goar agrees that one of HeartFlow's biggest potential hurdles is convincing clinicians that FFR_{CT} will increase, not reduce, the value of their practices. Adding to the complexity of this issue is that the interventional cardiology community is not a monolith; it includes physicians with wide variations in practice patterns, from key opinion leaders at academic medical centers who perform a broad range of PCIs, including the most complex procedures, to clinicians at community hospitals who may only see a handful of relatively simple cases. Each is likely to react differently to HeartFlow's approach.

"Some physicians are going to be threatened by this technology," St. Goar admits. "Others will appreciate the added value. Clearly, the interventionalists who are time-value sensitive are going to be empowered by it and will appreciate benefits such as the ability to optimally inform and educate patients." The HeartFlow technology will allow clinicians to show patients - possibly using a graphics app on an iPad - the details of their coronary anatomy, where their blockages are, where stents are needed, and what their anatomy will look like and how it will function after the procedure. *(See Exhibit 4.)*

In terms of how practice patterns may change, the fact that diagnostic angiograms could largely become a thing of the past is actually a welcome relief to many physicians. John Stevens points out that noted interventionalist Martin B. Leon, MD, of **Columbia University Medical Center**, has often said that if he doesn't have to do another diagnostic angiogram again in his life, he'd be a happy man. Yet, Fred St. Goar acknowledges that Leon's view "is not the norm" and that many interventionalists with small, independent practices "are certainly not going to embrace this technology quickly because it's going to be threatening to them." Indeed, since the introduction of FFR, a common adage in the cath lab is that if you want to intervene, you do IVUS; if you don't want to intervene, you do FFR – the thinking being that, in making determinations of whether to treat borderline lesions, IVUS

provides a qualitative view that can usually be interpreted as justifying stenting, whereas if a clinician thought the clinical indications were not robust enough for stenting, FFR provides quantitative data supporting that decision.

When it comes to adopting FFR_{CT}, the question will ultimately come down to whether HeartFlow changes the way cardiologists practice medicine, no matter if the motivation behind the status quo is clinical, i.e., feeling compelled to stent certain lesions even if there is only a small chance they are significant, or financial. Indeed, for all of the excitement generated by HeartFlow at this year's EuroPCR conference, the company also had its critics. Some of those views were summarized in a presentation by Bernard Meier, MD, of the Swiss Cardiovascular Center in Bern, who argued that coronary angiography is really the only tool an interventionalist needs. Meier highlighted FFR's low adoption rates and attributed them, at least in part, to the fact that FFR, like other imaging modalities including IVUS and OCT, increases radiation exposure, requires more contrast use, and increases costs, and ultimately "distracts from the overall picture, leaving behind unfinished work." Patients, he said, are only looking to physicians to make them feel better; "they aren't interested in our gimmicks."

The primary criticism of FFR_{CT} can be distilled down to a common concern of clinicians when faced with any new technology that will require them to change practice patterns: the notion that the new technology is a substitute for their experience in making clinical decisions. Fred St. Goar has heard this from his colleagues. "Critics are going to say 'My clinical judgment is better and more accurate in determining how to treat my patient than relying on this technology. I'm going to take to the cath lab the patients I want to take to the cath lab and I'm going to still do perfusion scans or exercise echos because that's what I've always done,'" he says.

But HeartFlow executives argue that these criticisms miss the point. "FFR_{CT} is not and never will be a substitute for a physician's judgment in clinical decision making," John Stevens says. "The patient's clinical history, physical exam, ECG and cardiac enzymes will be paramount, all of which require the physician's judgment to assess. FFR_{CT} is simply another, and we believe more precise, piece of information to help the physician make the best decision for the patient."

HEALTH CARE REFORM: A BOON TO HEARTFLOW

To a certain extent, this whole argument over adoption may largely turn out to be moot because ultimately cardiologists may not have a choice whether or not to employ FFR_{CT}. That is because, as Phil Young noted, HeartFlow's technology has the potential to demonstrate huge savings for the health care system as a whole. *(See Exhibit 5.)*

Here is yet another area in which the timing appears to be working in the company's favor. A decade ago, few people would have given much more than lip service to the health economics of a technology like FFRCT. But in today's climate of health care reform and comparative effectiveness, this issue is suddenly at the top of everyone's priority list.

The total cost of treating coronary heart disease in the US alone was estimated at $177 billion in 2009. HeartFlow estimates that combining FFR_{CT} with CCTA can save the US health care system around $13 billion, in what the company says is a conservative calculation. This savings is primarily generated from fewer patients being sent to the cath lab for both diagnostic and therapeutic treatment. "There are very few new technologies that can significantly improve patient outcomes and also actually save the system a great deal of money," John Stevens says.

If the company is, in fact, able to demonstrate cost savings of that magnitude, then cardiologists may find that the decision regarding whether to use FFR_{CT} and CCTA with certain patients may no longer be theirs to make. "This is going to make some physicians uncomfortable, but it is possible that there are going to be gatekeepers, such as insurance companies, who may require the use of this technology to determine who does or doesn't go to the cath lab," Fred St. Goar suggests.

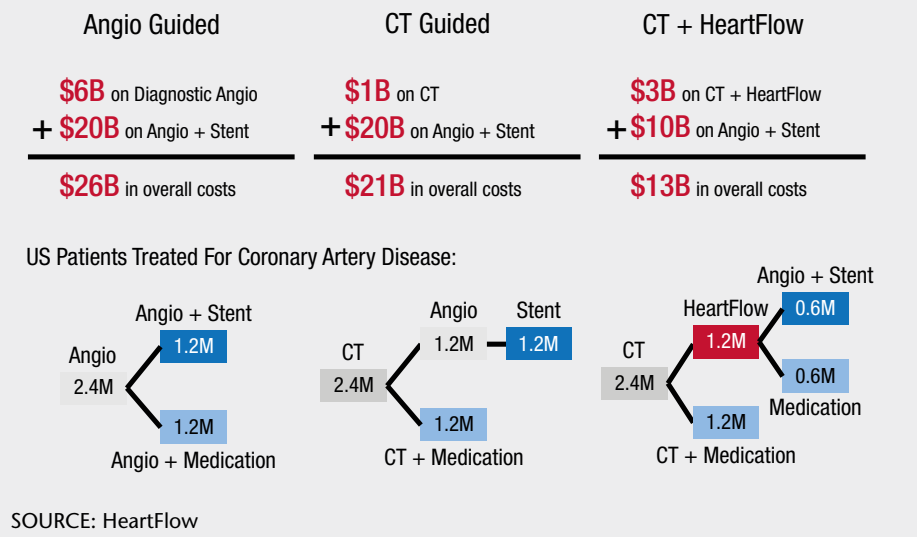
That raises the next important question for HeartFlow: how much data will those gatekeepers need in order to establish such a policy? St. Goar predicts that initial adopters are likely to be health care systems such as Kaiser or Sutter HealthCare that are already interfacing with their physician communities to limit costs. The larger insurance carriers may be inclined to wait and see how a gatekeeper approach plays out with patients, physicians and hospitals in terms of both clinical and financial outcomes.

John Stevens has already started talking to payors to familiarize them with HeartFlow's technology. He acknowledges that getting the right reimbursement will be critical to the company's success and this will be made more difficult by the fact that he can't point insurers to any similar products they can use as guidance. The hope is that the cost savings are compelling enough to generate coverage.

One area in which some critics argue HeartFlow may increase costs is through greater use of CT scans, a technology that is already the subject of much criticism for

EXHIBIT 5

Estimated US Cost Savings With FFR_{CT}



SOURCE: HeartFlow

overuse. Company executives contend that FFR_{CT} actually would enhance the value of CCTA by providing the functional significance that the current technology lacks. According to Stevens, "The primary reason why people argue that CT should not be used as much as it is and why payors don't uniformly cover CCTA is that the Achilles heel of those scans is their failure to define functional significance. We change the equation by providing that missing piece of information."

A TRUE PLATFORM, BUT WHERE DOES IT FIT?

HeartFlow's potential ability to change the traditional diagnostic paradigm in cardiology is a double-edged sword. It is always hard for a start-up company to bear the burden of pioneering any new technology, particularly one that requires a change in physician practice patterns.

Yet, in many ways, HeartFlow is not your typical medical device company, displaying many of the attributes of an IT start-up. The company can quickly conduct the clinical studies needed to support its technology because it can avoid the lengthy patient follow-up required in most device studies. Also, HeartFlow has the potential to scale up rapidly. "We don't have to teach a physician a new procedure or install a piece of capital equipment. We don't have to be in the cath lab stocking the shelves. This could go very quickly," John Stevens explains. For that reason, he views this as both an opportunity and a challenge. "There are so many things that are different here than with a typical device start-up that we're going to be very cautious as we start to make sure we've got the operational efficiencies where they need to be and make sure that the clinicians are getting exactly what they want when they want it," he says. In that way, Stevens is looking to avoid some of the mistakes Heartport made, allowing its sales effort to get out ahead of its clinical work.

HeartFlow expects to receive CE mark approval of its FFR_{CT} technology by the third quarter of this year and will then begin a gradual rollout in Europe. While there are some medical centers there that aggressively utilize CT, in general, Stevens says European interventionalists use noninvasive imaging less than their US counterparts, preferring to take patients right to the cath lab. "But European physicians are driven by the same economic and clinical outcomes considerations as in the US, which we think will work to our advantage," he notes.

The company is in the process of identifying a small number of prospective initial European customers that are high-volume CT centers for a planned fourth quarter product launch. HeartFlow will open a European headquarters to handle both commercial and clinical operations. According to Stevens, "We want to be able to offer real-time data analysis, which means having our clinical analysts based in Europe and then eventually in Asia, when we begin operations there."

In the US, FFR_{CT} is a PMA product, which somewhat surprised HeartFlow executives, who thought the technology would qualify for 510(k) approval. And as Phil Young points out, several years ago with a less risk-averse FDA, that probably would have been the case. The good news, according to Stevens, is that since HeartFlow is running a non-significant risk trial (largely because there is no implantable device involved), the regulatory path is expected to be more predictable than would otherwise be the case. The company expects to submit data from the DEFACTO trial in support of its PMA in early 2012 with the hope of commercializing in the US later that year.

Stevens is reluctant to say much about HeartFlow's sales model, other than revealing that in figuring out how to structure commercial operations, the firm is talking to people outside of the device industry and health care. The company also has hired Scott Ashworth as VP of sales and marketing. Ashworth previously headed **Siemens AG**'s global ultrasound sales and service organization.

Not resembling a typical medical device company also has its drawbacks. Most notably, it's not at all clear what the likely exit path will be for HeartFlow. It certainly doesn't appear to be an obvious fit with any of the large cardiovascular device companies; in fact, HeartFlow may be seen as competing with the existing businesses of several of these strategic players, not in terms of having competitive product offerings, but rather by offering a technology that could result in lower sales of existing cath lab products.

HeartFlow may actually be one of the few emerging technology companies that are well suited to remaining an independent, stand alone company. While start-ups often talk about running as if they will remain independent, the fact is that few could survive that way. HeartFlow could prove to be a true platform company, with technology applications in all of the major vascular sectors—neuro, carotid, peripheral, renal and coronary. The worldwide coronary diagnostic market alone is $20 billion. And that is what John Stevens and his team appear to be building toward. The company has raised $30 million to date and Stevens estimates that it can probably reach profitability with that level of funding, although he says HeartFlow may raise another financing round that will likely be led by one of several strategic partners who "are really interested in aligning interests more fully."

Phil Young believes HeartFlow is best suited to be a standalone company, whether or not it's owned by a large strategic. In Young's view, "This company's business model is so different from anything else that anybody is doing that the only effective way to capitalize on the huge opportunity is to run it as an independent company."

John Stevens is committed to HeartFlow remaining independent. "I can't imagine that we would have an early exit," he says, noting that it is different than many emerging companies. According to Stevens, "Most start-ups specifically design exits at times like this. We are disruptive and have the opportunity to improve outcomes, reduce risk and save money. We need to capitalize and achieve scale, and have great clinical data and be ready to commercialize. We want to see if we can make it happen." For the founders of HeartFlow, it's been a long time coming, but finally the timing may be on their side. [A#2011800105]

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