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EBR Systems: A Survivor's Tale

Innovating In A Conventional Market

—Can Leadless Pacing Revive CRM Growth?

KEY POINTS

- The cardiac rhythm management (CRM) market has been largely devoid of both major innovation and significant growth over much of the past decade, and many believe the two are linked.
- The leads that conventional CRM devices require has been their weak link.
- EBR Systems believes it has cracked the code with its leadless pacing technology, which appears to be effective in treating many heart failure patients for whom current CRT devices are ineffective.
- As a rare start-up in a mature sector, the company appears to have overcome early problems that forced it to suspend its initial clinical trial, with subsequent studies proving successful.
- By focusing on heart failure patients, EBR is hoping to attract the attention of one of a number of strategics—beyond just the Big 3 of CRM—looking for a share of this huge, growing market.

by
STEPHEN LEVIN

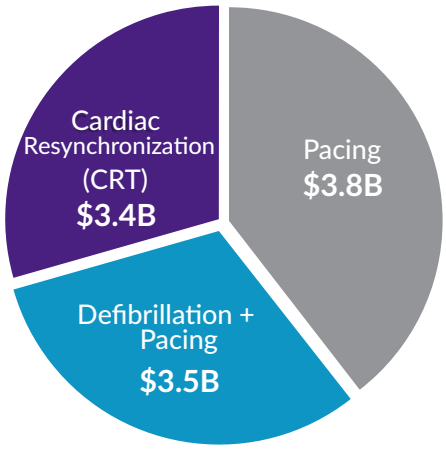
Cardiac rhythm management (CRM) has long been one of medtech's largest and most stable product sectors. Dominated globally by three major players—**Medtronic PLC**, **St. Jude Medical Inc.**, and **Boston Scientific Corp**.—whose respective market shares have remained largely stable for nearly a decade, CRM has also avoided any significant technology disruptions since cardiac resynchronization therapy (CRT) devices became available in the US in 2001.

In the process, this market has also largely followed a different innovation model than the traditional path common in most other medtech segments. Instead of the M&A model where venture-backed start-ups develop innovative new products and are then acquired by the major players, in CRM it is the strategics themselves that develop most new technology. While M&A certainly plays a role in that process, the large CRM players are nowhere near as dependent on acquisitions as most other large medtech companies to fuel their new product pipelines.

While that model has been effective in building what, according to the most recent available data, was an estimated $10.7 billion global market in 2013, CRM's growth over the past decade has slowed dramatically since the boom of the early 2000s, which was driven by the introduction of CRT devices (*see Figure 1*). Since then, pacemakers, which still comprise the largest of CRM's three major product segments, have basically been flat, registering consistent low single-digit growth, while the other two segments, CRTs and ICDs (implantable cardioverter defibrillators, which provide defibrillation and pacing), have been growing in the mid-single-digit range.

Figure 1

CRM: A $10.7 Billion Market in 2013



Source: EBR Systems

A major factor contributing to that slow growth has been the reluctance of physicians, due to the continued troubling non-responder rate of nearly one in three patients, to extend the use of CRT devices more broadly into the heart failure population eligible for reimbursement coverage, along with the continuing lack of reimbursement for a large part of the heart failure patient population. (Current estimates are that the penetration rate for reimbursement of potential CRT patients is only around 15-20%.) But industry executives suggest that the CRM space has also been limited by the lack of significant recent technology innovations that could help spur growth.

However, one area within CRM that has the potential to help drive growth has attracted at least a couple of start-ups: leadless and wireless devices. **Cameron Health Inc.**, which developed a subcutaneous ICD that did not require leads, garnered attention for its acquisition by **Boston Scientific Corp.** in 2012. Estimates are that Cameron was acquired for $150 million up-front, plus a potential earnout of more than $1 billion, of which an estimated additional $300 million has been paid. Less familiar is Sunnyvale, CA-based **EBR Systems Inc.**, which is developing a leadless pacing technology designed initially for patients not effectively treated with current CRT devices, a huge potential market in and of itself.

Lead failures continue to be the number-one complication in CRM. However, less widely acknowledged are the issues caused by an inherent shortcoming of wired leads—the location where they can be placed. Like all foreign bodies in the blood stream, leads are susceptible to clot formation that can result in emboli. It is for this reason that cardiac leads are placed in the right side of the heart (right atrium and right ventricle) or the coronary sinus (part of the venous system). This enables the lungs to filter emboli, rather than run the risk of emboli causing a heart attack or stroke. However, the right side of the heart is typically not the optimal place to stimulate the heart.

Leadless CRM technology is acknowledged to be a huge technical challenge, one much better suited to a large strategic than a venture-backed start-up, and the large CRM players have all pursued and continue to work on various leadless CRM technologies. Medtronic and St. Jude Medical both have leadless implantable pacemakers, the latter through its 2013 acquisition of **Nanostim Inc.** While those devices are designed for specific smaller segments of the pacing population, EBR is specifically looking to serve heart failure patients, a large and growing market, many of whom have no option with current treatments. EBR's story bears out the challenge of developing these complex devices, both in terms of how long it has taken and the problems encountered along the way. The company's ability to persevere after having to suspend its initial clinical trial and the sustained support of investors speak to the great clinical need, now and in the future, the market opportunities this technology can address, and the fact that EBR is one of the only companies well-positioned to solve this problem.

Using Sound Instead of Leads

In looking to reduce the shortcomings posed by electrical leads in CRM devices, EBR was taking on one of the industry's major concerns. Leads carry the current from the pulse generator (or "can"), which includes a power source and is generally located in a pocket created in the pectoral region of the chest, to the electrodes placed either inside (endocardial) or external (epicardial) to the heart. They are used with nearly all CRM devices, including pacemakers (which regulate bradycardia, when the heart beats more slowly or irregularly than normal), defibrillators (ICDs, initially developed to prevent sudden cardiac death by treating tachycardia, when the heart beats too quickly or erratically), and CRTs (which help treat heart failure (HF) by preventing the

ventricles from beating out of synchrony with one another—a condition known as dyssynchrony).

These electrical leads have long been perhaps the biggest problem facing the CRM industry. Every one of the three major CRM companies, which together control over 80% of the global market—Medtronic (about 40% share), St. Jude Medical and **Boston Scientific Corp.** (roughly 20-25% each)—has faced this issue and been forced to recall products as the result of lead failures. One such recall triggered a sell-off of Medtronic stock that reduced the company's market cap by $9 billion.

Lead failures also reduce patient confidence in CRM devices and slow product adoption as they can produce a variety of adverse clinical events. Lead failure typically results from the lead dislodging, fracturing or malfunctioning. One reported example occurred when a physician was testing an already-implanted device only to have it spark inside the patient's chest, emitting a puff of blue smoke, which was later traced to the lead's coating being worn away; fortunately, the patient wasn't hurt. It is not unusual for lead failures to produce serious problems, including infections, cardiac perforations, coronary sinus dissections, vein thrombosis, and heart valve damage. Even apparently benign lead failure situations that are identified before adverse events occur can prove problematic as lead removal can be a challenging procedure. The leads are barbed to prevent migration after placement, which can make removal difficult, sometimes requiring open surgery.

The potential benefits of developing leadless CRM devices have long been clear, but the technical challenges were known to be significant. Nonetheless, in 2003, three veterans of the CRM industry—Debra Echt, MD, an electrophysiologist (EP), Axel Brisken, an ultrasound physicist, and Richard Riley, a CRM engineer—set out to do just that when they founded EBR (the name comes from combining the first letters of each of their last names) with the idea of developing a leadless defibrillator. Echt had directed the arrhythmia practice at the Vanderbilt University School of Medicine and also worked with several medtech start-ups, including serving as chief medical officer of Cardiac Pathways Corp. (coronary mapping and ablation of arrhythmias), which was acquired by Boston Scientific for $115 million in 2001. (She is currently a consultant to EBR.) Riley became EBR's founding CEO and is currently COO, having formerly been VP of R&D at Cardiac Pathways, and previously was one of the managing engineers for Medtronic's pacemaker program. Brisken was an acoustic physicist at **Stanford University** and a key contributor at the intravascular imaging company **CardioVascular Imaging Systems**, acquired by Boston Scientific for $100 million. Allan Will, serial medtech CEO, founder and investor, initially financed the company, first through St. Paul Venture Capital and then Split Rock Partners. He later became chairman and was ultimately named CEO.

The trio's initial concept was to use ultrasound to defibrillate the heart. Ultrasound is a mechanical sound wave (one which cannot transmit its energy through air, requiring a medium like blood or tissue). The idea was to use ultrasound to mechanically thump the heart to defibrillate it. After pursuing that goal for nearly 18 months, EBR found that premise was clinically impractical, primarily because the energy requirements were too great. But in the process, they discovered a way to pace the heart and shifted their focus to pacing the left ventricle to treat heart failure patients.

In doing so, EBR recognized a need that follows a pattern in CRM, where a technology may solve one problem but leave other issues unresolved or even create new clinical issues. For example, the development of ICDs enabled pacing to be combined with defibrillation to help reduce sudden cardiac death. CRT technology used pacing in a new manner to treat heart failure by bringing the ventricles back into synchrony. These devices were built on the principles of standard pacing (the oldest and still the largest CRM market) but augmented their capabilities with defibrillation or left-sided pacing. But pacing chronically in the right ventricle can actually often cause a new problem—dyssynchrony, due to the location of the lead. As mentioned, pacemaker and ICD leads are placed in the right side of the heart, often at the apex of the right ventricle (RV), because placing leads in the left side increases the risk of blood clots. But the RV apex is not the natural place in the heart where an electrical pulse would typically start; normally it would begin on the left side in the interventricular septum and spread from there to the rest of the heart. While pacing from the RV apex allows more convenient access, as noted, it also can trigger dyssynchrony.

CRT devices, for all of their effectiveness in some patients, provide another example of a less-than-ideal solution. In developing CRT technology, engineers figured out that they could pace the left side of the heart by placing the lead in the coronary sinus (CS), thereby enabling stimulation of the left ventricle (LV) to resynchronize the ventricles, hence the therapy's name. According to Allan Will, there are several shortcomings to that solution: the path of the coronary sinus severely limits the locations able to be paced from within it; the CS is located on the exterior of the heart so pacing from that location is less effective hemodynamically than pacing from the endocardial (inside) surface of the heart; and lastly since it requires an additional lead running through the CS, it suffers from the typical lead issues previously mentioned. "Pacing endocardially gives you significantly improved hemodynamics, increasing cardiac output by around 20%," he says. "In our view, we saw the coronary sinus lead as the Achilles heel in CRT, causing some pretty significant failures in the treatment of heart failure patients."

One Technology's Failures Are Another's Opportunities

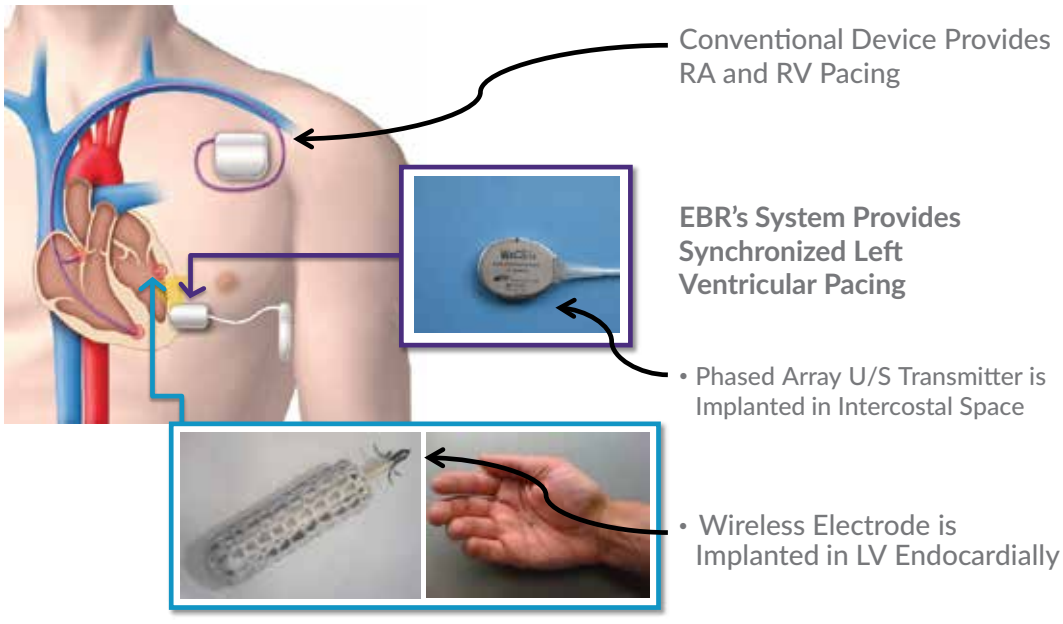
For all of the success of CRT, the technology still has major shortcomings, the most significant being an efficacy rate that would be considered disappointing by the standards of most widely adopted medical devices. The problem is that the only way to find out whether this treatment works on a specific patient is by actually implanting the device. According to Allan Will, "About 30% of the time, you put a CRT system in a patient—costing around $26,000—only to find out six months later that, although you are stimulating the left ventricle, you're not getting the heart to pump adequately to improve the patient's condition, so the patient doesn't respond to the therapy." These failures (referred to as non-responders) are generally for two reasons; either the lead is in the wrong location or the ventricle is too badly damaged by infarcts or other causes to respond to stimulation. The net result is that each year, in a $3.4 billion market, more than $1 billion spent on devices is wasted.

CRT placement is also procedurally challenging, with 5-10% of cases requiring more than a single procedure to place the CS lead. An additional 2-5% of patients annually suffer chronic CS lead issues and complications that require adjustment or surgical revision. One of the most frequent complications of epicardial CS pacing is that it accidentally stimulates the nearby phrenic nerve, which controls the diaphragm. This means that every time the device paces, the patient hiccups, thereby requiring repositioning of the lead. (That is one reason why quadripolar leads were developed recently by the large CRM companies. These leads have a selection of poles on the lead itself so that in the case of phrenic nerve pacing, the EP can change the combination of poles being used in order to avoid affecting the nerve and eliminating side effects.) But generally, Will explains, lead placement issues mean the EP has to either call the patient back in for another attempt or sometimes they'll refer the patient to a cardiac surgeon to place an epicardial lead by opening the chest and putting one on the outside of the heart. There are also some patients where lead placement proves too difficult to implant a device. For those patients who cannot be treated with CRT, there are often no other treatment options to stem the progressive cascade of heart failure with its cycle of repeated hospitalizations until their condition deteriorates to the point where they may become candidates for left ventricular assist devices (LVADs).

Presented with a large potential unmet clinical need and a receptive customer group in the form of clinicians who are frustrated at being unable to treat so many patients, EBR's solution was *WiSE* (Wireless Stimulation Endocardially) Technology. *WiSE* uses focused ultrasound to trigger a small wireless electrode (9mm long and 0.5mm in diameter) placed in the left ventricle (*see Figure 2*). EBR is initially targeting this group of conventional CRT failures. The company's system is implanted in patients who already have CRT or other pacing devices providing right atrial and ventricular pacing, with the *WiSE* device pacing the left ventricle synchronously. The EBR system has three components: a phased array ultrasound transmitter about the size of a conventional CRM device implanted in the intercostal space near the ribs using a surgical incision (a smaller next-generation device is being designed for less-invasive placement obviating the need for a surgeon); a replaceable battery, which powers the transmitter; and a tiny wireless electrode that is implanted endocardially in the LV using angiography. The electrode contains

Figure 2

EBR's Wireless Pacing – How it works



Source: EBR Systems

some 100 components, sealed in a titanium capsule. The tip of the electrode extrudes nitinol tines that hold it in place for the first 30-45 days, which is the time it takes for endocardial tissue to encapsulate the implant. The *WiSE* system automatically detects the other implant (the co-implant), whether that is a pacemaker, ICD or CRT, locates the target electrode in the LV, and sends the energy to pace the LV without using leads, converting the ultrasound to electricity and stimulating the heart at the electrode's location.

For all of the success of CRT, the technology still has major shortcomings, the most significant being an efficacy rate that would be considered disappointing by the standards of most widely adopted medical devices.

One of the more difficult technical challenges for EBR in developing the *WiSE* system was making it as energy efficient as possible, a constant issue for CRM companies continually looking to reduce the size of their devices, including the battery, which comprises perhaps the largest part of most implants. Unlike most pacemakers, which have batteries integrated into their boxes, EBR chose to separate its battery because the intercostal region where the *WiSE* transmitter is implanted does not have as much protective tissue covering the can as the pectoral area does, meaning the company needed a smaller footprint for its device. EBR's solution was to detach the battery and place it separately, connected to the transmitter by a cable. This approach also enables replacement of the battery without replacing the transmitter and gives the company the design flexibility to develop different capacity batteries independent of the transmitter.

By the very nature of being wireless, this device is transmitting energy less efficiently than if it were using a wire. That is also a reason the company needed to ensure that it targeted the energy as precisely as possible on the exact point to be stimulated. "We could direct the ultrasound broadly to ensure we hit our spot, but that would be wasting a great deal of energy," Rick Riley explains.

The *WiSE* device has sensors to determine exactly when the co-implant sends out a right ventricular pacing pulse so that it can immediately pace the left ventricle to bring the two into synchrony. In order to maximize energy efficiency, with each beat of the heart the *WiSE* system sends out a series of locating pulses, like sonar, and a search algorithm to identify the precise location of its electrode. It then directs enough energy at a one centimeter area at that location to stimulate the electrode and pace the left ventricle. This whole process takes only three milliseconds, enabling it to occur virtually simultaneously with the stimulation of the right ventricle. EBR has been continually improving the accuracy with which the system targets the electrode, which Riley says is now in the high ninety percent range.

Another challenge for EBR is that some clinicians have voiced concerns that the *WiSE* system is too cumbersome a solution, involving as it does, a second can. Riley points out that the history of CRM devices is one of continually shrinking boxes in subsequent generation devices, while also pointing out that, while perhaps cumbersome, EBR's system is the only therapy available for many patients who fail conventional CRT.

Wireless pacing is able to succeed where conventional CRT can't for several reasons, according to Riley. By placing an electrode inside the heart, he says that EBR's device is not impaired by the tortuous, smaller vasculature through which conventional coronary sinus leads must be placed. *WiSE* also benefits from the improved hemodynamics and cardiac output of endocardial placement as previously noted. Whereas current CS leads can only be placed in certain locations, the *WiSE* electrode can pace from any location on the endocardial surface of the LV. "We don't settle for just any location we can reach," Riley points out. "We go for the best location and we can test each possible location during the procedure to make sure it's optimal." In addition, he adds that endocardial LV pacing avoids phrenic nerve stimulation, and eliminating leads significantly reduces complications associated with pocket infections like endocarditis, caused by bacteria that travel from the implant pocket down the lead directly to the heart.

The procedure by which the *WiSE* device is implanted uses traditional interventional tools. The system employs a steerable sheath, much like a guiding catheter, that the EP can direct on the inside surface of the heart. A delivery catheter with the electrode attached to the tip is placed through that sheath. The EP touches the sheath to the ventricular wall and, without implanting the electrode, tests the pacing threshold just by placing the saline-filled tip against the LV tissue. When the EP finds a good location, he or she then pushes the electrode into the tissue, attaching it to the wall, monitoring the placement with angiography using contrast.

For a start-up like EBR looking to carve out its place in a sector—CRM—dominated by three major players, the population of failed conventional CRT patients is the perfect place to start for a number of reasons, most notably because the hurdle rate is low and it is a huge opportunity that has yet to be addressed. As Allan Will observes, "These patients are easily identified and don't have any alternatives, so we're

not competing head-to-head against the major players. In effect, we're solving a problem of theirs, so it's a great green-field market for us."

In terms of market size, EBR estimates CRT non-responders and lead failures to be a $5.3 billion opportunity with a $3.9 billion prevalence and $1.4 billion annual incidence rate (*see Figure 3*). And while EBR is still in the process of establishing the cost of the *WiSE* device, Will estimates it will be comparable to conventional CRT implants. Asked if he is concerned by the cost of *WiSE,* considering both the long-standing reimbursement battles that have plagued CRT generally and the pressure in the current healthcare economic climate to reduce medtech spending, Will acknowledges these potential obstacles but believes EBR is well-suited to deliver long-term cost savings. In his view, "Payors are always reluctant to cover expensive new devices, but we are actually offering a less-expensive alternative for heart failure patients who, left untreated, will undergo repeated costly hospitalizations." He goes on, "If we then take this to the next step and instead of just treating the failed patients, become a front-line therapy, the result could potentially be a success rate closer to 90% than 70%, which will also save money.

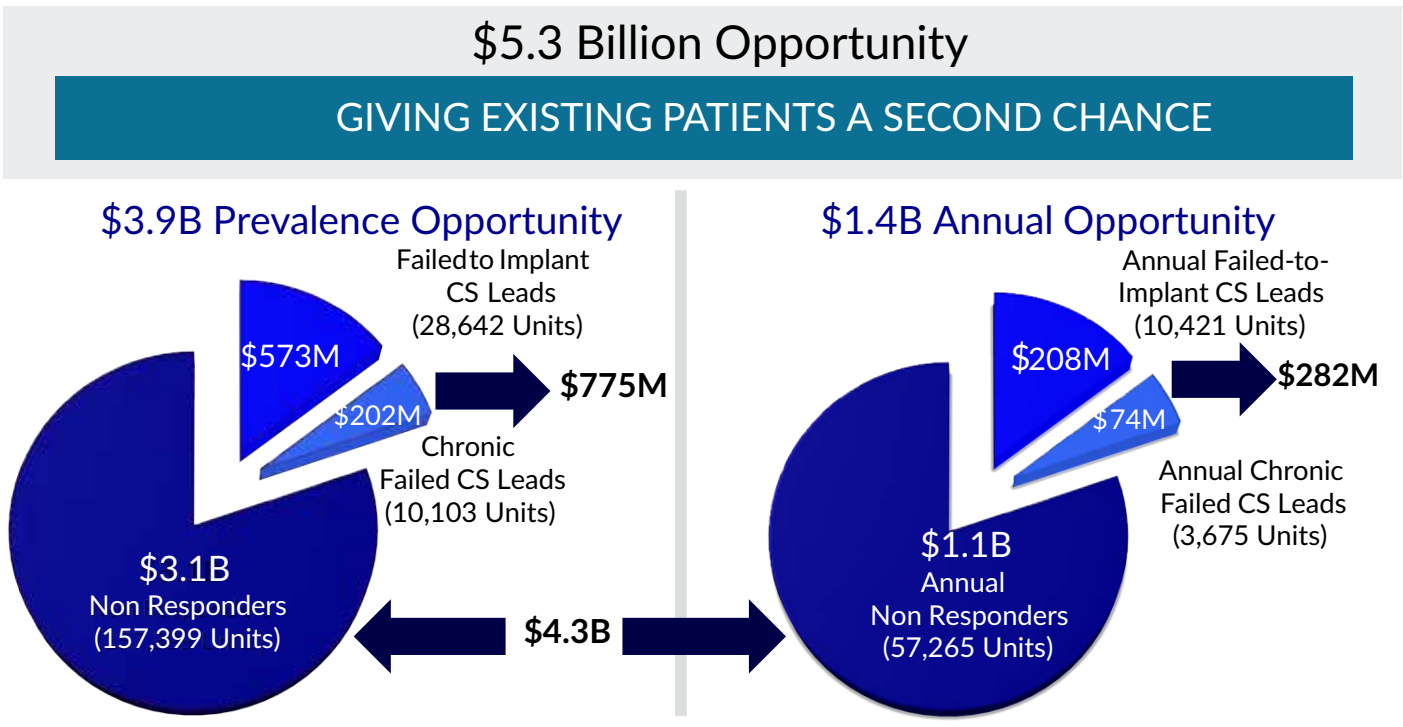
Delivery Issues Force Return to R&D Mode

It took EBR nearly eight years to get the *WiSE* system ready for clinical study. In February of 2011, the company began enrolling patients in its WiSE-CRT trial, which enrolled 17 patients and treated 13 at six European sites. While the device itself proved safe and effective, significant problems arose with the catheter delivery system, forcing EBR to suspend the trial. Specifically, there were three acute procedural pericardial effusion events in which the delivery catheter damaged the myocardium to the point where blood leaked into the pericardial sac. "We found that our delivery catheter was too rigid and sharp at the tip to be used safely," Allan Will acknowledges.

This setback forced the company to revert to R&D mode to re-design the delivery system. At first, the company thought it was a procedural issue before figuring out the problem resulted from the delivery system's design. Allan Will estimates that, all told, it took the company around six months to figure out the exact cause of the problem and fifteen months to re-design the system to solve the situation, which delayed them by two years in the clinic. This process also required restructuring EBR, including reducing the staffing from 25 to 12 (now 19),

Figure 3

Initial Market Entry: Failed Conventional CRT Patients



Source: EBR Systems

and necessitated the company taking out a bridge loan to finance the revisions.

The re-designed delivery system added a balloon at the tip of the catheter to make it softer against the endocardial wall to avoid punctures, thereby increasing the system's safety margin. EBR also made the new delivery catheter more precisely steerable to enable the EP to spend less time in the ventricle and improved the fixation of the transmitter.

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Despite the delivery system issues, the *WiSE* device itself proved effective in achieving the study's six-month secondary endpoint of reducing New York Heart Association HF class and/or global assessment, which was statistically significant. Eleven patients also showed reduced QRS duration, which is a measure of how well synchronized the ventricles are, and overall, ejection fraction, which is a measure of how much blood is pumped out of the heart, improved by an average of 28%. The *WiSE* system proved compatible with devices from all of the other manufacturers whose devices were used by patients in this trial (Medtronic, St. Jude Medical and **Biotronik**), and treated patients with a variety of conditions, including failed leads, chronic lead issues and non-responders, all without any unanticipated safety issues (specifically, no embolizations or strokes).

In Will's view, EBR's delivery system setback did not damage the company's credibility with clinicians as much as it did with investors and corporates. "We took a big hit not only because it cost us time but because it occurred at a period when venture capital was shrinking pretty dramatically and it cost us credibility with the venture community, as well as with some of the corporates." Will attributes the resulting loss of confidence among some large companies to the tradition-bound nature of the CRM industry. "There is a predominant 'not-invented-here' mindset in CRM, and EBR, by virtue of being ultrasonically-based, is a very different technology than these engineering teams are used to seeing, so any problem is likely to produce questions in their minds," he says. Another factor, in his view, was that the EBR system involves the left ventricle, which is a risky proposition for traditional CRM companies that are most comfortable staying on the right side of the heart.

Teaming Up to Divide and Conquer

While there is never a good time for a start-up to have to suspend its initial clinical trial, for EBR, the timing was particularly problematic given, as Allan Will notes, the corresponding overall declining state of medtech venture investing. In the best of times, a stopped study can cause investors to second-guess their backing of a start-up, especially one like EBR with an unconventional and potentially disruptive technology in a sector where innovation is traditionally incremental and generally the province of large companies looking to protect their existing product lines.

And 2011 was far from the best of times, with the sector still feeling the impact of the decline in device investing that paralleled the economic collapse since 2008. Venture capitalists were fleeing medtech in droves for greener pastures like biotech, IT and mobile health. Those who remained were husbanding limited reserves for existing portfolio companies and pulling the plug on those that had significant risk of any kind—financing, technology, clinical, regulatory or reimbursement. At the time, EBR faced challenges in each of those areas. Certainly, in the last few years, investor syndicates have shut the doors of many companies whose futures seemed a lot more certain than EBR's. Yet, the company managed to survive.

David Milne of SV Life Sciences, which, in 2006, was one of the early investors to back EBR, after the initial funding from St. Paul Ventures (later Split Rock Ventures), speaks for the board of which he is a member when he says that despite the problems with the delivery system, "the fundamental premise of the technology remained sound and had been proven in that first clinical study." Milne notes that "a delivery system problem is a lower risk to resolve compared to a problem with the implant itself. Solving this issue was very achievable with engineering, time and money, so the board decided it made sense to put more money in to fix the delivery system, which the team did on plan and on budget."

While continuing to support the company, EBR's board decided that the demands of re-doubling the engineering effort with only half the staff to fix the delivery system, along with the demands of fundraising, would be too much to expect of the CEO alone. The board decided to bring in a new CEO to focus on fundraising and strategic issues, allowing Rick Riley as COO to focus on the engineering efforts, which was his strength. This decision was made easier, Milne notes, because the ideal candidate was already serving as chairman, and in 2011, Allan Will was named CEO.

Will was ideally suited to assume the reins as CEO not just because he was familiar with EBR, having been a director since its inception, but also because of his extensive medtech operational background, along with his VC expertise. Will started in medtech in 1981 and has more than 25 years

of experience in operational roles. He was CEO of atherectomy pioneer Devices for Vascular Intervention (DVI), which was acquired by Eli Lilly in 1989 and later became part of Guidant; CEO of AneuRx, the aortic aneurysm stent graft company that was acquired by Medtronic in 1996; and co-founder of Adjacent Surgical (minimally-invasive surgical instruments), which was sold to **General Surgical Innovations** in 1996. Will was also founder, chairman and CEO of The Foundry medical device incubator, which has launched, among other companies, **Twelve Medical** (mitral valve replacement, recently acquired by Medtronic), Ardian (renal denervation, acquired by Medtronic), Evalve (mitral valve repair, acquired by **Abbott Vascular**), and Concentric Medical (stroke therapy, acquired by **Stryker Corp.**). In addition, Will was a venture capitalist for eight years at St. Paul Venture Capital and Split Rock Partners.

"It was pretty apparent that EBR had a small team that was still facing a lot of challenges, and we needed to increase their efforts to include outside fundraising, corporate relations with strategics, and starting to think about scaling up for European operations," Milne explains. In the board's view, that was just too much to layer on to the existing team. "They just didn't have the time and ability to do that, whereas Allan had the perfect skill sets for those external activities, so that Rick could concentrate on the engineering and product development. It played to their strengths," he says.

Milne believes that this type of corporate reorganization, taking advantage of the skills of key board members, will become increasingly common among start-ups that are already being stretched thin and in need of skilled executives to handle an ever-expanding range of issues. In his view, "We couldn't take a CEO like Rick Riley, who was deeply involved in the technical, regulatory and clinical issues, and then tell him to go out and raise money because then he would basically stop being an operating CEO and the company couldn't afford that."

The increasing need to divide what had previously been the responsibilities of a CEO is also being driven by the changing nature of fundraising. CEOs can no longer rely on going up and down Sand Hill Road in Palo Alto to meet with VCs or depend on existing syndicate investors to support the company in subsequent rounds. Fundraising can take the majority of a medtech CEO's available time. "This is no longer a world where CEOs can be successful on their own," according to David Milne. "The time and effort it takes to fund raise and build corporate relations is, in and of itself, almost a full time job in this new world. Boards are going to have to think smarter about how they staff their companies, including the use of skill sets on the board itself, and leverage those skills and their time more than they ever have."

In June of this year, EBR completed its $15.2 million Series E funding round, led by Emergent Venture Partners, headed by Thomas Fogarty, MD, who became a board member. This brought the company's total funding raised to $86 million. As noted, the company's first institutional round was led by St. Paul Venture Capital and also included Frasier Healthcare Ventures and De Novo Ventures. The Series B round was co-led by Split Rock (crossing over from St. Paul Venture Capital) and SVLS, and the Series C financing was led by Delphi Ventures with Series D funded by existing investors. EBR also has received significant personal backing from a number of leading medtech entrepreneurs, including Will.

Second Time's The Charm

After redesigning the delivery system, EBR went back into the clinic with a second European clinical study, SELECT-LV, conducted in patients who had failed conventional CRT. Vivek Reddy, MD, of New York's Mt. Sinai Hospital reported the preliminary results from this trial at the Heart Rhythm Society meeting this past May. SELECT-LV was conducted at six sites, implanting 34 patients in two phases: a safety phase with 12 patients implanted to ensure that the design changes were effective, and an extended phase of 22 additional patients implanted. Reddy reported that all 34 have reached 30 days, with all but one achieving the primary endpoint of being biventricularly paced. Twenty-six patients had reached six-months, 21 (or 81%) of whom met the efficacy endpoint of NYHA heart failure class improvement and/or global assessment. Considering that these patients had failed conventional CRT, these results are exciting.

While EBR is still in the process of collecting the data on this second trial, the early results appear to exceed the clinical results from the first trial, according to Allan Will, while successfully addressing the safety concerns caused by the original delivery system. The company used the data from the SELECT-LV study to support EBR's CE mark submission, with the WiSE-CRT trial used as supporting data. Following the anticipated CE mark approval, the company expects to continue to collect data on additional patients in Europe.

EBR is now in the process of defining its US strategy. The company has begun discussions with the FDA to determine the parameters for an IDE pivotal study, including how many patients the agency will require for what will certainly be a PMA, perhaps one with expedited approval since these patients have no other options.

Company officials believe that EBR has rebounded from the delivery system setback. Will acknowledges that "Anytime a company has struggled over its 12-year history and had some stumbles along the way, there is an overhang of why it has taken so long and thus it is hard to wipe the slate clean in everyone's minds." But in his view, that applies more to the investor community than to the clinical or corporate community. Will contends that the success of the second clinical trial confirms that this innovative technology

approach is safe and effective. EBR now has the data demonstrating the viability of using a wireless device placed in the left ventricle to provide CRT treatment to a broad array of patients, many of whom have no other therapies available to them.

Will contends that the success of the second clinical trial confirms that this innovative technology approach is safe and effective. EBR now has the data demonstrating the viability of using a wireless device placed in the left ventricle to provide CRT treatment to a broad array of patients, many of whom have no other therapies available to them.

At this point, Milne, who helped craft Boston Scientific's Cameron Health acquisition, believes that, upon receiving CE mark approval as expected and collecting additional patient data, the timing would be right for EBR "to build an operation outside the US, not just to generate revenue, but also to clearly demonstrate the range of patient indications this device serves and how it fits into different healthcare systems around the world because CRT is so widely accepted. You always want to add more clinical experience to your bag."

In terms of a US strategy, Milne's view is that, once the company finds out from the FDA what the IDE trial will look like, then EBR can determine whether there is "enough strategic interest in the company for them to partner with someone before making that IDE commitment or whether the company moves ahead without a strategic partner."

Having worked at several large medtech companies, Milne is of the opinion that "Coming up with something that reinvents an existing product platform is a difficult investment for a big company to make because it's very dilutive." He also questions whether the strategics have the expertise for this kind of innovation and, even if they do, "whether this would ever become a high enough priority for it to get funded."

One of the major advantages for EBR is that, ultimately, its wireless pacing technology goes beyond being simply a new left ventricular pacing therapy for failed conventional CRT patients, the company's initial therapeutic target. Allan Will suggests that, down the line, this technology can have a place as a front-line heart failure therapy enabling deeper penetration into the HF reimbursement guidelines with possibly superior efficacy, and may eventually even prove useful as a superior bradycardia therapy through multi-site wireless pacing.

By positioning its therapy squarely within the heart failure continuum, EBR enhances the company's value by placing it within the sights of a broader range of potential acquirers/partners than just the Big Three CRM companies. One only need refer to the recently announced acquisition by **HeartWare International**, a pure-play LVAD company, of **Valtech Cardio**, an Israeli mitral valve start-up with a major focus on heart failure, for upwards of $860 million, to demonstrate the potential value that strategics of different types place on possible HF therapies, with the added benefit of not having to initially compete directly with any of the Big Three. In addition to the current Big Three CRM companies, others with interests in heart failure include **Johnson & Johnson**, **Edwards Lifesciences**, and HeartWare.

In Allan Will's view, EBR is also helped by the success of Boston Scientific's acquisition of Cameron Health, the only recent comparator in terms of major CRM acquisitions. The two start-ups have other things in common: it similarly took Cameron a long time to exit following Boston's initial investment in the company, having hit some bumps along the way. Boston reportedly paid $150 million up-front, $150 million on US approval, and another $150 million in the first year of launch, indicating that Cameron may be generating dollar-for-dollar on that earn-out as the device appears to be generating about that same amount in revenue. It is also likely that Boston Scientific is getting product pull-through by virtue of having the Cameron device in its bag, which will generate additional business.

David Milne recalls presenting his proposed Cameron Health deal to the Boston Scientific board several years before Boston acquired Guidant and its CRM business. "The question they put to me was 'Why would an interventional cardiology company buy a CRM start-up?' Part of our thinking was that there was an opportunity for interventionalists to use a wireless defibrillation system to perform procedures, and if that premise was true, you didn't need to be a rhythm management company to sell that device; you needed to be an interventional cardiology company." Another part of the reasoning behind the Cameron investment was also based on the possibility of Boston Scientific eventually buying or merging with a CRM company. "The thought was that if we later got into the CRM business, then we would have Cameron as an additional platform, and if we didn't, this could give us access to getting into CRM without having to staff-up and become a full-fledged CRM player."

The opportunity for EBR's technology in heart failure surpasses the opportunity for pure wireless defibrillation. The experience of Cameron Health may well apply to EBR; it's something for potential acquirers to keep in mind.