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By Marion Webb

WHEN IT COMES TO TREATING ACUTE heart attack patients, primary percutaneous coronary intervention (PPCI) remains the gold standard of care. And while this life-saving procedure restores blood flow through the coronary artery, perfusion in all areas of the heart may not occur. In this article, we'll highlight three innovative medtech companies that have developed very different solutions to try to improve upon the current standard of care and hear perspectives from interventional cardiologists.

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When it comes to treating heart attack patients who have ST-segment elevation myocardial infarction (STEMI) caused by the sudden complete blockage of a coronary artery, "door-to-balloon" time is critical - this is the window of time between a patient's initial clinical assessment and them receiving life-saving percutaneous coronary intervention (PCI).

A recent study published in the *European Heart Journal* looked at 12,675 patients with STEMI and found that one death in every 12 patients could be prevented, if patients were treated within the recommended time of less than 90 minutes.

While hospitals have made great strides in reducing the time it takes for patients to receive emergency PCI -- considered the gold standard for treating STEMI patients -- a small, but significant number of patients continue to show impaired myocardial reperfusion despite successful opening of the obstructed artery.

This phenomenon called no reflow, caused largely by microvascular obstruction or MVO, is regarded as an independent predictor of death and myocardial infarction, according to a recent study published in the *Indian Heart Journal*.

MVO is complex and involves multiple factors, but doctors agree that early recognition and treatment while the patient is still in the cath lab is essential to achieve better outcomes. Current treatments including vasodilators and antiplatelet agents and mechanical strategies such as distal protection and aspiration thrombectomy have shown benefits, but many in the medical community say there is an unmet need for better solutions.

Several smaller medical device companies have developed innovative technologies to try to solve the MVO problem and offer patients additional benefits beyond the standard of care.

CorFlow Therapeutics

Swiss-based **CorFlow Therapeutics AG** believes its *CoFI (Controlled Flow Infusion) system* will allow interventional cardiologists to better detect and treat MVO in STEMI patients compared to using PCI alone.

Jon Hoem, CEO and co-founder of CorFlow, said CoFI is unique in that it addresses a huge problem that conventional medical therapies fail to address and also fits into the existing workflow of interventional cardiologists treating patients in the cath lab. *(Also see "Hindsight 20/20: Jon H. Hoem" - Medtech Insight, 6 Oct, 2017.)* (See Figure 1).

Photo Credit: Corflow

Figure 1
Jon Hoem, CEO and co-founder of CorFlow Therpeutics

"What makes MVO detection and treatment problematic

is that it is detected in only the worst case no-reflow patients which constitutes 4-5% of the patients after a stent has been placed," Hoem told *Medtech Insight*. "Studies suggest that MVO is present in roughly 50% of patients, which means that about 45% of patients remain undiagnosed and therefore untreated."

Under conventional methods, interventional cardiologists rely on angiographic and electrocardiographic indices to identify suboptimal microcirculation and estimate optimal myocardial perfusion.

"What makes MVO detection and treatment problematic is that it is detected in only the worst case no-reflow patients which constitutes 4-5% of the patients after a stent has been placed," said Jon Hoem, CEO of Corflow Therapeutics. "Studies suggest that MVO is present in roughly 50% of patients, which means that about 45% of patients remain undiagnosed and therefore untreated."

"But the interventional cardiologists only detect the worst cases on the angiogram," Hoem said. "The average MVO in all patients is around 1.9% of the left ventricular mass and these patients often remain undetected, because of the lack of an on-table diagnostic tool to detect MVO."

To precisely delineate both MVO and the infarct size as a percentage of the left ventricular mass, requires contrast enhanced cardiovascular magnetic resonance (CMR) imaging, a procedure that can only be done outside of the cath lab.

"When you diagnose MVO using CMR, it's too late to repair the damage," he said, adding that MVO often translates into worsening outcomes.

Studies have shown that STEMI in-hospital mortality rates still hover around 5-6% on average, increasing to 7-18% by one year and outcomes data suggest that some 25% of STEMI patients will develop heart failure within four years of their first heart attack, according to CorFlow.

CoFI's approach to detecting MVO is different in that it uses a proprietary algorithm to diagnose MVO by measuring real-time coronary dynamic microvascular resistance (dMVR) and heart response to infusing targeted drugs immediately after the patient has been treated with PCI.

This is how it works: The CorFlow catheter is placed into the coronary artery immediately after opening the coronary circulation with a stent and/or using thrombus aspiration, the tools of standard primary PCI. CorFlow's catheter is then placed into the stent and occludes the native coronary blood flow using an occlusion balloon and an algorithm to infuse a crystalloid in controlled flow steps. The CoFI system measures the pressure response to the controlled flow infusion, which is used to calculate dMVR and diagnosing the MVO. In those patients where MVO has been diagnosed, the therapeutic part of the system is used to infuse approved therapeutic agents, such as abciximab (ReoPro), at low rates into the affected area. After about 30 seconds of infusion, the balloon is deflated to allow the coronary circulation to return to its normal perfusion rate (Figure 2).

"We measure dynamic real-time vascular resistance and it's calculated by dividing the measured pressure response with the known flow rates we have infused," Hoem said. "We have been able to create MVO in the non-clinical setting and have documented that dMVR correlates with the MVO measured by CMR post procedure."

CorFlow's approach is substantially different from high-flow infusion technologies, which Hoem said have been attempted in the past and shown to be ineffective. He said the company will present two abstracts at the American College of Cardiology's 67th Annual Scientific Session from March 10-12, 2018 in Orlando, Florida.

One abstract will describe the method of measuring dynamic microvascular resistance and the other will show that MVO can be created non-clinically without the presence of thrombi. The results also show that minute reductions in coronary volume flow causes an expo-

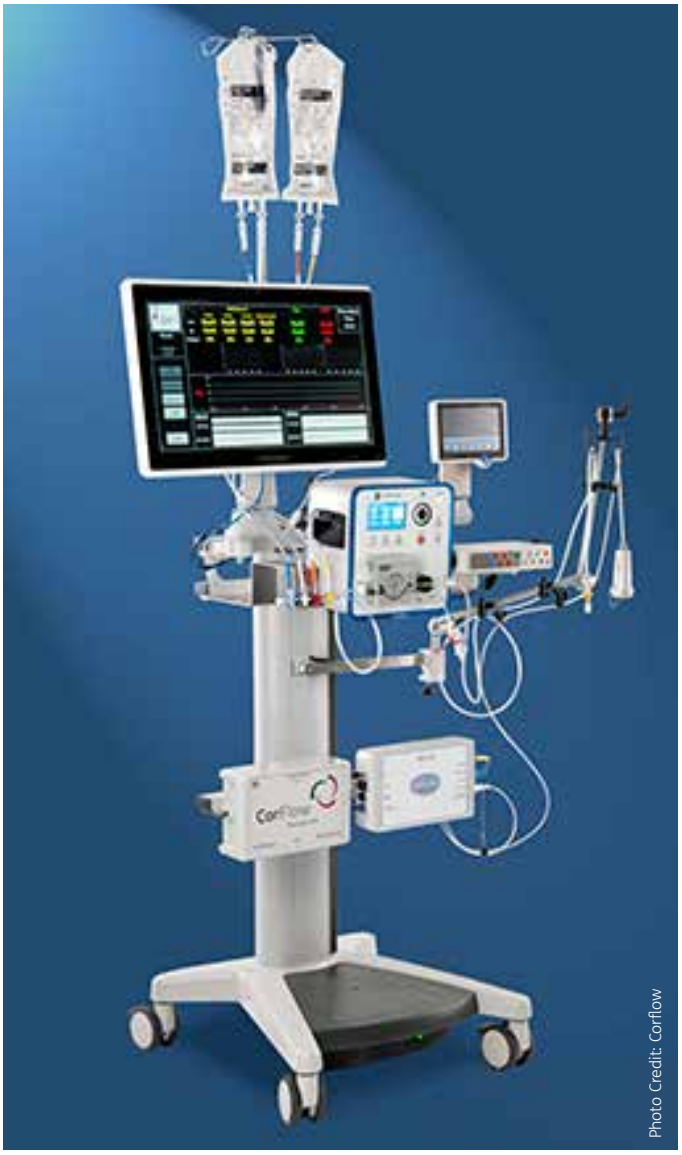

Figure 2
The CoFI System measures real-time vascular resistance

nential collapse of the coronary microcirculation and that epicardial revascularization alone isn't sufficient to open the collapsed coronary microcirculation, he said.

CorFlow, which was founded in June 2016, announced on Oct. 24, 2017 it raised $2.6m in a seed round financing led by private medical device investors including CoreValve and CardiAQ founders Jacques Séguin and Arshad Quadri and CoreValve and CardiAQ tech developer Jean-Claude Laborde. To date, the company has raised a total of $5m in funding.

Hoem said part of these proceeds will be used to finance the company's first 90-patient clinical trial at five to six centers in Europe. He said 15 non-STEMI patients will be enrolled to show that CoFI is effective in measuring dMVR. The following 90 STEMI randomized controlled study will explore diagnosing microvascular obstruction and potential therapy, comparing the technology to standard of care. If all goes as planned, the human trial will start in late Q3 or Q4 of 2018 with interim results being announced by Q2 of 2019.

Hoem said that CorFlow plans to raise $15m to develop a second-generation version of the CoFI system, which is more user-friendly for adoption in the cath lab before seeking CE mark approval for commercialization. If that strategy works out, he said, the company will file for CE mark approval of a Class III device in late 2020 or early 2021.

Miracor Medical Systems

Miracor Medical Systems GMBH, which was formerly led by Corflow's Hoem, announced in January 2018 it raised €25m as part of a Series D financing round to further develop and commercialize its *PiCSO* (Pressure-controlled Intermittent Coronary Sinus Occlusion) system for treating acute coronary syndrome and heart failure patients *(Also see "Medtech Money Flow: Weekly M&A And VC Deals, Jan. 1-7" - Medtech Insight, 8 Jan, 2018.) (Also see " Miracor's cardiac perfusion technology enters first human trial " - Medtech Insight, 10 Nov, 2010.)*.

Miracor said the funding will be used to finance a randomized clinical trial in Europe using its *PiCSO Impulse system*, work with the FDA to win approval for starting a clinical trial in the US in 2019 as well as start commercializing its product in Europe next year. The latest capital round was led by Ming Capital (Shenzhen, China) and co-led by a strategic unnamed investor. Other backers included the new Belgian and Walloon public investors SFPI, SRIW and Meusinvest, as well as existing investors Earlybird Venture Capital, Delta Partners, SHS Gesellschaft for Beteiligungsmanagement, Biomed Invest and Peppermint Venture Partners. As part of the deal, Austria-based Miracor Medical Systems GmbH merged with **Miracor Medical SA** and relocated its headquarters to Awans, Belgium.

Olivier Delporte, who took the helm of Miracor in July 2016, said the technology addresses some three million

infarct patients worldwide. He pegs the global market size at $10bn, saying it's a "massive market opportunity."

Since the company was founded in 2008 by Austrian cardio surgeon, Werner Mohl, and the European venture capital firms Earlybird and Delta Partners, it has conducted four clinical trials treating a total of 193 patients. Delporte has high hopes to win CE mark approval by 2019 and eventually file for premarketing approval in the US.

The PiCSO system, which consists of a balloon-tipped catheter and a driving console, is designed to improve blood flow to the heart muscle during PCI to help repair cardiac tissue in patients with acute myocardial infarct. The balloon catheter is inserted via the femoral vein into the coronary sinus, using a steerable guide sheath (Figure 3).

Delporte noted that this procedure is done in parallel with the standard stenting procedure and managed via the console, which takes its input from the ECG and coronary sinus pressure, using the company's Wien Algorithm, which constantly monitors the coronary sinus pressure and automatically sets the time when the catheter balloon is intermittently inflated to increase the pressure in the myocardium.

"When the pressure is increased, it leads to redistribution of blood flow, which leads to better myocardial perfusion," Delporte explained. "Every time the balloon is deflated (in a cycle of 10-15 seconds or maximally 30 seconds), there is a wash-out effect, evacuating the toxic metabolites during AMI in the microvasculature, which in turn, improves microcirculation and perfusion."

Last November, at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in Denver, Colorado, Miracor presented positive interim results of a prospective, parallel controlled UK study comprising 92 STEMI patients. The study compared 20 patients using the PiCSO device with 80 patients from the INFUSE-AMI control group with a 5-day cardiac MRI with the aim of showing the effects of PiCSO on infarct size. The findings showed that PiCSO reduced infarct size in STEMI patients by 47% compared to the control group and prevented deterioration of myocardial function after acute anterior STEMI.

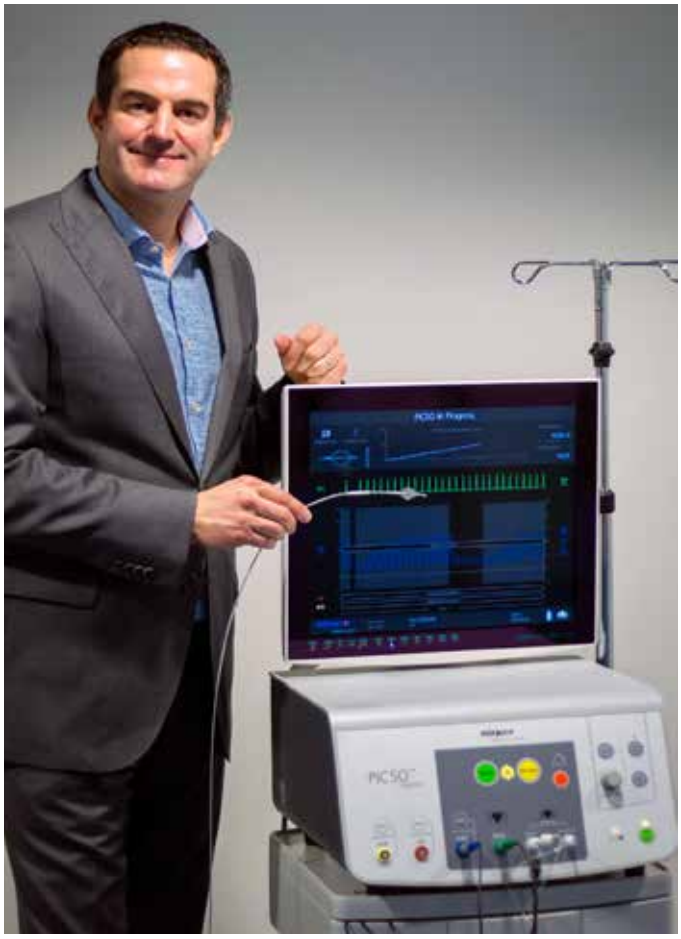

Photo Credit: Miracor

Figure 3
MiraCor's CEO Olivier Delporte shows the company's heart therapy PiCSO system

Miracor announced back in 2010 that it received the CE mark, but then it was not recertified after the initial five-year period; instead, regulators asked for more clinical trial data. Delporte said the company hopes that the results of the recently completed UK STEMI clinical study will be sufficient for EU regulators to grant recertification of PiCSO.

Asked about their EU marketing strategy, Delporte said the company hasn't announced details. But he aims at a controlled roll-out in selected countries rather than introducing PiCSO in all 15 EU countries.

"It's more about collaborating with a limited number of hospitals in the initial period of commercialization to have accelerated usage and a growing number of patients (being treated with PiCSO)," he said.

TherOx

Irvine, California-based **TherOx Inc.** has been developing a novel heart attack therapy based on delivering supersaturated oxygen to the damaged part of the heart immediately after conventional PCI therapy to reduce infarct size since its founding in 1995 *(Also see "Miracor Medical Systems GMBH" - Medtech Insight, 1 Oct, 2009.)*.

After multiple setbacks in trying to win regulatory approval in the US for its *Super Saturated Oyxgen* (*SS02*) treatment, the company's long-time president and CEO, Kevin Larkin, now hopes that the company's PMA application, filed last September, will be approved by mid-year (Figure 4).

The PMA application included data from TherOx's 100-patient IC-HOT (Evaluation of Intracoronary Hyperoxemic Oxygen Therapy) study at 15 US centers. The primary objective of the study was to collect confirmatory data supporting the safety and effectiveness of SS02 therapy in treating anterior STEMI patients who have undergone conventional PCI therapy within six hours of experiencing acute myocardial infarct symptoms. These findings were presented in October at TCT 2017 and confirmed earlier findings from the AMIHOT II study.

Larkin said that the company learned during an earlier patient trial (AMIHOT I) that six hours is really the "magic window" to show improvement in saving heart tissue. After submitting that data to the FDA, regulators asked the company to conduct another randomized patient trial (AMIHOT II) to show that the therapy would meet the safety and effectiveness endpoints *(Also see "Research Briefs: Gore Iliac Branch Trial; Svelte DES Trial; TherOx SSO2 Data" - Medtech Insight, 18 Nov, 2013.) (Also see "PMA Panel Asks TherOx For New Data On Cath-Lab-Based Oxygen Therapy" - Medtech Insight, 23 Mar, 2009.)*. Results from the AMIHOT II trial showed that SSO2 therapy, together with PCI, produced a relative reduction of 26% in infarct size compared to using PCI alone, Larkin said. The findings also showed a 53% greater likelihood of having a small (less than 5%) infarct among SS02 therapy patients. The findings were published in the medical journal *Circulation: Cardiovascular Interventions*.

Larkin said that there have been many attempts made with drugs and devices to reduce infarct size -- including using cooling catheters, thrombectomy and thrombolysis -- but none have been successful. He said that's because they're not addressing the underlying issue of the ischemic condition of oxygen deprivation.

The idea of delivering supersaturated oxygen to heart tissue came from a Detroit-based cardiologist who observed that treating AMI patients and stroke patients in hyperbaric chambers improved their recovery.

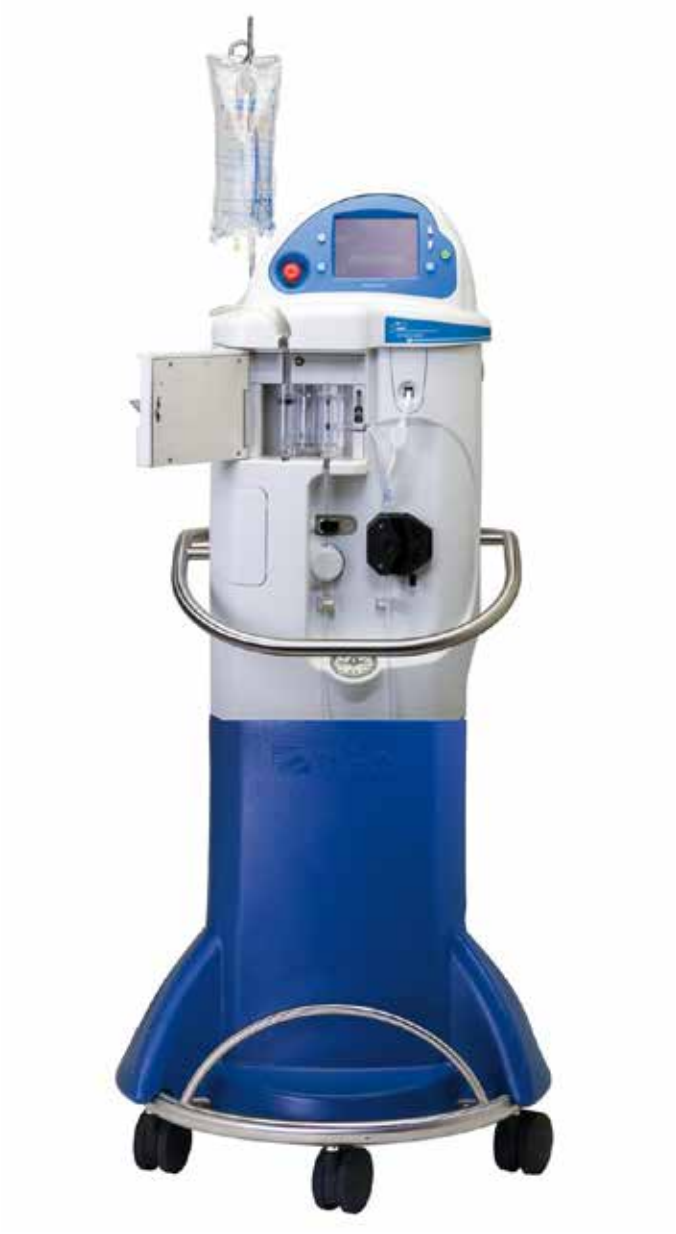

Photo Credit: TherOx

Figure 4
TherOx's SS02 system is currently under review for PMA approval by US FDA

Larkin said the company was founded to develop a hyperbaric equivalent by dissolving a large amount of oxygen in a smaller volume of saline to create the supersaturated oxygen solution that could then be infused in the coronary artery to help restore normal oxygen to the damaged tissue. It took TherOx years to overcome that initial technology hurdles.

> **"We've been doing intervention or stents for heart attacks for many, many years now, but for 30 years, we've never had anything adjunctive to do to improve the results," said interventional cardiologist Richard Schatz. "You can open up a blood vessel, but in about 30% of patients, the ventricle still falters. It doesn't recover completely for many reasons."**

"Five or six years were devoted to this – part of the trick is not just dissolving oxygen into blood and saline solution to create a supersaturated oxygen solution, but a big part of the research work involved dissolving an enormous amount of oxygen into this liquid, while not producing bubbles," Larkin told *Medtech Insight*. "Bubbles in the coronary artery would be deadly."

After testing the concept in animals, the company conducted the AMIHOT I controlled study where they treated patients up to 24 hours from symptom onset using the first-generation product. This study showed that patients who were treated with SS02 for up to six hours from symptom onset showed a demonstrable benefit in reducing infarct size, he said.

Additionally, this study and evidence from the broader scientific community showed that "right ventricular or inferior wall infarcts can actually undergo a fair amount of damage without functional effects whereas the left ventricular side showed significant differences," he said.

The company then developed a second-generation system using an angiographic type catheter that would be positioned in the left coronary ostium to infuse the left ventricle with supersaturated oxygen, not just the LAD artery, as was done with the first-generation system.

"After angioplasty and stenting in the primary artery, SSO2 has an angioplasty-like effect on the micro vessels by reversing microvascular obstruction," Larkin explained. "We've opened up all those little pipelines to get the myocardium restored to normal … faster and sooner than the normal arterial blood flow can do it." He said the SS02 system delivers oxygen 7 to 10 times the oxygen content than normal arterial blood carries — That's what stops the infarct from growing as it typically does with PCI alone."

Richard Schatz, one of the original investors in TherOx who works as an interventional cardiologist at the Scripps Clinic in La Jolla, California said that infusing SS02 therapy can save 30% or more of heart tissue that would otherwise deteriorate using PCI alone.

"We've been doing intervention or stents for heart attacks for many, many years now, but for 30 years, we've never had anything adjunctive to do to improve the results," Schatz told *Medtech Insight*. "You can open up a blood vessel, but in about 30% of patients, the ventricle still falters. It doesn't recover completely for many reasons."

Asked about the necessary training required to use TherOx's system, Schatz said it's very easy to use. "You put the catheter in the left main artery and let it percolate for an hour and dribble in supersaturated oxygen …"

He said the scientific data looks good. But he also expects that one of the biggest challenges in getting interventional cardiologists to adopt the technology — provided it is granted marketing approval — will be the extra 60 minutes of treatment time.

To date, TherOx has been financed largely by venture capital firms, Larkin said. The total VC funding is $140m with the biggest backers being New York-based New Science Ventures and Palo Alto, California-based DAG Ventures.

Challenges

Jeff Cavendish, an interventional cardiologist in San Diego, said that while many companies are trying to improve upon the current gold standard of PCI, he believes any new technology would have to be validated

in large randomized clinical trials comprising thousands of patients to see if they truly improve mortality.

He said microvascular obstruction (MVO) remains a complex issue, but feels that progress has been made in recent years.

Among the biggest improvements in recent years has been the reduction in door-to-balloon times for STEMI patients, which was driven by national campaigns of both, the American College of Cardiology and the American Heart Association. In 2004, the American College of Cardiology (ACC) guidelines stated that primary PCI should be performed within 90 minutes followed by a revision of the guidelines to further improve STEMI management.

"We've gotten pretty good at what we do and pretty fast — when we see an MVO, we address it pretty aggressively," Jeff Cavendish, interventional cardiologist told Medtech Insight.

"Today, most patients are taken to the cath lab right away, which wasn't the case 15 to 20 years ago," Cavendish said. Those improvements, in turn, have led to a lower mortality rate of heart attack patients. He said that while interventional cardiologists could certainly benefit from better techniques to detect and measure MVO, he feels that he has a reasonable sense of when MVO occurs using conventional PCI therapy and treats each patient accordingly.

"We've gotten pretty good at what we do and pretty fast — when we see an MVO, we address it pretty aggressively," Cavendish told *Medtech Insight*. He said that looking at the angiogram and evaluating the blood flow into the coronary microcirculation and the changes on the ECG, along with patients' symptoms resolving, allows interventional cardiologists to gauge MVO and then use current therapies such as vasodilators and antiplatelet agents in mitigating and addressing MVO.

He agrees with Hoem that CMR imaging is more sensitive in terms of detecting even the smallest amount of MVO, but said that interventional cardiologists assume that MVO is an issue with every STEMI patient, and thus, try to address it early on with medical therapies.

Hoem, however, said that the current practice is problematic, because doctors infuse the drugs through the guide sheath or a microcatheter without an occlusion balloon.

"You can think of this as a jet," Hoem said. "If you inject a drug by hand you get a short burst with a high flow rate and as you don't have an occlusion balloon in location in the coronary, and as the heart is beating, part of the drug will be washed out into the aorta and a majority of the drug will go into the collateral vessels where you have low resistance and it will never reach where you need it."

He said CorFlow infuses the drugs distal to the occlusion balloon and "we let the heart massage the drug into microcirculation where it's needed."

Cavendish said while the technology sounds interesting, he said he would want to see clinical data showing that CorFlow's method is superior to using conventional methods. The same goes for all other newer technologies as well.

"If you're going to conduct a study, you have to prove it's better than what we have," Schatz echoed. He said researchers and clinicians have been grappling with the issue of trying to reduce an infarct for many years. "I've been putting stents in for almost 30 years now and we've been doing infarcts for that long and we've never had a single therapy to improve the scar after an infarct."

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