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CorFlow Therapeutics

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**YEAR FOUNDED**

2016

**WHO'S BEHIND IT**

Robert S. Schwartz, MD, an interventional cardiologist and inventor who serves as Director of Education at the Minnesota Cardiovascular Research Institute and Senior Consulting Cardiologist at the Minneapolis Heart Institute; Prof. Martin T. Rothman, MD, who became VP of Medical Affairs for Medtronic's coronary and structural heart disease businesses after 37 years as a practicing interventional cardiologist, having also directed cardiac research and development at the London Chest Hospital and London NHS Trust; and Jon H. Hoem, who has founded/developed several innovative cardiovascular companies (including Medistim ASA), most recently as CEO of Miracor Medical Systems

**UNMET CLINICAL NEED**

Microvascular obstruction (MVO) has been recognized as a pathophysiological mechanism that leads to poor outcomes in many patients following an acute myocardial infarction, yet it cannot easily be diagnosed or treated

**SOLUTION**

The *CorFlow Controlled Flow Infusion (CoFI) System*, a single platform for the detection and treatment of MVO at the time of primary PCI that takes place within hours of acute MI

**FUNDING TO DATE**

$2.5 million in the seed round

# CorFlow Therapeutics: Targeting Microvascular Obstructions in Heart Attack Patients

***Many patients have a poor prognosis after suffering acute myocardial infarction, despite successful recanalization of the blocked coronary artery. Microvascular obstruction is emerging as a target for intervention in many of those patients, and CorFlow aims to be the first to develop a platform to diagnose and treat it.***

by
MARY STUART

When a patient suffers a heart attack due to the complete occlusion of a coronary artery, a situation that's known as ST-segment Elevation Myocardial Infarction (STEMI), the principle therapeutic strategy is to get the artery opened as quickly as possible to restore blood flow, since the longer the heart is deprived of blood, the more cardiac tissue will die. "Time is Muscle" is the guiding principle driving hospitals to decrease their "door-to-balloon" time—how long it takes to treat a STEMI patient with a percutaneous coronary intervention (PCI), and in recent years, the clinical community has done so with ever increasing success. Yet, interestingly, several studies show that these efforts have had little positive impact on STEMI mortality rates—in-hospital mortality hovers around 5-6%, on average, increasing to 7-18% by one year. In addition, outcomes data suggest that some 25% of STEMI patients will develop heart failure within four years of their first heart attack. Now, it's clearer than ever that opening the blocked coronary artery and restoring epicardial blood flow is not the complete solution for many patients.

> *Evidence is accumulating that microvascular obstruction is an independent predictor of a poor prognosis months and years after an AMI.*

Part of the answer might lie in addressing reperfusion injury, the tissue damage that occurs when the artery is reopened. Heart tissue that has been subjected to oxygen deprivation (ischemia) during STEMI undergoes cellular changes that make cells and tissues more susceptible to injury when blood rushes back into the area during reperfusion (which is a very simplistic explanation of a complex process that is also related to an individual's susceptibility to damage). Moreover, the infarct itself and the following reperfusion sometimes also cause the release of embolic debris, which can clog vessels in the microvasculature. Indeed, for at least two decades, microvascular obstruction (MVO) has been known to be implicated in the "no reflow" phenomenon after PCI—the failure of ischemic heart tissue to receive adequate blood flow even after recanalization of the occluded artery, as seen on the control angiogram—and poor prognoses for heart attack patients. Studies have shown that patients with no-reflow have larger left ventricular infarcts and greater rates of mortality than patients in whom normal flow is successfully restored.

Until recently, infarct size reduction was the chief therapeutic strategy for acute myocardial infarction (AMI) patients, and the means of achieving this goal has been the rapid restoration of epicardial blood flow. At this juncture however, the efficiency and success of PCI in so many patients has made it clear that there are patients who fare less well following the procedures, and there are other mechanisms that contribute to higher rates of mortality after an acute myocardial infarction.

One contributing mechanism that has been gaining attention at clinical meetings is MVO in the post-ischemic territory, the clogging of small (<200µm) distal vessels with atherosclerotic debris, blood clots, or platelet plugs. Evidence is accumulating that the presence of microvascular obstruction, as diagnosed with contrast-enhanced MRI post-procedure, is an independent predictor (distinct from infarct size) of a poor prognosis months and years after AMI. However, there is no clinically validated therapy for microvascular obstructions, nor any clinically feasible way to detect them.

**CorFlow Therapeutics AG** was founded in 2016 to solve the MVO problem with a single system that can both detect and treat microvascular obstructions in STEMI and non-STEMI patients in the cath lab. In September 2016, CorFlow raised a $2.5 million seed round from private investors who all have lifelong track records in interventional cardiology, says CEO and co-founder Jon H. Hoem.

The company is less than one year old, but its founders have been studying the phenomenon of microvascular obstruction for over fifteen years now. Interventional cardiologists and researchers Robert S. Schwartz, MD, who serves as Director of Education at the Minnesota Cardiovascular Research Institute and is Senior Consulting Cardiologist at the Minneapolis Heart Institute, and Martin T. Rothman, MD, who became VP of Medical Affairs for Medtronic's coronary and structural heart disease businesses after 37 years as a practicing interventional cardiologist (having also directed cardiac research and development at Barts Health NHS Trust in London), have devoted much of their careers to the problem, as has Jon H. Hoem, the former CEO of **Miracor Medical Systems GmbH**, which is also developing a device therapy for AMI.

Hoem says that for the experienced founding team, the most important requirement for a solution to this unmet medical need was "to fit the workflow that already exists for acute heart attack patients—that is, a technology that goes in over the guidewires already in place after the stent has been placed." While there are devices capable of revealing microvascular obstructions, such as gadolinium-enhanced cardiac MRI, or intracoronary pressure Doppler, or temperature guide wires, these are not easy to use during the emergent situation of an AMI. Says Hoem, "We wanted to pass what we at the company call 'the 2 AM test,' meaning that the technology could be used in the odd hours when some of these patients get to the cath lab."

Thus, CorFlow has developed a single system called *CoFI* (which stands for CorFlow Controlled Flow Infusion), which is delivered via a rapid-exchange pressure guidewire—the tool of standard PCI—into the target coronary artery. It doesn't require the use of contrast agents nor does it add many steps or additional skills to the workflow of primary PCI.

MVO affects as many as 45-55% of AMI patients following PCI despite the restoration of normal coronary flow in the infarct-related artery. The first order of business for CorFlow is the identification of those patients with MVO, so that appropriate treatment can be administered, because, as noted, some half of AMI patients don't develop MVO. (At this early stage in the field, where no clinically validated therapies exist specifically for MVO, appropriate patient selection is also important to get a clear signal of the efficacy of any new therapy and clinical trial.)

CorFlow's *CoFI* (pronounced "coffee") platform consists of a pressure-sensing guidewire, a catheter with an occlusion balloon and infusion lumen (the *RX CorFlow CoFI Catheter*), a drug infusion console, and a proprietary algorithm that measures, in real-time, coronary vascular resistance and the heart's response to flow infusions, parameters that clinicians were not previously able to measure in the cath lab (*see Figure 1*). When vascular resistance and other intra-coronary parameters suggest the presence of MVO, the patient can be treated with the same catheter, which can infuse drugs in the vicinity of the MVO while the coronary artery is still occluded with the *CoFI* catheter.

The bolus infusion of antiplatelet and other drugs at high flow rates is cur-

Figure 1

***CorFlow Controlled Flow Infusion System (CoFI)***

Source: CorFlow Therapeutics

rently one treatment strategy for MVO (again, never studied for this application in randomized, controlled clinical trials). However, the efficacy of that therapy is necessarily compromised by the simple fact that resistance in the microcirculation impedes the delivery of drug to the blockage; the drug will follow the path of least resistance in the coronary circulation. To get around this problem, the *RX CorFlow CoFI Catheter* uses an occlusion balloon to lock infused drug into the zone near the obstruction.

The procedure is as follows: immediately after the coronary circulation is restored by stent placement and/or thrombus aspiration, the CorFlow catheter is placed in the target coronary artery (it is possible to place it in either the right or left coronary artery). The vascular resistance is measured, and if MVO is diagnosed, then the occlusion balloon is inflated and a therapeutic agent is infused in the targeted coronary territory at low flow rates for about 30 seconds. The balloon is then deflated to allow perfusion to return to a normal state. Still in place, the *CoFI* System can measure the effect of the infusion on the obstruction; if MVO persists, the infusion can be repeated until the blockage is cleared.

Hoem notes that reperfusion causes many undesirable side effects besides distal blockages—for example, myocardial edema and endothelial swelling—and these conditions, which might also be implicated in poor patient prognoses, could be amenable to the infusion of particular drugs. But at this very early stage, says Hoem, the company has chosen to administer the approved antiplatelet drug *ReoPro* (abciximab), since it has been observed that many microvascular obstructions are platelet and fibrin plugs. "I'm not saying that we are sure that we have a therapeutic solution for 100% of the problem, but if it affects 40-50% of patients, we now have a way to get an appropriate concentration of *ReoPro*, or some other known platelet-removing drug, down into the microcirculation to resolve these plugs."

Indeed, since the company is developing a very novel approach for the diagnosis and treatment of MVO, Hoem says it has built its prototype with validated off-the-shelf-products, to minimize the number of variables at this stage. "After we have established proof-of-concept with our prototype, we will then deliver an integrated device that incorporates all of our learnings."

***The parameters that CoFI measures correlate with the Index of Microvascular Resistance, which is currently used to diagnose MVO in STEMI patients post-stent placement.***

It will be a long haul, and it began with the fact that there were no animal models mimicking human microvascular obstruction. The company believes, after developing many series of animals with researchers at the University Hospital in Zurich (the same hospital where Andreas Gruentzig did the first percutaneous transluminal angioplasty 40 years ago), that it is now working with a translational nonclinical model. "We have been able to reproducibly create microvascular obstructions, and we have confirmed that with MRI and histology. We know we are on the right track with regard to understanding what creates these microvascular obstructions in the animal model," Hoem says. Furthermore, the company is developing a benchtop microfluidic chip model to simulate MVO and thereby refine the diagnostic and therapeutic algorithms. The animal and benchtop models are key for CorFlow's understanding of the *CoFI* diagnosis and therapy.

CorFlow has collaborations in place to study the *CoFI* prototype in anticipation of its first-in-human clinical trial in Europe, planned for mid-2018. With a team at the Essex Cardiothoracic Centre in Basildon, UK, the company has found that the parameters that *CoFI* measures correlate with the Index of Microvascular Resistance (IMR), which currently is being used to diagnose MVO in STEMI patients post-stent placement. "In other words, we have a very simple method, without having to do any adenosine infusion or multiple measurements, to quickly diagnose these patients. It is an early sign that our simple parameters have value for clinicians," notes Hoem.

The first-in-human trial (called MOCA I, for MVO with *CoFI System* Assessment) will study 40 AMI patients with MVO, comparing the *CoFI* diagnosis to cardiac MRI. The company will follow that study up with a second 40-patient trial in which the patients diagnosed with MVO will be treated with the *CoFI System*.

Many unknowns still exist at this stage: for example, whether the animal models will truly mimic human experience, or the variables around drug administration (which drug, timing, dose are optimal). But by being early, CorFlow has been able to create what it believes will be a valuable intellectual property position. A group of investors who are cardiovascular insiders appears to be convinced; the company expects to close its seed+ financing round to finance the MOCA I clinical trial later this year.