DownStream® System
Device Description

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1 Overview

TherOx has developed a focal hyperbaric oxygen technology to treat ischemic myocardial tissue in heart attack patients. This novel focal approach, unlike hyperbaric chambers that rely on full-body exposure to pressurized oxygen gas, creates a solution of highly oxygen-enriched sterile saline called SuperSaturated Oxygen (SSO_2) solution, which is then mixed with a patient's arterial blood in an extracorporeal circuit and delivered directly to the coronary arteries through an SSO_2 delivery catheter. The procedure, called SSO_2 Therapy, is intended for anterior AMI patients treated with PCI/stenting within 6 hours of symptom onset.

The SSO_2 Therapy procedure utilizes three components: a computerized mobile hardware console, a single-use disposable cartridge, and an SSO_2 delivery catheter. The cartridge has a three-chambered main body that creates SSO_2 solution from inputs of hospital-supplied oxygen gas and physiologic saline, and mixes the SSO_2 solution with autologous patient arterial blood to create oxygen-enriched hyperoxemic blood. The cartridge has draw tubing to withdraw the patient blood and return tubing that attaches to the SSO_2 delivery catheter to return the hyperoxemic blood to the coronary artery. The aim of the treatment is to resuscitate stunned or damaged myocardium, reducing infarct size and thereby improving cardiac function and patient outcomes. An introduction to SSO_2 Therapy is provided herein, followed by detailed descriptions of all three required devices and the principles of operation. A glossary of terms is available in **Section 4**.

2 Introduction to SSO_2 Therapy

The clinical benefits of hyperbaric medicine are realized in a broad range of treatment modalities, including wound healing, ischemic stroke and global cerebral ischemia, cancer therapy, and acute myocardial infarction (AMI)[1]. A clinical course of hyperbaric oxygen therapy entails full-body pressurization at a facility with a pressurized chamber and staff dedicated to its operation and maintenance. The effectiveness of hyperbaric oxygen therapy in treating AMI has been explored in several pilot studies with encouraging results[2,3,4,5,6]. The documented benefits include improvement in global and regional heart function and metabolic markers, reduced restenosis, as well as reduced mortality rates, particularly in high-risk and cardiogenic shock patients. Despite a history of promising results in clinical research, the

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[1] Jain KK. Textbook of Hyperbaric Medicine. Hogrefe and Huber Publishers 1999.
[2] Cameron AJV, Huatton I, Kenmure ACF, *et al*. Haemodynamic and Metabolic Effects of Hyperbaric Oxygen in Myocardial Infarction. Lancet 1966;I:833-7.
[3] Thurston JG, Greenwood TW, Bending MR, *et al*. A Controlled Investigation into the Effects of Hyperbaric Oxygen on Mortality Following Acute Myocardial Infarction. Q J Med 1973;42:751-70.
[4] Swift PC, Turner JH, Oxer HF, *et al*. Myocardial Hibernation Identified by Hyperbaric Oxygen Treatment and Echocardiography in Post infarction Patients: Comparison with Exercise Thallium Scintigraphy. Am Heart J 1992;124:1151-8.
[5] Shandling AH, Ellestad MH, Hart GB, *et al*. Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction: the "Hot MI" Pilot Study. Am Heart J 1997;134:544-50.
[6] Sharifi M, Abdel-Karim I, Fares W, *et al*. Reduction in Clinical Restenosis by Hyperbaric Oxygen Therapy: A Year Later. Presented at the Transcatheter Cardiovascular Therapeutics Conference, September 15 – 19, 2003.

widespread use and acceptance of hyperbaric oxygen to treat AMI patients is limited. Hyperbaric chambers are physically incompatible with a Cardiac Catheterization Laboratory (CCL), and inhibit access to the patient during the critical early recovery phase.

To overcome these limitations, TherOx developed a method and device to deliver localized hyperbaric oxygen therapy directly to the affected area of the heart after acute myocardial infarction. The procedure follows completion of successful percutaneous coronary intervention (PCI) with stenting and fits into the treatment regimen and space limitations of the CCL. The apparatus (equipment) includes a hardware device called the DownStream® System, the DownStream® Cartridge, and a qualified SSO_2 delivery catheter. The DownStream Cartridge is loaded into the DownStream System by a health care professional (user). The cartridge is connected to the patient by a tubing set that connects to an arterial sheath on the draw side and to the SSO_2 delivery catheter on the return side. The SSO_2 delivery catheter is placed over a guidewire into the left main coronary artery (LMCA) by an interventional cardiologist (physician).

The novel concept of creating highly concentrated SSO_2 solution and combining it with arterial blood serves as a means of providing focal hyperbaric oxygen therapy. The techniques and design features developed by TherOx to control the mixing and delivery of supersaturated oxygen solutions ensure that this process does not generate gas emboli[7,8]. The hyperoxemic pO_2 level increases the available oxygen in blood plasma by nearly tenfold, thus providing additional oxygen transfer to ischemic myocardium. The patient's systemic arterial pO_2 level is not changed by administration of SSO_2 Therapy. The potential benefits of SSO_2 Therapy have been examined in pre-clinical and clinical studies; an overview of these studies is provided below.

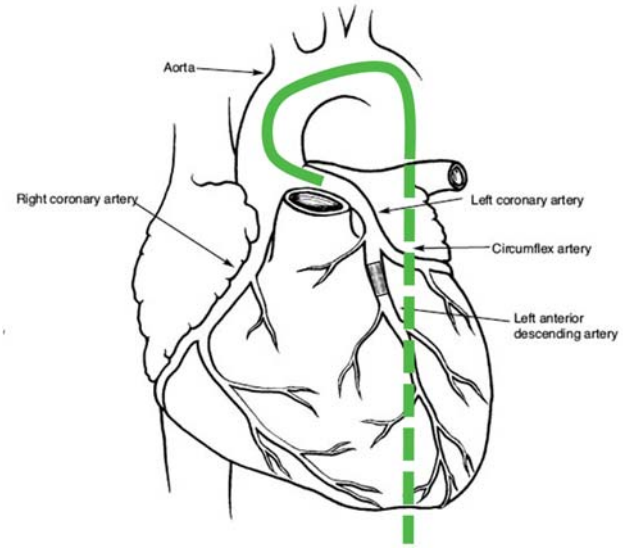
2.1 Clinical Studies of SSO_2 Therapy

Initially, TherOx developed a method for delivering SSO_2 Therapy at 75 ml/min directly into the target coronary artery using an infusion catheter placed through a guide catheter for positioning. Using this method, TherOx conducted three FDA-sanctioned clinical studies for treatment of AMI patients. The first study was a pilot effort conducted on twenty-nine patients; study results included promising trend data towards improved left ventricular ejection fraction and wall motion score in SSO_2 Therapy treated subjects[9], and served as a foundation for the AMIHOT I multi-center randomized trial. No safety concerns were noted during the pilot study. The AMIHOT I study was a randomized trial that examined outcomes in AMI subjects treated with SSO_2 Therapy following PCI with stenting as compared to a Control group receiving PCI with stenting alone for patients experiencing inferior or anterior AMI treated within 24 hours. Study results showed improvement in infarct size reduction, reduced ischemic

[7] Brereton GJ, Crilly RJ, Spears JR. Nucleation in Small Capillary Tubes. Chemical Phys 1998;230;253-65.
[8] Creech JL, Divino V, Patterson W, *et al.* Injection of Highly Supersaturated Oxygen Solutions without Nucleation. J Biomech Eng 2002:124;676-83.
[9] Dixon SR, Bartorelli AL, Marcovitz PA, *et al.* Initial Experience with Hyperoxemic Reperfusion after Primary Angioplasty for Acute Myocardial Infarction. J Am Coll Cardiol 2002:39(3);387-92.

burden, and left ventricular contractility for patients with anterior wall infarctions treated within six hours of symptom onset. This promising AMIHOT I patient cohort was the target population for the pivotal AMIHOT II study. The AMIHOT II study demonstrated that SSO_2 Therapy administered adjunctively following PCI with stenting reduces infarct size with no statistically significant difference in 30-day Major Adverse Cardiac Events (MACE).

Subsequently, TherOx's discussion with key interventional cardiologists and thought leaders revealed that in current practice, delivering the infusion more proximally and away from the PCI injury zone is preferred to the sub-selective approach with the infusion catheter. TherOx made improvements upon the SSO_2 Therapy delivery platform. **Figure 1** shows the current approach to SSO_2 Therapy delivery.



SSO_2 Therapy Delivery (Femoral access)

Figure 1. SSO_2 Therapeutic Delivery Approach

A primary difference is the delivery point change for the infusion, from the sub-selective coronary artery to a proximal position in the left main coronary artery (LMCA). By moving the infusion point proximally, patient safety is improved due to elimination of mechanical manipulation near the PCI injury zone. The infusion may be performed through a catheter in the LMCA. The SSO_2 delivery catheter is discussed in **Section 3.3**. In addition, the infusion is performed in a higher flow main artery, reducing concerns about restricting flow in part of the sub-selective target vessel. Consequently, a second difference with the improved therapy is an increase in infusion flow rate to 100 ml/min in the LMCA.

A 20-patient pilot study was conducted to evaluate the current approach. Study results included promising trend data towards further reduction in infarct size in SSO_2 Therapy treated subjects. No safety concerns were noted during the pilot study, which served as a foundation for the IC-HOT 100-patient trial to confirm the current approach.

The principle of operation is conceptually simple:

- Hospital-supplied oxygen gas is dissolved in physiologic saline under high pressure; the resultant highly oxygenated solution is called SSO_2 solution.

- SSO_2 solution (3.5 ml/min) is combined with the autologous arterial blood (96.5 ml/min) in an extracorporeal circuit, providing hyperoxemic blood at a flow rate of 100 ml/min with an elevated pO_2 level of 1000 mmHg. A sixty-minute procedure requires 210 ml of fluid loading, representing a minimal amount clinically.

- Hyperoxemic blood is infused into the target coronary artery through the SSO_2 delivery catheter for sixty minutes. Existing patient connections, including the femoral introducer sheath, can be used for blood withdrawal and coronary access. It is also possible to place the delivery catheter using radial artery access, using femoral access for blood withdrawal.

2.2 Intended Use

The TherOx DownStream System, DownStream Cartridge, and SSO_2 delivery catheter are indicated for: The preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.

3 Device Description

The equipment required for SSO_2 Therapy includes three components: the re-usable electromechanical console DownStream System (Model DS-1), the single-use disposable DownStream Cartridge (Model DSC-2), and a qualified SSO_2 Delivery Catheter. These components work in unison to perform the processes of SSO_2 Therapy delivery and blood circulation to support hyperoxemic blood delivery. A detailed description of these components is provided herein.

3.1 DownStream System

The DownStream System ("system") is the electromechanical console that controls the cartridge and monitors performance and safety during administration of SSO_2 Therapy. The system is

AC Mains operated (AC-powered) and stationary during therapy, but has wheels and is internally powered for mobile operation. The DownStream System is shown in **Figure 2**.

Figure 2. TherOx® DownStream® System

The major subsystems of the system are the Cartridge Control Subsystem (CCS), Display Subsystem (Display), Power Supply Subsystem (Power Supply), and Oxygen Supply Subsystem (Oxygen Supply). **Figure 3** functionally describes the system.

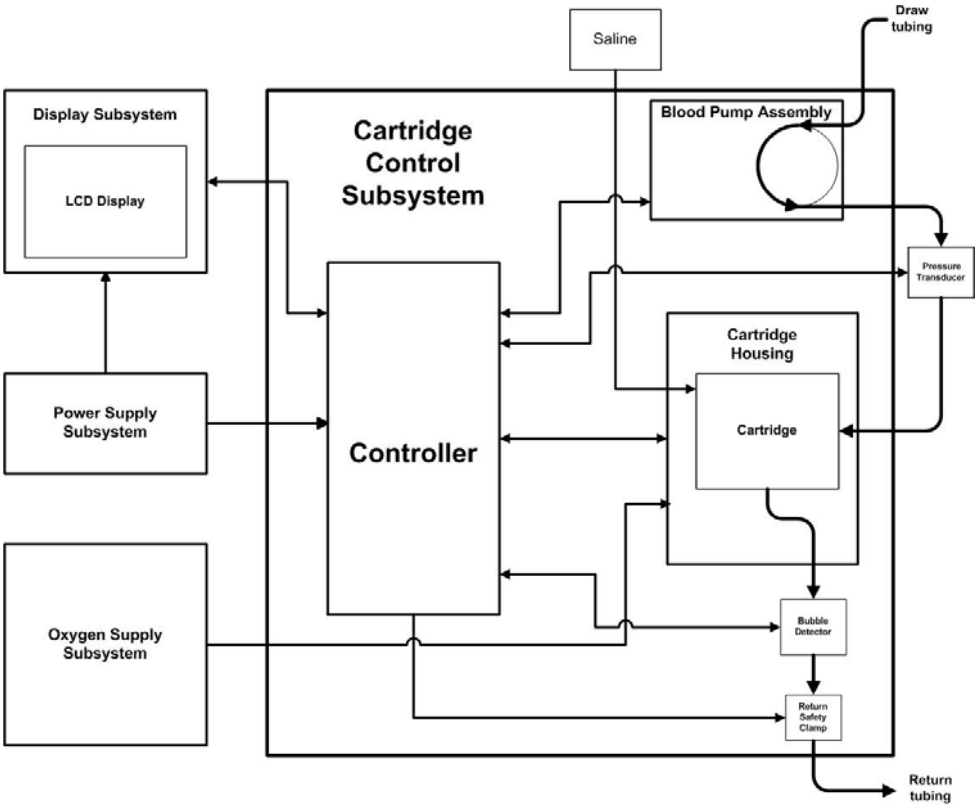


Figure 3. DownStream® System Diagram

3.1.1 Cartridge Control Subsystem (CCS)

The Cartridge Control Subsystem (CCS) is the electromechanical assembly mounted within the DownStream System electronics enclosure. A view of the CCS is shown in **Figure 4**. The CCS has a Printed Circuit Board Assembly (CC PCBA) that monitors and controls the operation of the Cartridge during SSO_2 solution preparation and administration of therapy. The CCS has a Cartridge Housing that houses and operates the Cartridge. An Oxygen Valve controls the flow of oxygen to the Cartridge. A Piston Actuator operates the piston (syringe) inside the Cartridge. A Blood Pump operates on the Cartridge draw tubing to withdraw arterial blood from the patient and pump it through the Cartridge return tubing. A modular jack on the front panel of the CCS connects to the Cartridge Transducer assembly. A combination flow probe/bubble detector on the front panel of the CCS attaches to the exterior of the cartridge return tube. A Prime switch and Emergency Stop switch located on the Display are also part of the CCS.

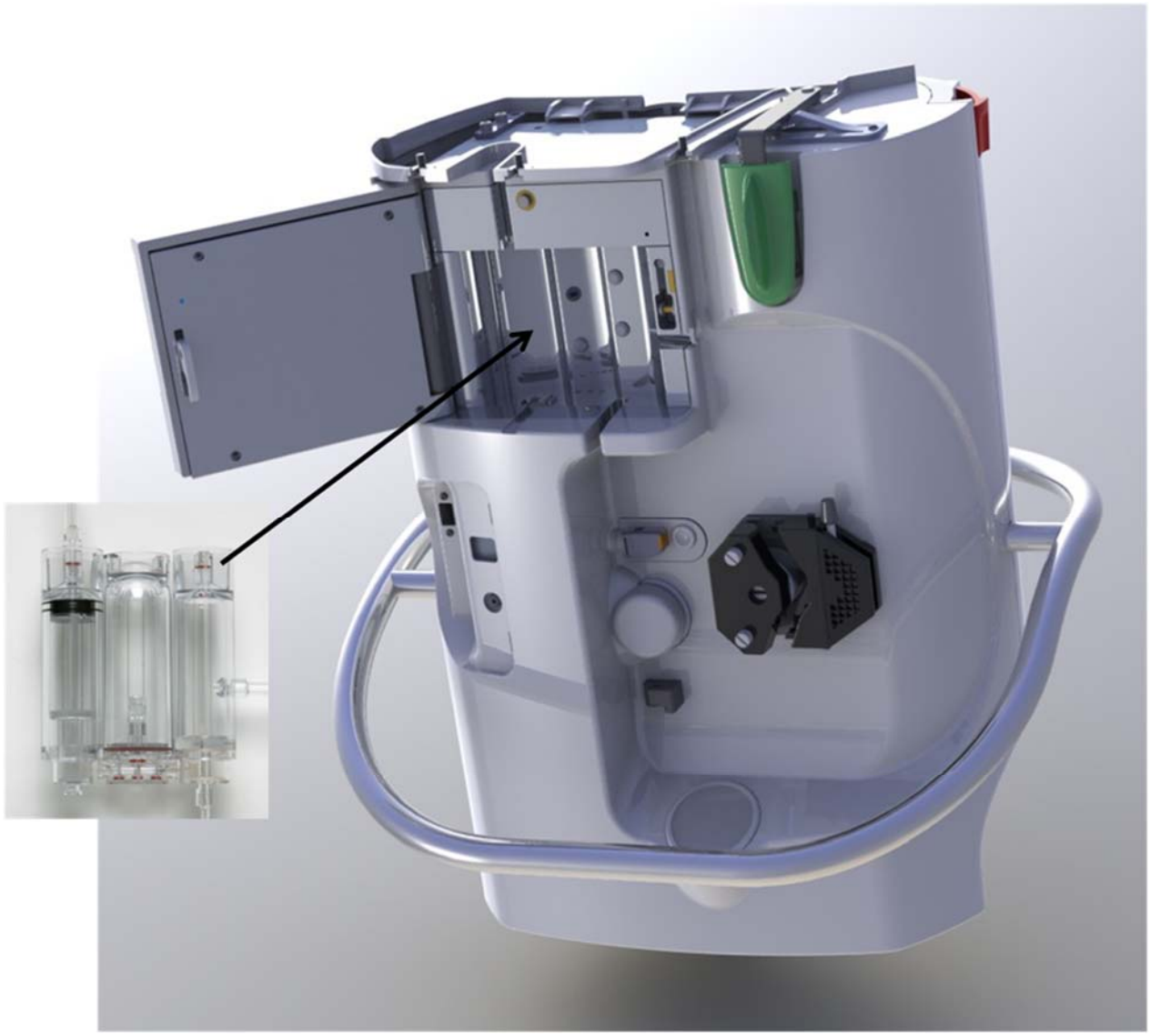


Figure 4. Cartridge Control Subsystem (CCS)

3.1.1.1 Cartridge Controller Printed Circuit Board Assembly (CC PCBA)

The CC PCBA monitors display communication, digital signals from sensors and switches, and analog signals from transducers. Powered electromechanical components within the CCS (Blood Pump, Piston Actuator and all solenoids) are operated by the CC PCBA. A block diagram representing the key components of the CC PCBA is shown in **Figure 5**.

The CC PCBA's two 8051 microcontrollers are the CC 8051 and the CI 8051. The CC PCBA has a Digital Signal Processor (DSP) that contains software to perform bubble detection and flow measurement. The CC PCBA also has a Field Programmable Gate Array (FPGA) logic device that receives commands from the CC 8051, operates powered electronics, and contains Safety Interlock circuitry.

The CC 8051 (Cartridge Control 8051) microcontroller runs the software to control system operation (state machine). The CC 8051 communicates serially with the Display software (via COM port), the DSP (Bubble Detector software) and the CI 8051 (Cartridge Interface 8051). The CC 8051 monitors digital and analog signals from within the CCS and the other subsystems. The CC 8051 receives digital signals from the Cartridge Detect sensor, Door Latch sensor, Pump Lever sensor, Power Lever sensor, Battery status and Power status. The CC 8051 receives analog signals from the Temperature sensors, Oxygen Pressure transducer, and Piston Pressure Transducer (load cell), battery voltage and 24VDC supply voltage. The CC 8051 receives blood flow rate and bubble detection data from the DSP. The CC 8051 receives data from the CI 8051 microcontroller, which processes the signal from the cartridge pressure transducer and stores and retrieves system data in the cartridge PROM. The CI 8051 microcontroller and all associated circuitry are electrically isolated from the CCS electronics to provide patient isolation. The CC 8051 also receives level sensor data, motor encoder data and Safety Interlock status data from the FPGA.

The FPGA receives digital inputs (commands) from the CC 8051 and operates all 24VDC powered electronics. The FPGA controls the five Cartridge valve actuator solenoids, in addition to the Door Lock Actuator, Pump Lock Actuator, Return Clamp and the Oxygen Valve. The FPGA also controls the Piston Actuator stepper motor and Blood Pump servomotor with feedback from optical encoders. The Safety Interlock within the FPGA provides logical input and output functions to enable or disable DownStream System operation based on the monitored inputs. The FPGA device continuously performs this safety function. The Safety Interlock output from the FPGA controls the operation of all solenoids and motors; it can shut down the system safely by disabling 24V.

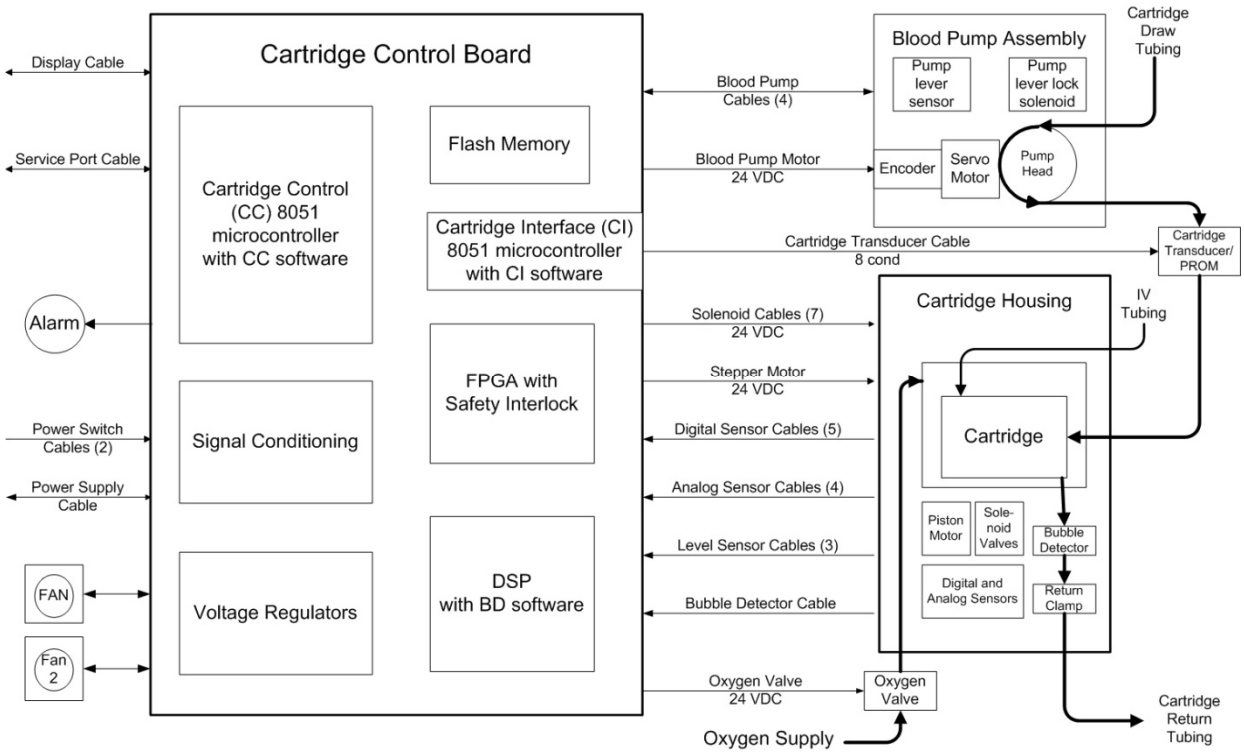


Figure 5. Cartridge Control Subsystem (CCS) Diagram

3.1.1.2 Safety Interlock

The function of the Safety Interlock is to provide a safe response to potential unsafe conditions or out-of-range operating parameters that are detected during the delivery of SSO_2 Therapy. In the DownStream System, the Safety Interlock is an autonomous function incorporated into the FPGA. The Safety Interlock continuously monitors parameters critical to safe system operation. When unsafe conditions are detected, the safety interlock stops therapy by disabling 24 VDC. This safety interlock response initiates several system operations. First, the response automatically disables the blood pump with the pump head locked, which isolates the patient draw line from the system. Second, the response closes the return clamp, isolating the patient return line from the system. In addition, the response disables SSO_2 solution flow, closes the O_2 flow valve, and depressurizes the cartridge by venting the oxygen within the cartridge.

3.1.1.3 Cartridge Housing

The Cartridge Housing is an anodized aluminum enclosure that contains the pressurized Cartridge during operation. The four major parts of the housing assembly are the receiver

block, top plate, bottom plate, and door. The Cartridge Housing door is opened by pulling the door handle down and forward (when it is unlocked). Slots in the Cartridge Housing provide clearance for the cartridge draw tubing, return tubing and IV tubing. The cartridge is automatically aligned with all mechanical interfaces and sensors within the Cartridge Housing when the housing door is closed.

Cartridge Housing Oxygen Supply: Mechanical hardware for the cartridge oxygen inlet is mounted on the top plate of the Cartridge Housing. This plate contains an oxygen port that automatically connects to the cartridge oxygen inlet when the cartridge is installed in the housing. After the cartridge is inserted, the closed door to the Cartridge Housing contacts an actuator that pushes the port into contact with the top of the cartridge. When the door is opened, a spring retracts the port for cartridge loading and unloading.

Cartridge Housing Solenoid Actuators: The Cartridge Housing has solenoid-operated actuators that control the cartridge needle valves, vent valves, and door lock actuator. Five valves within the Cartridge are controlled by (3) Needle Valve Actuators and (2) Vent Valve Actuators. Each valve actuator mechanism has a pin on one end of a lever and a pull-type solenoid on the other. The Oxygen vent valve has a spring that pushes the pin away from the vent valve to maintain the valve open when the solenoid is not energized. For the other four valves, a spring preloads the lever, pushing the pin against the cartridge needle valve or vent valve to maintain the valve closed when the solenoid is not energized. When energized, the solenoid pulls the pin away from the needle or vent valve, allowing the valve to open from pressure inside the cartridge. The door lock has a spring that engages the lock mechanism when the solenoid is not energized.

Cartridge Level Sensors: Three ultrasonic level sensors mounted in the Cartridge Housing receiver block monitor liquid levels within the cartridge chambers. These level sensors are: 1) SSO_2 low level (SSO_2 solution at low level), 2) BMC low level (blood at low level), and 3) BMC high level (blood at high level). Each sensor detects the presence or absence of liquid level within the cartridge at specific locations. When the cartridge is installed in the housing, the spring-loaded sensors press against the cartridge to provide proper coupling for transmission and reception of the ultrasonic signal.

Cartridge Housing Digital Sensors: The Cartridge Housing has digital sensors to detect the presence of a cartridge and to detect if the housing door is fully closed. The Cartridge Detect sensor is a reflective IR sensor that reflects off of the outside surface of the cartridge for detection. The Door Closed sensor is a Hall Effect sensor that detects a magnet in the door handle when the handle is fully latched.

Cartridge Housing Analog Transducers: The Cartridge Housing has analog transducers for measuring temperature (a primary sensor plus a redundant sensor) and oxygen pressure. The temperature sensors are thermistors. The oxygen pressure transducer has a diaphragm with a strain gauge circuit to produce an analog measurement.

3.1.1.4 Oxygen Valve

The Oxygen Valve is solenoid-operated and controls the flow of oxygen from the oxygen supply to the cartridge. The valve is normally closed. The valve is pulsed open in feedback with the oxygen pressure transducer to maintain the oxygen pressure in the cartridge at the desired set point.

3.1.1.5 Piston Actuator

A Piston Actuator operates the piston (syringe) inside the cartridge. The Piston Actuator has a Piston Ram, Ball Screw, Stepper Motor, Stepper Motor encoder, Piston Travel Sensors, and Load Cell.

Piston Ram: The Piston Ram is slotted to engage a key on the cartridge piston when the cartridge is installed into the Cartridge Housing.

Ball Screw: The Ball Screw attaches Stepper Motor to the Piston Ram; it converts the rotary motion of the Stepper Motor into linear motion needed to operate the Piston Ram.

Stepper Motor: The stepper motor has a rotary output that is reduced in speed and increased in torque by a gearbox.

Stepper Motor Encoder: The stepper motor has an optical encoder to detect motor speed and direction.

Piston Travel Sensors: Two slotted IR sensors are used to detect the top and bottom position of the Piston Ram.

Load Cell: A Load Cell measures the force applied to the Cartridge Piston by the Piston Actuator. The Load Cell is a compression type donut Load Cell that uses strain gauge circuitry to produce analog measurements.

3.1.1.6 Blood Pump

The Blood Pump interfaces with the outside surface of the cartridge draw tubing and thus does not have direct blood contact. The system user inserts the cartridge into the Cartridge Housing, the draw side tubing into the Pump Head and the return side tubing into the flow probe during system set-up. The Pump Head is mounted on the front panel of the System enclosure, while the Pump Motor, Pump Motor Encoder, Pump Head Lock, and Pump Head Closed Detector are mounted inside the Electronics Enclosure. A description of these Blood Pump components is provided below:

Pump Head: MasterFlex™ EZ-Load pump head is a three-roller peristaltic pump head that mounts on the front of the system enclosure. The occlusion setting is fully occlusive for the tubing, so the pump head functions as tubing clamp when stopped. The peristaltic pump features an over-center, cam-actuated mechanism with a handle to facilitate loading of tubing. The Pump Head couples to the Pump Motor.

Pump Head Lock: The pump head has a solenoid actuated lock that prevents opening of the pump head during operation.

Pump Motor: The Blood Pump drive has a DC servomotor with a gearbox (31:1 gear reduction). The motor operates on 24 VDC.

Pump Motor Encoder: The Blood Pump has an optical encoder with a resolution of 500 counts per revolution to measure pump speed and direction.

Pump Head Closed Detector: The Blood Pump has a sensor to detect if the pump head is closed. This IR sensor detects a reflective feature when the pump head is in the closed position. The Blood Pump drive will not turn when the Pump Head is not closed.

3.1.1.7 Cartridge Transducer Interface

The CCS has a modular jack on the front of the system enclosure for connection to the cartridge transducer. During setup, the system user inserts the cartridge pressure transducer connector into the modular jack on the front of the system main enclosure.

BMC Pressure: The analog pressure transducer input (BMC pressure) on the cartridge is monitored by the CCS.

PROM Memory: The CCS reads/writes to the PROM memory on the cartridge.

3.1.1.8 Bubble Detector / Flow Probe

The CCS has a Flow Probe mounted on the front of the system enclosure that is used as both a bubble detector and flow meter by the CCS. Transonic Systems, Inc. (Ithaca, NY) supplies the Flow Probe. The Flow Probe is an ultrasonic transducer that clamps onto the return tubing. The system user inserts the return tubing of the cartridge in the Flow Probe during initial system set-up.

Bubble Detector software algorithms operating on the DSP measure the electrical signal attenuation that occurs when a bubble passes through the transducer. Signal attenuation can be described as a drop in voltage of the received signal and the characteristic time to recover to a

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steady signal. The magnitude of the signal attenuation is proportional to bubble size. The software calculates the bubble size and corrects the bubble size for the BMC pressure (measured in proximity of the bubble detector probe), since the bubble volume increases as its local pressure is reduced. The Bubble Detector detects individual bubbles with diameter $\geq$ 100 μm, and quantifies the cumulative bubble volume during therapy. The Bubble Detector software also monitors signal strength continuously, ensuring the return tubing is properly loaded in the bubble detector probe. If the cumulative bubble volume reaches 10 μl during the 60-minute treatment, or if the signal strength is out of range, the Bubble Detector initiates a system shutdown.

The Bubble Detector software also provides blood flow measurement in the cartridge return tubing. The Bubble Detector software utilizes "time of flight" technology to generate flow rate using the Flow Probe.

3.1.1.9 Return Clamp

The CCS operates the return tubing clamp. The return tubing clamp isolates the patient from blood flow in the cartridge. This pinch clamp is normally closed; the system user loads the cartridge tubing into the clamp during initial system set-up.

3.1.1.10 Prime Switch

The CCS has a Prime switch mounted to the Display enclosure that the user must press and hold to start the pump motor and initiate blood flow.

3.1.1.11 Emergency Stop Switch

The CCS has an Emergency Stop (E-Stop) switch mounted on the Display enclosure. The CCS disables all powered electronics (24VDC) upon manual actuation by the system user. The E-Stop switch latches when pressed and must be manually disengaged.

3.1.2 Display Subsystem

The Display Subsystem is the user interface for the DownStream System. A keypad provides user control of system operation. An LCD display provides visual feedback, and a speaker provides audible feedback for the user. Users are cardiologists and nurses administering the treatment in the Cardiac Catheterization Laboratory (CCL). Display Subsystem is shown in **Figure 6**. The user has seven keys (buttons) on the Display Subsystem that control system operation. An LCD display provides visual feedback, and a speaker provides audible feedback for the user. **Figure 7** provides a functional overview (block diagram) of the Display.

Figure 6. Display Subsystem

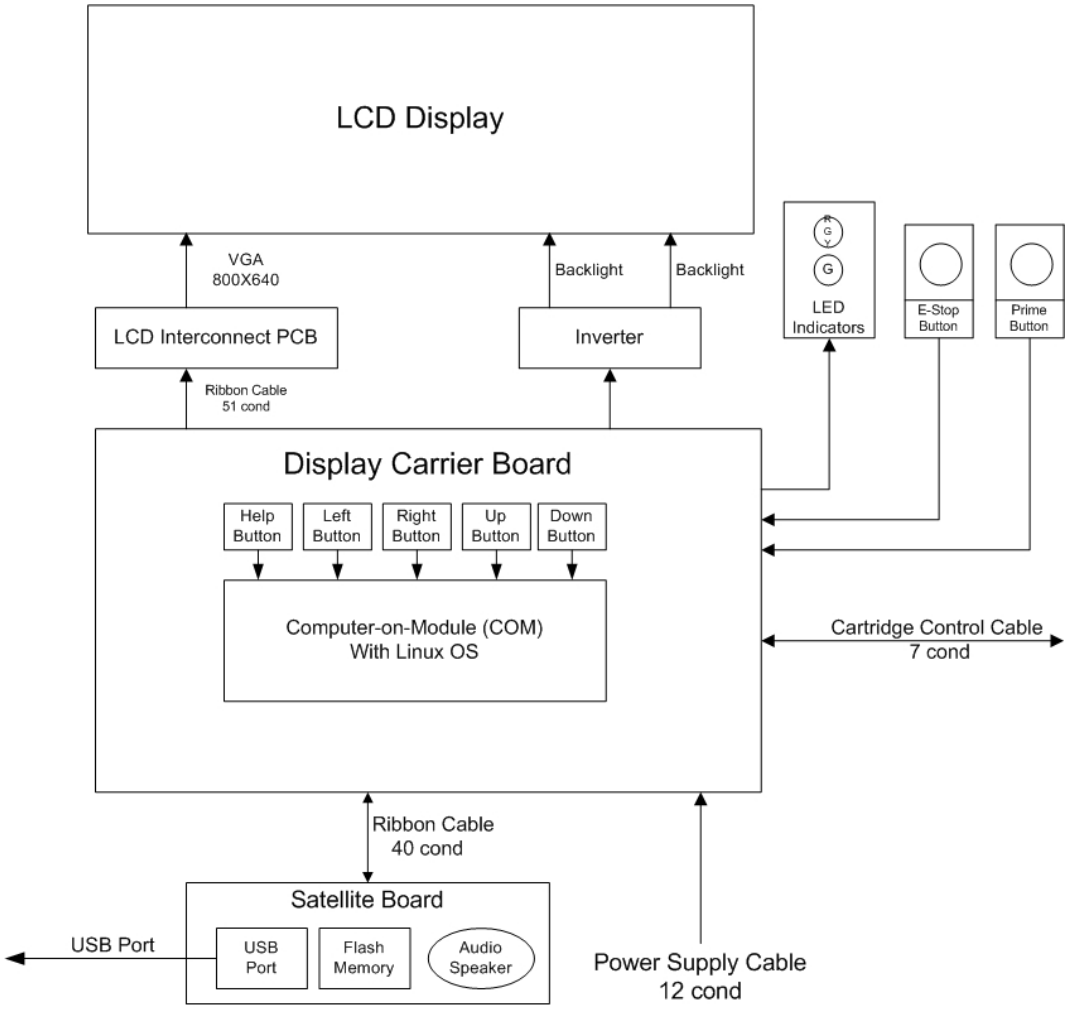

Figure 7. Display Subsystem Diagram

3.1.3 Power Supply Subsystem

The Power Supply Subsystem (Power Supply) is an electronic assembly that provides DC power to the subsystems within the System. The Power Supply receives power from the AC Mains or an internal battery. Component features of the Power Supply include: appliance inlet receptacle with fuses, medical grade 15 VDC power supply, battery charger, DC-to-DC power supplies, and a battery. The Power Supply is shown in **Figure 8**. The Power Supply Subsystem continuously supplies power to the CCS and Display Subsystem. The Power Supply can use either AC Mains or internal battery back-up to provide necessary system power. The battery provides at least one half hour of operation when fully charged. When connected to AC Mains, the system automatically charges the battery. The DC-to-DC power supplies provide fixed voltages for use by electronic subsystems within the DownStream System. **Figure 9** provides a functional overview (block diagram) of the Power Supply.

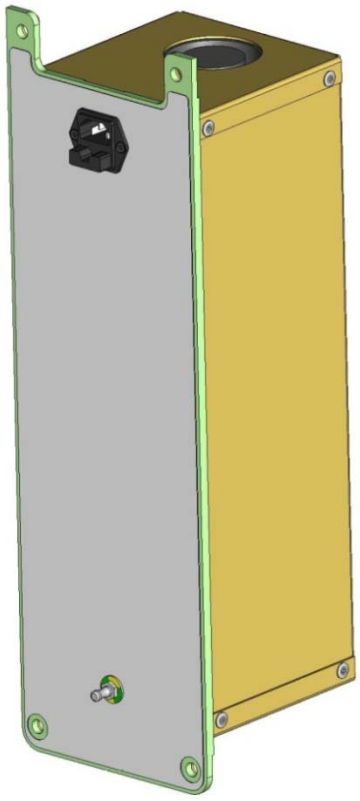

Figure 8. Power Supply Subsystem

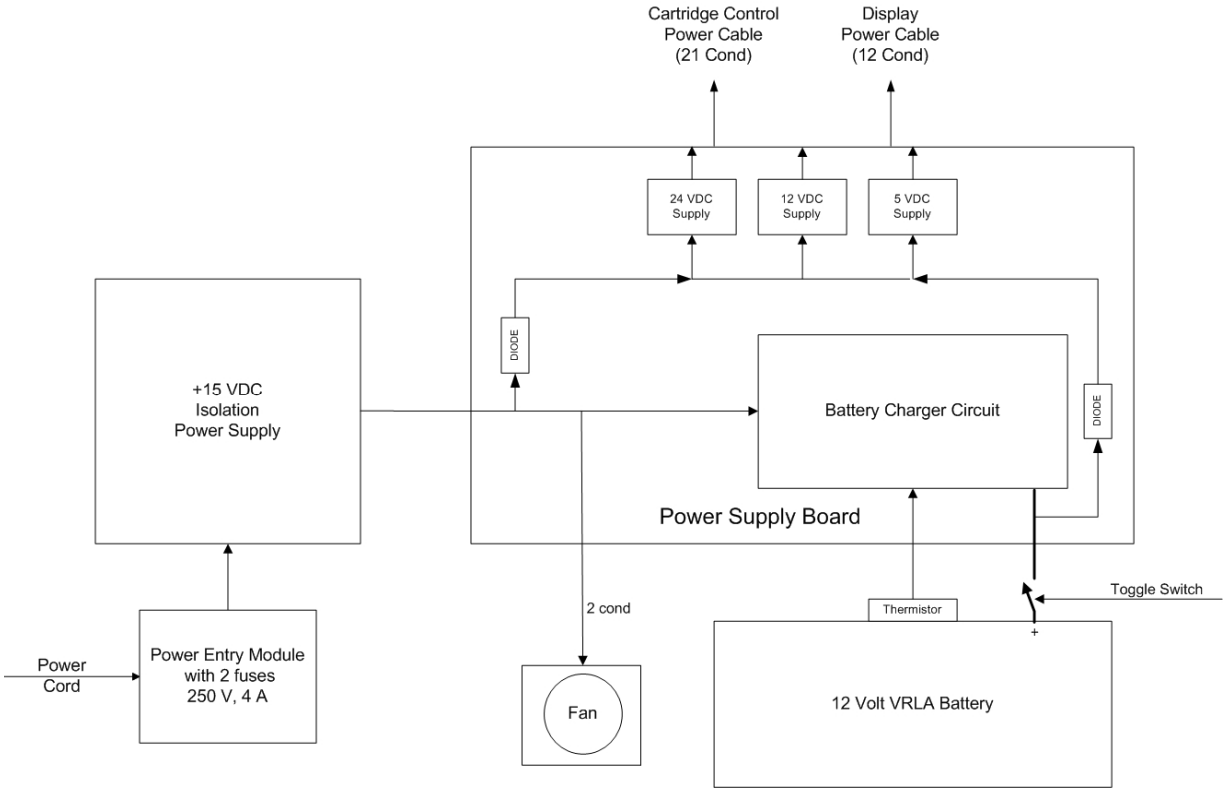

Figure 9. Power Supply Subsystem Diagram

3.1.4 Oxygen Supply Subsystem

The Oxygen Supply Subsystem (Oxygen Supply) is a mechanical assembly that provides regulated oxygen to the CCS. The Oxygen Supply uses pressurized oxygen from a medical grade E-bottle, which it regulates to 750 ± 50 psig. Component features of the Oxygen Supply include: E-bottle (yoke-type) connection, oxygen regulator with 900 psig relief valve, bottle pressure gauge, and oxygen filter. The Oxygen Supply is shown in **Figure 10**. The Oxygen Supply can support over 50 treatments on one E-bottle.

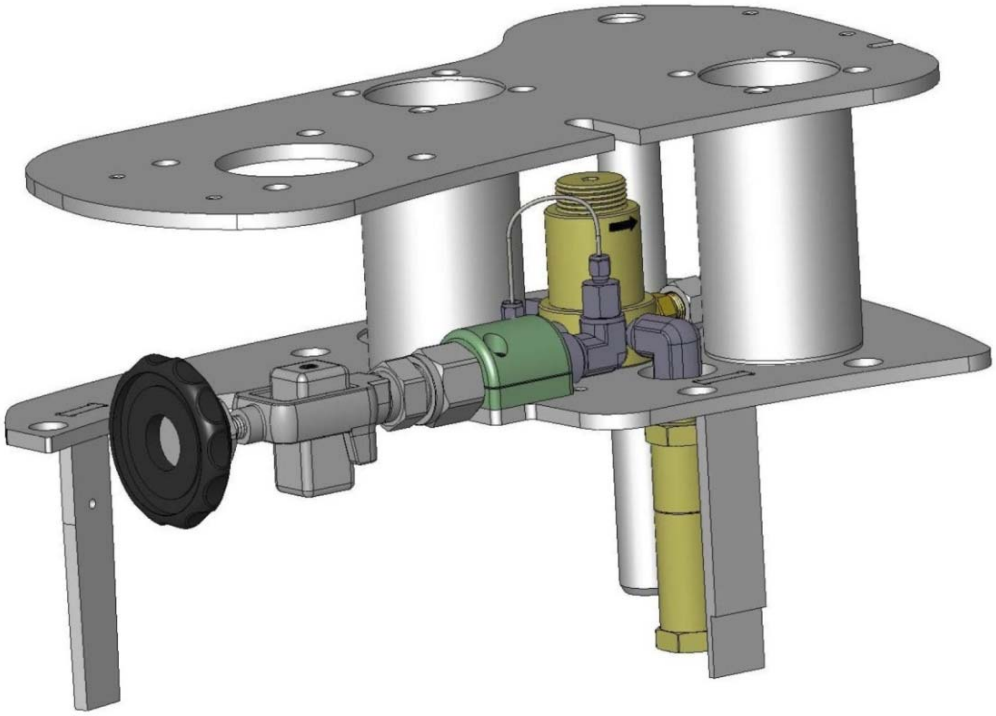

Figure 10. Oxygen Subsystem

3.1.5 System Operation

The DownStream System is operated by a trained health care professional (user). Treatment is initiated in the Cardiac Catheterization Laboratory (CCL). The Display guides the health care professional (user) through setup and clinical operation. The user loads the cartridge into the Cartridge Housing. The system controls the flow of gas and liquid through the cartridge. It controls the saline and SSO_2 solution flow in the cartridge with a motorized piston actuator and

needle valve actuators. The system controls blood flow in the EC circuit with a peristaltic blood pump and a return clamp. The system also controls oxygen supply to the cartridge and depressurizes the cartridge upon shutdown by actuating vent valves in the Oxygen Chamber and BMC. The cartridge is shown loaded into the system in

Figure 11. Procedural operating parameters are programmed into the Cartridge Pressure Transducer during the manufacturing process and are read by the system during operation.

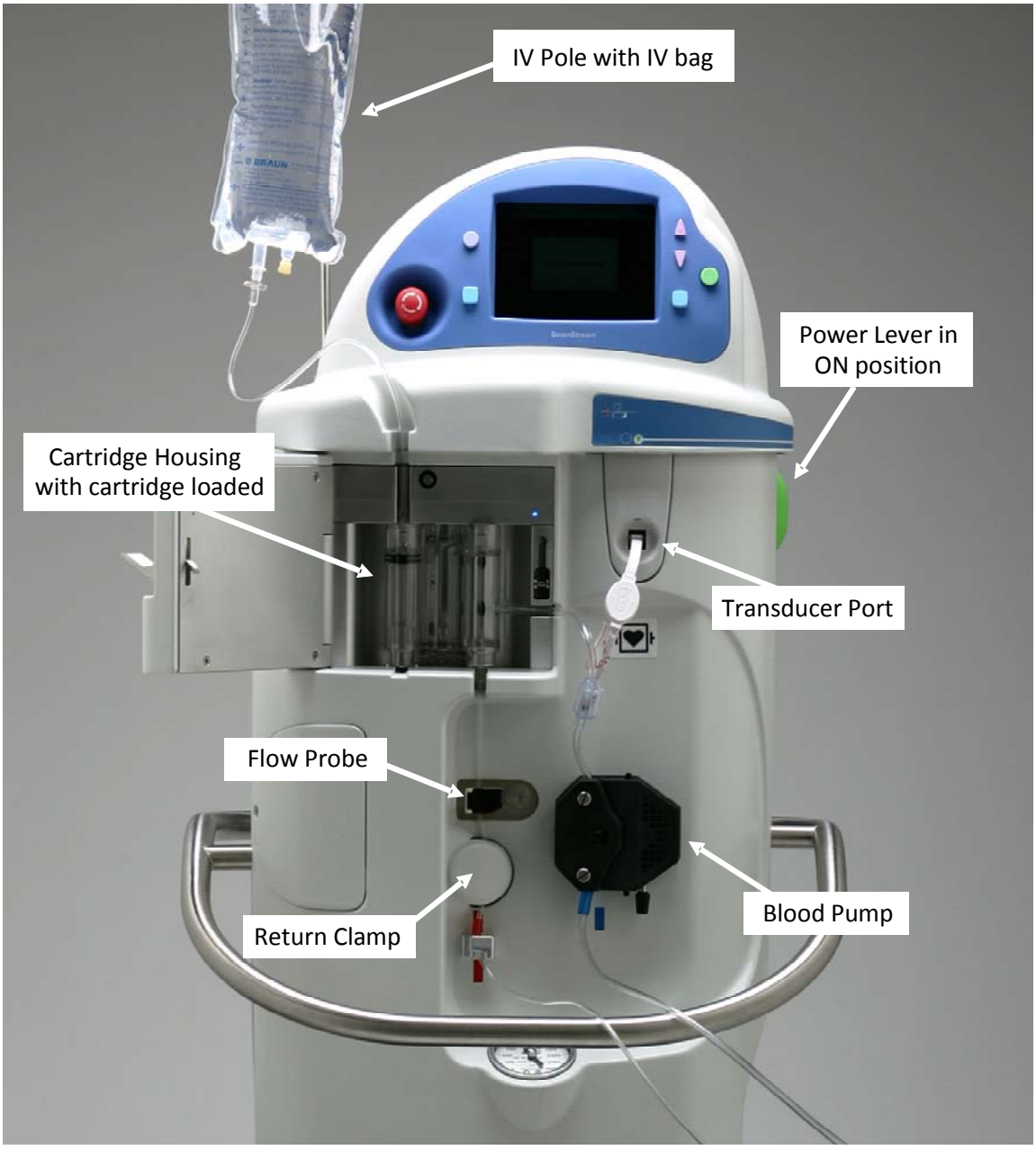

Figure 11. Cartridge Loaded into System

The user loads the DownStream Cartridge into the Cartridge Housing, and then door is closed and latched. The user spikes the cartridge IV line into a saline bag hanging from the IV pole. The user inserts the transducer jack into the transducer port, loads the draw tubing into the blood pump, and loads the return tubing through the flow probe and return clamp.

3.1.5.1 Cartridge Preparation (Prep)

After the cartridge has been loaded into the Cartridge Housing, the user has spiked the saline IV bag, and the Cartridge Pressure Transducer is connected to the system, the user can Prep the cartridge. At the beginning of the Prep sequence, the system reads the operating parameters from the Cartridge Pressure Transducer, setting the SSO_2 infusion duration to 60 minutes and the blood flow rate to 100 ml/min. The purpose of Prep is to check the Fill, Flush and Flow Valves, to saline prime the fluid path in the high-pressure side of the cartridge, establish the minimum liquid level, and pressurize with oxygen. Prep is fully automated after user initiation. The CCS piston actuator drives the cartridge piston down to draw liquid from the saline bag, stopping at the bottom of stroke limit sensor. Then the CCS piston actuator drives the cartridge piston upward to expel any air in the Piston Chamber and to fill the cartridge Oxygen Chamber with saline fluid, until it reaches the top of stroke limit sensor. During the first upward stroke after saline has been drawn into the Piston Chamber, the system checks the Fill, Flush and Flow Valves for leaks. These piston up/down cycles continue until liquid is pushed from the Piston Chamber into the Oxygen Chamber. After the SSO_2 Low level sensor detects the liquid level in the Oxygen Chamber, the SSO_2 System interrupts the sequence. The CCS returns the piston to the top position, verifies SSO_2 solution level, and pressurizes the Oxygen Chamber from the CCS Oxygen Supply. After oxygen pressure exceeds 560 psig, Prep is completed. The user must press the Continue Button to proceed to Blood Path Priming.

3.1.5.2 Blood Path Priming

Prior to initiating blood priming, the physician places the SSO_2 delivery catheter into the patient's left main coronary artery through an arterial sheath. The cartridge draw tubing is connected to the sidearm of a femoral artery sheath (it can be the same sheath, as discussed later in Section 3.3.2, Patient Connections). Priming the EC circuit requires two health care professionals; the user operates the system while the interventional cardiologist performs a wet connection between the return tubing and the SSO_2 delivery catheter after blood priming the return tubing.

Blood priming is initiated when the user presses and holds the Prime switch. This action starts the Blood Pump. During priming, the Blood Pump head rotates at the target speed of 107 RPM with the BMC vent closed and the return clamp closed to verify proper loading of the tubing set. When the BMC vent opens, the BMC is depressurized and priming continues until Blood Level is achieved in the BMC Chamber. When level is achieved, the return clamp opens, the BMC vent valve closes, and the Blood Pump head rotates at half the target speed (54 RPM). Priming is completed after the SSO_2 delivery catheter is connected and steady-state flow is achieved,

when the BMC pressure exceeds a minimum threshold and the Bubble Detector achieves adequate signal strength, and the blood pump returns to the target speed of 107 RPM.

3.1.5.3 Blood Circulation

After blood priming, the Blood Pump withdraws arterial blood at a flow rate of 96.5 ml/min, achieving a return pressure greater than 800 mmHg. The method of flow control is a constant pump head speed of 107 RPM to achieve the set point of 100 ml/min (which includes 3.5 ml/min SSO_2 solution flow). A secondary flow measurement (using the flow probe) is monitored by the system as a redundant safety check to ensure that the blood flow rate is within 33% of the set point of 100 ml/min. When not delivering SSO_2 solution, the system performs saline flush cycles into the BMC Chamber (see Cartridge Flush below).

3.1.5.4 SSO_2 Solution Delivery

The CCS monitors SSO_2 solution level within the cartridge Oxygen Chamber. The SSO_2 solution low-level sensor detects low level when the SSO_2 solution reservoir volume is less than or equal to 5 ml. Detection of low level initiates a fill cycle. The fill cycle starts when the Piston Actuator drives the piston upward to build pressure in the Piston Chamber. After the Piston Pressure (derived from a Load Cell signal) reaches the Oxygen Pressure (derived from Oxygen Transducer signal), the piston begins to deliver saline to the Oxygen Chamber. After a full delivery stroke (3 ml) has been reached, the Piston Actuator changes direction and returns to the bottom of stroke. The fill cycle occurs approximately once per minute during SSO_2 solution delivery.

The SSO_2 flow needle valve actuator remains open throughout the fill cycle, maintaining a constant SSO_2 solution flow rate. The CCS controls the dissolved oxygen concentration (SSO_2 concentration) by controlling the dilution valve actuator during each fill cycle. In other words, a portion of the saline is expressed through the atomizer nozzle, oxygenating it completely, while the remainder of the saline flow is pumped directly into the reservoir. By controlling the relative amounts of these two flows, the SSO_2 concentration is easily controlled.

If the dilution needle valve actuator is open, saline enters through the dilution port. The mix ratio of atomized saline to dilution saline determines the output SSO_2 solution concentration. The CCS software monitors temperature, target oxygen pressure, Fill Cycle Time, blood flow rate, and the arterial pO_2 range setting to determine the SSO_2 concentration set point and thus the ratio of atomization to dilution in the two flows as described above.

3.1.5.5 Cartridge Flush

The purpose of the cartridge flush is to prevent blood from entering into the SSO_2 delivery path when blood is in the BMC but SSO_2 solution is not flowing. The cartridge flush is accomplished by a repeating flush cycle. The cycle starts when the Piston Actuator drives the

piston upward to build pressure in the Piston Chamber until the piston pressure reaches high pressure threshold. After the pressure is reached, the Piston Actuator stops and the flush needle valve actuator opens, enabling saline to flow through the SSO_2 delivery path. When pressure decays to a low pressure threshold, the flush needle valve actuator closes, and the Piston Actuator returns to the bottom of stroke. After the piston returns to the bottom of stroke, another flush cycle starts. This flush cycle is repeated four times per minute, flushing approximately 0.75 ml/min saline into the BMC.

3.1.5.6 Blood Flow Interruption Response and Recovery (Intraprocedure)

The system is designed to detect interruptions in extracorporeal circuit blood flow (e.g., from tube set handling) and to enable recovery to normal operation. The system continuously monitors blood flow parameters in the extracorporeal circuit during blood circulation (described in **Sections 3.1.5.3 – 3.1.5.5**). Specifically, the system monitors peak circuit pressure (BMC Pressure from cartridge transducer) and blood flow rate. When the peak circuit pressure is maintained between 800 – 1700 mmHg and the blood flow measurement is between 66 – 133 ml/min, the system allows SSO_2 Therapy to proceed. If circuit pressure or flow rate go beyond their ranges (*e.g.*, from a temporary tubing restriction), SSO_2 Therapy is disabled and the system displays a message for the operator while recovering pressure and flow into the operating range. If circuit pressure or flow rate does not recover within 30 seconds, or if circuit pressure thresholds of greater than 1800 mmHg or less than 650 mmHg are reached, the system stops the blood pump and initiates a 99-second timeout. In order to continue therapy, the operator must restart the blood pump within 99 seconds (by pressing the Prime button), or the system will automatically end the procedure. If the operator attempts to restart the system but the cause of flow interruption is still present, the system stops the blood pump again and restarts the 99-second timer. If the extracorporeal circuit does not attain normal circuit pressure and flow rate within 200 seconds of entering the recovery mode, the system will end the procedure automatically when the blood pump stops. This recovery mechanism allows therapy to proceed in the event that a momentary stoppage occurs due to flow restriction and does not require the use of a second cartridge.

3.1.5.7 Cartridge Unload

The cartridge is depressurized after system shutdown, and after depressurization the CCS unlocks the Cartridge Housing door. When the Unload command is received from the User Interface, the vent valve actuators open to depressurize the cartridge. The Piston Actuator is commanded to the home position. When the oxygen pressure is below 10 psig and the Piston Actuator is in the top position, all needle and vent actuators open, the door unlocks, and the door may be opened for manual cartridge removal.

3.2 DownStream Cartridge

The DownStream Cartridge ("cartridge") is a sterile, single-use device component that creates SSO_2 solution from saline and oxygen, and then mixes SSO_2 solution with arterial blood to produce hyperoxemic blood. The cartridge has three distinct chambers and three tubing sets. The three chambers are: Piston Chamber, Oxygen Chamber, and Blood-Mixing Chamber (BMC). The cartridge is shown in **Figure 12**.

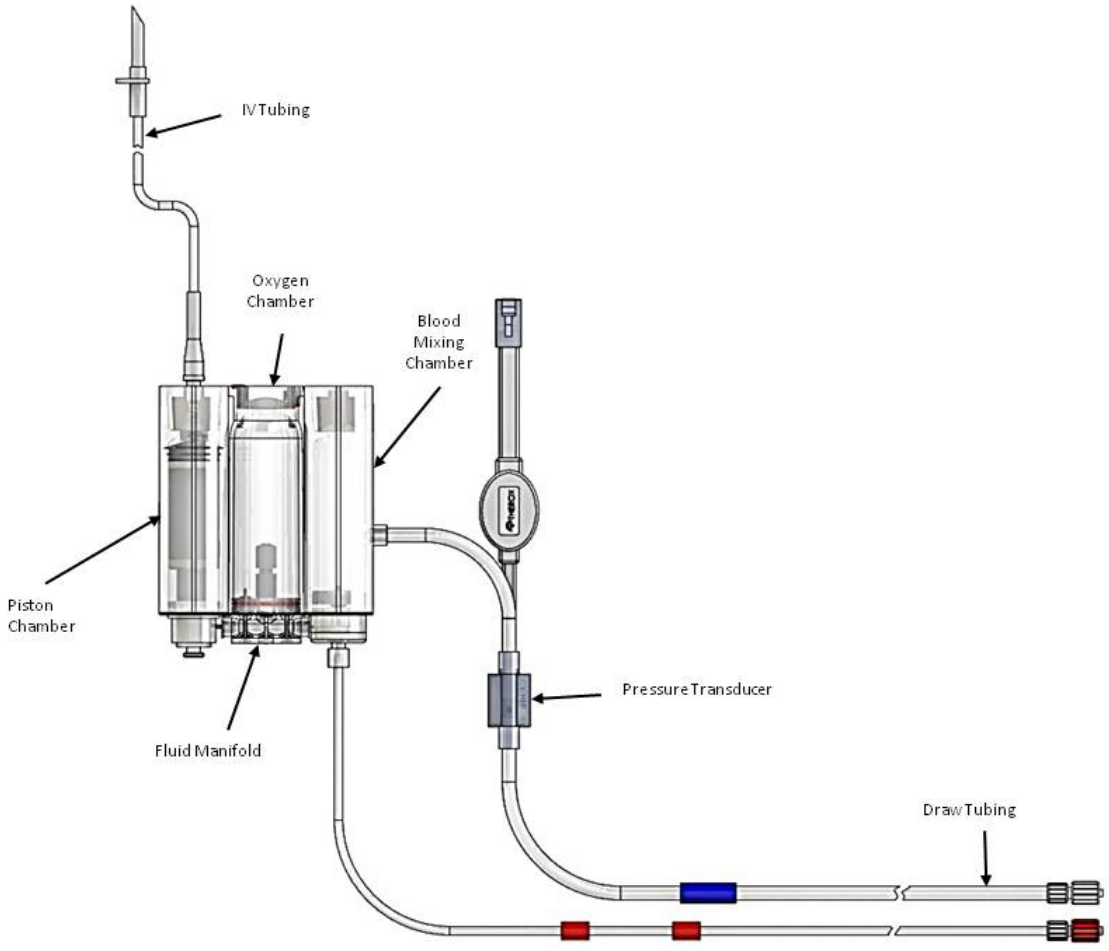

Figure 12. TherOx® DownStream® Cartridge

A Fluid Manifold in the Oxygen Chamber provides the fluid path between the three chambers. The IV tubing set connects the Piston Chamber to a 1-liter bag of sterile saline provided by the hospital. The draw tubing set connects the BMC to an arterial draw sheath (blood from the patient), and the return tubing set connects the BMC to the SSO_2 delivery catheter (hyperoxemic

blood to the patient). The cartridge housing is constructed from molded polycarbonate. The tubing sets are constructed from polyvinyl chloride (PVC). **Figure 13** depicts the fluid flow paths through the cartridge and the fluid flow control features.

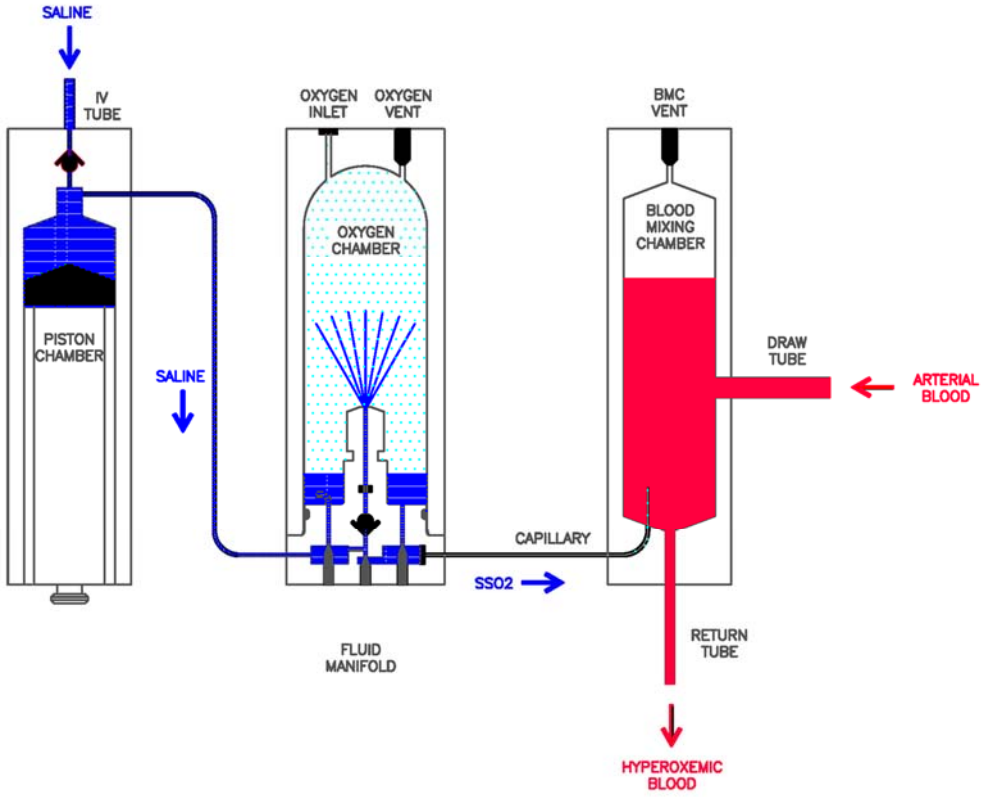

Figure 13. DownStream® Cartridge Fluid Schematic

3.2.1 Cartridge Features

3.2.1.1 IV Tubing and Piston Chamber

The Piston Chamber operates as a syringe pump. The piston mechanically engages the piston actuator during cartridge installation. The piston draws saline supplied from an IV bag on the downstroke, then pressurizes and pushes the liquid out to the Fluid Manifold on the upstroke. The system user connects the IV bag to the Piston Chamber IV tubing with a bag-piercing device (spike) on the tubing. A check valve in the inlet to the Piston Chamber prevents backflow of liquid to the IV bag when the chamber is pressurized (piston upstroke). A small tube at the outlet of the Piston Chamber connects to the Fluid Manifold. The Fluid Manifold prevents backflow of liquid to the Piston Chamber when the chamber is depressurized (piston downstroke). The piston provides 3 ml of saline per stroke (approximately one stroke per minute) during SSO_2 Therapy.

3.2.1.2 Oxygen Chamber

The Oxygen Chamber contains pressurized oxygen regulated to 625 psig by the DownStream System oxygen supply. The Oxygen Valve under the control of the CCS regulates this pressure. The Oxygen Chamber has an inlet that seals against the DownStream Cartridge Control Subsystem (CCS) oxygen port when a cartridge is installed in the CCS housing. The oxygen inlet has a 0.2 μm filter. The Oxygen Chamber also has a vent valve, which is controlled by the CCS.

3.2.1.3 Fluid Manifold

The Fluid Manifold directs saline and SSO_2 solution flow through the three chambers of the cartridge as shown in **Figure 13**. The Fluid Manifold is operated to mix the necessary proportions of normal saline and SSO_2 solution in order to achieve the required concentration of dissolved oxygen for SSO_2 Therapy. The Fluid Manifold has one inlet from the Piston Chamber and one outlet to the capillary. The Fluid Manifold has three ports allowing access to the Oxygen Chamber: a dilution port inlet, a nozzle inlet, and an outlet from the SSO_2 solution reservoir. Saline entering the oxygen chamber through the nozzle is atomized and oxygenated (nearly saturated) by the oxygen gas in the chamber. Saline entering through the dilution port enters below the liquid level of the SSO_2 solution reservoir, thus is not oxygenated. The SSO_2 solution collected in the SSO_2 reservoir is a mixture of oxygenated and non-oxygenated saline. The relative amounts of oxygenated and non-oxygenated saline are controlled in order to achieve the desired oxygen concentration of the effluent. SSO_2 solution exits the reservoir to the capillary outlet. The oxygen gas pressure provides the driving force for fluid flow.

The Fluid Manifold controls the fluid path with three needle valves and one check valve (ref. **Figure 13**). The dilution valve (V1) controls the entrance to the dilution port. The flush valve (V2) allows the piston chamber to deliver saline directly to the capillary. The SSO_2 flow valve (V3) controls the flow of SSO_2 solution from the SSO_2 reservoir to the capillary. The check valve allows forward flow to the nozzle, but automatically closes when the piston moves downward, allowing the Piston Chamber to be filled from the saline bag.

The Fluid Manifold seals to the Oxygen Chamber with an O-ring. Upon system set-up, vertical clearance between the DownStream Cartridge and the CCS housing permits the system user to insert the cartridge. When the Oxygen Chamber is pressurized, the Fluid Manifold pushes downward and closes this vertical clearance. This action locks the DownStream Cartridge in place for control of the piston and full engagement of all valves to their respective valve actuators in the CCS. Pressure inside the Oxygen Chamber also opens the needle valves and oxygen vent valve when the CCS actuators are retracted.

3.2.1.4 Capillary

The capillary is a piece of single-lumen fused silica tubing that delivers SSO_2 solution to the blood-mixing chamber (BMC) at a rate of approximately 3.5 ml/min. The inlet to the capillary

has a 2-μm filter frit protecting the capillary from possible particulate contamination. The capillary delivers the SSO_2 solution from the Oxygen Chamber into the BMC in a continuous, controlled manner that maintains the oxygen in a solubilized state. The design features developed to control the mixing and delivery of supersaturated oxygen solutions ensure that this process does not generate gas emboli[7,8].

3.2.1.5 Blood-Mixing Chamber (BMC)

The BMC mixes SSO_2 solution, bubble-free, with the patient's normoxemic arterial blood to create hyperoxemic blood. Arterial blood pumped from the patient via the draw tubing enters the BMC through a tangential inlet, inducing swirling flow. This swirling flow provides effective mixing of the inflowing arterial blood with the inflowing SSO_2 solution from the capillary. After mixing, the resultant hyperoxemic blood flow has a pO_2 level between 760 - 1240 mmHg. The hyperoxemic blood flows out of the bottom of the BMC into the return tubing.

The BMC has a vent valve that is used to establish the proper level in the BMC for mixing blood and SSO_2 solution. Pressure inside the BMC opens the vent valve when the actuator is retracted. The BMC, which has a finite liquid level height and a substantial fraction of trapped air at the top of the chamber, provides a gas trap for bubbles introduced into the draw tubing. This air cushion at the top of the chamber also effectively acts as a pulse dampener for the peristaltic pump.

3.2.1.6 Draw Tubing and Return Tubing (Blood Path)

The blood path has 1/8” I.D. draw tubing that is sized to fit the Blood Pump head and provide minimal pressure drop upstream of the pump head. The blood path also has 3/32” I.D. return tubing is sized to fit into the flow probe.

The draw and return tubing ends (with luer fittings) are in a sterile pouch and are handed to the physician in the sterile field during set-up. The system user loads the draw tubing into the pump head and draw tubing clamp during set-up. The user also loads the return tubing into the flow probe and return clamp during set-up.

3.2.1.7 DownStream Cartridge Pressure Transducer Assembly

The draw tubing is equipped with in-line disposable pressure transducer. The pressure transducer is supplied by Merit® Medical (Salt Lake City, Utah). The pressure transducer, a Programmable Read Only Memory (PROM) device and a cable with a modular connector form the DownStream Cartridge Pressure Transducer Assembly. The modular connector of the assembly interfaces with a modular jack on the front of the DownStream System. During use, the DownStream System writes to the PROM, which prevents reuse of the cartridge.

3.2.2 Cartridge Operation

The cartridge is inserted into the CCS Cartridge Housing by the user. The CCS Preps the cartridge automatically at user command and controls SSO_2 Solution delivery and concentration. SSO_2 solution produced in the cartridge is mixed with patient blood at a rate of 3.5 ml/min during 60 minutes of SSO_2 Therapy. The peristaltic Blood Pump circulates arterial blood through the Extracorporeal Circuit (EC) comprised of the cartridge draw tubing, Blood Mixing Chamber (BMC), return tubing, and the SSO_2 delivery catheter at a nominal flow rate of 100 ml/min. When blood is circulating but SSO_2 solution is not flowing, the CCS flushes normoxic saline through the cartridge into the blood path at a rate of 0.75 ml/min.

3.3 SSO_2 Delivery Catheter

The qualified SSO_2 Delivery Catheter ("catheter") is a 5F (O.D.) over-the-wire commercially-available catheter that is equipped with a standard luer fitting at the proximal end for attachment to the return line of the cartridge. The SSO_2 delivery catheter has been cleared for coronary use and has been qualified by TherOx for delivery of SSO_2 Therapy. The catheter has an outer diameter (O.D.) of 5F and has a length of 100 cm with a single endhole for fluid output and is shaped to facilitate placement in the left main coronary ostium using a femoral or radial access site. The catheter produces a nominal circuit pressure between 1000 to 1400 mmHg at a return blood flow rate of 100 ml/min. The catheter is placed in the ostium of the LMCA using a guidewire by the trained physician and is connected to the cartridge after blood priming. An example of a qualified catheter is the 5F Boston Scientific Impulse® coronary diagnostic catheter.

3.3.1 Catheter Features

Catheter Size: 5F **Catheter Length:** 100 cm

Luer Hub: A female luer hub enables attachment of the DownStream Cartridge return tubing to the catheter.

Tip Shape: The distal tip shape is designed for placement in the LMCA using a femoral or radial approach, typically from the Judkins Left (JL) class of tip shapes.

Fluoroscopic Visibility: The catheter is radiopaque for visualization under X-ray fluoroscopy**.**

3.3.2 Patient Connections

The DownStream Cartridge draw tubing luer hub connects to the sidearm of a femoral arterial sheath. The preferred sheath placement is coaxial (in one femoral artery) using a 7F femoral arterial sheath as shown in **Figure 14**. Alternatively, the operator may use a second 5F radial arterial sheath for the SSO_2 Delivery Catheter as shown in **Figure 15**. For the coaxial approach, TherOx provides a recommended 7F Merit Medical Custom Sheath Introducer for placement in the femoral artery (otherwise, a standard 8F sheath may be used). The cartridge draw tubing is connected to the side arm of the sheath and the axial port of the sheath is used for catheter placement. The SSO_2 delivery catheter is placed over a guidewire to the desired infusion location in the LMCA. The guidewire is removed prior to initiation of blood flow. When extracorporeal blood flow is initiated, the SSO_2 Delivery Catheter and DownStream Cartridge return tubing are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. The term 'wet connection' requires that both devices are fully blood-primed and free of trapped air bubbles. The cartridge return tubing luer fitting connects to the luer hub of the SSO_2 delivery catheter. The SSO_2 Delivery Catheter set-up options are shown in **Figure 14** and **Figure 15** below.

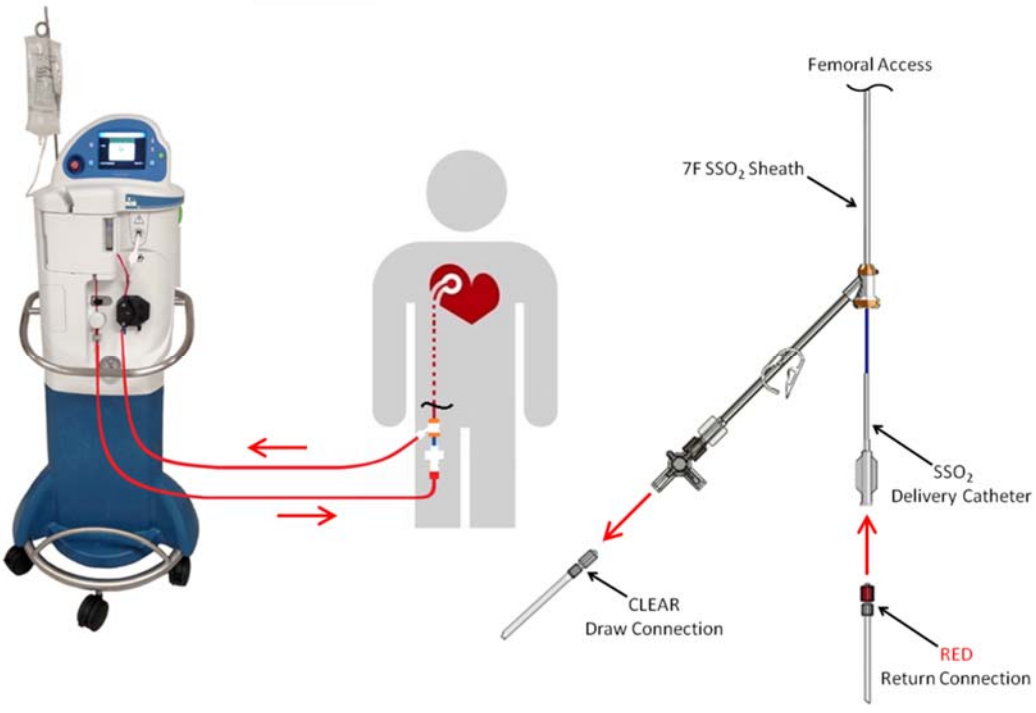

Figure 14. SSO_2 Delivery Catheter Set-Up (coaxial femoral access site approach)

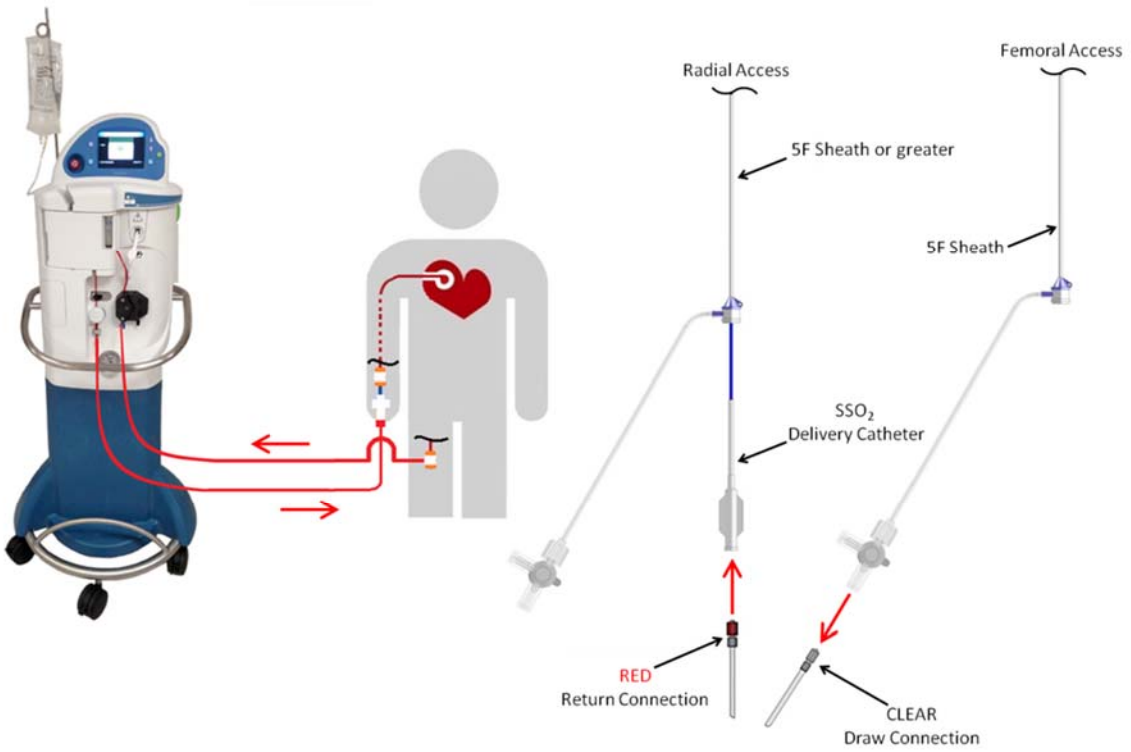

Figure 15. SSO_2 Delivery Catheter Set-Up (radial access site delivery –femoral access site draw approach)

4 Glossary of Acronyms and Terms

AMI: Acute myocardial infarction.

AMIHOT I: "Acute Myocardial Infarction With HyperOxemic Therapy"; a randomized clinical trial conducted by TherOx using SSO_2 Therapy. The AMIHOT I study focused on anterior or inferior STEMI patients treated with PCI within 24 hours of symptom onset.

AMIHOT II: "Acute Myocardial Infarction With HyperOxemic Therapy II"; a randomized clinical trial conducted by TherOx using SSO_2 Therapy. The AMIHOT II study focused on anterior STEMI patients treated with PCI within 6 hours of symptom onset.

BMC: "Blood Mixing Chamber" of the DownStream Cartridge.

CCS: "Cartridge Control Subsystem" of the DownStream Cartridge.

CCL: "Cardiac Catheterization Laboratory."

Delivery Catheter: A qualified 5F diagnostic catheter indicated for coronary use.

DownStream System: TherOx DownStream System, a computerized mobile hardware device.

DownStream Cartridge: TherOx DownStream Cartridge, a single-use disposable cartridge.

Introducer Sheath: A 7F Merit Medical Custom Sheath Introducer (Merit part number K15-00147) or a standard 8F sheath for femoral access.

PCI: Percutaneous coronary intervention.

PROM: "Programmable Read-Only Memory" of the DownStream Cartridge.

SSO_2 Therapy: The preparation and delivery of hyperoxemic autologous blood to coronary arteries immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.

STEMI: "ST-Segment Elevation Myocardial Infarction."

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