SuperSaturated Oxygen Therapy for STEMI

Moving beyond epicardial vessel patency for enhanced myocardial salvage.

BY JACK L. MARTIN, MD, FACC

In April 2019, the FDA approved the TherOx DownStream System for the delivery of SuperSaturated Oxygen (SSO_2) Therapy (TherOx, Inc.) to ischemic regions perfused by the left anterior descending coronary artery. The TherOx DownStream System is intended for use immediately after left anterior descending artery percutaneous coronary intervention (PCI) with stenting that is completed within 6 hours of the onset of ST-segment elevation myocardial infarction (STEMI). This approval represents an important milestone in acute myocardial infarction therapy because SSO_2 Therapy is the first adjunct device or drug in the reperfusion era to achieve the elusive goal of infarct size reduction.[1,2]

Early reperfusion therapy in STEMI has led to a progressive improvement in mortality over several decades.[3] However, despite achieving epicardial vessel patency, myocardial salvage is frequently suboptimal and is associated with severe left ventricular (LV) dysfunction as well as increased morbidity and mortality.[4,5] The mechanisms responsible for extensive myocardial necrosis, despite restoration of epicardial vessel patency, are multifactorial and include microcirculatory dysfunction and reperfusion injury.[4-6] SSO_2 Therapy studies in experimental models demonstrate the potential to favorably impact these factors. When applied after ischemia and reperfusion, SSO_2 Therapy results in capillary vasodilatation, reduced endothelial cell edema, increased tissue-level perfusion, and infarct size reduction.[6-8]

CLINICAL DEVELOPMENT

After the safety and feasibility of SSO_2 Therapy was demonstrated in early human studies,[9-11] the AMIHOT I trial randomized 269 patients after successful PCI for STEMI to receive either SSO_2 Therapy or normal post-PCI care.[12] This study included patients with occlusion of any major epicardial vessels who underwent reperfusion therapy by primary PCI ≤ 24 hours from symptom onset. A post hoc analysis demonstrated that patients with anterior STEMI who were treated with SSO_2 Therapy and reperfused within 6 hours of symptom onset had a smaller infarct size than those in the control group (9% of left ventricle vs 23% of left ventricle, respectively). They also had greater improvement in regional wall motion and ST-segment elevation resolution compared with the control group. Based on these findings, the AMIHOT II trial randomized 301 patients with anterior STEMI that was reperfused within 6 hours of symptom onset to either standard care followed by SSO_2 Therapy or standard care alone.[1]

The primary efficacy endpoint in AMIHOT II was infarct size evaluated for superiority in the intention-to-treat population, measured at 14 to 21 days post-treatment by Tc-99m-sestamibi single-photon emission computed tomography (SPECT). This prespecified analysis involved the formal pooling of AMIHOT I and AMIHOT II infarct size data. A highly statistically significant absolute reduction in infarct size of 6.5% met this prespecified efficacy endpoint, as seen in Figure 1. Previous studies in the fibrinolytic era have demonstrated a strong association between this degree of infarct size reduction and mortality.[13,14]

Additionally, the infarct size reduction in AMIHOT II is more than the 5% reduction associated with favorable clinical outcomes for PCI compared with thrombolytic therapy.[15,16] A meta-analysis of randomized trials in the PCI era of STEMI care demonstrated that infarct size measured within 1 month after primary PCI is a strong predictor of all-cause mortality and rehospitalization for heart failure within 1 year.[17] This relationship between infarct size and outcomes has held true throughout the reperfusion era of STEMI care, from thrombolytic therapy to successful mechanical reperfusion. For these reasons, infarct size reduction remains an important and highly relevant primary efficacy endpoint in contemporary PCI trials.

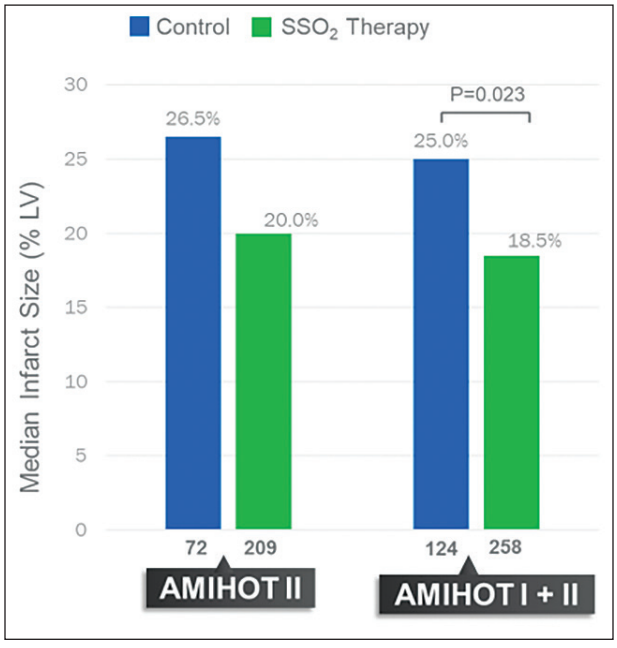

Figure 1. AMIHOT II median infarct size (% LV).

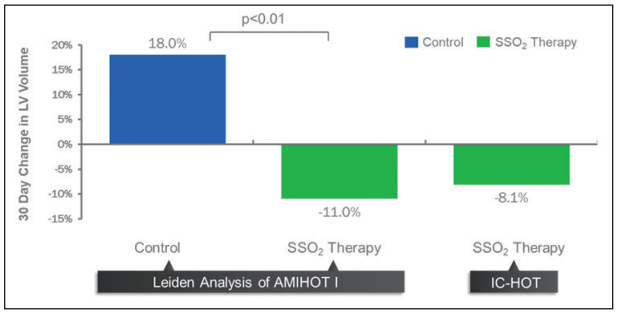

Figure 2. IC-HOT cardiac MRI LV volume results.

AMIHOT II met its prespecified safety endpoint of noninferiority for the composite of major adverse cardiovascular events at 30 days in the intention-to-treat and per-protocol populations, with a nonstatistically significant numeric increase in safety events.[1]

The IC-HOT trial is a single-arm, open-label safety trial in which SSO_2 Therapy was administered after stent implantation in 100 patients with anterior STEMI presenting within 6 hours of symptom onset.[18] The primary endpoint was the 30-day composite rate of net adverse clinical events—including death, reinfarction, clinically driven target vessel revascularization, stent thrombosis, severe heart failure, or thrombolysis in myocardial infarction major/minor bleeding—compared against an objective performance goal of 10.7%. This primary endpoint was met with a net adverse clinical events rate of 7.1% at 30 days; there were no deaths, one instance of stent thrombosis, and one case of severe heart failure.

The IC-HOT 1-year clinical outcomes were compared with those of the INFUSE-AMI trial in a propensity-matched population. In IC-HOT, SSO_2 Therapy resulted in a highly statistically significant reduction in all-cause mortality and hospitalization for heart failure at 1-year follow-up.[19]

Imaging data from IC-HOT shed light on the potential mechanisms that contribute to these favorable long-term clinical outcomes. The IC-HOT trial MRI data demonstrated a reduction in LV volumes from day 4 to day 30, which is consistent with echocardiographic data from AMIHOT I (Figure 2).[10] This is an additional favorable prognostic finding because LV enlargement is strongly associated with death and heart failure after STEMI.[10] The reduction in LV volume over 30 days in SSO_2-treated patients is consistent with recovery toward normal conditions (premyocardial infarction), and it is in contrast with the LV dilatation expected in standard-of-care patients based on previous data.[10] The IC-HOT MRI data also evaluated microvascular obstruction, which is an independent predictor of myocardial salvage and mortality.[20] The 0.3% microvascular obstruction at day 4 compares favorably with historical controls and is consistent with favorable effects of SSO_2 Therapy on the downstream circulation.

CLINICAL IMPLEMENTATION AND FUTURE DIRECTIONS

The TherOx DownStream System consists of an electromechanical console, a single-use disposable cartridge, and a 5F angiographic-style delivery catheter (Figure 3). The cartridge is inserted into the DownStream System for SSO_2 Therapy. The cartridge and attached SSO_2 catheter form a simple circuit for blood flow: normoxic arterial blood is pumped from the patient, oxygenated to hyperbaric levels, and then returned to the coronary arteries via the SSO_2 delivery catheter. During infusion, the catheter tip is located in the ostium of the patient's left main coronary artery with a return blood flow rate of 100 mL/min at a pO_2 level of 760 to 1,000 mm Hg.

In parallel with the AMIHOT and IC-HOT trials, the TherOx DownStream System underwent sequential modifications to enhance ease of use and safety. This included a more intuitive console with improvements to avoid unintended system shutdown for possible bubble- or flow-related signals. The delivery system has also been modified to avoid the need for subselective infusion catheter placement in the left anterior descending coronary artery and permit infusion into the left main coronary with a 5F catheter. The delivery catheter change allows for arterial blood to be drawn from a 7F femoral sheath that contains the infusion catheter and avoids the need

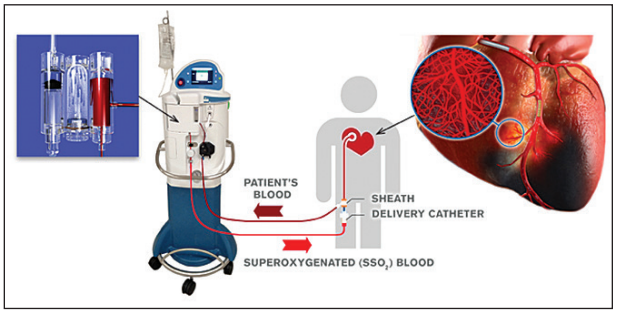

Figure 3. The TherOx DownStream System.

for larger sheaths or an additional contralateral arterial draw line. The use of a 5F infusion catheter also facilitates the application of SSO_2 Therapy in cases where PCI is performed through a radial approach.

With these advancements in technology, SSO_2 Therapy can be readily adopted in all catheterization laboratories performing PCI for STEMI. Importantly, and unlike other potential adjunctive therapies to PCI that are evaluated in STEMI trials, SSO_2 Therapy does not delay door-to-balloon times because it is applied after successful PCI accomplished by standard techniques. This adoption will facilitate the collection of real-world data to complement data from previous and ongoing post-approval studies. Previous SSO_2 Therapy trials excluded patients with cardiogenic shock, but future trials will address this additional important unmet need.

CONCLUSION

SSO_2 Therapy is the first adjunct drug or device therapy to demonstrate further infarct size reduction beyond that achieved by timely PCI in patients with STEMI. It can be safely and seamlessly adopted in cardiac catheterization laboratories that perform primary PCI, and it does not affect door-to-balloon times, given that it is delivered after the completion of PCI with stenting. The reduction in infarct size meets a long-term unmet need to further improve clinical outcomes. Future directions include the study of this technology in additional populations, including those with cardiogenic shock. ■

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Disclosures: None.