Policy Number	**MED202.074**
Policy Effective Date	**02/15/2025**
Policy End Date	**12/31/2025**

Hyperoxemic Reperfusion Therapy

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Hyperoxemic reperfusion therapy (also known as supersaturated oxygen infusion therapy, super oxygenation therapy, aqueous oxygen therapy, or intracoronary hyperoxemic perfusion) **is considered experimental, investigational and/or unproven** for all indications.

Policy Guidelines

None.

Description

Heart disease is the leading cause of mortality in the United States, accounting for more than half of all deaths. Coronary artery disease is the most common cause of heart disease. In a 2023 update on heart disease and stroke statistics from the American Heart Association, it was estimated that 720,000 Americans have a new coronary attack (first hospitalized myocardial infarction [MI] or coronary heart disease death) and approximately 335,000 have a recurrent attack annually. (1) In the case of acute MI, early and successful revascularization can effectively prevent loss of contractile myocardial muscle mass, decrease the infarct size and improve clinical outcomes. However, reperfusion may paradoxically lead to exacerbated and accelerated injury in the myocardium, referred to as myocardial ischemia-reperfusion (I/R) injury. While inflammation is already induced during ischemia, the restoration of blood flow and oxygen delivery further activates inflammatory signaling pathways.

Hyperoxemic Reperfusion Therapy
Hyperoxemic reperfusion therapy is a treatment in which arterial blood is removed, supersaturated with oxygen, and then reinfused into the person's blood stream at the site of cardiac injury. It has been proposed for use in conjunction with percutaneous coronary intervention (PCI) following an anterior acute myocardial infarction (AMI).

Regulatory Status
The FDA granted premarket approval (PMA) (P170027) for the TherOx Downstream® System (TherOx Inc.) in April of 2019 "for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of PCI with stenting that has been completed within 6 hours after the onset of AMI symptoms caused by a left anterior descending artery infarct lesion." (2)

FDA product code: MWG

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The

quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Review of Evidence

Dixon et al. (2002) conducted a pilot study to evaluate the feasibility and safety of intracoronary hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction (AMI). (3) In a multi-center study of patients with AMI undergoing primary angioplasty (PTCA), hyperoxemic blood (pO(2): 600 to 800 mm Hg) was infused into the infarct-related artery for 60 to 90 minutes after intervention. The primary end points were clinical, electrical and hemodynamic stability during hyperoxemic reperfusion and in-hospital major adverse cardiac events. Global and regional left ventricular (LV) function was evaluated by serial echocardiography after PTCA, after aqueous oxygen (AO) infusion, at 24 hours and at one and three months. Twenty-nine patients were enrolled (mean age: 58.9+/-12.6 years). Hyperoxemic reperfusion was performed successfully in all cases (mean infusion time: 80.8+/-18.2 min; mean coronary perfusate pO(2): 631+/-235 mm Hg). There were no adverse events during hyperoxemic reperfusion or the in-hospital period. Compared with baseline, a significant improvement in global wall motion score index was observed at 24 hours (1.68+/-0.24 vs. 1.48+/-0.24, $p < 0.001$) with a trend toward an increase in ejection fraction (48.6+/-7.3% vs. 51.8+/-6.8%, $p = 0.08$). Progressive improvement in LV function was observed at one and three months, primarily due to recovery of infarct zone function. The authors concluded that intracoronary hyperoxemic reperfusion is safe and well tolerated after primary PTCA. These preliminary data support the need for a randomized controlled trial to determine if hyperoxemic reperfusion enhances myocardial salvage or improves long-term outcome.

Trabattoni et al. (2006) sought to assess left ventricle function recovery, ST-segment changes, and enzyme kinetic in ST-elevation myocardial infarction (MI) patients treated with intracoronary hyperoxemic perfusion (IHP) after primary percutaneous coronary intervention (PCI) and compare them with the results obtained in control patients. (4) Twenty-seven anterior ST-elevation MI patients treated < or = 12 hours after symptom onset by primary PCI were subjected to selective IHP into the left anterior descending coronary artery for 90 minutes. They were compared with 24 anterior ST-elevation MI control patients matched in clinical and angiographic characteristics and treated with conventional primary PCI. LV function recovery was evaluated by serial 2-dimensional (2D) contrast echocardiography. Left anterior descending coronary artery recanalization was successful in all patients. After IHP (100% successful, duration 90 +/- 5.4 min), patients showed a 4.8 +/- 2.2 hours shorter time-to-peak creatine kinase release ($P = 0.001$), a shorter creatine kinase half-life period (23.4 +/- 8.9 hours vs. 30.5 +/- 5.8 hours, $P = 0.006$), and a higher rate of complete ST-segment resolution (78% vs. 42%, $P = 0.01$). A significant improvement of mean LV ejection fraction (from [44 +/- 9]% to [55 +/- 11]%, $P < 0.001$) and wall motion score index (from 1.77 +/- 0.2 to 1.39 +/- 0.4, $P < 0.001$) was observed at 3 months in IHP patients only.

In a 2007 prospective, multicenter study, O'Neill et al. sought to determine whether hyperoxemic reperfusion with aqueous oxygen (AO) improves recovery of ventricular function after PCI for AMI. (5) Two hundred sixty-nine patients with acute anterior or large inferior AMI undergoing primary or rescue PCI (<24 hours from symptom onset) were randomly assigned after successful PCI to receive hyperoxemic reperfusion (treatment group) or normoxemic blood autoreperfusion (control group). Hyperoxemic reperfusion was performed for 90 minutes using intracoronary AO. The primary end points were final infarct size at 14 days, ST-segment resolution, and delta regional wall motion score index of the infarct zone at 3 months. At 30 days, the incidence of major adverse cardiac events was similar between the control and AO groups (5.2% vs. 6.7%, p = 0.62). There was no significant difference in the incidence of the primary end points between the study groups. In post-hoc analysis, anterior AMI patients reperfused <6 hours who were treated with AO had a greater improvement in regional wall motion (delta wall motion score index = 0.54 in control group vs. 0.75 in AO group, p = 0.03), smaller infarct size (23% of left ventricle in control group vs. 9% of left ventricle in AO group, p = 0.04), and improved ST-segment resolution compared with normoxemic controls. Authors concluded that intracoronary hyperoxemic reperfusion was safe and well tolerated after PCI for AMI, but did not improve regional wall motion, ST-segment resolution, or final infarct size. A possible treatment effect was observed in anterior AMI patients reperfused <6 hours of symptom onset.

Stone et al. (2009) performed a prospective, multicenter trial in which 301 patients with anterior ST-segment elevation myocardial infarction (STEMI) undergoing PCI within 6 hours of symptom onset were randomized to a 90-minute intracoronary supersaturated oxygen (SSO2) infusion in the left anterior descending artery infarct territory (n=222) or control (n=79). (6) The primary efficacy measure was infarct size in the intention-to-treat population (powered for superiority), and the primary safety measure was composite major adverse cardiovascular events at 30 days in the intention-to-treat and per-protocol populations (powered for noninferiority), with Bayesian hierarchical modeling used to allow partial pooling of evidence from AMIHOT I. Among 281 randomized patients with tc-99m-sestamibi single-photon emission computed tomography data in AMIHOT II, median (interquartile range) infarct size was 26.5% (8.5%, 44%) with control compared with 20% (6%, 37%) after SSO2. The pooled adjusted infarct size was 25% (7%, 42%) with control compared with 18.5% (3.5%, 34.5%) after SSO2 (P(Wilcoxon)=0.02; Bayesian posterior probability of superiority, 96.9%). The Bayesian pooled 30-day mean (+/-SE) rates of major adverse cardiovascular events were 5.0+/-1.4% for control and 5.9+/-1.4% for SSO2 by intention-to-treat, and 5.1+/-1.5% for control and 4.7+/-1.5% for SSO(2) by per-protocol analysis (posterior probability of noninferiority, 99.5% and 99.9%, respectively). Researchers concluded that among patients with anterior STEMI undergoing PCI within 6 hours of symptom onset, infusion of SSO2 into the left anterior descending artery infarct territory results in a significant reduction in infarct size with noninferior rates of major adverse cardiovascular events at 30 days. Several study limitations were noted, one being that although the 6.5% median (4.5% mean) reduction in infarct size with SSO2 represents a greater improvement in myocardial recovery than with thrombolytic (tPA) therapy compared with streptokinase, or with primary PCI compared with tPA, much larger studies than AMIHOT II

would be required to detect an improvement in survival given the currently achieved low mortality rates with contemporary primary PCI.

Hanson et al. (2015) sought to evaluate the feasibility and safety of catheter based SSO2 delivery via the left main coronary artery (LMCA) following primary PCI. (7) Patients with acute anterior STEMI presenting within 6 hours of symptom onset were enrolled at three centers. Following successful LAD stenting, SSO2 was infused into the LMCA via a diagnostic catheter for 60 minutes. The primary safety endpoint was the 30-day rate of target vessel failure (composite of death, reinfarction, or target vessel revascularization). Cardiac magnetic resonance imaging (cMRI) was performed at 3-5 and 30 days to assess infarct size. Twenty patients with acute anterior STEMI were enrolled. The infarct lesion was located in the proximal LAD in 7 cases (35%) and the mid LAD in 13 cases (65%). Following primary PCI, SSO2 was delivered successfully in all cases. Target vessel failure within 30 days occurred in 1 patient (5%). Median [interquartile range] infarct size was 13.7% [5.4-20.6%] at 3-5 days and 9.6% [2.1-14.5%] at 30 days. Researchers concluded that following primary PCI in acute anterior STEMI, infusion of SSO2 via the LMCA is feasible, and is associated with a favorable early safety and efficacy profile.

David et al. (2019) evaluated the safety of SSO therapy selectively delivered to the left main coronary artery (LMCA) for 60 minutes after PCI in patients with anterior STEMI. (8) SSO therapy was administered to the LMCA after stent implantation in 100 patients with anterior ST-segment elevation MI and proximal or mid-LAD occlusion presenting within 6 hours of symptom onset. The primary endpoint was the 30-day composite rate of net adverse clinical events (NACE) (death, reinfarction, clinically driven target vessel revascularization, stent thrombosis, severe heart failure, or TIMI major/minor bleeding) compared against an objective performance goal of 10.7%. Cardiac magnetic resonance imaging was performed at 4 and 30 days to assess infarct size. SSO delivery was successful in 98% of patients. NACE at 30 days occurred 7.1% of patients (meeting the primary safety endpoint of the study); there were no deaths, only one stent thrombosis and one case of severe heart failure. Median [interquartile range] infarct size was 24.1% [14.4%, 31.6%] at 4 days and 19.4% [8.8%, 28.9%] at 30 days. Authors concluded that following primary PCI in acute anterior STEMI, infusion of SSO via the LMCA was feasible and was associated with a favorable early safety profile.

Chen et al. (2020) performed a prospective, open-label, single arm study, evaluating the 1-year clinical outcomes of intracoronary supersaturated oxygen (SSO2) treatment after primary percutaneous coronary intervention (pPCI) in patients with anterior ST-segment elevation myocardial infarction (STEMI) based on its demonstration of infarct size reduction in the IC-HOT study. (9) The IC-HOT study was a prospective, open-label, single-arm study in which 100 patients without cardiogenic shock undergoing successful pPCI of an occluded left anterior descending coronary artery were treated with a 60-min SSO2 infusion. One-year clinical outcomes were compared with a propensity-matched control group of similar patients with anterior STEMI enrolled in the INFUSE-AMI trial. Baseline and postprocedural characteristics were similar in the two groups except for pre-PCI thrombolysis in myocardial infarction 3 flow, which was less prevalent in patients treated with SSO2 (9.6% vs. 22.9%, p = .02). Treatment

with SSO2 was associated with a lower 1-year rate of the composite endpoint of all-cause death or new-onset heart failure (HF) or hospitalization for HF (0.0% vs. 12.3%, p = .001). All-cause mortality, driven by cardiovascular mortality, and new-onset HF or HF hospitalization were each individually lower in SSO2 -treated patients. There were no significant differences between groups in the 1-year rates of reinfarction or clinically driven target vessel revascularization. The study concluded infusion of SSO2 following pPCI in patients with anterior STEMI was associated with improved 1-year clinical outcomes including lower rates of death and new-onset HF or HF hospitalizations. Three study limitations were identified: 1) Analysis from a modest-sized propensity-matched cohort rather than a large randomized controlled trial; 2) The study population represents a selected cohort of patients; therefore, findings of this study may not apply to all patients with STEMI, such as those with cardiogenic shock, nonanterior MI, and others who did not undergo pPCI with stenting within 6 hrs. of symptom onset, and 3) Some details regarding the clinical presentation such as hemodynamic instability and HF symptoms and the completeness of revascularization were not available. Appropriately powered randomized trials are warranted to demonstrate the effect of SSO2 treatment on outcomes in patients with anterior STEMI after successful pPCI.

ECRI

In 2021, ECRI evaluated the TherOx DownStream Supersaturated Oxygen Therapy System for MI. (10) ECRI found that "adding TherOx therapy to PCI and stenting within 6 hours of AMI symptom onset in patients with anterior STEMI may reduce infarct size at up to 30-day follow-up based on evidence from 2 RCTs and 1 nonrandomized comparison study. However, these studies do not demonstrate whether adding TherOx to PCI and stenting within 6 hours of treatment improves patient-oriented outcomes (i.e., mortality, reinfarction rates, target vessel revascularization rates, stroke rates) more than PCI and stenting alone. Additional RCTs reporting long-term follow-up (>3 years) are needed to demonstrate TherOx's comparative effectiveness, but none are ongoing." (Evidence is inconclusive: too few data on outcomes of interest)

Summary of Evidence

At this time, there are a limited number of peer-reviewed published clinical studies evaluating the safety and efficacy of HR therapy for the treatment of individuals with myocardial infarction (MI). Overall study results indicated that hyperoxemic reperfusion resulted in no significant differences in primary outcome measures when compared with controls. Additional well-designed studies with appropriate comparators and long-term results are necessary to establish the clinical utility of hyperoxemic reperfusion therapy in individuals with MI.

Practice Guidelines and Position Statements

There are no professional guidelines and position statements that would likely influence this medical policy.

Ongoing and Unpublished Clinical Trials

A literature search in January 2025 did not identify any clinical trials that might influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0659T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. Feb 21 2023; 147(8):e93-e621. PMID 36695182
2. U.S. Food and Drug Administration. TherOx DownStream System (P170027) (April 2, 2019). Available at <https://www.accessdata.fda.gov> (accessed January 3, 2024).
3. Dixon SR, Bartorelli AL, Marcovitz PA, et al. Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction: results of a pilot study utilizing intracoronary aqueous oxygen therapy. J Am Coll Cardiol. Feb 2002; 39(3):387-392. PMID 11823074
4. Trabattoni D, Bartorelli AL, Fabbiocchi F, et al. Hyperoxemic perfusion of the left anterior descending coronary artery after primary angioplasty in anterior ST-elevation myocardial infarction. Catheter Cardiovasc Interv. Jun 2006; 67(6):859-865. PMID 16649231
5. O'Neill WW, Martin JL, Dixon SR, et al. Acute myocardial infarction with hyperoxemic therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. J Am Coll Cardiol. Jul 2007; 50(5):397-405. PMID 17662390
6. Stone GW, Martin JL, de Boer MJ, et al. Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. Circ Cardiovasc Interv. Oct 2009; 2(5):366-375. PMID 20031745
7. Hanson IV, David SW, Dixon SR, et al. "Optimized" delivery of intracoronary supersaturated oxygen in acute anterior myocardial infarction: a feasibility and safety study. Catheter Cardiovasc Interv. Oct 2015; 86(1):S51-S57. PMID 25512256
8. David SW, Khan ZA, Patel NC, et al. Evaluation of intracoronary hyperoxemic oxygen therapy in acute anterior myocardial infarction: The IC-HOT study. Catheter Cardiovasc Interv. Apr 2019; 93(5):882-890. PMID 30265429

9. Chen S, David SW, Khan ZA, et al. One-year outcomes of supersaturated oxygen therapy in acute anterior myocardial infarction: The IC-HOT study. Catheter Cardiovasc Interv. May 1, 2021; 97(6):1120-1126. PMID 32649037
10. ECRI Institute. TherOx DownStream Supersaturated Oxygen Therapy System (Zoll Medical Corp.) for Myocardial Infarction. Plymouth Meeting (PA); ECRI Institute; 2021 Jan. (Clinical Evidence Assessment).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
02/15/2025	Document updated with literature review. Coverage unchanged. Reference 1 added and reference 2 removed; others updated.
03/15/2024	Reviewed. No changes.
03/15/2023	Document updated with literature review. Coverage unchanged. Reference 10 added.
10/15/2022	Reviewed. No changes.
07/15/2022	New medical document. Hyperoxemic reperfusion therapy (also known as supersaturated oxygen infusion therapy, super oxygenation therapy, aqueous oxygen therapy, or intracoronary hyperoxemic perfusion) is considered experimental, investigational and/or unproven for all indications.