EuroIntervention
2025;21:e774-e775
published online e-edition July 2025
DOI: 10.4244/EIJ-E-25-00031

EDITORIAL

Supersaturated oxygen therapy to reduce myocardial infarct size: time to pay attention!

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Reperfusion therapy in ST-segment elevation myocardial infarction (STEMI) improves prognosis principally by reducing infarct size (ISz)[1]. However, while primary percutaneous coronary intervention (PCI) restores epicardial blood flow in most patients with STEMI, microvascular perfusion and myocardial salvage are frequently suboptimal. In patients with extensive areas at risk (AAR), such as those experiencing anterior myocardial infarction (MI), the resulting large infarctions may lead to adverse left ventricular (LV) remodelling, heart failure (HF), and death[2]. Reducing door-to-balloon times (DBT) to ~90 minutes has reduced ISz and mortality after STEMI; however, further DBT reductions have not clearly improved prognosis[3].

Microvascular obstruction (MVO) is a major cause of suboptimal myocardial salvage after primary PCI[4]; reperfusion injury is the other likely major contributor[5]. Unfortunately, numerous pharmacotherapies and device-based approaches have failed to reduce no-reflow, reperfusion injury and ISz in humans[5,6]. The one exception to date has been supersaturated oxygen (SSO_2) therapy.

In the SSO_2 procedure, the patient's own blood is hyperoxygenated to a level where its partial pressure of oxygen is 7-10 times normal (760-1,000 mmHg), and this is administered to the myocardial infarct zone after reperfusion. SSO_2 has been shown to reduce MVO and improve regional myocardial blood flow by decreasing capillary endothelial cell swelling, and to reduce indices of reperfusion injury and apoptosis. Among 301 randomised patients with anterior STEMI in the pivotal AMIHOT II trial, ISz – measured by technetium-99m (99mTc) single-photon emission computed tomography (SPECT) as a percentage of total myocardial mass at 14 days – was reduced following successful primary PCI from a median of 25.0% in controls to 18.5% in patients in whom SSO_2 was administered selectively to the left anterior descending artery for 90 minutes via an infusion catheter (p=0.02)[7]. Although there was no difference in the 30-day primary safety endpoint between groups, haemorrhagic complications and access site-related events, mostly haematomas, were more frequent in the treatment group. To further reduce complications, an "optimised" SSO_2 approach was developed to afford use of a smaller infusion catheter (5 Fr) to deliver SSO_2 at the origin of the left main and with a shorter infusion duration (60 minutes). In the IC-HOT single-arm study (n=100), the 30-day rate of net adverse clinical events, including Thrombolysis in Myocardial Infarction major or minor bleeding, was only 7.1% in patients with anterior MI treated with optimised SSO_2. This was less than the objective performance goal of 10.7%, and only 1 patient (1.0%) developed target lesion failure[8]. ISz after SSO_2, as assessed by cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement, was consistent with that from AMIHOT II. SSO_2-treated patients from IC-HOT had reduced rates of death or HF hospitalisation compared with a propensity-adjusted control group[9]. On the basis of these studies, the U.S. Food and Drug Administration approved SSO_2 for the treatment of anterior STEMI after successful PCI within 6 hours of symptom onset.

Few studies have examined whether SSO_2 reduces ISz in clinical practice. In this issue of EuroIntervention, König et al[10] report the results from a carefully performed multimodality imaging study in 20 haemodynamically stable patients with anterior STEMI in whom SSO_2 was administered for 60 minutes after primary PCI. An additional 20 similar patients treated by operators not yet using SSO_2 served as a non-randomised control group. Within the first week after PCI, AAR was determined by 2 methods (CMR and fibroblast activation protein inhibitor positron emission tomography), and ISz was determined by 2 methods (CMR and 99mTc-tetrofosmin SPECT).

Article, see page e810

Baseline clinical characteristics, ischaemic times, AAR and PCI success rates were similar between the two groups. The mean ISz by CMR assessment was 32.3±6.9% with control treatment and 20.4±13.1% after SSO_2 (p=0.005), and by SPECT imaging, the mean ISz was 29.2±14.4% with control treatment and 17.4±17.2% after SSO_2 (p=0.014). The myocardial salvage index determined by CMR increased from 19±16% in controls to 47±27% with SSO_2 treatment (p=0.003). MVO assessed by CMR was also markedly lower after SSO_2 compared with controls. Additionally, 6-month LV ejection fraction (LVEF) was improved in the SSO_2 group (58.2±5.6% vs 49.9±6.2%; p=0.009).

The authors should be congratulated for completing a real-world study of SSO_2 therapy in clinical practice. Specifically, the use of three different sophisticated imaging modalities that demonstrated consistent results in AAR, ISz, and myocardial salvage is beyond impressive. The improvement in LVEF at 6 months with SSO_2 has not, to our knowledge, been demonstrated before and complements the reduced ISz finding. Nonetheless, the results from this single-centre, non-randomised, non-adjusted small study must, on their own, be considered exploratory. In this regard, the ISz reduction in the present study was even more impressive than in AMIHOT II (~40% compared with ~26%), which might be explained by between-study differences in patients, residual differences between groups, and unmeasured confounders.

Based on these and other data, a large-scale randomised trial of SSO_2, powered to demonstrate a reduction in death and HF hospitalisation after primary PCI in anterior STEMI, is warranted. Absent such a trial, ISz is accepted by many as a powerful surrogate of death and HF after STEMI. SSO_2 is the only therapy to date shown in a pivotal trial and post-approval studies to reduce ISz, with an effect size from AMIHOT II that might translate to an ~25% decrease in 1-year mortality[2]. As "optimised" SSO_2 has few complications and is delivered post-PCI (thereby not delaying reperfusion), it is time interventionalists start paying attention and increase the use of SSO_2 in high-risk patients with large anterior STEMI.

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Conflict of interest statement

G.W. Stone has received speaker honoraria from Medtronic, Amgen, and Boehringer Ingelheim; has served as a consultant to Robocath, Daiichi Sankyo, Vectorious, Miracor, Apollo Therapeutics, Cardiac Success, Occlutech, Millennia Biopharma, Ablative Solutions, Oxitope, Elixir, Impulse Dynamics, Asceneuron, Myochron, Remote Cardiac Enablement, Valfix, Zoll, HeartFlow, Shockwave Medical, Adona Medical, Abbott, HighLife, Elucid Bio, Aria, Alleviant, FBR Medical, Colibri, Bioventrix, and MedHub; and has equity/options from Cardiac Success, Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWAVE, Orchestra Biomed, Aria, Valfix, and Xenter; his employer, Mount Sinai Hospital, receives research grants from Shockwave Medical, Biosense Webster, Bioventrix, Abbott, Abiomed, Cardiovascular Systems Inc, Philips, Vascular Dynamics, Pulnovo, V-Wave, and PCORI (via Weill Cornell Medical Center). O. Akinmolayemi has no conflicts of interest to declare.

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